UNIVERZA V LJUBLJANI
BIOTEHNIŠKA FAKULTETA

Matej PLANKAR

KOHERENCA V BIOLOŠKIH SISTEMIH IN NJENE APLIKACIJE V BIOLOŠKE ZNANOSTI

DOKTORSKA DISERTACIJA

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COHERENCE IN BIOLOGICAL SYSTEMS AND ITS APPLICATIONS TO LIFE SCIENCES

DOCTORAL DISSERTATION

Ljubljana, 2013

How natural scientists manage to know so surely that they are part of a nature that in itself knows nothing is to me a complete mystery.

Jesper Hoffmeyer

Doktorska disertacija je zaključek doktorskega Podiplomskega študija bioloških in biotehniških znanosti iz področja biologije. Doktorsko delo je bilo opravljeno na Inštitutu BION v Ljubljani.

Na podlagi Statuta Univerze v Ljubljani ter po sklepu Senata Biotehniške fakultete in Senata Univerze v Ljubljani z dne 4. 11. 2010 je bilo potrjeno, da kandidat izpolnjuje pogoje za neposreden prehod na doktorski Podiplomski študij bioloških in biotehniških znanosti ter opravljanje doktorata s področja biologije. Za mentorja je bil imenovan prof. dr. Igor Jerman.

Komisija za oceno in zagovor:

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Datum zagovora: 15. 5. 2013

Podpisani se strinjam z objavo svoje naloge v polnem tekstu na spletni strani Digitalne knjižnice Biotehniške fakultete. Izjavljam, da je naloga, ki sem jo oddal v elektronski obliki, identična tiskani verziji.

Doktorska disertacija je rezultat lastnega raziskovalnega dela.

Matej PLANKAR

KLJUČNA DOKUMENTACIJSKA INFORMACIJA

ŠD Dd
DK 577.3:53:6(043.3)=163.6
KG Koherenca/samoorganizacija/rak/kognicija/nevronske oscilacije
AV PLANKAR, Matej, univ. dipl. biol.
SA prof. dr. JERMAN, Igor, univ. dipl. biol.
KZ SI – 1000 Ljubljana, Jamnikarjeva 101
ZA Univerza v Ljubljani, Biotehniška fakulteta, Podiplomski študij bioloških in biotehniških znanosti, področje biologija
LI 2013
IN KOHERENCA V BIOLOŠKIH SISTEMIH IN NJENE APLIKACIJE V BIOLOŠKE ZNANOSTI
TD Doktorska disertacija
OP V, 113 str., 196 vir.
IJ sl
JI sl/en
AI S koherenco označujemo sinhronizirano ritmično aktivnost oscilirajočih elementov. Koherenca je emergentna in konvergentna lastnost kompleksnih sistemov in omogoča učinkovit pretok energije, daje potencial za kodiranje informacij in omogoča komunikacijo dolgega dosega med različnimi sistemi. Koherentne biološke ritme najdemo na različnih organizacijskih ravneh, v zadnjih nekaj letih pa vse večjo težo pridobiva zlasti koherenca molekulske dinamike, saj na nekaterih molekulskih sistemih dokazano usmerja pretok energije, ki se porablja za biološke procese. S teoretičnega vidika je biološki pomen molekulske koherence poznan in napovedan že dolgo časa in mnogi teoretični modeli predvidevajo pomembno vlogo koherence pri organizaciji bioloških procesov. Pri aplikaciji koncepta koherence na biološke sisteme smo se osredotočili na dva organizacijsko izrazito kompleksna procesa, na izvor in razvoj raka ter na dinamiko nevronskih oscilacij. Pokazali smo, da rak ni enostavno določen z mutacijami specifičnih genov, temveč je sistemska bolezen, ki se sočasno razvija na mnogih sodoločujočih se organizacijskih ravneh kot progresivna organizacijska motnja. Ta karakterizacija je skladna s koherenčno hipotezo raka, ki pravi, da je lahko motnja v koherentni molekulski dinamiki dejavnik, ki vpliva na razvoj raka in ki združuje dosedanje v znanstveni literaturi ločeno predstavljene modele v enoten konceptualni okvir. Na področju kognitivne nevroznanosti smo naredili celovit pregled koherence nevronskih oscilacij kot enega temeljnih mehanizmov informacijskega procesiranja v možganih, ki je funkcionalno povezan z vsemi osnovnimi kognitivnimi funkcijami. Kljub temu pa nekatere hitre makroskopske modulacije nevronske aktivnosti ostajajo nepojasnjene z obstoječimi modeli, zato nekateri raziskovalci predlagajo nesinaptične molekulske interakcije dolgega dosega kot možno razlago. Teoretično modeliranje molekulske dinamike pa tudi nedavni eksperimenti nakazujejo, da je možen nosilec takih interakcij intranevronski matriks, saj omogoča visoko kooperativen oziroma koherenten prenos energije. Predstavili smo pregled teh modelov in pokazali, da molekulska koherenca načeloma lahko funkcionalno dopolnjuje koherentne nevronske oscilacije.

KEY WORDS DOCUMENTATION

DN DD
DC 577.3:53:6(043.3)=163.6
CX Coherence/selforganisation/cancer/cognition/neuronal oscilations
AU PLANKAR, Matej, univ. dipl. biol.
AA prof. dr. JERMAN, Igor, univ. dipl. biol.
PP SI – 1000 Ljubljana, Jamnikarjeva 101
PB University of Ljubljana, Biotechnical Faculty, Postgraduate Study of Biological and Biotechnical Sciences, Field: Biology
PY 2013
TI COHERENCE IN BIOLOGICAL SYSTEMS AND ITS APPLICATIONS TO LIFE SCIENCES
DT Doctoral Dissertation
NO V, 113p., 196 ref.
LA sl
AL sl/en
AB Coherence denotes synchronised rhythmic activity of oscillating elements. Coherence is an emergent and a convergent propery of complex systems, and it enables efficient energy flow, provides a potential for information coding, and allows communication between different systems. Coherent biological rhythms are found at various organisational levels. The coherence of molecular dynamics has recently gained significant attention in biological scientific community since it was experimentally confirmed to guide the flow of energy utilised for biological processes in certain molecular systems. Biological meaning of molecular coherence has been predicted for a long time, and many theoretical models suggest its generic role in organising biological processes. In applying the principle of coherence to biological systems we focussed to two organisationally highly complex phenomena, namely to the cancer origin and development, and to dynamics of neuronal oscillations. We show that cancer is not simply determined by mutations at specific genes, but rather is a systems disease that develops at multiple organisational levels as a progressive organisational disorder. This characterisation is consistent with the coherence hypothesis of cancer, which predicts an impairment of coherent molecular dynamics as a factor contributing to cancer development. The coherence hypothesis unites theoretical models so far separately proposed under a common conceptual framework. Within the field of cognitive neuroscience we reviewed neuronal oscillatory coherence as a fundamental mechanism of information processing in the brain, which functionally underlies all basic cognitive functions. However, very transient macroscopic modulations of neuronal activity remain unexplained by conventional models, and some researchers suggest that nonsynaptic long-range molecular interactions could provide an explanation. Theoretical modelling as well as recent experimental corroboration indicate that the intraneuronal matrix allows highly cooperative, or coherent, modes of energy transfer. We review those models and show that coherence of molecular dynamics may functionally complement coherent neuronal oscillations.

KAZALO VSEBINE

1 PREDSTAVITEV PROBLEMA IN HIPOTEZE

1.1 UMESTITEV RAZISKOVALNE TEME V ZNANSTVENI IN TERMINOLOŠKI KONTEKST

Vprašanje o zakonitostih življenja sodi med temeljne naravoslovne probleme in ga lahko uvrstimo ob bok vprašanjem o naravi zavesti ali izvoru vesolja. Sodobni pogledi na temeljni ustroj življenjskih procesov segajo v začetke novoveške filozofije. Descartesov substančni dualizem (stroga ločitev realnosti na dve temeljni, medsebojno izolirani substanci, materialno in duševno) velja za eno največjih prelomnic v zgodovini znanosti, saj je izločil subjektivnost iz znanstvenega raziskovanja in omogočil prodor sodobne pozitivistične znanosti, ki temelji na empirični metodi (Favareau, 2007). Strogi dualizem je zaznamoval tudi pojmovanje življenja, ki je postalo izrazito mehanicistično: organizme so začeli obravnavati kot deterministične stroje oz. avtomate, podvržene slepim mehanskim silam, ki jih vodijo fizikalni zakoni in se konceptualno ne razlikujejo od neživih objektov, k čemer je v veliki meri pripomogel razvoj fizike in astronomije v 17.stoletju. Metodološki redukcionizem, ki se je oblikoval znotraj tovrstnega mehanicističnega naravoslovja, je omogočil mnoga temeljna odkritja o zgradbi in delovanju organizmov in tudi danes prevladujoče usmerja razvoj bioloških znanosti. Obenem pa ontološki redukcionizem (fizikalni determinizem, atomizem) in njegova izpeljava na biologijo – zlasti genski determinizem, ki pojmuje gene za osnovne enote in determinante življenjskih procesov – pomembno sooblikuje ideološko podstat bioloških znanosti in je vplival zlasti na razvoj nekaterih molekularno bioloških znanosti, npr. genetike in biotehnologije.

V razsvetljenstvu se je začel oblikovati drugačen, v marsičem nasprotujoč pogled na življenje, katerega temeljna značilnost je postala organizacijska avtonomnost: organizmi obstajajo sami od sebe in sami za sebe, so subjekti narave. Immanuel Kant je imel organizme za avtonomne celote z lastnim (notranjim) smotrom, nedostopnim naši presoji. Menil je, da se organizmi izognejo determiniranosti, ki jo vsiljujejo mehanski zakoni, saj za njih velja dvojna vzročnost, poleg »progresivne« (materialna in mehanska) velja tudi »regresivna« (formalna) vzročnost[1]: organizmi so zanj celote, ki so produkt svojih sestavnih delov, a prav tako so ti deli odvisni od svojega vzajemnega so-delovanja in so-določanja, torej so v razmerju do celote svoj lasten vzrok in posledica. »Le kadar je

[1] Danes govorimo o krožni (ang. circular) oziroma spuščajoči se (Gregorčič, 2010) vzročnosti (ang. downward causation) (Noble, 2008; 2010).

izpolnjen ta pogoj, bo tak produkt organizirano in samo-organizirano bitje, ki ga lahko enačimo z naravnim smotrom« (prosti prevod po Van de Vijver, 2006).

Čeprav je že Kant opisal posebnost organizacije živij bitij in jo označil kot samoorganizacijo, je ta koncept zaradi pomanjkanja metodoloških orodij, pa tudi zaradi vitalističnih konotacij, ostal na obrobju znanosti vse do približno sredine 20.stol., ko se je začela razvijati multidisciplinarna teorija kompleksnosti: sprva pod okriljem kibernetike, kjer je bil zlasti pomemben William Ross Ashby, kasneje pa nelinearne termodinamike (Ilya Prigogine), sinergetike (Hermann Haken) in kibernetike drugega reda (npr. Bateson, von Foerster, Maturana). Na razvoj teh disciplin so močno vplivale matematične teorije, ki so se jim postopoma priključevale: teorija kaosa, bifurkacij, samoorganizirane kritičnosti, samoorganiziranih mrež. V zadnjih dveh desetletjih (za mejnik nekateri pojmujejo odkritje oziroma matematično formalizacijo samoorganizirane kritičnosti) postaja teorija kompleksnosti vse bolj samostojna znanstvena disciplina, ki opisuje veliko skupino dinamičnih pojavov v bioloških, fizikalnih, kemijskih, računalniških, ekonomskih, sociooloških in kognitivnih sistemih, pri čemer uporablja lasten nabor teoretičnih konceptov in metodoloških orodij (De Wolf in Holvoet, 2005; Goujon, 2006; Kauffman, 2008; Solé in Goodwin, 2000; Sporns, 2007). Z uporabo teorije kompleksnosti v bioloških sistemih se ukvarja sistemska biologija[2] (Noble, 2010; Saetzler in sod., 2011).

Kompleksnost v splošnem označuje visoko stopnjo interakcij med mnoštvom elementov dinamičnega sistema, ki zaradi notranjih preprek povzročijo zmanjšanje števila naključnih interakcij in povečanje števila kooperativnih interakcij, s čemer se poveča organiziranost sistema kot celote (De Wolf in Holvoet, 2005; Di Marzo Serugendo in sod., 2004). Različna merila kompleksnosti povzema Sporns (2007) in zajemajo algoritemske ocene informacijske bogatosti ter strukturna in organizacijska (npr. hierarhičnost) merila. Kompleksnost je torej tesno povezana s samoorganizacijo. Organizacija sistema se navadno ne povečuje zvezno, pač pa z nenadnimi spremembami blizu kritičnih točk

[2] Tu velja opozoriti na dvoje različnih pojmovanj sistemske biologije (O'Malley in Dupré, 2005): na t.i. pragmatično sistemsko biologijo (ki bi jo v slovenščini morda ustrezneje označili kot biologijo sistemov), ki se ukvarja z matematičnim modeliranjem in statistično obdelavo molekulskih mrež podatkovnih sistemov, t.i. -ómike (genomi, transkriptomi, proteomi, metabolomi, itd.) in interakcij med njimi ter je metodološko redukcionistična, in na t.i. sistemsko teoretično biologijo (ali konstruktivno sistemsko biologijo (Kaneko, 2006)), ki za razumevanje bioloških procesov uporablja teorijo kompleksnosti in je konceptualno holistična, kar pomeni, da kot znantveno teoretično paradigmo privzema ontološki emergentizem oziroma njegovo biološko zvrst, organicizem. Izraz sistemska biologija je sicer v svojem izvornem (holističnem) pomenu utemeljil von Bertallanfy (1969). Kljub temu mnogi raziskovalci, delno zaradi sinergije med obema pristopoma in delno verjetno tudi zaradi nedorečenega izrazoslovja, pojem sistemske biologije uporabljajo nespecifično (glej npr. »Whole-istic Biology«, tematska izdaja Science, 2002).

nestabilnosti, ki jim pravimo zlomi simetrije (Anderson, 1972) in v termodinamičnih sistemih ustrezajo faznim prehodom (Nicolis in Prigogine, 1977). S termodinamičnega vidika (s tem vključujoč tudi biološke sisteme) so kompleksni sistemi disipativne strukture, tj. odprti sistemi daleč od termodinamičnega ravnovesja, ki za povečanje in vzdrževanje notranje organizacije izkoriščajo pretok energije iz okolice v sistem, navzven pa izvažajo (disipirajo) entropijo (Feltz in sod., 2006; Karsenti, 2008; Kauffman, 2008; Nicolis in Prigogine, 1977; Solé in Goodwin, 2000).

Ena temeljnih lastnosti naravnih sistemov, ki omogoča nastanek kompleksnosti – in torej eden od mehanizmov samoorganizacije – je, da se spontano vzdržujejo na kritični meji med stabilnostjo (redom) in nestabilnostjo (determinističnim kaosom), čemur pravimo samoorganizirana kritičnost (ang. self-organised criticality), za katero je značilna statistična porazdelitev kritičnih dogodkov brez lastne časovne in prostorske skale (potenčni zakon, ang. power law; v podobnih oblikah tudi Zipfov zakon, Paretovo pravilo, laično pravilo 80-20), ki vzdržujejo kompleksnost. Kljub temu da je pojav samoorganizirane kritičnosti matematično dobro utemeljen, pa splošni kriteriji, ki bi določali pogoje, v katerih bo sistem izkazoval samoorganizirano kritičnost, niso znani (Bak in sod., 1988; Kauffman, 2008).

Druga temeljna značilnost kompleksnih sistemov je mnoštvo možnih stanj sistema, ki jih matematično opišemo kot atraktorje, tj. stabilna stanja, proti katerim ireverzibilno teži dinamika sistema v danih začetnih in mejnih (robnih) pogojih. Temeljna značilnost atraktorjev je robustnost, tj. sposobnost upiranja sistema zunanjim motnjam, in je eden osnovnih dejavnikov stabilnosti bioloških procesov (Kitano, 2004). Fenomenološko atraktorji ustrezajo emergentnim lastnostim sistema, torej lastnostim na višjih organizacijskih ravneh, ki se dinamično porajajo (vznikajo) iz interakcij med elementi sistema in jih posamezni elementi nimajo[3] (Gregorčič, 2010; Heudin, 2006; Kauffman, 2008; Nicolis in Rouvas-Nicolis, 2007). Množico atraktorskih bazenov in trajektorij med njimi imenujemo evolucijska (izvorno pa epigenetska (Waddington, 1942)) pokrajina in označuje množico stanj, ki jih lahko sistem zaseda in prehaja med njimi, v kolikor se spremenijo začetni ali mejni pogoji, tj. mrežna topologija v matematičnem oziroma notranje prepreke sistema v termodinamičnem smislu (Huang, 2009; Nicolis in Rouvas-Nicolis, 2007).

[3] Omenjena opredelitev emergence je splošna in zgolj orientacijska. V teoriji znanosti ločimo več tipov emergence, ki imajo različne epistemološke in ontološke posledice (Gregorčič, 2010).

Čeprav imamo lahko emergenco in samoorganizacijo v osnovi za neodvisna pojma s svojimi značilnostmi, sta zlasti v tradiciji sistemske biologije in torej v biološkem kontekstu tesno povezana in soodvisna. Navadno pojmujemo emergenco kot posledico samoorganizacije, torej kot lastnost dinamičnega sistema, medtem ko samoorganizacija označuje sámo dinamiko oziroma soodvisno delovanje njegovih elementov, katerega posledica je večja organiziranost sistema in s tem tudi pojav emergenih lastnosti (De Wolf in Holvoet, 2005).

Ena najznačilnejših emergentnih lastnosti kompleksnih sistemov je koherenca (slov. ubranost, usklajenost, skladnost). V širšem pomenu koherenca označuje značilno in konsistentno povezavo (korelacijo) med elementi, ki daje sistemu identiteto, torej vzdržuje značilen vzorec oziroma vedenje sistema kot celote (De Wolf in Holvoet, 2005). V ožjem pomenu pa koherenca označuje usklajenost ritmičnih značilnosti populacije elementov in je sorodna sinhronizaciji. Sinhronizacija (sočasnost, ožje tudi uglasitev) pomeni uskladitev notranjih ritmov oscilirajočih elementov ali oscilatorjev, tj. objektov z definirano fazo in frekvenco, zaradi njihove vzajemne interakcije. Matematično sinhronizacija označuje fazno konsistenco, stabilnost faznih razmerij med oscilatorji, in nastane s prenastavitvijo faze ali frekvence v sistemu sklopljenih oscilatorjev. V naravnih sistemih, vključno bioloških, s sinhronizacijo oziroma koherenco običajno označujemo najbolj tipičen primer fazne konsistence, kjer vsi ali večina elementov v sistemu oscilira sočasno oziroma v isti fazi (posledično pa tudi z isto ali pa harmonično frekvenco), pri čemer pa sinhronizacija v naravnih sistemih nikoli ni popolna, saj je zaradi termodinamične odprtosti vedno prisotna določena mera šuma (Osipov in sod., 2007; Pikovsky in sod., 2001).

V matematični teoriji sinhronizacije je prvo temeljno odkritje prispeval Winfree (1967), ki je dokazal, da se šibko sklopljeni oscilatorji z limitnim ciklom in statistično porazdelitvijo lastnih frekvenc spontano fazno sinhronizirajo, kadar je varianca njihovih frekvenc pod določenim kritičnim pragom. Kasneje sta Watts in Strogatz (1998) matematična orodja sinhronizacije uporabila na mreži, tj. strukturi z definirano povezljivostjo elementov, kar imamo za začetek sodobne teorije kompleksnih mrež, ki se danes množično uporabljajo za modeliranje dinamičnih procesov na vseh področjih znanosti, v biologiji na primer za modeliranje dinamike genskih in metaboličnih mrež, nevronskih oscilacij, fizioloških ritmov, populacijske dinamike in prehranskih mrež v ekologiji (Arenas in sod., 2008).

Pomenske razlike med koherenco in sinhronizacijo niso enotne, izrazna nedoslednost pa se še poveča v njunem odnosu s pojmoma samoorganizacije in emergence. Ponekod, zlasti v matematični teoriji sinhronizacije, se pretežno uporablja pojem sinhronizacije, koherenca

pa redkeje in sinonimno sinhronizaciji (Arenas in sod., 2008; Pikovsky in sod., 2001). V nevroloških krogih s koherenco navadno mislimo fazno konsistenco nevronskih oscilacij, kjer imajo različni oscilatorni sistemi lahko različne, a konsistentne fazne zamike, sinhronizacija pa je poseben primer koherence s skupno fazo (Senkowski in sod., 2008). V fiziki se pretežno uporablja pojem koherence, s katero opisujemo valovne značilnosti oscilatornih sistemov, ki so lahko bolj ali manj fazno sinhronizirani. V kontekstu kompleksnih sistemov se koherenca navadno uporablja v svojem širšem pomenu in sicer kot podpomenka emergence (De Wolf in Holvoet, 2005), sinhronizacija pa kot podpomenka samoorganizacije (Arenas in sod., 2008). Zaradi potrebe po čim jasnejšem izrazoslovju se v doktorskemu delu držimo slednje (analoške) razmejitve pojmov, pri čemer pa koherenco pojmujemo fizikalno, torej kot posledico oziroma emergentno lastnost sinhronizacije kot vrste samoorganizacije.

1.2 KOHERENCA V BIOLOŠKIH SISTEMIH

Organizmi so disipativni sistemi z visoko stopnjo vzdražnosti, katerih odzivanje na zunanje in notranje motnje mora biti natančno in učinkovito regulirano v času in prostoru. Fizikalni pomen samoorganizacije je čim učinkovitejše zmanjševanje energijskih gradientov, saj organizacija sistema v splošnem povečuje pretok energije in izmenjavo informacij z okolico (Fath in sod., 2001; Margulis in Sagan, 2003; Perez Velazquez, 2009). Specifičnost koherence je kolektivna sumacija izhodnih stanj posameznih elementov, kar v splošnem omogoča močan odziv sistema na šibke zunanje dražljaje, učinkovito komunikacijo med različnimi sistemi ter kodiranje informacij s fazo ali frekvenco oscilacij. Biološki pomen samoorganizacije kot tudi koherence gre torej pripisati zmanjšanju nekoreliranih prostostnih stopenj oziroma naključnih interackij med elementi na račun usklajenega vedenja sistema, kar omogoča daljnosežni red in učinkovito koordinacijo bioloških procesov v času in prostoru (Ho, 2008; Lloyd, 2005; Perez Velazquez, 2009; Plankar in sod., 2013).

Kooperativne oscilatorne pojave ali biološke ritme, ki imajo značilnosti sinhronizacije oziroma koherence, najdemo na različnih ravneh biološke organizacije (Glass, 2001). Na celični ravni je značilen primer ritmično sproščanje kalcija iz znotrajceličnih zalog in zunajceličnega prostora v citosol (s periodo od nekaj sekund do več kot minute), ki ima lahko obliko potujočih valov; za nastanek oscilacij je bistvena dinamika razgradnje in sinteze sekundarnega obveščevalca IP3, ki je odvisna od koncentracije kalcija in ima lahko učinek pozitive ali negativne povratne zveze na njegovo sproščanje (Dupont in sod., 2011). Znani in zlasti pri kvasovkah dobro raziskani so tudi metabolični cikli, periodična nihanja

med oksidirajočo in reducirajočo fazo celičnega metabolizma s periodo med 40 min in nekaj ur, s katerimi je sinhronizirano tudi izražanje večine genov in presnovnih molekul v značilnih, med seboj izključujočih fazah, posledično pa tudi celične delitve. V določenih pogojih gojenja pride tudi do medcelične sinhronizacije metaboličnih ciklov v celotni kulturi, kar se kaže na primer v izraziti ritmični dinamiki koncentracije kisika in nekaterih presnovnih molekul (Bianchi, 2008; Lloyd, 2005; Tu in sod., 2005). Na fiziološki ravni so dobro poznani dnevni (cirkadiani) ritmi, za katere je značilna sinhronizacija endogenega periodičnega nihanja določenega fiziološkega procesa z dnevno-nočnim ritmom, pa sinhronizacija ritmovnikov, ki dajejo frekvenco srčnemu ritmu, živčno-mišična sinhronizacija, ki omogoča lokomocijo, ter nevronska sinhronizacija, ki je eden temeljnih mehanizmov informacijskega procesiranja v možganih. Različni fiziološki ritmi se lahko sinhronizirajo tudi med seboj, npr. srčni in respiratorni ritem med športno aktivnostjo (Glass, 2001). Primeri usklajenega vedenja z značilnostmi sinhronizacije med organizmi pa so npr. zaznavanje kvoruma pri bakterijah, skupinske strategije plenjenja, usklajeno zvočno ali svetlobno signaliziranje, paritveni obredi, dinamika večjih skupin živali (ribje ali ptičje jate, črede rastlinojedov, krdela zveri ali roji žuželk), pa tudi posebni primeri kot npr. sinhronizacija menstrualnih ciklov.

Nedavno se je za razumevanje bioloških procesov začela uveljavljati tudi koherentna dinamika molekul in submolekulskih elementov, ki jo nadalje imenujmo molekulska koherenca. Biološki pomen molekulske koherence je prvi predvidel Herbert Fröhlich (1968), katerega model – sicer v okviru statistične mehanike – predvideva, da ob nadkritičnem dotoku metabolične energije v sistem sklopljenih oscilatorjev, ki v biološkemu sistemu odgovarja sistemu termično vzbujenih električnih dipolov, pride spontano do neravnovesne porazdelitve nihajnih načinov, kjer se večina energije preusmeri v oscilacije določene frekvence. Po sklopitvi z mehanskimi vibracijami molekule nastane t.i. koherentna ekscitacija, kjer se molekula obnaša kot enoten električni dipol. Fröhlich (1975; 1977) je predvideval, da koherentni režim omogoča selektivne resonančne interakcije med molekulami z visoko specifičnostjo in učinkovitostjo na osnovi frekvenčnih vzorcev elektromagnetnega polja, ki jih oddajajo koherentne ekscitacije dipolov. V novejšem času se s teoretičnim izpopolnjevanjem Fröhlichovega modela intenzivno ukvarja zlasti češka skupina biofizikov, ki ga umešča v molekulsko dinamiko mikrotubulov in biologijo raka (Cifra in sod., 2011; Cifra in sod., 2010; Pokorný, 2009).

V osemdesetih letih se je s konceptom molekulske koherence začela ukvarjati italijanska skupina fizikov, katere glavniki predstavniki so Giuliani Preparata, Giuseppe Vitiello in Emilio Del Giudice, ki so Fröhlichov model dopolnili in razširili v domeni kvantne fizike (Del Giudice in sod., 1988). Pokazali so, da se mikroskopske domene koherentnih

elektronskih vzbujenih stanj pojavijo spontano v vseh kondenziranih snoveh z nadkritično polarizacijsko gostoto zaradi sklopitve z vakuumskimi fluktuacijami elektromagnetnega polja. Skupina se je osredotočila zlasti na modeliranje vodnih molekul in pokazala, da tekočo vodo tvorita koherentna faza, v kateri se energija elektronov v vzbujenem stanju močno približa ionizacijski energiji, ter nekoherentna faza, v kateri prevladuje difuzijski režim, razmerje med obema fazama pa je odvisno od temperature in stopnje strukturiranosti molekul (Arani in sod., 1995). Kasneje je skupina koherenco aplicirala tudi na dinamiko preprostih metaboličnih ciklov, kjer voda zaradi visoke energije elektronov v koherentni fazi domnevno deluje kot katalizator oksido-redukcijskih procesov (Brizhik in sod., 2009; Del Giudice in sod., 2005; Del Giudice in sod., 2010).

Z vidika prenosa metabolične energije od mesta sprostitve (npr. hidrolize ATP) do mesta njene uporabe je pomemben tudi koncept solitona, lokalizirane vibracijske ekscitacije, ki se v nasprotju s klasičnimi vibracijami ne termalizira in lahko na ta način prenaša metabolično energijo na daljše razdalje. Obstoj solitonov v beljakovinskih α-heliksih kot mehanizma prenosa ekscitacijske energije je teoretično napovedal Davydov (1976) in ga uporabil za modeliranje mišične kontrakcije. Njegov model je na bioloških sistemih bolj sistematično uporabil Scott (1992), kasneje pa so koncept solitona razširili in ga uporabili tudi na drugih bioloških strukturah (Davia, 2006; Mershin in sod., 2006; Satarić in Tuszyński, 2003), med drugim za modeliranje t.i. ionskih valov na površini citoskeletnih filamentov kot domnevnega mehanizma za njihovo električno prevodnost (Priel in Tuszyński, 2008; Tuszyński in sod., 2004).

Do nedavnega je bilo neposredno eksperimentalno proučevanje molekulske koherence nemogoče zaradi tehnoloških omejitev. O obstoju koherentne molekulske dinamike so pričale zlasti indikacije endogenih koherentnih elektromagnetnih polj, bodisi njihove meritve v neposredni bližini celic, ki imajo tehnične omejitve, bodisi posredne – preko atermičnih vplivov šibkih zunanjih elektromagnetnih polj na rast celic ter druge fiziološke procese v močni odvisnosti od parametrov polja, ali pa na dinamiko dielektričnih materialov v neposredni bližini celic (Cifra in sod., 2011; Grundler in Kaiser, 1992; Hölzel, 2001; Hyland, 1998; Hyland, 2005; Kirson in sod., 2007; Pokorný, 2001). Pojav ultrašibke biolominiscence, izredno šibkega sevanja fotonov iz vseh metabolično aktivnih bioloških sistemov, je prav tako posredni dokaz koherentne molekulske dinamike, o čemer pričajo spektralne lastnosti biofotonov, na primer enakomerna porazdelitev njihovega števila vzdolž celotnega merljivega frekvenčnega spektra ali pa dinamika upada sevanja zakasnjene luminiscence, tj. po obsevanju s kratkim svetlobnim pulzom (Popp in Beloussov, 2003).

Eksperimentalni preboj se je začel z uporabo dvodimenzionalne laserske spektroskopije, ki z uporabo izredno kratkih laserskih pulzov omogoča neposreden vpogled v dinamiko prenosa vzbujenih stanj med molekulami (Nagy in sod., 2006). Engel in sodelavci (2007) so prvi neposredno izmerili kvantno koherenco celotnega FMO kompleksa[4] zelenih žveplovih bakterij pri nizki temperaturi. Obstoj kvantne koherence na drugih delih fotosintetskega sistema (antenski kompleks, reakcijski center) nekaterih bakterij in alg ter pri fiziološki temperaturi so potrdile nadaljnje raziskave (Collini in sod., 2010; Lee in sod., 2007; Panitchayangkoon in sod., 2010; Panitchayangkoon in sod., 2011). Vsem raziskavam je skupna interpretacija, da je svetlobno vzbujena ekscitacijska energija elektronov za kratek čas porazdeljena po celotnem kompleksu, kar omogoča sočasno vzorčenje vseh možnih stanj oz. poti prenosa ekscitacijske energije med molekulami (zaradi značilnega kvantnega pojava superpozicije) in s tem njen ponor v reakcijski center s skoraj popolnim izkoristkom. Ta mehanizem se bistveno razlikuje od do sedaj predpostavljenega klasičnega mehanizma (Försterjeva teorija spektralnega prekrivanja ekscitacij), ki predvideva, da elektroni preskakujejo med posameznimi vzbujenimi stanji na poti do reakcijskega centra, pri čemer izgubljajo energijo (Engel in sod., 2007; Scholes in sod., 2011).

Poleg fotosintetskih sistemov obstajajo močna znamenja za funkcionalno (netrivialno) vlogo makroskopske kvantne koherence tudi pri nekaterih čutilnih sistemih, npr. pri magnetorecepciji nekaterih ptičev (Gauger in sod., 2011; Lambert in sod., 2012; Ritz, 2011) in prepoznavanju vonjev (Brookes in sod., 2007; Franco in sod., 2011; Lambert in sod., 2012). Koherenten prenos vzbujenih energijskih stanj postaja relevanten tudi pri bolj splošnemu razumevanju biokemijskih procesov, npr. pri prenosu vibracijske energije vzdolž beljakovinskih α-heliksov (Dijkstra in sod., 2011; Kobus in sod., 2011) ter vzdolž vodikovih vezi v vodi (Mulkidjanian in sod., 2006; Yang in Skinner, 2010), pa tudi pri transportu elektronov na dolge razdalje (Bandyopadhyay, 2010; Lambert in sod., 2012; Sahu in sod., 2013; Skourtis in sod., 2011). Kljub temu razmahu v zadnjih nekaj letih pa so eksperimentalne raziskave molekulske koherence trenutno na ravni, ko še ne moremo podati končnih odgovorov o njenem splošnem obsegu in pomenu za biološke procese.

Fizikalne interpretacije molekulske koherence in pojavov, ki so z njo povezani, niso enotne in se razlikujejo že v osnovnem teoretičnem izhodišču. Večina raziskovalcev interpretira

[4] Fenna-Matthews-Olson kompleks je beljakovinski trimer, pri katerem vsak monomer veže osem bakterioklorofilnih molekul, in povezuje tók svetlobno vzbujenih elektronskih ekscitacij med antenskimi pigmenti in reakcijskim centrom (Wikipedia: Fenna-Matthews-Olson complex).

nedavne eksperimentalne rezultate s kvantno mehaniko, ki proučevani sistem opisuje z valovno funkcijo, ki kvantnim stanjem elementov pripisuje verjetnostne amplitude s pripadajočimi fazami. V kvantno koherentnem sistemu so fazne relacije med elementi usklajene, kar omogoča koherentno superpozicijo elektronskih in vibracijskih energijskih stanj (Arndt in sod., 2009; Fleming in sod., 2011; Scholes, 2010). Zaradi neizogibnih termičnih interakcij z zunanjim okoljem se koherentna stanja zelo hitro izpovprečijo, čemur pravimo kvantna dekoherenca (Zurek, 1991), zato so kvantne lastnosti fizikalnih sistemov načeloma omejene na zelo majhne prostorsko-časovne skale, tipično atome in manjše molekule.

Kljub temu pa poznamo mnoge primere makroskopskih koherentnih sistemov, kjer so prostorsko-časovne skale koherence praktično neomejene: superprevodni, superfluidni in magnetni materiali, kristali, Bose-Einsteinov kondenzat in laserska svetloba. Za opisovanje tovrstnih sistemov, za katere je značilna stabilnost kljub njihovi visoki urejenosti, je po mnenju nekaterih raziskovalcev primerna kvantna teorija polja (Vitiello, 2001). V nasprotju s kvantno mehaniko opisuje kvantna teorija polja tudi fazne prehode in torej večfazne sisteme kot je npr. tekoči helij (Landau, 1941), v okviru katerih pojmuje tudi nastanek koherentnih stanj. Druga posebnost te teorije pa je, da koherentno stanje pojmuje kot osnovno (in torej stabilno) energijsko stanje sistema, ki ima neomejeno število možnih fizikalno neekvivalentnih realizacij, iz česar izhaja potencial za informacijsko kodiranje. Ta potencial ima lahko tudi biološki pomen, npr. za specifično prepoznavanje molekul na osnovi frekvenc elektromagnetnega polja, v čemer se ta teorija sklada s Fröhlichovo teorijo koherentnih ekscitacij (Del Giudice in sod., 2005; Del Giudice in Tedeschi, 2009; Preparata, 1995; Vitiello, 2001).

Kljub temu da je poznavanje koherentne molekulske dinamike šele na začetku eksperimentalnega preboja in za njihovo interpretacijo še ni enotne fizikalne teorije, teoretični koncept molekulske koherence ponuja globlje in predvsem bolj sistemsko razumevanje nekaterih bazičnih bioloških procesov, še zlasti če ga pojmujemo v okviru biološke samoorganizacije. Obenem nam nudi elegantne rešitve nekaterih bazičnih bioloških problemov, npr. prenosa vzbujenih stanj med mestom sprostitve in mestom porabe metabolične energije ali pa visokega izkoristka nekaterih biokemijskih procesov. Poleg tega ponuja tudi uporabna raziskovalna izhodišča, na primer pri zdravljenju nekaterih bolezni z uporabo nihajočih elektromagnetnih polj, ki ima že relativno dolgo zgodovino uporabe (Rosch in Markov, 2004).

1.3 NAMEN IN HIPOTEZE

Silen razmah sodobne znanosti povzroča, da se vedno bolj diferencira v visoko specifične, vsebinsko ozke struje z lastnim izrazoslovjem ter metodološkimi in teoretičnimi izhodišči. Ta razmah je po eni strani pričakovan in nujno potreben za razvoj, po drugi strani pa se pojavlja problem komunikacije med različnimi disciplinami in s tem tudi težnja po ohranitvi enotnih raziskovalnih izhodišč. Tako je npr. pojav molekulske koherence v organizmih v splošnem še vedno slabo poznan, kljub temu da je dokazana njena vloga pri organizaciji vsaj nekaterih bioloških procesov. Po drugi strani pa fiziki, ki raziskujejo koherenco, pogosto slabo poznajo biološko ozadje raziskovanih struktur in posledično površno ovrednotijo biološki pomen svojih rezultatov, kar zmanjšuje preglednost raziskovanja. Eden glavnih namenov doktorskega dela je zato s povezovalnim in multidisciplinarnim pristopom prispevati k ustvarjanju skupnega komunikacijskega prostora med fizikalnimi in biološkimi interpretacijami biološke samoorganizacije.

Drugi namen dela je umestitev koherence kot teoretičnega koncepta v biološke znanosti. Osredotočili smo se na dve področji bioloških znanosti, na izvor in razvoj raka ter na dinamiko nevronskih oscilacij. Obe področji sta po biološkem pomenu ter načinu organizacije popolnoma različni, skupna značilnost pa tudi osnovni razlog za izbor pa je njuna izrazita organizacijska kompleksnost. Kljub relativno dobremu poznavanju in dolgoletnemu raziskovanju na obeh področjih pa osnovni dejavniki tako za razvoj raka kot tudi temeljni mehanizmi makroskopske nevronske dinamike še niso sistemsko pojasnjeni, kar je dodaten motiv za njun izbor. Koncept koherence skušamo prikazati ne le kot fizikalni mehanizem, pač pa kot organizacijski princip, ki pomembno vpliva na biološko organizacijo ter v ožjem pomenu neposredno soustvarja življenje. Zato je osnovno izhodišče doktorskega dela, oziroma njegova temeljna predpostavka, da ima fizikalni pojav koherence tudi biološki pomen in vpliva na dinamiko ter organizacijo bioloških procesov na več organizacijskih ravneh. V dispoziciji doktorske disertacije smo postavili tri delovne hipoteze, ki se nanašajo na tri različna raziskovalna področja in izhajajo iz omenjenega temeljnega izhodišča.

Hipoteza o samoorganizaciji pravi, da je biološka koherenca konkretna materialno-fizikalna manifestacija samoorganizacijskih procesov bioloških sistemov kot dinamičnih kompleksnih sistemov daleč od termodinamičnega ravnovesja.

Hipoteza o raku pravi, da je raka moč sistemsko razumeti kot razvojno motnjo v dinamiki in organizaciji specifičnih koherentnih procesov na celični ravni, ki motijo oz. zavirajo energijske in informacijske tokove.

Hipoteza o kogniciji pravi, da je koherenca eden ključnih fizikalnih pojavov, dejavno udeleženih pri organizaciji kognitivnih procesov tako na nevronski kot tudi na internevronski ravni ter smiselno dopolnjuje že obstoječe nevrološke modele kognicije, ki temeljijo na kemičnih sinapsah in nevronskih skupnostih.

V sprejetih člankih (Poglavje 2) analiziramo in umeščamo molekulsko koherenco v biologijo raka (Sekciji 2.1 in 2.2) in v kognicijo (Sekcija 2.3). V razpravi in sklepih (Poglavje 4) povzemamo v strnjeni obliki glavne ugotovitve objavljenih del in analiziramo zastavljene hipoteze.

2 ZNANSTVENI ČLANKI

2.1 O IZVORU RAKA: ALI LAHKO IGNORIRAMO KOHERENCO?

Avtorji: Matej Plankar, Igor Jerman, Rok Krašovec

Izvirni naslov: *On the origin of cancer: Can we ignore coherence?*

Publikacija: *Progress in Biophysics & Molecular Biology (2011) 106, 380-390.*

Ključne besede: *cancer systems biology, cancer epigenetics, cancer attractor, cancer bioenergetics, biological coherence, microtubules*

Izvleček: V zadnjem času se je nabralo več spoznanj, ki niso povsem skladna z genetsko deterministično paradigmo o izvoru raka, med katerimi sta najpomembnejši nespecifična narava tumorigenih mutacij in t.i. ne-celično avtonomni dejavniki razvoja tumorja. Epigenetika in sistemska biologija predstavljata dve področji, ki sta precej vplivali na razumevanje raka in katerima je skupna karakterizacija raka kot nespecifične progresivne destabilizacije metaboličnih procesov. Koherentna dinamika nekaterih celičnih podsistemov je bila dolgo časa predpostavljena kot mehanizem daljnosežne koordinacije bioloških procesov, vendar le teoretično. Šele nedavno pa je preučevanje molekulske koherence pristalo v središču pozornosti, saj je bila izmerjena na nekaterih fotosistemih in po mnenju raziskovalcev neposredno vpliva na prenos energije med molekulami. Nekateri teoretični modeli pa tudi eksperimentalna opažanja nakazujejo, da bi razvoj raka lahko bil povezan z okvaro koherentne dinamike določenih struktur, med katerimi so tudi mikrotubuli. V prispevku povzemamo te modele in predlagamo možne povezave med okrnjeno koherenco in progresivno destabilizacijo molekulskih in genskih regulatornih mrež.

Progress in Biophysics and Molecular Biology 106 (2011) 380–390

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

Review

On the origin of cancer: Can we ignore coherence?

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ARTICLE INFO

Article history:
Available online 29 April 2011

Keywords:
Cancer systems biology
Cancer epigenetics
Cancer attractor
Cancer bioenergetics
Biological coherence
Microtubules

ABSTRACT

A growing number of inconsistencies have accumulated within the genetically deterministic paradigm of the origin of cancer. Among them the most important are the nonspecific nature of cancer mutations and the non-cell-autonomous factors of cancer initiation and progression. Epigenetic aspects of cancer and cancer systems biology represent novel approaches to cancer aetiology and converge in the notion that cancer is characterized by a nonspecific progressive destabilization of multiple molecular pathways. The coherent behaviour of certain cellular subsystems has been theoretically predicted for a long time to have a general role in coordinating biological processes. However, it has only recently gained major scientific interest when it was measured on photosynthetic complexes at physiological temperatures and confirmed to have a direct effect over the dynamics of the energy transfer. Several theoretical and experimental considerations suggest that cancer might be associated with the absence or impairment of the proper coherent dynamics in certain biological structures, most notably in the microtubules. We review those models and suggest that impaired coherence might largely contribute to the progressive destabilization of the molecular and gene regulatory networks, thus connecting different non-genetic aspects of cancer.

Contents

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doi:10.1016/j.pbiomolbio.2011.04.001

1. Introduction

Cancer is one of the most complex and thoroughly researched diseases, characterized by an abnormal cell growth and tissue organization. Cancer research has gone through a long history of fashions (Harris, 2005), and although many theories have been proposed, there is still a lot of confusion surrounding its molecular origin (Seyfried and Shelton, 2010). A growing number of contradictions and paradoxes have accumulated within the current genetic paradigm of cancer, making a unified aetiology impossible (Sonnenschein and Soto, 2008; Baker and Kramer, 2007). Cancer research demands a more systemic and multidisciplinary approach, with as many perspectives as possible combined and synthetically evaluated.

Here we integrate three approaches to the biology of cancer in the search of its systemic origin: molecular biology, systems biology, and the emerging concept of biological coherence. We briefly review some of the major inconsistencies in the current genetic paradigm of cancer and point out that a more integrative approach is needed. Cancer epigenetics and cancer systems biology represent two such approaches and converge in the notion that cancer is primarily characterized by a global and nonspecific progressive disorganization of multiple molecular pathways and gene regulatory networks (Clark, 1995; Feinberg et al., 2006; Kreeger and Lauffenberger, 2010). However, the nonspecific nature of the inductive agent does not mean that the common aetiology of cancer is inaccessible. The third approach, the concept of coherence in biological systems, has been theoretically predicted for a long time (Fröhlich, 1968a) and elaborate theoretical models have been proposed. However, it gained major scientific interest only recently when it was experimentally measured and confirmed that coherence directly coordinates the dynamics of specific biochemical processes in photosynthetic systems (Engel et al., 2007; Collini et al., 2010).

It is theoretically predicted that coherence represents the underlying physical mechanism for the proper coordination of many biological processes at different levels of biological organization (Abbott et al., 2008; Jaeken, 2006). Several theoretical considerations have linked different aspects of improper or insufficient coherence within the cell or between cells to cancer. We review some of those models and suggest that impairment of coherent dynamics may represent one of the general factors underlying the systemic disorganization of molecular and gene regulatory networks in cancer. Coherence may contribute to a more synthetic view on cancer, as well as connect different non-genetic aspects of this complex disease.

2. Searching for the molecular origin of cancer

In the early history of cancer biology, two important discoveries set out two major paradigms of the origin of cancer, which still divide modern science. The genetic paradigm arose when in 1914 Theodor Boveri proposed that the observed abnormal nuclei in malignant cells arise because of "impairment of certain chromosomes" (Boveri, 2008). A few years later, upon the observation that the vast majority of tumours display a unique metabolic phenotype, namely aerobic glycolysis (glycolytic energy metabolism despite oxygen availability), Otto H. Warburg proposed that the prime cause of cancer is a mitochondrial dysfunction, followed by replacement of oxygen respiration in normal body cells by a fermentation of sugar (Warburg, 1930). Together with the early propositions regarding developmental aspects of cancer (Waddington, 1935), the non-genetic paradigm gradually arose with the emphasis on metabolic, bioenergetic, developmental, and systems aspects of cancer.

2.1. Monoclonal genetic alteration

Since the 1950s the genetic paradigm has received a major boost. In 1976, Nowell proposed a refined version of the somatic mutation theory, the clonal evolution model of tumour progression (Nowell, 1976), which is still acknowledged as a current doctrine of cancer biology. According to the clonal evolution model, tumours expand as a clone from a single mutated cell, and clinical progression is the result of sequential accumulation of random somatic genetic changes, generating increasingly aggressive subpopulations within the expanding clone, able to liberate themselves from homeostatic control mechanisms (Nowell, 2002). The clonal evolution model has been supported by the systematic discovery of oncogenes, which promote tumour development by activation, or gain of function, and tumour suppressor genes which act by inhibition, or loss of function. Together with stability (or caretaker) genes that maintain the integrity of the genome, they represent a class of "cancer genes" that are able to collectively or independently transform normal cells to cancer cells by affecting relatively few distinct pathways (Volgenstein and Kinzler, 2004).

One of the major and well-documented arguments for the clonal evolution model has been clonal expansion of tumour cells with specific genetic, karyotypic or phenotypic traits (Bedi et al., 1996; Fialkow, 1979; Nowell, 1976; Little, 2010). However, while clonal expansion reflects a selective growth advantage of the specific genome (or more correctly, gene expression profile), this does not mean that there are any cancer-specific mutations, or that cancer initiates from a single clone. In colon cancer, one of the most studied cancers, no known mutations have been defined as necessary and sufficient for specific stages of cancer progression, other than a few "gatekeeper" mutations (Feinberg et al., 2006), and even those act more like predispositions rather than being definitive of specific phases of tumour development (Volgenstein and Kinzler, 2004). In other words, no specific gene mutation has been a completely reliable diagnostic for any specific type of tumour (Seyfried and Shelton, 2010; Soto and Sonnenschein, 2005). As it was recently demonstrated by systematic sequencing of cancer genomes, tumours of the same type, as well as cells within the same tumour, show great heterogeneity among the sets of mutated genes with very little overlap. Only a few mutations are found in the majority of tumours or cells within the same tumour, whereas the vast majority of mutations are found in specific tumours or specific cells within individual tumour, resembling a statistical distribution (Fox et al., 2009; Wood et al., 2007).

2.2. Genomic instability

Taking into account the extensive time that the clones would need to develop malignant tumours, a mutator phenotype hypothesis has been proposed by Loeb (1991), suggesting an increase in mutation rates due to defective stability genes. Indeed it was shown that different forms of genomic instabilities, such as chromosome or microsatellite instability, make a clear contribution to cancer and are thought to serve as a fuel for tumour progression by inducing genomic rearrangements (Holland and Cleveland, 2009; Schvartzman et al., 2010). It was also suggested that a specific karyotype as a whole, not specific mutations, initiates and evolves to define a specific cancer genome (Duesberg et al., 2005; Li et al., 2009; Heng et al., 2009).

Mutations in the mitotic checkpoint genes, hypothesized to cause chromosome instability *in vivo*, seem however to be excluded, and thus its molecular origin remains unclear (Holland and Cleveland, 2009). More importantly, it has become evident in recent years that interactions of the specific karyotypes with various genetic contexts and microenvironments found in different

tissues, crucially determine the course of tumour development. In one tissue, a given karyotype may promote tumour development, whereas in another tissue, tumour incidence may be suppressed. The fate of the specific karyotype is thus inherently context-dependent and as such the subject of tissue-level control (Holland and Cleveland, 2009; Schvartzman et al., 2010).

2.3. Microenvironmental factors

The so called non-cell-autonomous, or microenvironmental factors in tumour development represent the second major objection to the genetic paradigm of the origin of cancer. The crosstalk between the solid tumour and its connective tissue microenvironment, the tumour stroma, has been recognized for a long time as the key factor in tumour development. Stroma, once activated, secretes various growth factors, inflammation factors, proteases and other components that promote cancer development by inducing cell growth, angiogenesis, degradation and remodelling of the extracellular matrix and basal lamina (the latter is considered to be the hallmark of malignancy), and in addition act in a paracrine way to influence tumour cells to secrete further tumour promoting factors (Mueller and Fusenig, 2004).

In the classical view, concomitant with the cell-autonomous somatic mutation theory, the tumour stroma is viewed as being primarily activated by various growth factors secreted by tumour cells, and thus its role in tumour development is secondary to already present tumorigenic mutations (Jacks and Weinberg, 2002; Mueller and Fusenig, 2004). However, there is convincing evidence that the carcinogen-exposed stroma can autonomously transform non-tumorigenic epithelial cells *in vivo*. For example, Maffini et al. (2004) have shown that the mammary gland stroma treated with a chemical carcinogen can transform normal epithelial cells regardless of themselves being treated or mutated. Similarly, the ability of non-irradiated mammary gland epithelial cells to progress to tumours was dramatically increased when transplanted to the stroma treated with ionizing radiation, compared to non-irradiated stroma (Barcellos-Hoff and Ravani, 2000; Barcellos-Hoff, 2008).

While modified tissue microenvironment can autonomously induce tumour in normal cells, normal tissue structure can on the other hand actively delay, suppress or even reverse tumour development. Tumour reversion, or normalization, has been acknowledged for a long time, especially in the ability of embryonic tissues to induce reversion and complete integration of teratoma cells into normal animal tissues (Illmensee and Mintz, 1976). In subsequent studies it was shown that tumour reversion is a generic phenomenon since normal somatic tissues may also suppress or reverse tumour progression of inoculated neoplastic cells, and the reversion is dependent on tumour malignancy as well as the host tissue characteristics (Hochedlinger et al., 2004; Maffini et al., 2005; McCullough et al., 1998). Using 3D cultures, it was convincingly demonstrated that by manipulating the function of only one or two molecules involved in intercellular signalling, cells could repeatedly switch between the malignant, and normal epithelia forming phenotype, together with complete reorganization of the cytoskeleton and redistribution of cell adhesion molecules – thus stressing the crucial role of intercellular communication in cancer (Kenny and Bissell, 2003).

Tumour reversion by itself strongly contradicts any irreversible, genetically deterministic models of the origin of cancer, and further emphasizes the role of tissue structure and integrity (Bizzarri et al., 2008; Bissell and Radisky, 2001; Ingber, 2008; Rubin, 2006; Soto and Sonnenschein, 2005; Weaver and Gilbert, 2004). In sum, the emerging picture of the non-cell-autonomous aspects of cancer shows that tumours can be experimentally both induced and reversed by manipulating signalling interactions responsible for maintaining cell and tissue communication and integrity, independently of genetic mutations. Induced mutation (or genomic instability) is merely one of the many possible ways to initiate cancer (Ingber, 2008).

2.4. The epigenetic progenitor theory

To account for some of the outlined problems of the genetic paradigm, the epigenetic progenitor model has been proposed recently as an alternative model for the unified cancer aetiology, uniting the cancer stem cell theory with the cancer epigenetics (Feinberg et al., 2006). Cancer stem cell theory maintains that cancer ultimately initiates and promotes from a population of either dedifferentiated cells with renewed stem-like properties, such as the ability of unlimited division, or directly from tissue specific adult stem cells and their descendant tissue progenitor cells (Clarke and Fuller, 2006; Tan et al., 2006). The stem cell theory of cancer could well account for the therapeutic refractoriness and dormant behaviour of many cancers, as well as the observed primary cancer and metastatic tissue phenotypic heterogeneity (Visvader and Lindeman, 2008).

On the other hand, great advances have been made in characterizing a plethora of epigenetic alterations in pre-malignant tumours, which act by modifying gene expression patterns and typically include global DNA hypomethylation, local hypermethylation of gene promoters, histone hypoacetylation, loss of genomic imprinting, etc. (Feinberg et al., 2006; Hitchler and Domann, 2009; Jones and Baylin, 2007). Some of these modifications may directly promote tumours by forming mutation hot spots or by inducing genomic instability (Jaenisch and Bird, 2003). However, the general assertion of the epigenetic progenitor model is that tissue progenitor cells are the early targets of epigenetic changes that gradually accumulate over time due to variety of nonspecific environmental or endogenous factors, long before clinical tumours arise. When an initiating (or gatekeeper) mutation occurs, its effects might be uncontrollably exacerbated by the background of epigenetically modified gene expression patterns, and therefore the risk of developing malignancy would be much higher compared to an epigenetically stable genetic network. An increased epigenetic plasticity would progressively uncover genetic variants with a selective growth advantage, but which are potentially deleterious for the whole organism. It is thus the *epigenetic* instability that accumulates with time and leads to irreversible genetic changes and genomic instability[1] (Feinberg et al., 2006; Prehn, 2005). The implication of this theory is that it is the instability of gene expression *per se* that ultimately leads to cancer, and that specific gene mutations may accelerate, but might not be a necessary condition for, tumour initiation or progression.

As epigenetic changes are much more dynamic (compared to genetic) and reversible, the epigenetic progenitor model can explain a number of problems associated with the somatic mutation theory: the high correlation of cancer with age and environmental exposure (or latency of cancer onset), tumour reversion (since epigenetic changes are reversible), the non-specificity of tumour-promoting mutations, and the phenotypic heterogeneity of primary cancer cells and metastases (Feinberg et al., 2006). In addition, many of the well-known carcinogens, traditionally

[1] We note that epigenetic plasticity may in principle also work as a sort of buffer that compensates for the induced genetic changes, hence increasing the robustness of tumour cells, as pointed out by Heng et al. (2009). However, a more general picture is that over-increased epigenetic plasticity (epigenetic instability) would act as a genome-destabilizing factor in cancer (Feinberg et al., 2006).

thought to induce tumours through mutagenesis, are now known to act epigenetically (Trosko and Upham, 2005).

While the epigenetic progenitor theory presents itself as a unifying aetiology of cancer, there is however one rarely articulated, but crucial aspect regarding epigenetics. The epigenome has been hypothesized to provide an interface between the environment and the nuclear genes (Wallace and Fan, 2010). The concept of epigenetic control is inherently non-deterministic since, in principle, every possible molecular event, either cellular or environmental (e.g., xenobiotics), including stochastic metabolic perturbations can, more or less directly, influence gene expression through the epigenetic molecular machinery (Herceg, 2007; Jaenisch and Bird, 2003). Thus epigenetics (as defined in the strict sense of cellular epigenetic inheritance by Jablonka and Raz (2009)), together with other recently discovered mechanisms of gene expression control, such as through riboswitches (Serganov and Patel, 2007) and non-coding RNAs (Mattick, 2004), opens up a huge space of the metabolic control over gene expression dynamics, and functionally reverts the focus from the genes to metabolic networks (see Shapiro, 2009 for further discussion). This necessitates the need for an integrative systems approach in search of the primary, systemic origin of cancer.

3. Cancer as a systems developmental disorder

Strict reductionistic methodology asserts that genes in principle act independently of each other and code for well-defined products with well-defined functions. Hence, biological causation should be completely determined by the genes and can only be one-way (the central dogma of molecular biology). Consequently, metabolic pathways are drawn as separate linear diagrams with the flux of metabolites being determined by the kinetics of the rate-limiting step, and ultimately representing fulfilments of linear genetic programs (Bizzarri et al., 2008).

3.1. Systems biology

With the rise of non-linear thermodynamics and complexity theory, together with computational modelling, such a linear view of biological causation began to change drastically. Organisms began to be seen as organized hierarchies of dissipative structures, dynamic self-organizing structures that maintain order far from the thermodynamic equilibrium (Nicolis and Prigogine, 1977). In other words, under the constant flow of energy and information, complex systems – defined as made up of a sufficiently large number of simple elements, able to undergo local interactions – tend to autonomously create higher-order structures with reduced degrees of freedom, to most efficiently reduce the physical gradients in order to extract metabolic energy (Feltz et al., 2006).

The interconnectedness of synchronously interacting elements in dynamic systems accounts for their complex behaviour. Some of their most distinctive properties, as opposed to linear systems, are: (1) *collective behaviour*, a meaningfully synchronized dynamics of the elements and a collective response to perturbations because of their interdependency; (2) *robustness*, ability to resist, adapt or return to their initial state due to external perturbations; (3) *multistability*, their ability to attain multiple stable states, or attractors; (4) *downward* (*circular*) *causation*, the ability of higher-order structures to influence dynamics of lower-order structures or elements, and vice versa; and (5) *context dependency*, the non-specificity of individual elements to produce a specific systems response (Feltz et al., 2006; Kaneko, 2006; Kauffman, 2008).

All of these properties strongly apply to living systems. Complexity in organisms arises from a large number of interacting molecules, extensive crosstalk between pathways, from feedback circuitries, and from nonlinear relations between interacting molecules, making it impossible to predict behaviour on the basis of changes in a linear pathways diagram (Hornberg et al., 2006). Changing one component may affect hundreds or thousands of other components, and not just those downstream. Understanding biological mechanisms in disease development therefore demands a systems approach that goes beyond one-at-a-time studies of single components to a global analysis of the structure, function and dynamics of molecular networks (Bizzarri et al., 2008; Cusick et al., 2005). The realisation that changing the DNA is a biochemical process leads to the understanding that it is subject to regulation like other cellular activities and responsive to different cellular and environmental stimuli. Hence, the emphasis has to be on what the *cell* does with its genome, and not what the genome directs the cell to execute (Shapiro, 2009). The genome is not a deterministic execution program, but more like a database from which the dynamics of intra- and intercellular metabolic networks actively choose the desired information according to the current needs of the system (Atlan and Koppel, 1990; Noble, 2010).

3.2. Cancer attractors

To account for such a systems view on life, the field of cancer systems biology is starting to emerge (Kreeger and Lauffenberger, 2010). One of the formally most elaborated theories within this field is the cancer attractor model, proposed by Huang and Ingber (2007) and Huang et al. (2009). Briefly, gene expression patterns can be formally represented as a multidimensional gene regulatory network of active and non-active elements (the genes) that influence their activity in a reciprocal manner. When the number of elements becomes large, complex behaviour emerges. The crucial property of such a network is multistability, meaning that only certain patterns of expression are stable and thus form the distinct stable states, or attractors, of the mathematical phase space describing the network topology. Attractors correspond to particular cell types, an idea first put forth by Stuart Kauffman (1969). If the system is mildly perturbed, e.g. by natural stochastic molecular fluctuations that influence the gene expression (Blake et al., 2003; Raser and O'Shea, 2005), it manages to sustain a quasi-stable expression profile within the borders of the attractor. However, if perturbation is strong enough, or persists for a sufficient period (such as genetic or epigenetic changes), the perturbed molecular network dynamics may result in a change of the "shape" of the attractors and thus rewire the whole network architecture, making it susceptible to further changes which can, eventually, cause the shift of the system to another attractor.

There are many potential attractors in the huge phase space of the gene regulatory network, such as apoptotic attractors, or early developmental attractors that stabilize embryonic or stem-like gene expression profiles, which have been occupied in the history of each differentiated cell lineage and which may promote proliferation, extracellular matrix remodelling, migration etc. When the perturbation is sufficient, there is a chance that such an attractor suddenly becomes available and causes drift down "the potential" to eventually self-stabilize as a distinct attractor with a specific tumour promoting expression profile. Additional perturbation is needed to further distort such an attractor to gradually express the full phenotype of the malignant tumour. Cancer attractors may operate at cellular or tissue level and thus may encompass many cells to account for the non-cell-autonomous aspects of cancer biology (Huang and Ingber, 2007).

The cancer attractor model is supported by a substantial amount of experimental data. For example, microarray measurements of the entire transcriptomes of lung carcinomas reveal distinct genome-wide expression subclasses for various tumour types,

which could correspond to different attractors. There is no continuum with smooth transitions between different transcriptomes, as would be expected from the progressive (epi)genetic alterations driven by selective pressures (Bhattacharjee et al., 2001; Guo et al., 2006). More generally, the attractor concept offers a formal theoretical framework for developmental branching of cell phenotypes – from highly potent stem and progenitor cells to stable tissues with cell-type specific gene expression patterns – cancer being a sort of a dead end deviant trajectory not completing the proper development (Brock et al., 2009; Chang et al., 2008; Huang et al., 2009). It can also be seen as a systemic explanation of the long acknowledged phenomenon of genetic robustness, or resilience of phenotypes with respect to genetic variation (de Visser et al., 2003) – and in the case of cancer, the cancer robustness to resist anticancer therapies (Kitano, 2004). Most importantly, the cancer attractor model naturally unites genetic and non-genetic aspects of cancer development, as well as offers a systems framework for tumour reversion and other non-cell-autonomous aspects of cancer (Ingber, 2008; Huang et al., 2009). In essence, the concept of epigenetic instability in the epigenetic progenitor model of Feinberg et al. (2006), and rewiring of the gene regulatory network in the cancer attractor model of Huang et al. (2009), describe the same process of *progressive destabilization* within the interactive molecular networks' architecture, thought to represent the *nonspecific* molecular origin of cancer, which subsequently promotes genomic instability and manifests, in the late phases of tumour development, as the phenotypic hallmarks of cancer (Hanahan and Weinberg, 2000).

3.3. Cancer as a developmental disorder

Ultimately, the systems biology approach understands cancer as a developmental disorder, as the price the organism pays for evolving complex, multicellular organization (Huang et al., 2009). Developmental aspects of cancer frequently converge with the notion of a field in the sense that tissue context has the organizing capacity (Bizzarri et al., 2008; Sonnenschein and Soto, 2008; Potter, 2007; Prehn, 2005; Rubin, 1985; Waddington, 1935). But is the field merely a useful metaphor to conceptualize the autonomy of mutual relations within and between cells and their environments, or could it have some form of a physical manifestation? Stated differently, what exactly is this orchestrated control that enables each normal cell to respond to both intrinsic and environmental stimuli by regulating the gene expression and metabolic processes properly, and which ceases to operate in malignant cells? If the unifying concept in cancer is neither the nature of the initiating agent nor the necessity of mutation, but instead similarity in the development and progression, and its essence is progression with progressive self-disorganization, a form of abnormal morphogenesis (Clark, 1995), then what is the specific basis in terms of physical substance for such self-disorganization? What exactly is disorganized that was previously organized? The emerging concept of coherence offers exactly such a unifying materialization of the "field effect", based on non-linear thermodynamics and quantum physics, and thus fully complements the systems biology approach.

4. The concept of biological coherence

Concepts like spontaneous synchronization, order out of chaos and negentropy have been present in biology for a long time, as has the concept of the field (Bischoff, 2003). Erwin Schrödinger, one of the pioneers of quantum physics, was the first to point out that statistical mechanics alone, together with its macroscopic consequence, diffusion, could not sufficiently explain the remarkable energy efficiency of biological systems due to the "small numbers" problem. He argued that despite the huge number of molecules in a single cell, eventually, due to their versatility and compartmentalization, the number of interacting molecules of the same species is generally much too small to obey macroscopic statistical laws, imposed by the thermal noise. He concluded that some other organizing factor must be ultimately responsible for the high efficiency of living systems and that living nature is very likely to harness the quantum properties of matter (Schrödinger, 1944). Others have also pointed out fundamental inadequacy of statistical mechanics to explain biological order (Del Giudice et al., 2005; Jaeken, 2009; McClare, 1971; Pokorný, 2001; Vitiello, 2001).

After more than 60 years, Schrödinger's intuition has been experimentally confirmed. Engel et al. (2007) have for the first time directly measured quantum coherent energy transfer through the entire bacteriochlorophyll complex of green sulphur bacteria, which is composed of several protein monomers and light pigments. According to the authors, the measured coherence time (660 fs) is long enough to guide the dynamics of the biochemical reactions of the complex. Specifically, the coherence allows the complex to sample vast areas of the energy phase space simultaneously (by exploiting the quantum phenomenon of superposition), to find the most efficient path for light energy transfer to the reaction centre. This mechanism contrasts with a semi-classical "hopping" mechanism through which the electron excitation would move stepwise between different excited states, dissipating energy at each step, where only one state could be occupied at any one time (Engel et al., 2007). Since 2007, several subsequent studies have confirmed this result with almost identical conclusions (Lee et al., 2007; Mercer et al., 2009). In 2010, functional macroscopic quantum coherence has been measured for the first time at physiological temperatures on cryptophytic algae antennae complexes about 5 nm wide (Collini et al., 2010; for more background information, see Scholes (2010)).

On the other hand, much indirect evidence indicates the generic presence of coherent endogenous electromagnetic fields in living organisms, behaving classically compared to quantum entangled states in the photosystems. These include, for example, a strong frequency-dependent growth rate of bacteria, indicating resonant electromagnetic interactions (Grundler and Kaiser, 1992; Giladi et al., 2008), coherent nanomechanical vibrations in the yeast cell wall (Pelling et al., 2004), strong dielectrophoretic behaviour of particles in the vicinity of cells (indicating the presence of endogenous electromagnetic fields), and direct measurements of electromagnetic fields around different cells (Hölzel, 2001). Different means by which cells generate and communicate by electromagnetic fields, as well as methodological difficulties regarding detection of those fields, have been reviewed by Cifra et al. (2011).

We will broadly define biological coherence as a synchronized behaviour of coupled elements within a biological system, either of quantum or electromagnetic origin, able to influence biological processes in a biologically meaningful way. Since the 1960s, several elaborate models of coherence have been developed. Arthur T. Winfree (1967) was the first to mathematically prove that in the system of weakly coupled oscillators with a random frequency distribution, under specific parameters the system undergoes spontaneous collective synchronization whereby all oscillators become synchronized in phase and in frequency and thus coherent. Around the same time Herbert Fröhlich showed how such order could be established in a biological environment by the same principle due to non-linear electromagnetic coupling of oscillating electric dipoles of biological macromolecules with the heat bath (Fröhlich, 1968a, 1968b; Šrobár, 2009). In essence, the phenomenon resembles energy pumping to a solid state laser system, where critical energy pumping is required for the phase transition from ordinary, non-coherent light, to coherent laser light. Fröhlich predicted

that coherence would allow for a highly specific recognition and efficient interactions between biological macromolecules via the principle of resonance, or frequency-specific coupling, as opposed to classical models based on far less efficient Brownian (statistical) motion and van der Waals interaction (Fröhlich, 1975, 1978).

In the 1980s, Fröhlich's model has been further elaborated by an Italian group of physicists within the framework of the quantum field theory (Del Giudice et al., 1988). In this model, coherent state is described in terms of a quantum phase transition of the many-body system, as one of the multiple physically distinct ground states, resembling the well-known Bose-Einstein condensate but existing at physiological temperature (see Vitiello, 2001 for a qualitative discussion). Any form of energy as diverse as vacuum electromagnetic fluctuations, light, mechanical vibrations, or metabolic energy (e.g., from ATP hydrolysis) may, in principle, excite the coherent phase transition (Del Giudice et al., 2005).

The theory was first applied to cell water, but later extended to encompass biological macromolecules, since they generally satisfy basic temperature and polarisation density conditions, as determined by quantum field theory (Brizhik et al., 2009; Del Giudice and Tedeschi, 2009; Del Giudice et al., 2005, 2009). Moreover, quantum electronic coherence has been hypothesized to provide the fundamental physical mechanism explaining how the quasi-free electrons, vital for the redox processes, arise due to resonant coupling with electromagnetic fields. Such quasi-free electrons would significantly increase the probability of quantum tunnelling, an increasingly accepted physical mechanism underlying biochemical reactions (Del Giudice and Tedeschi, 2009; Nagel and Klinman, 2009). As in Fröhlich's model, the specificity of reactions would depend on the resonant frequency coupling between the reactants. The suggested model is, however, different due to different theoretical frameworks (Arani et al., 1995; Del Giudice et al., 2005).

In sum, theoretical models predict that, although the biological environment, traditionally considered "warm, wet and noisy", and hence unable to support any functionally significant quantum phenomena, generally meets the basic criteria for macroscopic, biologically meaningful quantum coherence. Coherence, either quantum or electromagnetic, is increasingly being acknowledged as not only allowing, but ultimately coordinating the dynamics of biological processes (Abbott et al., 2008; Jaeken, 2006). Specific implications of coherence in biological processes have been shown for water (Arani et al., 1995; Chaplin, 2006; Marchettini et al., 2010; Ho et al., 2006), cell physiology (Jaeken, 2006, 2007, 2009), biological macromolecules (Brizhik et al., 2009; Del Giudice et al., 2005; Del Giudice and Tedeschi 2009; Fröhlich 1975, 1978; Vitiello, 2001), the cytoskeleton (Mershin et al., 2006; Mavromatos et al., 2002; Jaeken, 2007), neurodynamics (Hameroff, 2006; Jibu et al., 1994; Vitiello, 2001), and cancer (Hameroff, 2004; Fröhlich, 1978; Pokorný, 2009a, 2009b; Popp, 2009).

5. Coherence and cancer

Within the framework of cancer biology described in Sections 2 and 3, we suggest that if the systemic origin of cancer is characterized by global and nonspecific progressive disorganization of the integrative molecular and gene regulatory network dynamics, and if coherence does indeed represent an important physical mechanism for the proper coordination of biological processes, then the lack of coherence, or even disturbance in proper coherent dynamics, will in some way contribute to cancer development.

5.1. Fröhlich's theory of cancer and thermodynamics

Several attempts have been made so far to explicitly connect cancer with biological coherence. Fröhlich himself was the first to predict a general principle of how cancer could arise due to the absence of proper coherent dynamics. He considered groups of cells, perhaps as large as individual organs, to be connected through a global coherent oscillation, excited via the cell membrane displacements whose wavelength would be much larger than the dimensions of a cell. The global oscillation would "lock" the cells into collective phase relations, stabilizing them due to their synchronized mechano-electric dynamics. If a component cell of such a system – for whatever reason – loses its proper frequency, this would not have a major effect on the global coherent excitation. However, if the number of such cells exceeds a certain critical value, the global coherent excitation would be weakened to such an extent as to be incapable of exerting these stabilizing influences over the group of destabilized cells. Then, a phase transition would occur to a disordered state of uncontrolled cell division, followed by a change of adhesive forces to the surrounding tissue, which Fröhlich identified with cancer (Fröhlich, 1978; Hyland, 2009; Pokorný, 2009a, 2009b).

This general approach fits well with the thermodynamic interpretation of cancer in that such a group of cells would gradually become an autonomous dissipative system, a sort of a thermodynamic "parasite" which utilizes the global energy of the organism for its own development (Hauptmann, 2002; Molnar et al., 2005). Indeed, because the total free energy of ATP hydrolysis is similar in normal and malignant cells (despite differences in the mechanisms of energy production, see Section 5.2), the loss of coherence would result in excessive energy input without its proper dissipation (Brizhik et al., 2009). The consequence of such an energetic "overload" would be a distortion of dissipative structures, impaired self-organizing potential of the metabolic networks, higher entropy of the system, and increased thermal noise – an entropic hallmark of cancer (Berretta and Moscato, 2010; Hauptmann, 2002; Klimek, 2001; van Wijk et al., 1984).

5.2. Bioenergetics and cancer

Is there a way Fröhlich's general framework can be interpreted within the recent findings in cancer biology? A possible underlying factor connecting coherence and progressive disorganization of molecular and genetic networks in cancer is cellular bioenergetics. The flow of energy through the cell is primarily mediated by the mitochondrion. The bioenergetic view of cancer maintains that cancer arises from impaired oxidative phosphorylation in mitochondria, an idea proposed almost a century ago by Warburg, but which has only recently regained scientific interest. It was confirmed that more than 95% of carcinomas manifest the bioenergetic signature of cancer, an increased ratio of glycolytic, compared to respiratory proteins (Acebo et al., 2009).

Damage to the respiration machinery can arise from any number of nonspecific influences, such as chemical carcinogens, radiation, low level hypoxia, inflammation, reactive oxygen species, or inherited mutations. Damage may include abnormalities in mitochondrial inner membrane (affecting proton motive gradient), mitochondrial DNA, the tricarboxylic acid (TCA) cycle, and the electron transport chain. As a result, the cell redirects its metabolism for the synthesis of ATP through glycolysis (aerobic glycolysis, or Warburg effect) and glutaminolysis. However, a prolonged aerobic glycolysis results in an atypical redox status, disrupted calcium homeostasis, and would generally increase genomic instability (Seyfried and Shelton, 2010).

In fact, it has been shown that all of the six classical phenotypic hallmarks of cancer (Hanahan and Weinberg, 2000) can be functionally connected to impaired respiration apparatus (Kroemer and Pouyssegur, 2008; Seyfried and Shelton, 2010). Further, several connections have been recently established between metabolic

defects and cancer epigenetics. For example, epigenetic enzymes themselves are redox sensitive, and in addition rely heavily upon metabolic and dietary factors, such as NAD^+, α-ketoglutarate, folate, S-adenosylmethionine, ATP, and acetyl-CoA (Hitchler and Domann, 2009). Generally, bioenergetic regulation of nuclear gene expression acts in such a way that when energy availability is low, chromatin becomes dephosphorylated and deacetylated, gene expression subsides, and the cell ceases growth. Hence,-bioenergetics provides an important interface between the environment and the epigenome (Wallace and Fan, 2010).

5.3. The role of microtubules

The mitochondria provide energy through the electrochemical gradient across the inner mitochondrial membrane (about −180 mV), which powers the cell and the body. The static electric field surrounding mitochondria is also used to regulate calcium homeostasis, cellular pH, substrate compartmentalization, and import of proteins into the mitochondrion (Wallace, 2010).

However, it may provide yet another role. More than 50% of acetyl-CoA free energy is not utilized for ATP production in mitochondria, and this energy flows out of mitochondria mostly in the form of thermal energy, light, and ultraviolet radiation. Since mitochondria are located around microtubules, a major component of the cytoskeleton, a considerable part of their energy output is absorbed by them. It was pointed out by a Czech group of biophysicists that the strong electric field surrounding mitochondria provides conditions for the nonlinear energy transfer via the Fröhlich's mechanism, and the electromagnetic energy efflux provides the major energy source to excite the microtubules in the coherent state (Cifra et al., 2010; Pokorný, 2009a, 2009b; Pokorný et al., 2011). Microtubules have been long considered the prime cellular nanostructures to support functional coherent dynamics due to their mosaically ordered dipolar structure with piezoelectric, ferroelectric, and other biophysical characteristics (Mershin et al., 2006; Tuszyński et al., 1997). Theoretical analyses of microtubule electro-mechanical vibrations indeed predict that they can support a wide range of frequencies (from kHz to THz) with different coherent modes, able to produce a complex dynamic electromagnetic field, which can influence molecular processes in the cell (Cifra et al., 2010; Wang et al., 2006).

Various mechanisms that supposedly arise as a result of the coherent dynamics in microtubules have been proposed as necessary for organizing cellular processes, such as transport of energy and metabolites, metabolic interactions, and information processing. For example, the generated coherent electromagnetic field can promote non-random transfer of ions and charged molecules in the vicinity of the filament (Pokorný et al., 2005; Pokorný, 2001). Such transfer would be highly facilitated through the ordered (polarized) water surrounding the filament, which has a vital role in cell physiology (Del Giudice et al., 2005; Jaeken 2007; Pollack, 2002; Priel et al., 2006). Given sufficient thermal isolation, it is predicted that various kinds of coherent vibrational waves (solitons) would also promote highly efficient excitation transfer along the filament and thus facilitate metabolic interactions (Mershin et al., 2006; Scott 1992; Vitiello, 2001). Information processing through quantum superposition of the electron clouds in tubulin monomers, and in the microtubule interior, has been also predicted to have a functional role in coordinating cellular interactions (Abbott et al., 2008; Hameroff, 2006; Jibu et al., 1994; Mershin et al., 2006).

It is clear that these mechanisms do not exclude each other and cooperation of different processes at different levels of organization is expected. However, they all depend on the coherent states in the microtubules. There has been a considerable criticism as to whether microtubules could support coherence times long enough to influence biological processes, either due to unavoidable thermal agitation (Tegmark, 2000), or due to insufficient energy pumping (McKemmish et al., 2009). It has been argued that the stabilizing effects of the structured water, electromagnetic energy input from mitochondria, and nonlinear interactions have not been properly evaluated in those models (Cifra et al., 2010). However, very recent preliminary measurements on isolated microtubules strongly support coherent condensation and coherent electron transport along the whole filament, with resistance independent of its length, and at physiological temperature (Bandyopadhyay, 2010).

It is thus reasonable to assume that a gradual weakening or distortion of the coherent dynamics in microtubules as a result of impaired energy flow will have a significant influence over the dynamics of the interactive metabolic networks in the cell – especially considering the fact that the cytosolic enzymes of many metabolic pathways are concentrated as supramolecular clusters (metabolons) associated with the cytoskeleton, or cytomatrix in general (Shepherd, 2006). Destabilization of molecular processes, if sustained, will inevitably affect the gene expression patterns, promote genomic instability, and thus cancer development (Fig. 1). Impaired coherent dynamics would further destabilize energy flow and information processing in a self-reinforcing manner so as to gradually push the whole system out of the reach of the control mechanisms that usually direct the cells towards apoptotic expression profiles (or attractors), toward less and less organized states resembling immature mesenchymal cells – in accordance with the cancer attractor and epigenetic progenitor models. When a critical threshold is reached, transition to malignancy would occur.

Centrosomes have also been suggested to be involved in cancer development due to impaired coherent dynamics. Centrosomes are the primary microtubule-organizing centers in animal cells and become the core structures in mitosis where they direct formation of the mitotic spindle. It was shown that centrosomal defects, such as multiplication or enlargement, often occur early in tumour development and may directly promote genomic instability (Pihan et al., 2003). Hameroff (2004) has argued that impairment of the coherent modes in the mitotic spindle during cell division would result in improper communication between the centrosome pairs, followed by abnormal separation of the chromatids, that is, aneuploidy. Thus, a possible direct connection between the coherence,

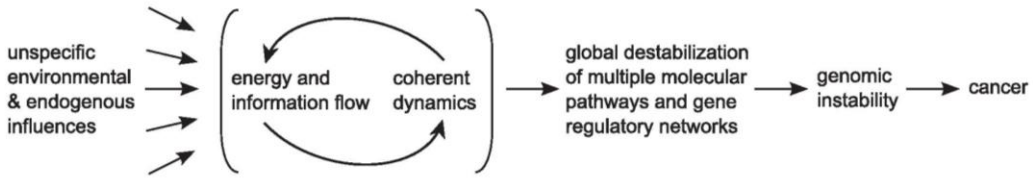

Fig. 1. Role of coherence in the systemic view on cancer development. Any number of nonspecific influences may induce a self-reinforcing loop between impaired coherence and disturbed energy/information flow within a cell and between cells. Sufficient perturbation results in a global destabilization of multiple molecular pathways, gene regulatory networks, and the genome.

and genomic instability, generally considered as necessary for cancer development (see references in Section 2.2) has been suggested. The origin of impaired coherence was, however, not discussed in this theory, but within the above framework, it can be inferred that weakened or disturbed coherent modes in the microtubules may well account for impairment of coherent dynamics in the mitotic spindle as a whole.

As already discussed, disturbed cellular signalling pathways, adhesion properties, or induced mechanical stress can also contribute to cancer development, independently of the cellular bioenergetic status (Ingber, 2008). The cytoskeleton and other structural elements of the cell form an interconnected, tensionally integrated (tensegrity) system, which is able to collectively coordinate distinct gene expression profiles – and thus cellular fate – in response to structural and mechanical perturbations, via mechanotransduction (Ingber, 2003, 2006). With several types of cell junctions, cell adhesion molecules, such as integrins, and the extracellular matrix, the whole tissues and organs form a continuous, functionally coherent network. Given the strong relationship between mechanical and electromagnetic excitations (Tuszyński et al., 1997), we can assume that by chemically or mechanically disturbing these elements, coherent modes will be affected, which would destabilize the coordinated energy and information processing in a similar way to impaired bioenergetics. Indeed, cancer is typically accompanied by various defects in the structure of the cytoskeleton, which affect the mechanical properties of the cell (deformability, stiffness, and elasticity), cell adhesion properties, and signalling interactions between cells (Ingber, 2008; Suresh, 2007). This may give a new perspective on the non-cell-autonomous aspects of cancer.

5.4. Biophotons

Indirect experimental connection between the coherence and cancer has been shown in the field of biophotonics. Biophoton emission (ultra-weak photon emission from living organisms) displays some unique characteristics, such as nonlinear spectral distribution, distinct photon count statistics, hyperbolic relaxation dynamics (in terms of delayed luminescence), and self-transparency, which imply its coherent origin (Popp and Beloussov, 2003).

Emission correlates well with biological rhythms, tissue damage, age, and cancer. While normal cells showed a decreasing (total) emission with an increasing cell density, the photon emission of tumour cells increased, and the increase was more distinct, the more malignant the tumour cells. Further, as the cell density increased, the degree of incoherence (measured as deviations from hyperbolic relaxation) decreased in normal cells, but strongly increased in tumour cells (Schamhart and van Wijk, 1987; Scholz et al., 1988; Popp, 2009). These observations cannot be explained in terms of linear optics, as with increased optical density of the tissue, the saturation may be understandable, but not the decrease after saturation. However, they accord with the idea of coherent communication not only between neighbouring cells, but among the members of a cell population (Cifra et al., 2011; van Wijk, 2001). Popp (2009) has argued, based on comparing stimulating and inhibiting factors on cell growth, that biophoton emission is not the consequence, but the cause of cell division, because only its complex bioinformational character could work as an information source. Thus, the implication is that cancer will arise when integration of new cells in a population by cell division results in a decreased coherence and/or communication between the cells (van Wijk, 2001), in accordance with Fröhlich's original theory.

In sum, from the systems view, energy and information flow in organisms are both primary factors contributing to cancer if impaired, in the form of damaged oxidative phosphorylation in mitochondria, or disturbed signalling networks and tissue integrity. It is not yet clear to what extent can each of those primary factors autonomously contribute to cancer development. However, energy and information, as cardinal concepts in biology can directly affect, as well as be affected by, an impairment of the coherent dynamics (Fig. 1). As microtubules are becoming the focus point in the models regarding the coherence aspect of cancer and coherence research in general, the scope of functional coherence in microtubules will very likely be one of the crucial features determining the general role of coherence in living systems.

6. Conclusions

It is becoming clear that even with potentially unlimited insight into the dynamics of genetic changes, cancer could not be sufficiently explained, and neither could it be explained in terms of separate linear molecular pathways alone. During the last decade, scientific attention has turned dramatically towards the metabolic, bioenergetic, developmental, and systems biology aspects of cancer, reflecting a gradual paradigm shift towards its non-genetic origin. Coherence is a well-known concept in physics, but has only recently witnessed a general acknowledgement in biological scientific communities. We have argued here that coherence may be one of the general underlying factors that contributes to cancer development by destabilizing energy flow and information processing, causing a progressive and nonspecific disorganization of the molecular and gene regulatory networks, as a systems "hallmark" of cancer. Coherence may connect different non-genetic aspects of cancer into a more integrative understanding of this pathology.

Perhaps a more pragmatic reason not to ignore coherence is the fact that new cancer therapies might emerge. As the coherent dynamics is associated with specific frequencies of either endogenous electromagnetic fields (Pokorný et al., 2005) or electromagnetic potential (Brizhik et al., 2009; Del Giudice et al., 2005), an impairment of coherent dynamics in cancer would result in the loss of normal, tissue-specific frequencies, while some new, tumour-specific frequencies may appear. A model of cancer-specific frequencies, caused by a shift in the resonant recognition frequencies of certain oncogenic products, has been recently proposed (Cosic and Pirogova, 2007). Specific frequencies could in principle be used for the selection of tumour cells either to destroy them, or to restore impaired control mechanisms and reprogram them into normal tissues.

Bioelectromagnetic medicine has a long history and many frequency-based therapies are routinely used for a variety of pathologies (Rosch and Markov, 2004). Important advances have been made in the field of electromagnetic cancer therapy. Kirson et al. (2007, 2009) have successfully inhibited various rat and human primary tumours and lung metastases with low intensity (sub-thermal) alternating electric field in the low frequency range (30–300 kHz). The hypothesized mechanism for interaction is the classical electromagnetic effect of dielectrophoresis, in which a gradient of the induced field prevents the correct orientation of the spindle during cell division and eventually causes apoptosis. However, assuming the presence of electromagnetically coherent modes in microtubules would provide an about 1.5 orders of magnitude stronger electrical field (Cifra et al., 2010). This would make them more susceptible to interference with exogenous electromagnetic fields of sub-thermal intensities.

In the same study, inhibiting tumour-specific frequencies have also been reported (100 kHz for melanoma and 200 kHz for glioma). Tumour-specific frequencies imply qualitative differences between individual tumours, difficult to explain by classical

electromagnetics (e.g., by using models of the cell shape-dependent distortion of field intensities), since the biological environment is highly heterogeneous. They are, however, in accordance with the resonant frequency interactions typical of coherent systems. Others have also reported tumour-specific modulation frequencies, though in different frequency ranges (Barbault et al., 2009; Costa et al., 2009).

The recent discovery of quantum coherence in photosynthetic systems, as well as preliminary results supporting coherent energy transport along microtubules, do represent a proof of principle, and these possibly have huge implications for the life sciences. If it indeed turns out that coherence plays a functional role in microtubules, or possibly even represents a generic factor coordinating the dynamics of functional molecular networks (such as protein-protein and protein-DNA interactions), then we will have to give it serious consideration in the understanding of fundamental biological processes, just like diffusion, or electrochemical excitability. It is already proposed that coherent systems are dissipative structures, and therefore represent the self-organizing capacity of matter (Marchettini et al., 2010; Vitiello, 2001), acting independently of natural selection. We believe that only a multidisciplinary systems approach can tackle the many empirically open questions and allows us to obtain a more synthetic understanding of cancer.

Acknowledgements

First author is financially supported by the European Union, European Social Fund and OP ESS 2007–2013.

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2.2 VLOGA KOHERENCE PRI SISTEMSKEM POGLEDU NA RAZVOJ RAKA

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Izvirni naslov: *The role of coherence in a systems view of cancer development*

Publikacija: *Theoretical Biology Forum (2012) 105, 15-46.*

Ključne besede: *cancer, coherence, systems biology, self-organisation, quantum electrodynamics*

Izvleček: Razumevanje raka je na paradigmatskem razpotju, kar odpira vrata novim hipotezam o njegovem izvoru. Mnoga dognanja s področij tkivnega mikrookolja, energijskega metabolizma, epigenetike, sistemske biologije in termodinamike nakazujejo, da rak ni genetsko determinirana bolezen. Ena temeljnih značilnosti karcinogeneze je postopna deregulacija bioloških procesov na mnogih organizacijskih ravneh: genomski, metabolični, tkivni in celo organizemski. Stalen tók energije in informacij predstavlja temeljno gonilno silo biološke samoorganizacije, zato lahko motnja tega toka predstavlja sistemski vzrok za razvoj raka. Nekatere fizikalne teorije smatrajo koherenco molekulske dinamike kot pomemben princip biološke samoorganizacije, ki lahko razloži visoko učinkovitost bioloških procesov. Nedavni tehnološki napredek je omogočil neposredno merjenje koherentnega prenosa energije med molekulami, ki je bil do sedaj dokazan na več molekulskih sistemih, zato lahko princip koherence načeloma apliciramo v sistemsko biologijo raka. V prispevku predpostavimo koherenčno hipotezo raka, v kateri združujemo do sedaj predpostavljene teoretične modele, ki predvidevajo vzročno povezavo med različnimi vidiki okrnjenega koherentnega prenosa metabolične energije in razvojem raka, in katerim dodajamo tudi lastno hipotezo, ki temelji na teoriji kvantne elektrodinamike. V prispevku poskušamo prikazati, kako lahko teoretični koncept molekulske koherence povezuje različne vidike razvoja raka in na ta način združuje biološke in fizikalne pristope k razumevanju te kompleksne bolezni.

THE ROLE OF COHERENCE IN A SYSTEMS VIEW OF CANCER DEVELOPMENT

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Keywords: cancer, coherence, systems biology, self-organisation, quantum electrodynamics.

Abstract: *Theories of cancer origin are going through a paradigm shift, opening cancer research to new hypotheses. Accumulating evidence from the tissue microenvironment research, from bioenergetics, epigenetics, systems biology and thermodynamics tends to converge in characterising cancer as essentially a genetically non-deterministic disease. Instead, it is characterised by progressive disorganisation at a variety of organisational levels, from the genome and metabolic networks, to tissue integrity. As biological self-organisation is fuelled by the continuous supply of energy and information, these represent systemic roots of cancer origin, when compromised. The coherence of molecular dynamics has been recognised as an organising principle behind the long-range coordination of biological processes which can explain the remarkable efficiency of biological systems. Recent methodological advances have enabled the rapid accumulation of experimental evidence pointing to coherence as indeed playing an active role in mediating the flow of energy and information in diverse molecular systems, which is sufficient reason to apply it to a systems view on cancer development. We review theoretical models of how impaired coherence dynamics could lead to cancer as well as propose a new hypothesis based on the quantum electrodynamic theory of coherence. We discuss how the concept of coherence could connect different aspects of cancer and possibly represent their underlying theoretical framework, thus combining biological and physical approaches to understanding this complex pathology.*

Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
Dokt. disertacija. Ljubljana, Univ. v Ljubljani, Biotehniška fakulteta, 2013

1. Introduction

Cancer research is going through what some aptly refer to as paradigm instability [1]. A growing list of inconsistencies and contradictions [2], together with a constant changing of trends in search of «the cancer genes» [3], have made it clear that the current genetically deterministic paradigm of cancer is inadequate to describe its unified etiology. On the other hand, a growing body of cancer research points in another direction. During the last decade, several approaches towards the non-genetic origin of cancer have been developed, focused upon diverse biological frameworks (Section 2. 2): the tissue microenvironment, bioenergetics, epigenetics, systems biology, and thermodynamics. Such an abundance of different contexts, however, does not simplify matters, but makes a unified cancer etiology even more elusive. On the one hand, for example, cancer can be primarily understood as a disease of tissue organisation and integrity [4]; on the other, it seems that it is primarily a metabolic disease [5]. Both aspects have substantial experimental support, but which of them, or any other, is more fundamental? Are they causally connected or could they initiate cancer independently and, crucially, is there something that they all have in common? Current knowledge of cancer molecular biology does not allow conclusive answers to these questions.

We argue here that the self-organising properties of energy and information flow in organisms provide a systems root of carcinogenesis, towards which different aspects of carcinogenesis may converge. Network modelling of self-organisation has become a widely acknowledged and powerful tool for explaining biological order [6, 7, 8]; however, self-organisation does not only pertain to topological order, but it also has its dynamic manifestation, synchronisation [9]. Synchronisation is a natural tendency of objects to adjust their internal *rhythms* to a collective operational regime due to their mutual interactions, and it has become one of the main research disciplines in non-linear science [10, 11, 12]. Synchronous behaviour of coupled elements enables a powerful response of a system to external stimuli, efficient coordination between different systems (e.g., temporal compartmentalisation), information encoding, and it generally maximises energy and information flow throughout the system, thus increasing the organising potential of biologcal processes [13, 14, 15]. Synchronisation phenomena have been described at all basic levels of biological organisation, from the precisely coordinated gene expression and metabolic cycles (such as glycolytic and redox cyles in yeast), to synchronised physiological rhythms, e.g. circadian cycles or coherent brain oscillations, and inter-organismal synchronisation, e.g. quorum sensing, synchronised signalling, social group dynamics, etc.[1]

We shall focus here on another recently emerging level of synchronous behaviour, namely of electrically active components within single molecules or molecular complexes, a phenomenon generally referred to as coherence. Erwin Schrödin-

[1] An interested reader may find further examples of synchronised dynamics in organisms in [9, 13, 15, 16, 17, 18, 19, 20].

Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
Dokt. disertacija. Ljubljana, Univ. v Ljubljani, Biotehniška fakulteta, 2013

ger in his famous essay [21] clearly pointed out that biological order could not be sufficiently explained exclusively by statistical laws, and that some other organisational principles must be ultimately responsible for maintaining the long-range order and energy efficiency. In the 1960s, such a long-range order was recognised by Herbert Fröhlich as coherent molecular excitations [22, 23]. In the 1980s, the theory of biological cohererence was further elaborated by the Italian group of physicists in the framework of quantum field theory [24, 25, 26, 27, 28, 29, 30]. Although these models pointed out the fundamental role of coherence in biology, it has been viewed as trivial in terms of exerting biologically meaningful effects in organisms, and neglected mostly due to lack of conclusive experimental evidence. This picture has changed considerably since 2007, when an elementary form of coherence, quantum coherence, was for the first time experimentally measured and demonstrated to directly coordinate a specific biochemical process [31]. The field of biological coherence, or «quantum biology», to which it is often referred, has since become a mainstream research field (Section 3. 1).

The application of coherence, or more specifically insufficiency or impairment of coherent dynamics, to cancer, was first suggested by Fröhlich [32, 33]. Recently, several papers further elaborated on this hypothesis, however mainly from the physics perspective [34, 35, 36, 37, 38]. Here, we aspire to develop a synthetic biological framework for applying the coherence as an organisational principle into a systems view on cancer biology. We review the existing hypotheses regarding the putative role of cohrence in cancer, together with our own physical interpretation based on quantum electrodynamics theory. It is not our intent to provide conclusive mechanistic role of coherence in cancer, as such an endeavour is yet premature due to lack of conclusive experimental evidence. Nonetheless, we aim to provide a basic conceptual framework for the long-range order in organisms upon which diverse aspects of this overwhelmingly complex disease – still far from being understood – could converge.

2. Genetic vs. non-genetic origin of cancer

From the molecular biology perspective, theories of cancer origin can be divided between two fundamental paradigms, the genetic and the non-genetic. The difference between them is epitomised by the role of mutations: in the genetic paradigm, mutations are causative, or determinative; in the non-genetic paradigm, they are permissive [39]. Whereas the genetic approach lends the full autonomy and explanatory power to the genes and the pathways they determine, the non-genetic approach emphasizes the complexity of integrative dynamic interactions among the system's components, whose emergent properties maintain a dynamic circular causation between the genotype and phenotypic traits, meaning that there is no preferred level of organisation that could independently determine biological function [40, 41, 42, 43, 44]. Because of its immense complexity, it may not be presumptuous to assert that cancer research reflects the historic paradigmatic opposition between the reductionist and systems biology approaches [45, 46, 47].

Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
Dokt. disertacija. Ljubljana, Univ. v Ljubljani, Biotehniška fakulteta, 2013

2.1. *The limited explanatory power of the genetic paradigm of cancer*

The genetic paradigm of cancer asserts that genetic alterations (mutations *s.l*) are the prime cause of cancer initiation and progression. A mutation can occur either at the level of a single gene, which may be an oncogene, tumour suppressor gene, or stability (caretaker) gene [48], or it can occur at the level of the genome. In the latter case, mutations arise from increased rates of genomic restructuring, because the whole genome is typically destabilised in most cancers [49, 50]. In either case, the genetic paradigm asserts that mutations would impose changes in specific steps of specific molecular pathways that would linearly determine the phenotype and thus the fate of the cell. Accumulating mutations are then gradually selected via selection pressures (e.g., hypoxia) such that only the clones with the most adaptive mutations will survive and multiply, progressively liberating themselves from homeostatic control mechanisms or, in other words, satisfying conditions for the classical phenotypic hallmarks of cancer [51] to emerge. This classical theory of cancer, borrowed from Darwinian evolution, is known as the clonal evolution model [52, 53] and is generally acknowledged as the current doctrine of cancer development. There are two major arguments that support the clonal evolution model: the clonal expansion of cells, bearing specific genetic, karyotypic, or phenotypic traits within primary tumours [52, 54, 55] or metastases [56], and a plethora of 'cancer' mutations, associated with either specific clones, cancer types, or cancer in general [48, 57].

2.1.1. The gene-centric approach to cancer

While the clonal expansion correctly acknowledges selective growth advantage of a specific clone bearing a distinct gene expression profile, this does not necessarily mean neither that cancer initiates from a single mutated cell (see, e.g., [58, 59, 60]), nor that genetic mutations are required for cancer initiation. In the strict gene-centric view of clonal evolution, it is proposed that only a few defined driver mutations, corresponding to discrete histopathological steps of tumour progression, suffice to induce a fully malignant transformation *in vivo* [57, 61]. However, very few specific mutations have been defined as a completely reliable diagnostic markers [5, 58, 62, 63]. For example, translocation between chromosomes 9 and 22 (the Philadelphia chromosome) which results in Bcr-Abl chimeric protein, is considered a definitive diagnostic marker of chronic myelogenous leukemia, a type of haematological malignancy.[1] In some cancers, specific germ-line or somatic mutations result in nearly 100% penetrance, e.g., *APC* or *MYH* in colorectal tumours, *RB1* in retinoblastoma, or *KIT* in gastrointestinal stromal tumours. In familial adenomatous polyposis, a type of hereditary colorectal cancer, mutations that activate the

[1] Nonetheless, a careful analysis demonstrated a low background of the hybrid gene in leukocytes from the majority of normal adults, indicating that other events may be necessary for a malignant transformation [64, 65].

Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
Dokt. disertacija. Ljubljana, Univ. v Ljubljani, Biotehniška fakulteta, 2013

Wnt/β-catenin signaling pathway (mostly at the *APC* or *CTNNB1* genes) are considered necessary, and thus causative, for tumour initiation.[1] In the majority of cancers, however, distribution of point mutations, obtained by sequencing many cancer genomes, tells us more about their heterogeneity, nonspecificity, and variability in their number, than it reveals on common genetic patterns. Only a few clonal mutations are typically present in a substantial number of tumours of the same cancer type, whereas the majority are found in individual tumours [70, 71, 72], or even in individual cells within the same tumour [73], resembling the power-law (i.e., statistical) distribution.

The reason why some genes are more frequently mutated or aberrantly expressed than others is because they often act as important hubs in the gene regulatory network. For example, *p53*, the most frequently mutated gene in cancer, may indirectly regulate several thousand genes [74] and undergoes as many as 50 post-translational modifications [75]. Similarly, many other genes commonly associated with cancer (e.g., *MYC, RB1, BRCA1*) turn out to be pleiotropic regulators of constitutive cell processes, such as cell cycle control, DNA repair, cell signalling, metabolism, or the genome integrity [76, 77, 78]. Mutations of such genes simultaneously deregulate multiple molecular pathways, often with synergistic consequences on the phenotype. In sum, as it seems that every individual tumour has its own complex mutational spectrum with only a few commonly mutated or aberrantly expressed tumour-associated genes, it seems unlikely that consistent and reliable patterns of mutations will be found for most cancers, which is supported by the cancer genome sequencing studies.

2.1.2. The genome-centric approach to cancer and genomic instability

As an alternative model of the clonal evolution theory, some researchers explain that cancer is not gene-specific, but rather a genomic, or karyotypic, disease [79,80,81]; it is not specific genes, but specific karyotypes as a whole that are subjects to selection pressures, and as such quasi-stably evolve towards the malignant phenotype. Common to this approach is that instability of the genome represents the major driving force for evolution and genetic heterogeneity of cancer. Genome instability refers to elevated rates of genomic restructuring, such as changes in chromosome number (aneuploidy), segmental chromosomal rearrangements (translocations, duplications, inversions and deletions), instability of repetitive sequences [82], and single catastrophic events, such as the recently described phenomenon of chromothripsis [83].

A plethora of factors with variable specificity can generally cause genomic instability: aberrant expression of caretaker genes, such as DNA repair genes and mitotic checkpoint genes [50,82,84], ionizing radiation [85], centrosome amplifications [86],

[1] In a minority of cases, Wnt/β-catenin pathway is not deregulated [66, 67]. Also interestingly, a recent study demonstrated that the Wnt/β-catenin pathway is regulated by signalling from the tumour microenvironment, indicating that it might not be predominantly cell-autonomously controlled [68]. In any case, however, other genetic or epigenetic events, resulting in complex expression signatures of clinical tumours, are required [69].

pathogenic infections [87], aberrant epigenetic patterns (Section 2. 2. 4), mitochondrial dysfunction (Section 2. 2. 3), and even changes in cell adhesion properties [88]. This suggests that genomic instability could not be solely ascribed to underlying mutational events, but rather is a systemic pathological state, reflecting a fundamental inability of a cell to maintain homeostasis. In other words, maintaining DNA integrity is an active process that requires precise metabolic control and energy expenditure [89, 90].

Because the genes influence expression of many other genes in a highly reciprocal manner, expression patterns will change due to rewiring of the gene regulatory network [39]. For example, single chromosome aneuploidy typically causes global and unspecific transcriptional dysregulation, as well as changes of phenotypic traits that are often convergent, i.e., independent of the chromosome identity [91, 92, 93]. Specific contributions of individual genes to phenotype thus become difficult to predict, as they are inherently dependent on the context of a genome as a whole [44, 94]. Even classical cancer-associated genes such as *RAS* may function both as oncogenes and tumour suppressor genes in the same cell type, depending merely on the timing of the mutation [48].

While the karyotypic theories account well for the genetic heterogeneity and unspecific nature of cancer mutations, they do not address the systemic cause of genomic instability. Generalising the latter to environmental stress, carcinogens, or aneuploidy may not be a sufficient explanation of the origin of cancer. Karyotypes are themselves context dependent: in one tissue, a given karyotype may promote tumour development, whereas in another tissue tumour incidence may be suppressed. The fate of a specific karyotype is thus subject to tissue-level context and is hence non-cell-autonomous [49, 84]. In sum, although genome-centric theories explain many observed genetic features of cancer, without proposing a systems background for genome instability, they nonetheless represent an alternative theory within the genetically deterministic paradigm of cancer.

2. 2. *The non-genetic aspects of cancer*

2.2.1. Cancer as a systems disease

Shapiro [44] has lucidly challenged the central dogma of biology by demonstrating a plethora of novel concepts of biological complexity that argue against genetic determinism. First, the highly dispersed (chromosome or even genome-wide) nature of exons and regulatory sequences, alternative splicing, and continuum of overlapping transcription has blurred the traditional concept of the gene to such an extent as to even challenge its ontological status [95]. Second, pleiotropic function of many genetic loci, together with their complex reciprocal and environment-dependent regulation, constrains them and makes the gene expression highly dependent on the gene regulatory network as a whole [7, 39]. Third, a plethora of post-translational modifications, together with the modular nature of many proteins and their conformational plasticity, enables immense combinatorial potential [44,96,97]; combined with the 'fuzzy' nature of protein interactions, this allows them to form

Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
Dokt. disertacija. Ljubljana, Univ. v Ljubljani, Biotehniška fakulteta, 2013

complex, multifunctional, dynamically interacting networks (e.g., metabolic compartments) with highly dispersed structural and catalytic specificity that could not be fully prescribed by the genes [42, 98]. Fourth, the inherent context-dependency of the functions of many proteins and signal molecules [48, 63, 94], of whole molecular pathways [99, 100], or even of cells and tissues [101, 102], further implies the fundamental non-determinacy of biological function.

Taken collectively into account, this fundamentally challenges the purely materialistically determined meaning of biological information – as defined in quantitative terms by Shannon [103] – but rather encourages a semiotic approach that takes into consideration its qualitative aspect, which is inherently context-dependent, i.e., relational [104]. Organisms spontaneously create new symbols with new meanings, and do not merely transmit or preserve existing information, as perceived from an information theory perspective (see selected chapters in [105] and [41]). Finally, the noise, whether in the form of stochastic environmental interactions, molecular fluctuations, or gene expression dynamics [106], must be appreciated as an ultimate creative force, rather than destructor, allowing the emergence of new information and open-ended evolution [107].

Continuous turnover of energy and information represents the basic fuel for biological self-organisation. Order is dynamically self-stabilized at multiple organisational levels, with no absolute level or direction of causation representable by a linear diagram [42, 43, 45, 108]. It is important to realise that the natural genetic engineering is a biochemical process, meaning that it is subject to regulation and responsive to environmental stimuli like other cellular processes [90]. In the same sense that there is no gene for the rhythm of a pacemaker [42], or coherent brain oscillations which represent a dynamic physical basis of cognition [17, 18], there is no gene or a linear pathway for cancer, because cancer is, like any physiological rhythm, a dynamic emergent process.

We argue that cancer is essentially non-genetic disease, characterised by a global and unspecific impairment of energy and information flow through the system, as manifested in genomic, transcriptomic and proteomic dysregulation [109, 110]. As open systems far from thermodynamic equilibrium, organisms spontaneously evolve towards maximum rate of energy turnover (its net production, transformation and dissipation) and informational richness (structural complexity) that can be supported by their environments (see discussion by Fath and co-workers [111]). Their phenotypic properties emerge from a delicate balance between positive and negative feedback forces and hence are highly susceptible to fluctuations in energy flow. Any sufficiently large perturbation in the normal flow of metabolic energy at any organisational level will destabilise its dynamic properties and force the system to occupy alternative paths of energy dissipation on account of structural complexity [112, 113]. As carcinogenesis is characterised by such (self-)disorganisation morphologically [60, 114, 115, 116], thermodynamically [117, 118, 119, 120], informationally [110, 121], and molecularly [58, 109, 110], energy and information are the primary systemic roots that initiate it, if disturbed. We start by a basic overview of the non-genetic aspects of cancer and then proceed towards the coherence hypothesis.

2.2.2. Tissue organisation

The significant role of the connective tissue microenvironment (the stroma) in the development of sporadic carcinomas has been widely acknowledged for more then a decade [116, 122, 123, 124, 125]. The stroma, composed of activated fibroblasts, immune cells and other specific cell types secretes a variety of growth factors, proteinases, cytokines, and other signalling molecules that promote carcinogenesis by inducing epithelial cell growth, angiogenesis, degradation and remodelling of the extracellular matrix and basal lamina, and in addition act in a paracrine way to influence epithelial cells to secrete further tumour promoting factors [126].

In the traditional, cell-autonomous view consistent with the clonal evolution theory, the tumour stroma is considered to be activated by various factors secreted by cells already bearing tumorigenic mutations [126, 127]. However, it has been demonstrated *in vivo* by tissue recombination that stroma treated with a chemical carcinogen [128] or ionizing radiation [129, 130] can autonomously induce transformation of, respectively, normal, or immortalized (but non-tumorigenic) epithelial cells, whether these had been treated or mutated themselves or not. These findings resemble the well-known late and bystander effects of ionizing radiation that can initiate cancer in non-targeted cells [89], and which may be explained by non-mutational heritable loss of normal cell signalling and tissue architecture [131]. Overexpression of stromelysin, an extracellular matrix proteinase that likewise disrupts the structural integrity of epithelia and intercellular signalling, can directly lead to transformation of phenotypically normal cells [132]. These studies clearly suggest how tissue structure and integrity – as emergent properties of biological organisation – exert a downward causative influence over individual cells and thus contribute to cancer development, when compromised [4, 60].

While a modified tissue microenvironment can autonomously induce tumours in normal cells, normal tissue structure can on the other hand actively delay, suppress or even reverse tumour development. Various adult or embryonic tissues can reverse injected malignant cells into normal phenotypes of corresponding tissues, indicating that tumour reversion is a generic phenomenon [133, 134, 135, 136]. Using 3D cultures, it was demonstrated that by manipulating the function of a single molecule involved in epithelium-extracellular matrix communication (integrin or dystroglycan), cells could repeatedly and reversibly switch between a disorganised state with increased malignant potential, and a normal epithelia-forming phenotype, together with complete reorganisation of the cytoskeleton and redistribution of cell adhesion molecules [137]. In sum, the phenomenon of tumour reversion further supports the role of tissue integrity and intercellular communication in carcinogenesis, while it strongly contradicts the view that sporadic carcinomas, which represent the majority of human cancers, are necessarily determined by genetic mutations. Gene (or genome) mutations are merely one of the many possible ways to induce cancer [60].

Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
Dokt. disertacija. Ljubljana, Univ. v Ljubljani, Biotehniška fakulteta, 2013

2.2.3. Energy metabolism

Energy metabolism is primarily organised by the mitochondria. The bioenergetic aspect of cancer maintains that cancer arises from an impaired oxidative phosphorylation. This idea was first proposed by Otto H. Warburg [138], who noticed that cancer cells use glycolysis as their main source of energy despite oxygen availability. Interest in aerobic glycolysis has only recently been revived, when it was confirmed that the vast majority of carcinomas manifest the 'bioenergetic' proteomic signature of cancer, as indicated by an increased ratio of glycolytic, compared to respiratory proteins, which accords with increased glucose intake and morphological impairment of mitochondria [139, 140]. As a consequence of this glycolytic switch, the whole metabolic network reorganises in such a way as to promote cell growth and proliferation (see [140, 141] for reviews). Importantly, the emergence of all of the classical phenotypic hallmarks of cancer [51] can be mechanistically traced to this metabolic reprogramming [5, 141].

Damage to oxidative respiration can arise from a number of unspecific influences, such as chemical carcinogens, radiation, hypoxia, inflammation, reactive oxygen species, and mutations. Damage may include structural abnormalities in the mitochondrial inner membrane (which disturbs the proton motive gradient and transport of electrons), components of the tricarboxylic acid cycle, or the electron transport chain [5]. As a consequence of damaged respiratory apparatus, mitochondria normally initiate apoptosis when damage becomes critical [142]. Cancer cells, however, evade apoptosis by definition, and aberrant expression of many metabolic regulators, which also act anti-apoptotically (e.g., MYC, HIF, Akt), is involved in this process [5, 143]. Abnormal expression of metabolic regulators may reveal robust, evolutionary conserved gene expression profiles and signalling pathways (i.e., retrograde signalling) that promote cell survival [5, 144]. However, impairment of oxidative phosphorylation and prolonged dependence on glycolysis also severely disturbs cell homeostasis and will generally lead to genomic instability [5, 145, 146].

2.2.4. Epigenetics

Cancer is characterised by global and unspecific epigenetic[1] modifications. There are four main epigenetic mechanisms: DNA methylation, covalent histone modifications, nucleosome remodelling, and non-coding RNAs [148]. All of these are known to contribute to aberrant cancer cells' epigenome, which is typically characterised by a genome-wide hypomethylation and site-specific hypermethylation, global histone post-translational modifications, changes in nucleosome positioning and replacement with histone variants, and widespread changes in expression of many miRNAs [58, 148, 149, 150]. As a result of these modifications, gene expression patterns in cancer cells are globally dysregulated [58, 148].

[1] Epigenetics is considered in strict molecular sense as the «structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states» [147].

A cell's epigenome is thought to provide an interface between the environment and the genome [151]. As epigenetic enzymes are highly susceptible to a variety of metabolic and dietary cofactors [152], many unspecific environmental influences can perturb gene expression dynamics by modifying epigenetic molecular machinery, meaning that epigenetic modifications are primarily determined by environmental and metabolic interactions, and not by the genes. The list of known environmental epigenetic modulators is potentially unlimited [153, 154], and also includes many classical chemical carcinogens traditionally thought to be mutagenic [155]. Considering the fact that epigenetic modifications are highly dynamic (unstable) and lack locus specificity, epigenetic dysregulation in cancer is not only global, but also highly non-specific.

Epigenetic modifications of gene expression may in principle by themselves induce cancer. Carcinogenic epigenetic switch (transdifferentiation without a change in DNA sequence) has been recently demonstrated on immortalized cells [156] and is also suggested to occur via impaired oxidative phosphorylation, thus establishing a direct link between cancer epigenetics and metabolism [152, 157]. In most cases, however, carcinogenesis is also associated with genome instability, and epigenetic dysregulation can cause genome instability in several ways: by destabilising monoallelic gene expression patterns, through alterations in expression of pleiotropic genes, by destabilising satellite DNA, or by activating mobile genetic elements [158]. Thus, as epigenetic plasticity becomes progressively unstable due to stochastic environmental perturbations, epigenetic instability may in turn translate into instability of the genome [58].

2.2.5. Cancer attractors of the gene regulatory network

The idea that the essential determinant of a cell's phenotype is its integrative gene expression profile, formally represented by attractor states of the gene regulatory network was first proposed by Stuart Kauffman [8]. Its application to cancer has been recently elaborated by Sui Huang and co-workers [39, 159, 160]. The gene expression profile is a specific configuration – among many combinatorial possibilities – of the gene regulatory network that self-stabilises as a consequence of the network topology and stochastic environmental interactions. The two most important characteristics of such network are multistability, meaning that a single network may give rise to many stable states or attractors; and robustness, ability of the system to resist or return to initial stable state when perturbed. Transcriptomic dynamics in different cell lines have indeed revealed convergent behaviour of transcriptomic trajectories, as well as return of the noise-induced deviations of a specific expression profile to the same transcriptome – both hallmarks of attractor states [7, 161, 162].

In normal development, various pleiotropic signals have a potential to redefine reciprocal influences between the genes such as to differentially instruct separate cell lines to switch the gene expression profiles to progressively differentiated cell types [39, 162, 163]. However if environmental or stochastic endogenous perturbations exerted on the gene regulatory network (in the form of mutations, epigenet-

Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
Dokt. disertacija. Ljubljana, Univ. v Ljubljani, Biotehniška fakulteta, 2013

ic modifications, loss of tissue integrity, etc.) are strong enough, or persist for a sufficient period, they may rewire the network topology in such a way as to redirect the gene expression dynamics towards some other, potentially pathological, sub-attractor. There are many unoccupied potential attractors in the huge phase space of the network of thousands of genes that are either non-viable and would generally lead to cell death or, alternatively, to immature, less-differentiated phenotypes that have been occupied in the developmental history of each cell. When the phenotype is attracted to such an immature expression profile, it may further 'explore' its potential and evolve towards progressively more aggressive, carcinogenic phenotype, or cancer attractor (see [39, 159, 160] for an in-depth discussion).

Cancer attractor theory has been supported by microarray measurements of the entire transcriptomes of lung carcinomas that reveal distinct genome-wide expression subclasses corresponding to specific cancer types, which plausibly represent distinct attractors. There is no continuum with smooth transitions between different transcriptomes, as would be expected from the progressive (epi)genetic alterations driven exclusively by selective pressures, implicated by the clonal evolution model [164, 165]. In sum, under the conceptual framework of complex dynamic systems, cancer is understood essentially as a systems developmental disorder, a dead-end deviant trajectory not completing proper development. Cancer attractor theory provides a systemic framework for tumour reversion and other non-genetic aspects of cancer, since attractors operate at the tissue level as well [159]. Most importantly, it naturally unites them with cancer genetics [160].

2.2.6. Entropy, thermodynamics and information theory

As pointed out in previous sections, cancer is characterised by the progressive destabilisation of the genome, aberrant gene expression patterns, dysregulated metabolic pathways, and compromised tissue integrity. Such global and unspecific loss of organisation, whether at the genome, cell, or tissue level, has been directly linked with increased entropy [110, 166, 167]. Entropy accumulation can be interpreted in terms of information theory as degradation and loss of cell- and tissue-specific information [121, 168] or, alternatively, in a thermodynamic sense as a reduced energy dissipation [117] and concomitantly its 'overload' [118, 119]. Both concepts converge towards the «entropic hallmark» of cancer, elaborated in a bioinformatic study by Berretta and Moscato [110]. Thus energy and information as fundamental biological concepts are, although probably the least understood, important when it comes to the relationship between organisation and disorganisation in pathology.

3. Coherent molecular dynamics and cancer

3.1. *Overview of molecular coherence*

Many researchers, starting with Erwin Schrödinger and his famous essay [21], have pointed out that statistical mechanics could not explain a remarkable biological order and energy efficiency. For example, a well-known biological problem is the

transport of metabolic energy along biological polymers over distances (typically, between energy release by ATP hydrolysis and its utilisation for biochemical work), which is difficult to model by thermal dispersion [30, 169]. Research in this field has increasingly focused towards the non-thermal (i.e., coherent) modes of energy transfer, however without systematic experimental conclusions yet [170, 171]. Next, the «kT problem» encapsulates the difficulty of explaining the non-thermal biological effects of weak electromagnetic fields, whose energy may be far below the average energy of thermal fluctuations [172, 173]. Moreover, the classical theory of ion partitioning in a cell that is based on energy consuming membrane pumps is known to be incompatible with some well-established experimental observations, e.g., cells may retain ionic balance after the membrane dysfunction [97, 174, 175, 176]. Similarly, the turnover rate of proton pumps is higher than the rate at which protons could be supplied via bulk diffusion models [177, 178]. Some of these inconsistencies could be at least partially explained if interfacial water near charged surfaces with different physico-chemical characteristics to bulk water [175, 179, 180, 181] is acknowledged to exert an electrodynamic role on charge transport.

In the quantum electrodynamic (QED) approach to living matter [27, 29] the second law of thermodynamics demands that electrochemical energy is funnelled into collective degrees of freedom in order to enable biochemical work, instead of thermalising. Such collective, or synchronised, behaviour of coupled elements is known as coherence. Alfred T. Winfree was the first to mathematically prove that phase synchronisation of coupled oscillators with random frequency distribution occurs *spontaneously* in conditions of weak coupling and low frequency dispersion [182]. Herbert Fröhlich, considered today as the pioneer of biological coherence [183], applied this principle to the biological environment by theoretically demonstrating spontaneous synchronisation of oscillating electric dipoles within biological macromolecules due to their nonlinear coupling with a heat bath under a sufficient supply of metabolic energy [22, 184]. The coherent molecular vibrations thus produced will generate endogenous electromagnetic fields, imposing a non-Brownian (directional) component upon the motion of ions and polarisable metabolites, as well as entail molecular recognition and interactions based on frequency-specific resonant coupling between the reactants [173, 185, 186, 187]. Such electrodynamic principles could complement the long established doctrine of molecular recognition that has based on thermal motion and molecular topology (the «lock-and-key» principle). Indeed, this has been supported by the recent demonstration in a study on *Drosophila* that vibrational spectra of odourant molecules are more significant for their recognition by the receptors than their topology [188].

The recent groundbreaking experiments on photosynthetic systems [31, 189, 190] have, however, provided conclusive evidence that long-lived macroscopic quantum coherent states indeed exist in the 'warm and noisy' biological environment. Specifically, these experiments demonstrate that light-induced excitation energy is collectively shared among the light-harvesting molecules, which allows simultaneous sampling of an entire energy phase space, to find the most effective sink for energy transfer to the reaction center. This mechanism is fundamentally different from the

Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
Dokt. disertacija. Ljubljana, Univ. v Ljubljani, Biotehniška fakulteta, 2013

semi-classical 'hopping' mechanism through which the electronic excitation would move stepwise between different excited states – dissipating energy at each step – and where only one state could be occupied at any one time [31, 191].

These experiments initiated a wide interest on the role and scope of quantum physics and coherence in biology [192, 193, 194, 195, 196]. Apart from photosynthetic systems, strong indications of macroscopic coherent dynamics of specific biological significance have been observed in an avian navigation system [197], odour recognition [188, 198] and vision [199]. Other phenomena of more general biological significance include the long-range coherent transport of electrons in proteins [200, 201, 202], hydrogen tunnelling in enzyme catalysis [203], and coherent vibrational energy transfer in proteins and water [171, 204, 205].

3.2. *The Coherence Hypothesis of Cancer*

If the the concept of the long-range interactions imposed by coherent dynamics turns out to be a generic principle of biological organisation, rather than a mere 'quantum effect' restricted to specific biochemical systems, then it will have to be acknowledged as a means of orchestrating the flow of energy and information in organisms. As argued above, impairment of this flow by structural or functional, environmental or endogenous perturbations at any specific level of organisation will directly destabilise the self-organising potential of a cell or tissue. As cancer is primarily characterised by an unspecific progressive self-disorganisation, rather than by a specific inductive agent [114], then impairment of the proper coherent dynamics at some specific level could be causally connected to such self-disorganisation. There may be a number of ways how an impaired coherence could lead to cancer, and given the current state of our knowledge these are open to theoretical speculation. In the following we review the hypotheses on the role of coherence in cancer proposed so far, as well as suggest our own view of 'cancer physics' based on quantum electrodynamics.

3.2.1. Fröhlich's Global Coherent Excitation

The first explicit hypothesis of the role of coherence in cancer was presented by Fröhlich [32, 33]. He suggested that a so-called global coherent excitation could emerge from electrically polar structures of sufficient size and polarisation density,[1] having a lower frequency whose wavelength would span across the tissue and exert the long-range attraction between cells, thus electro-mechanically stabilising the whole tissue. However, when a critical number of cells cease to be in resonance with the global excitation, they will no longer be under tissue control and will express their tendency to divide, which Fröhlich identified with cancer. This possibility has been further analysed by Pokorný [35] who showed that a disturbed cellular EM field would reduce adhesive forces between malignant cells and cause them to invade healthy tissue (see discussions by Hyland [206] and Pokorný [35]).

[1] Fröhlich originally suggested that the DNA-protein complex could represent such a source; in his time the electric properties of MTs were not yet recognised.

Such an electrodynamic characterisation is consistent with the microenvironmental aspects of cancer (Section 2. 2. 2), most notably to the Tissue Field Organisation Theory [4] as it is in accordance with both of its main premises, namely that carcinogenesis takes place primarily at the tissue level, and that a default state of a cell is proliferation [63]. Moreover, this theory proposes an abnormal morphogenetic *field* as a systemic cause of cancer. We strongly suggest that the long-range interactions represent a direct manifestation of the field in that they entail long-range correlation over a defined spatio-temporal domain in a purely physical sense, and thus could effectively complement diffusion-based models of morphogenesis that inherently must rely on «regularities only in the average», to paraphrase Schrödinger. The concept of coherence could thus importantly refine the traditional concept of the morphogenetic field.

Fröhlich's hypothesis has received indirect experimental support by measurements of ultraweak photon emission. Specifically, drastic differences between tumour and normal cells were observed in terms of photon count and the coherence properties of biophotons [37, 207, 208], which is consistent with the concept of intercellular communication via coherent fields and its subsequent loss in pathology (see further discussions on non-chemical modes of biological signalling by Cifra and co-workers [173], van Wijk [209], Funk and co-workers [210], and Rossi and co-workers [258]).

3.2.2. Mitochondrial Dysfunction

Originating from the Fröhlich's theory of coherence, Pokorný and co-workers have linked impaired coherence to bioenergetic aspect of cancer (Section 2. 2. 3). An electrochemical gradient across the inner mitochondrial membrane of about -180 mV provides not only metabolic energy, but also gives rise to a static electric field that extends far from the mitochondria [211]. This field is used to regulate calcium homeostasis, cellular pH, substrate compartmentalization, and import of metabolites into the mitochondrion [142, 157]. Pokorný [35, 36] suggests it might provide yet another role. More than 50% of acetyl-CoA free energy is not utilised for ATP production and flows out of mitochondria in the form of electromagnetic radiation. Together with the electric field, which provides nonlinear conditions for dipole interactions, this energy is considered necessary to excite coherent electromagnetic oscillations in the microtubules (MTs), which are typically closely associated with mitochondria [212]. Without this energy output from healthy mitochondria, a coherent electromagnetic field generated by the MTs would be weakened to such an extent that it would no longer be able to provide the organising potential for cellular processes.

Evidence of endogenous coherent electromagnetic fields has been obtained by examining the external frequency-dependent growth rate of bacteria, by studying dielectrophoretic behaviour of particles in the vicinity of cells, and by direct measurements of electromagnetic fields around different cells [173, 213, 214, 215, 216]. Some studies point to MTs as the field generators, and moreover their susceptibility to an external oscillatory electric field that could prevent division of malignant cells [35, 216, 217]. Theoretical analysis of electro-mechanical dipole vibrations in

Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
Dokt. disertacija. Ljubljana, Univ. v Ljubljani, Biotehniška fakulteta, 2013

MTs indeed predicts a wide range of frequencies from kHz to THz with various longitudinal coherent modes. Coherent oscillations thus produced will generate an electromagnetic field with complex spatio-temporal geometry, strong enough to be able to influence the flow of charged or neutral (polarisable) metabolites in the vicinity of the filaments and spatial distribution of intracellular components [186, 218]. Recently, strong indications of the coherent behaviour of MTs have been obtained by measuring their conductive properties [200,202]. These considerations support the application of bioelectromagnetic therapies on the basis of defined frequency-specific electromagnetic fields [219, 220, 221, 222].

The potential significance of intact MT vibrations in maintaining proper cell and tissue organisation may also be reflected in the fact that cancer cells are commonly accompanied by various defects in the structure of the cytoskeleton, which affect their mechanical properties (deformability, stiffness, and elasticity), adhesion properties, and tissue-level signalling [60,223,224]. The cytoskeleton, in addition to its classical structural-mechanical role, integrates many signalling pathways, influences the gene expression, coordinates membrane receptors and ionic flows, and localizes many cytosolic enzymes and signalling molecules, while at the same time it represents an immense, electrically active catalytic surface for metabolic interactions [212, 225, 226, 227, 228, 229, 230, 231]. Together with cell adhesion molecules and the extracellular matrix, it forms a tensionally integrated system throughout the tissues and organs, which is able to coordinate gene expression via mechanotransduction [228, 232]. Given the strong relationship between mechanical and electromagnetic excitations in the MTs (piezoelectricity) [233, 234] and their well-established organising potential, a weakened EM field may thus influence both cell and tissue aspects of carcinogenesis.

3.2.3. Impairment of the Centrioles

Hameroff [34] took a different starting point by hypothesising that impaired coherent dynamics in the centrioles may contribute to cancer by directly destabilising the genome (Section 2. 1. 2). Centrioles are barrel-shaped microtubule-based supramolecular structures in the vicinity of the nucleus, essential for the fidelity of chromatid separation during mitosis (although not necessary for mitosis itself). The exact mechanism of their contribution to correct chromatide separation, and hence the genome stability, is not fully understood; the current view is that they provide the necessary mechanical support to pericentriolar material (an amorphous protein mass that together with a pair of centrioles formes the centrosome) to maintain structural stability of the mitotic spindle, and thus the proper chromatid separation [235].

An alternative view is that the dynamics of mitotic spindle is ultimately orchestrated by some long-range correlation, that is, by a field [236]. Hameroff [34] suggests that such a correlation could manifest via quantum coherent states in the centrioles and their presumed resonant waveguide properties, as corroborated by Albrecht-Buehler [237]. Impairment of coherence in the mitotic complex would increase the probability of error in the mirror-like activity of the chromatid separa-

Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
Dokt. disertacija. Ljubljana, Univ. v Ljubljani, Biotehniška fakulteta, 2013

tion, promoting genome instability, or it could compromise the integrity of the centrioles themselves, which indeed often occurs early in tumour development [86, 238]. Alternatively the field could originate from the vibrations of the mitotic spindle's MTs (see above), however this approach has not yet been elaborated in terms of fidelity of chromatide separation.

3.2.4. Quantum Electrodynamic (QED) Approach to Cancer

In this section we provide our own approach to cancer physics based on quantum field theory, which provides the most fundamental physical description of condensed matter currently available.[1] Elaborating on this approach, water is understood as fundamental substance for organising biochemical processes [24, 26, 27, 28, 29, 239, 240]. Consequently, the organising potential of cell water is proposed to play an important role in carcinogenesis. Here we give a qualitative summary of this aproach.

In QED the following theorem can be proven: an ensemble of a large number N of molecules (which have, as is well known, a nontrivial internal spectrum) becomes dynamically unstable when the density N/V exceeds a threshold at a temperature T below a critical value. The ensemble evolves from a gas-like configuration where molecules are independent, into a new configuration having a well-defined phase, where all molecules fluctuate in unison between two individual configurations in tune with a self-produced electromagnetic (EM) field. The collective dynamics spans over a region (Coherence Domain, CD) whose size is the wavelength $\lambda = hc/\Delta E$ of the EM mode and frequency in the free space is $\nu = \Delta E/h$; h is the Planck constant and c is the speed of light. Within the CD, the field frequency ν is renormalised by the interaction with molecules to a lower value so that the squared mass of the field photons

$$m^2 = h^2\,(\nu^2 - c^2/\lambda^2) < h^2\,(\nu_0^{\,2} - c^2/\lambda^2) = 0$$

becomes negative. In the above inequality ν_0 is the frequency of the free EM field *in vacuo*, where photons have zero mass. The consequence of the above result is that within the CD photons acquire an imaginary mass so that they are unable to propagate and appear as the cohesion energy of the molecules. The CD thus becomes a self-produced cavity for the EM field, which fuses with the matter field of an ensemble of excitable molecules, hence giving rise to a unique field describing the collective dynamics of the molecules that behave as a single object [24,26,29].

Stability of the coherent configuration is kept by its lower energy level, namely by the existence of an energy gap, the difference in energy between an independent (non-coherent) and correlated (coherent) molecular configuration. In order to

[1] Vitiello [30] explicitly points out that quantum field theory is an appropriate theoretical framework applicable to complex systems such as organisms, because it allows description of multiple coexisting phases and phase transitions, which is not the case in quantum mechanics. This is especially relevant in the context of recently initiated theoretical research on «quantum biology» (Section 3. 1) that implicitly acknowledges quantum mechanics as the only relevant framework. See Vitiello [30] and Del Giudice [28] for a discussion and historical overview on this matter.

Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
Dokt. disertacija. Ljubljana, Univ. v Ljubljani, Biotehniška fakulteta, 2013

destroy the coherent configuration, it is necessary to supply the system with energy equal or larger than the energy gap (0.26 eV). At a given temperature *T*, thermal dynamics through the molecule collisions pushes a fraction of the molecules out of tune, so that there is a continuous balance between the coherent and non-coherent phase, as in the Landau model of super fluid helium [241]. A peculiar property of quantum field theory is that it describes the coherent state as a stable (low energy) and at the same time ordered state, having low entropy; thus no energy is required for the maintenance of order [30].

A specific property of water is that the coherent oscillation occurs between the ground molecule configuration, where electrons are very tightly bound (12.62 eV), and an excited configuration, where one electron is so loosely bound to be almost free (12.07 eV) – just one half of an eV below the ionization threshold. Consequently, a water CD contains an ensemble of almost free electrons kept coherent by the underlying molecular dynamics, and which can be further excited, giving rise to coherent excited states (vortices). This allows the CD to become a physical system able to collect environmental noise with high entropy, and transform it into low entropy, high grade energy able to perform electrochemical work, implementing the Prigogine requirement of dissipativity [112, 242].

Quantum electrodynamics further predicts a picture of living matter, which accounts for a decisive role of water. Biological polymers present in the interstices between CDs are subjected to the tails of the coherent EM (evanescent) fields, protruding from the CDs. According to general theorem of electrodynamics, molecules able to oscillate at the same frequency of the CD field are strongly attracted and therefore able to react chemically [27, 28]. Hence, in an extended coherent region a diffusive regime of molecules is replaced by a selective dynamic regime, where molecules can recognise and interact on the basis of frequency codes. Biological dynamics appears therefore as a close interplay between electromagnetism and chemistry, where fields are able to make the molecules interact through resonance, and molecules are able to regulate the field frequency through their reaction energies.

According to the general scheme outlined above, water molecules in bulk are predicted to give rise to CDs having size of 0.1 microns [24]. In biological environments, however, these CDs are presumed to give rise to extended domains constrained by the particular level excited by the metabolic energy flow, and may extend to the size of molecular complexes or even a whole cell or tissue [240]. Since the excitable spectrum of a CD is very rich [243], a variety of extended domains can emerge that may assume fractal (nested) architecture, as analysed by Vitiello [244]. Extended domains imply two important consequences, namely a defined size of the coherent system, and the appearance of spatial order. In order to have precise frequency matching, the relative positions of reacting molecules must assume a specific spatial configuration, corresponding to biological structures.[1] When the co-

[1] The recent experiments on photosynthetic systems provide an example where spatial arrangement of the component molecules within a coherent system must be carefully controlled in order to optimize the flow of energy [191].

herence is switched off, this order would break down and the system's size would no longer be defined, as it is primarily determined by the wavelength of an EM mode.

In the context of carcinogenesis we hypothesise the following. Once selected molecules react chemically, the output chemical energy is absorbed by the surrounding water, which will change its frequency spectra and cause an emergence of a new configuration [240]. In a homeostatically balanced system this is a self-organised process driven by metabolic energy that gives rise to time-dependent metabolic sequences across the levels of extended domains. However, when energy input exceeds the energy gap at some specific level of an extended domain (that is, other than the basic level), coherence at this particular level will dissolve, which would prevent energy dissipation. If continued, this process will occur in a degenerative way so as to further erode the rich frequency spectra of an extended domain, destroying its fractal architecture. As a result, individual CDs may coalesce under the action of short range forces. The normal flow of energy is interrupted, the spatio-temporal organisation is lost, and a diffusive regime becomes dominant.

A specific case of this hypothesis may be provided by the following prediction. Consider a tissue as an ensemble of microspheres (i.e., cells) having on their surfaces a nonvanishing density of positive or negative charge. QED predicts that plasma oscillations of electric charge will emerge, whose frequency (and thus energy) is

$$\omega_p = A \frac{e}{\sqrt{m}} \sqrt{\frac{Z}{V}}$$

and increases with the square root of plasma density Z/V. Plasma oscillations may couple with the coherent EM field when A is smaller than 1.88, where A=1 corresponds to the ideal case of a perfectly homogenous plasma (Chapter 5 in Preparata [29]). Each sphere will produce a CD having a defined radius. If the CDs remain in contact, an extended CD will appear, keeping in tune the total amount of charge of the spheres [245]. Coherence emerges when surface electric charge density ϱ satisfies the condition

$$\varrho \leq \frac{4\pi^2}{\alpha} (m_e \delta)^{\frac{1}{2}} \left(\frac{r}{d}\right)^2 \frac{\sqrt{2}}{d^3}$$

and moreover the distance d among neighboring spheres is equal to the wavelength λ of an EM mode responsible for the electron plasma oscillation, where d is the distance among the spheres, r is their radius, m_e electron mass, δ thickness of a charged layer on sphere surface, and α is a coupling constant which in natural units is 1/137. This will induce attraction among the components of a coherent system and may completely account for the observed attraction among similarly charged spheres that spontaneously form stable colloidal crystals, reaching at least 8 kT at d of about 2 microns [246]. Thus according to QED it is possible to satisfy conditions for the coherent state by convenient choices of ϱ and d.

The model could then be applied to an ensemble of cells where coherence may account for the stability of a healthy tissue. However, when charge density ϱ would

Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
Dokt. disertacija. Ljubljana, Univ. v Ljubljani, Biotehniška fakulteta, 2013

exceed an upper threshold, coherence would break down, corresponding to the loss of tissue stability and reduced attraction forces between the cells, in accordance with Fröhlich's and Pokorný's models that are specifically relevant for the tissue aspects of cancer. The model predicts that tumour cells should have a higher surface charge density than normal cells, which may be experimentally tested; some observations indeed seem to give support along this line [247, 248]. Moreover, in this framework a malignant transformation could be described in principle as a phase transition phenomenon [249], where surface charge density could serve as an order parameter. The hypothesised loss of fractal metabolic dynamics could be another – and perhaps a more general [97,250] – pathological feature implicated by this framework.

4. Conclusions

Although it is currently difficult, if not impossible, to show how different biological aspects of cancer might be causally connected, their common denominator is a global and unspecific progressive disorganisation at a variety of organisational levels, and it may manifest as loss of tissue organisation and intercellular signalling, aberrant epigenetic regulation and gene expression profiles (or abnormal attractors of the gene regulatory network), dysregulated metabolic pathways (in terms of transcriptomic and proteomic signatures), instability of the genome, increased informational and thermodynamic entropy, and impairment of oxidative energy flow. The concept of long-range dynamic order, epitomised by the coherent molecular dynamics, may provide a synthetic theoretical framework for different aspects of carcinogenesis from both biological and physical perspectives. Increased entropy is an immediate consequence of impaired coherence, and a subsequent decline of energy dissipation may exert an imbalance in metabolic and gene regulatory networks, disrupting normal flow of energy and information that percolates from one organisational level to the other and manifests as different biological aspects of cancer. The exact nature of such a self-reinforcing interplay between energy and information remains to be elucidated. Nonetheless, energy surplus exceeding the energy gap could provide a physical basis for such a general loss of dissipativity in pathology. We assert that if cancer is recognised as a systems disease [47, 108, 110, 251], these aspects must be taken in consideration as well.

It is important to realise that by acknowledging that cancer is not a genetically deterministic disease, it could be neither explained nor cured on the basis of *exclusive* knowledge of mutated or dysregulated genes. In the context of emerging targeted anticancer therapies, taking into account the huge genetic heterogeneity and adaptivity of each individual tumour [73], we can expect that «a minor subclone resistant to targeted inhibitor» [57] will likely become the rule rather than the exception, and thus a more systemic treatment might be necessary [92, 252, 253, 254]. What needs to be seriously taken into account as an alternative is the concept of the field in life sciences, which has lurked too long in the shadow of vitalism, but is now reemerging in the form of long-range dynamic order [255, 256]. There is probably no hypothetically more efficient means of energy and information processing

than through coherence, and ignoring the possibility that life has evolved to use this potential is ignoring the potential for cancer treatment. Albert Szent-Györgyi [257] stated that life as such should not exist, because what we observe are merely material systems that have a wonderful property of being alive, but not life itself. It should be clear by now that what he meant was that the secret of life lies not in its molecular details, but in the organisational principles behind them which hold organisms together and set them apart.

Acknowledgements

This work was in part financed by the European Union, European Social Fund and was implemented in the framework of the Operational Programme for Human Resources Development for the Period 2007-2013, Priority axis 1: Promoting entrepreneurship and adaptability, Main type of activity 1.1.: Experts and researchers for competitive enterprises.

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Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
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2.3 PRINCIP KOHERENCE V MNOGONIVOJSKEM INFORMACIJSKEM PROCESIRANJU V MOŽGANIH

Avtorji: Matej Plankar, Simon Brežan, Igor Jerman

Izvirni naslov: *The principle of coherence in multi-level brain information processing*

Publikacija: *Progress in Biophysics & Molecular Biology (2013) 111, 8-29.*

Ključne besede: *neuronal synchronisation, molecular coherence, functional connectivity, neuronal cytoskeleton, counterions, dissipative brain dynamics*

Izvleček: Sinhronizacija je postala pomembno matematično orodje za opisovanje biološke organizacije na mnogih ravneh. Sinhrona podpražna in nadpražna oscilatorna aktivnost nevronov znotraj ali med različnimi nevronskimi skupnostmi je danes priznana kot eden temeljnih načinov informacijskega procesiranja v možganih. Koherentne nevronske oscilacije korelirajo z vsemi osnovnimi kognitivnimi funkcijami, posredujejo lokalno in daljnosežno mednevronsko komunikacijo in modulirajo sinaptično plastičnost. Kljub temu pa ni znano, kako lahko izredno hitre in kompleksne spremembe funkcionalne nevronske povezljivosti, ki jo usmerja nevronska koherenca, pojasnimo izključno s sinaptičnimi mehanizmi prenosa informacije. Vse več raziskav nakazuje, da intranevronski matriks, ki je sestavljen iz citoskeletnih filamentov in različnih povezovalnih beljakovin, strukturno in funkcionalno povezuje nevronske sinapse in sodeluje pri prenosu živčnih prenašalcev, konsolidaciji spomina in t.i. električnemu signaliziranju. Teoretično modeliranje kot tudi nedavni eksperimentalni dokazi nakazujejo, da intranevronski matriks lahko deluje kot nosilec visoko kooperativnega prenosa energije in informacijskega procesiranja z značilnostmi koherence. Predpostavljamo, da koherentna molekulska dinamika v znotrajceličnem in zunajceličnem matriksu filamentoznih elementov lahko vzpostavlja dinamična stanja visokega reda, ki modulirajo funkcionalno povezljivost nevronov preko membranskega potenciala. Koherenca lahko na ta način predstavlja skupni imenovalec nevrofizioloških in biofizikalnih pristopov k informacijskemu procesiranju v možganih na različnih organizacijskih ravneh, iz katerih vzrašča kognicija kot njena temeljna manifestacija.

Progress in Biophysics and Molecular Biology 111 (2013) 8–29

Contents lists available at SciVerse ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

Review

The principle of coherence in multi-level brain information processing

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ARTICLE INFO

Article history:
Available online 17 August 2012

Keywords:
Neuronal synchronisation
Molecular coherence
Functional connectivity
Neuronal cytoskeleton
Counterions
Dissipative brain dynamics

ABSTRACT

Synchronisation has become one of the major scientific tools to explain biological order at many levels of organisation. In systems neuroscience, synchronised subthreshold and suprathreshold oscillatory neuronal activity within and between distributed neuronal assemblies is acknowledged as a fundamental mode of neuronal information processing. Coherent neuronal oscillations correlate with all basic cognitive functions, mediate local and long-range neuronal communication and affect synaptic plasticity. However, it remains unclear how the very fast and complex changes of functional neuronal connectivity necessary for cognition, as mediated by dynamic patterns of neuronal synchrony, could be explained exclusively based on the well-established synaptic mechanisms. A growing body of research indicates that the intraneuronal matrix, composed of cytoskeletal elements and their binding proteins, structurally and functionally connects the synapses within a neuron, modulates neurotransmission and memory consolidation, and is hypothesised to be involved in signal integration via electric signalling due to its charged surface. Theoretical modelling, as well as emerging experimental evidence indicate that neuronal cytoskeleton supports highly cooperative energy transport and information processing based on molecular coherence. We suggest that long-range coherent dynamics within the intra- and extracellular filamentous matrices could establish dynamic ordered states, capable of rapid modulations of functional neuronal connectivity via their interactions with neuronal membranes and synapses. Coherence may thus represent a common denominator of neurophysiological and biophysical approaches to brain information processing, operating at multiple levels of neuronal organisation, from which cognition may emerge as its cardinal manifestation.

Contents

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0079-6107/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.pbiomolbio.2012.08.006

1. Introduction

The tendency of natural systems to achieve order and harmony in their behaviour is a manifestation of open systems' self-organising capacity, existing everywhere in nature (Osipov et al., 2007). Synchronisation, a process whereby objects of a different nature adjust their internal rhythms to a collective operation regime due to their mutual interactions, is one of the most captivating phenomena encountered in complex systems, and has become a major scientific tool to explain this tendency. Technically, synchronisation refers to the establishment of stable phase relationships among the oscillating components within a system of coupled oscillators due to phase locking or frequency entrainment, whose oscillatory characteristics are more generally described as the coherence.[2] Synchronisation phenomena are encountered in areas as diverse as physics, chemistry, engineering, biology, medicine, economics, and social sciences, which implies its deep significance and explanatory power (Arenas et al., 2008; Osipov et al., 2007; Pikovsky et al., 2001).

Organisms are highly excitable dissipative systems whose responses to external and internal perturbations and energy flow throughout the system must be precisely and efficiently coordinated in time and space. Synchronisation phenomena have been observed at all basic levels of biological organisation – from the precisely coordinated gene expression and metabolic cycles (for example, glycolytic oscillations) to collective physiological rhythms[3] and social interaction dynamics.[4] The functional significance of coherent oscillatory dynamics lies in the *collective summation* of outputs of individual elements, which enables a powerful response to a weak external input, efficient communication between different systems (that is, transfer of energy and information) and encoding information in terms of the phase, frequency, or amplitude of the oscillating system. In other words, the power (or meaning) of coherence arises from a reduction in the uncorrelated degrees of freedom into a collective operation mode, which enables long range order and coordination of biological processes (Arenas et al., 2008; Bianchi, 2008; Binhi and Rubin, 2007; Goldenfeld and Woese, 2011; Ho, 2008; Klevecz et al., 2008; Strogatz, 2003; Winfree, 2001). Coherence and synchronisation are thus important concepts in biological organisation and systems biology (Plankar et al., 2011).

Synchronised oscillations of large neuronal groups, whose frequency range spans several orders of magnitude, represent one of the most prominent characteristics of brain information processing (Buzsáki and Draguhn, 2004). It has been proposed for over twenty years that dynamic neuronal interactions rely on precise temporal coordination of single neuronal discharges and population activity in distributed neuronal assemblies. This phenomenon, generally termed neuronal synchrony, has been found to correlate strongly with cognitive functions: perception, attention, sensorimotor integration, learning, memory, consciousness, decision making etc., and pathological synchrony patterns appear in many different brain disorders. It is strongly argued that coherent neuronal oscillations are not merely an epiphenomenon, but have a direct functional relevance and a causal role in encoding representations, coordinating neuronal communication and regulating synaptic plasticity (Fell and Axmacher, 2011; Fries, 2009; Fries et al., 2007; Jensen et al., 2007; Senkowski et al., 2008; Singer, 2009; Uhlhaas et al., 2009; Uhlhaas and Singer, 2010).

There is however another type of coherence that may also be important for neuronal information processing, but which operates at the level of individual molecules and molecular complexes. The coherence of molecular dynamics has long been theoretically elaborated (Del Giudice et al., 1985; Fröhlich, 1968; Ricciardi and Umezawa, 1967), only recently gaining wider acceptance, when quantum coherence was experimentally demonstrated to directly coordinate energy flow, maximising efficiency of excitation transfer in several photosynthetic complexes (Collini et al., 2010; Engel et al., 2007; Lee et al., 2007). On the other line of research, the neuronal cytoskeleton or, more generally, the intraneuronal matrix (Woolf et al., 2009) – is increasingly acknowledged to have an important role in modifying the gating properties of ion channels and in coordinating neuronal plasticity (Janmey, 1998; Priel et al., 2010; Woolf, 2006; Woolf et al., 2009). Moreover, much theoretical and experimental effort has been focussing on the coherent properties and long-range signal transfer within cytoskeletal elements, most notably in the microtubules (Bandyopadhyay, 2010; Cifra et al.,

[2] Although not identical, the terms coherence and synchronisation are often used interchangeably. Throughout this review, we will use both according to their traditional use in respective fields.

[3] These include, for example, heart contraction, brain oscillations, circadian rhythms, hormonal secretion, locomotion, etc.

[4] Common examples are synchronised signalling in crickets and fireflies, the dynamic behaviour of dense groups of animals, such as bird flocks or fish schools, bacterial quorum sensing, collective hunting strategies, etc. An interested reader may find further examples in the cited literatute.

2010; Jibu et al., 1994; Mershin et al., 2006; Priel et al., 2006a; Sahu et al., 2011; Tuszyński et al., 1997). It is hypothesised that such intrinsic information processing capacity could provide the neurons with greater autonomy in response (Woolf et al., 2009), complementary to their classical membrane-dependent characteristics.

Here we take an integrative approach, combining neuroscientific and biophysical disciplines to develop the hypothesis that coherence is a generic property of dynamic brain information processing, operating at different levels of neuronal organisation. Moreover, as synchronisation is a form of "temporal[5]" self-organisation, it may represent a biological organising principle from which cognitive functions emerge as its highest-order manifestation. The article's aim is not to establish conclusive mechanistic roles of coherent phenomena in cognition, nor to reiterate yet another version of the "quantum mind" theory; rather, we aim to provide a synthetic review of the recent progress in theoretical and experimental research, pointing out the many information processing contexts in which coherence could shape a dynamic ordering of the brain's integrative operation, bringing together utterly different scientific disciplines that independently recognised its importance. By partially relying on the synthetic approach of the dissipative brain dynamics theory (Freeman and Vitiello, 2006), we also speculate on how neuronal and molecular coherent oscillations could functionally interact by taking into account the electrodynamic properties of the intra- and extracellular filamentous matrices.

2. Neuronal coherence as a fundamental mode of cortical information processing

Sherrington (1941) and Adrian (1942) hypothesised that brain processing likely involves some sort of a "population code" with collective properties not readily observable in the summed responses of single neurons. Currently, the most accepted view on how this might be achieved is through the integration of information based on neuronal synchrony (Womelsdorf et al., 2007). Although synchronisation of neurons or neuronal subgroups can also arise via strong common inputs that occur irregularly, oscillation-based synchrony is the most energy-efficient and established mechanism suited for temporal coordination and for response transmission (Buzsáki and Draguhn, 2004; Winfree, 2001) and could complement the slower and less flexible firing rate strategy for coding information (Singer, 2009). Mechanistically, oscillations in fact induce an alternation between membrane states of inhibition and increased excitability in neighbouring neurons, biasing neurons to increase spike timing precision and hence mediate their synchronisation (Buzsaki, 2006; Fries, 2005; Singer and Gray, 1995).

2.1. Origins and modulatory influences

2.1.1. Generation of neuronal oscillations

Neuronal oscillation is a periodic wave-like variation of neuronal electromagnetic (EM) activity in the central nervous system, characterised by frequency (i.e., delta, theta, alpha, beta, gamma), amplitude, and phase (the angle of deflection of an oscillation). Neuronal oscillations are generated by intrinsic mechanisms of individual neurons via the self-generated (pacemaker) ionic currents or resonant properties of the membrane potential,[6] and/or by the internal recurrent network interactions (Buzsaki, 2006; Wang, 2010). While irregular, or stochastic activity is predominantly displayed in individual neurons (Wang, 2010) the interplay of both intrinsic and network mechanisms collectively generates rhythmic patterns of subthreshold and suprathreshold (spikes) potentials (Llinas et al., 1991; Steriade et al., 1990). The firing patterns or spike trains generated in such oscillatory networks are considered fundamental for information coding in the brain (Buzsáki and Draguhn, 2004; Schnitzler and Gross, 2005). Rhythmic firing patterns activate post-synaptic neurons, generating post-synaptic potentials (excitatory and inhibitory post-synaptic subthreshold potentials; EPSPs and IPSPs, respectively) which, when sufficiently summated and synchronised, give rise to oscillations of local gradients of electric potential in the extracellular space, known as local field potentials (LFPs) (Niedermeyer and Da Silva, 2005; Schnitzler and Gross, 2005).

At the level of a local neuronal assembly, oscillatory activity in groups of neurons generally arises from feedback (re-entrant) synaptic connections between the excitatory principal neurons, e.g., pyramidal neurons, input-driven by different sources, and inhibitory interneurons. The mutual feedback results in synchronisation via a collective periodic modulation of membrane excitability, and therefore of the firing probability or sub-threshold oscillations of target neurons. The inhibitory system affects a wide target neuronal pool of excitatory neurons, imposing upon them narrow time windows in which they can fire, which is especially relevant for the generation of synchronous local gamma oscillations (Cardin et al., 2009; Fries, 2009; Whittington et al., 2011). On the other hand, ultra fast gamma (100–200 Hz) oscillations are presumably generated via inhibitory interneuronal networks by themselves (Wang, 2010).

The local assemblies interact with the larger-scale feedback loops (Canolty and Knight, 2010; Donner and Siegel, 2011; Varela et al., 2001). Here, synchronous activity arises from excitatory–excitatory and excitatory–inhibitory feedback loops between distant brain regions, involving cortico-cortical, thalamo-cortical, cortico-subcortical, or cortico-hippocampal connections (Bollimunta et al., 2011; Buzsaki, 2006; Steriade, 2000). The frequency of oscillations is dependent on intrinsic neuronal characteristics, network size and connectivity, and information flow variables, such as coupling strength and time delay (Cardin et al., 2009; Nunez and Srinivasan, 2006; Zeitler et al., 2009). Theta rhythm, for example, originates from cortico-hippocampal loops or as a pacemaker drive within the hipocampus (Buzsaki, 2006; Goutagny et al., 2009; Miller, 1991; Wang, 2010). Alpha rhythms classically originate from thalamo-cortical loops, where they are modulated by intrinsic thalamic mechanisms, but they may also be autonomously established in the visual cortex circuits themselves (Lopes da Silva and Storm van Leeuwen, 1977; Steriade et al., 1990). The neuronal oscillators that generate the beta rhythm are presumably located in the cortex and operate via excitatory–inhibitory feedback similar to that of gamma oscillations, although beta typically operates over a longer range (Hipp et al., 2011; Lopes da Silva, 1991; Wang, 2010).

Technically, two oscillatory signals are considered coherent (synchronised/phase-locked/phase-coupled) when there is a consistent relationship between the phases (phase coherence) and/or power (spectral coherence) of the two signals over time (Fell and Axmacher, 2011; Lachaux et al., 1999; Rappelsberger and Petsche, 1988; Senkowski et al., 2008), albeit not necessarily in phase, i.e., with a zero phase difference[7] (zero lag) between them.

[5] As opposed to "topological" forms of self-organisation, epitomised by network modelling (e.g., Barabási and Oltvai, 2004; Huang, 2009; Kauffman, 1993).

[6] An intrinsic membrane potential pacemaker is typically based on a biphasic dynamics of depolarising and hyperpolarising ionic currents mediated by various transmembrane channels. Some neurons are not oscillators, but may have resonant membrane properties that increase their responsiveness to a specific frequency of stimulation (Alonso and Llinás, 1989; Hu et al., 2002; Hutcheon and Yarom, 2000).

[7] The phenomenon of zero-lag despite conduction delays between distant neurons represents a specific challenge for neuroscience. Although several mechanisms have been proposed, there is as yet no general consensus regarding its explanation (see Uhlhaas et al., 2009 for a discussion).

Coherence may refer to correlations between the spikes in different regions, between spikes in one region and LFP in the same or another region ("spike-field coherence") (Fries et al., 2001; Jutras et al., 2009; Womelsdorf et al., 2007) or between LFPs in different regions (Fell and Axmacher, 2011; Fries, 2005; Varela et al., 2001). Cross-frequency coupling of the phase or amplitude is also a common mode of neuronal synchronisation and gives rise to nested functional interactions of slow and fast rhythms (Axmacher et al., 2010; Canolty and Knight, 2010; Lisman, 2010; Roopun et al., 2008).

Various external and intrinsic contexts can trigger and modulate oscillatory patterns, e.g., periodic external stimuli (typically, light flashes or sounds), task- or event-related[8] non-periodic sensory or cognitive stimulation, or motor preparation and output. The oscillatory signal is phase-locked if there exists a stable phase relationship with an external event (stimulus onset) or other signal. Phase resetting refers to a shift in the phase of an ongoing oscillation, which can lead to phase-locking to the stimulus or it can modulate the phase coherence level with respect to other oscillatory signals (Jensen and Lisman, 1998; Kahana, 2006; Klimesch et al., 2007; McCartney et al., 2004; Rizzuto et al., 2003; Senkowski et al., 2008; Tass, 2007; Varela et al., 2001). Brief durations of phase resetting are typically followed by relatively longer periods of phase stability in a range from tens to hundreds of milliseconds, giving rise to multistable spatio-temporal patterns of neuronal activity with rapidly alternating periods between coherent and incoherent states (Breakspear et al., 2004; Fell et al., 2001; Freeman and Rogers, 2003; Friston, 2000; Rodriguez et al., 1999; Roelfsema et al., 1997; Thatcher et al., 2009).

On the other hand, synchronisation can arise spontaneously by interaction of signals from internal sources corresponding to some self-generated cognitive action (Başar, 1999; Başar et al., 1999) or even in the absence of any obvious task (the "resting-state activity"[9]). When signal processing of the external world input is inhibited, such as in sleep, this is subserved by large-scale synchronisation of low-frequency oscillations (Steriade, 2000). Thus the basic patterns of oscillatory synchrony are very much state-dependent (Fries et al., 2001; Palanca and DeAngelis, 2005; Thiele and Stoner, 2003; Van Der Togt et al., 2006). Ongoing oscillations in turn affect neuronal processing of subsequent external stimulus perception and other behavioural or mental events (Busch et al., 2009; Haider et al., 2007). For example, ongoing activity in the alpha rhythm in visual areas at rest could be a reflection of an "idling rhythm", enabling the brain to react more quickly to unexpected novel stimuli (Hari and Salmelin, 1997).

Whereas phasic oscillatory patterns are transient and usually correlate with volitional task- or event-related cognitive performance, tonic neuronal oscillations are slower, less volition-dependent and more related to global brain states such as fatigue, distress, neurological disorders, circadian rhythms, arousal, etc. (Canolty et al., 2006; Haider and McCormick, 2009; Pfurtscheller and Lopes da Silva, 1999; Pfurtscheller et al., 1996; Sirota et al., 2008). For example during slow-wave sleep, tonic responses result from spontaneous background activity mediated by dense local connectivity patterns from which slow oscillations (<1 Hz) emerge (Chen and Fetz, 2005; Poulet and Petersen, 2008; Steriade et al., 1993b).

The spatio-temporally integrated oscillations, which comprise both phase-locked and non-phase-locked (intrinsic or induced) oscillatory components, exhibit changes in amplitude and power spectra that depend on both the number of functionally involved neurons and their synchronization level in a specific frequency band. Globally summated signals give rise to macroscopic brain rhythms, categorised into distinct frequency bands: delta (1–3 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (14–30 Hz), gamma (30–80 Hz), fast (80–200 Hz), and ultra fast (200–600 Hz) (Schnitzler and Gross, 2005), each with specific functional and behavioural correlates, activating contexts, mechanisms, spatial scales, and inter-relations (Niedermeyer and Da Silva, 2005; Nunez and Srinivasan, 2006; Whittington et al., 2000). Generally, higher frequency oscillations operate more locally and are thought to represent the neuronal code for cognitive content, whereas large networks are integrated during slow oscillations, which predominantly mediate processual aspects of cognition, collectively resulting in highly interdependent and parallel information processing at multiple spatio-temporal scales (Buzsáki and Draguhn, 2004; Jensen and Lisman, 2005).

2.1.2. Modulation of neuronal oscillations

Neuronal oscillations are primarily mediated by chemical synapses, where GABA is the most important neurotransmitter in inhibitory systems, whereas excitatory synapses use mainly glutamate and acetylcholine. Different neuromodulatory systems via ascending projections from deep brain nuclei can additionally regulate the neurotransmitter levels (e.g., norepinephrine, acetylcholine, serotonin or dopamine) thereby modulating oscillations on a slower time scale. The neuromodulators typically influence the global state of arousal, e.g., wakefulness, sleep, and finely tune cognitive functions by modulating different brain waves (Berridge and Waterhouse, 2003; Goard and Dan, 2009; Montague et al., 2004; Rodriguez et al., 2004; Steriade, 2000). For example, acetylcholine concentration increases in attentive states and has been shown to play a crucial role in affecting oscillatory synchronisation patterns in the gamma band (Rodriguez et al., 2004).

Electrical synapses, gap junction mediated neuronal connections, which predominantly couple type-specific interneuronal networks in the cortex, also actively contribute to electrotonic neuronal synchronisation (Connors and Long, 2004; Hormuzdi et al., 2004; Wang et al., 2010). The mechanisms of their regulation are still poorly understood, but their main advantages are their rapidity and bidirectionality of signal transfer, which makes them very suitable for synchronising the sub- and suprathreshold activity of neurons (Bartos et al., 2007; Bennett and Zukin, 2004; Hestrin and Galarreta, 2005). Apart from their role in electrically coupling the neurons, they also participate in transmission of chemical signals (Connors, 2009; Wang et al., 2010).

Neuronal synchronisation, however, is not modulated exclusively by the neurons themselves. Approximately half of human brain tissue volume is composed of astrocytes, a type of glial cell that globally connect different brain regions, whose active role in brain information processing has only recently been fully recognised. Astrocytes comprise a brain-wide astro-glial network coupled via the gap junctions (Giaume et al., 2010). As excitable cells with neurotransmitter receptors, capable of releasing their own chemical messengers, gliotransmitters, they cooperate with both pre- and post-synaptic neurons in a recently proposed novel functional unit, the tripartite glutamatergic synapse (Araque et al., 1999).

[8] "Induced" and "evoked" activity (Başar, 1999; Başar et al., 2001; Niedermeyer and Da Silva, 2005); for example, induced gamma oscillations may increase during object representation (Tallon-Baudry and Bertrand, 1999). Event-related synchronisation and desynchronisation are frequency-specific oscillatory activity responses with highly specific functional roles (Başar et al., 1999; Pfurtscheller and Lopes da Silva, 1999), non-phase-locked to events, as opposed to event-related potentials.

[9] Baseline ongoing 1–80 Hz electrophysiological oscillations and slow (<0.1 Hz) fluctuations of functional imaging signals mediated by the brain intrinsic "default networks", which cannot be considered as mere noise, but reflect certain self-referential and other inner (mental and emotional) states (Cabral et al., 2011; Fox and Raichle, 2007; Freyer et al., 2009; Mantini et al., 2007).

Intracellular calcium waves represent a prominent feature of astrocytes' excitability. They are initiated in astrocytic processes of individual astrocytes, but may under proper synaptic input, as imposed and sustained by the synchronous neuronal oscillations, elicit intercellular waves, spreading coherently throughout the astro-glial network (Pereira and Furlan, 2009). Importantly, feedback from active astrocytes can in turn modulate not only synaptic plasticity, but also the dynamic properties of high-frequency neuronal oscillations, and they thus contribute to EEG signals (see a review by Pereira and Furlan, 2010 and references therein). There is a strong indication that coherent calcium waves are frequency and amplitude modulated, which implies their capability of encoding information (De Pittà et al., 2009; De Pittà et al., 2008). In a model by Pereira and Furlan (2010),[10] it is hypothesised that their modulatory potential is utilised for integration of neuronal signals based on wave interference patterns, which implies a long-range (field-like) interaction. The authors further suggest that some macroscopic coherent process might be required for such complex integration which, in addition to chemical signals from tripartite synapses, likely incorporates ephaptic (see below) signals from endogenous EM fields as well (Banaclocha, 2007; Pereira and Furlan, 2010).

The recent research on external brain stimulations by transcranial magnetic stimulation (Thut and Pascual-Leone, 2010a,b; Thut et al., 2011), transcranial electric stimulation (Kirov et al., 2009; Marshall et al., 2006) and stimulation by weak EM fields (Bawin et al., 1996; Deans et al., 2007; Ozen et al., 2010) has shown that neuronal oscillations can also be modified by these externally induced rhythmic stimulations, which latter also affect cognitive and behavioural responses. EM field-mediated interactions between juxtaposed neurons have been demonstrated in the cortex even at very weak naturalistic EM stimulation, affecting the APs, PSPs and spike-field correlations even though electric fields caused very small (below stochastic fluctuations) changes in the membrane potential of individual neurons (Anastassiou et al., 2010, 2011; Aur et al., 2010; Fröhlich and McCormick, 2010; Ozen et al., 2010). For example, intra- and extracellular recordings in the rat brain *in vivo* showed that both spiking and subthreshold activity were under the combined influence of forced fields and network activity, where an imposed voltage gradient as low as 1 mV/mm at the recording sites was sufficient to phase-bias neuronal spiking (Ozen et al., 2010) – a strong indication of a feedback loop between neuronal activity and endogenous electric fields. Such EM field-mediated neuronal interaction is also known as ephaptic coupling.

The early studies of Adey and others (Adey, 1975, 1981, 1993) corroborated that externally applied weak (non-thermal) EM fields may exert significant biological effects and influence behavioural responses in the nervous system (Adey, 2003; Bawin et al., 1996; Gavalas-Medici and Day-Magdaleno, 1976; Gavalas et al., 1970). The hypothesised mechanisms of these effects focussed upon modulations of the membrane proteins and ionic flows, calcium signalling, free radicals, charged molecules in the extracellular space, etc. (Adey, 1981, 2003; Blackman et al., 1985, 1982),[11] by asserting that sensitivity to weak low-frequency EM fields could be a generic property of cells and tissues serving for intrinsic communication and amplification of weak initial triggers (Adey, 1981, 1993). The suggested concept was that the threshold sensitivity of excitable tissues to EM fields is mediated by highly cooperative properties of a population of elements, arising from the non-linear electrodynamic properties of biological tissues and resonant responses, rather than by a single detector (Adey, 1992, 1998, 2003).

Both lines of research together suggest that weak EM fields can modulate macroscopic oscillations at the network level, and may thus influence oscillations that generated them in the first place, giving rise to emergent properties of synchronous oscillations that could not be simply deconstructed to the contributions of single components (Fröhlich and McCormick, 2010). This brings a new perspective to the possibility that not only external, but also endogenous EM fields could contribute to information processing in the brain by non-synaptic mechanisms (Anastassiou et al., 2011; Fröhlich and McCormick, 2010; Ozen et al., 2010). Some researchers even suggest that fluctuating ionic gradients and the resultant patterns of EM fields, in combination with neuronal synchronisation as a "binding agent", could represent the substrate of cognitive representation and consciousness (Cook, 2008; McFadden, 2002).

We may expect that significant ephaptic effects *in vivo* indeed require synchronous neuronal activity and a precise spatial arrangement of many neighbouring neurons (Connors, 2009). Nonetheless, the mechanisms of network entrainment by weak EM fields remain unclear. As pointed out, the emergent properties of neuronal networks as a whole are clearly more sensitive than the measurable effects of EM fields in single neurons, which were safely below normal membrane noise (Deans et al., 2007). It is possible that the network dynamics can change due to a direct effect on membrane potential fluctuations by a stochastic process, or alternatively, via highly cooperative dynamics originating at the subcellular level that could collectively amplify the effects of an EM field, as anticipated by Adey and here further elaborated. This may be yet another reason to examine more closely the functional connection of neuronal synchronisation and various endogenous electrodynamic processes.

2.1.3. Methods for analysing synchronised oscillations

Electro-magnetic activity in the brain can be measured as the summed LFPs across a large brain area with the millisecond-range temporal resolution of electroencephalography (EEG), electrocorticography (ECoG) and magnetoencephalography (MEG), all capable of monitoring the high speed of of cognitive processing. To obtain a better spatial resolution, single- or multi-unit microelectrode recordings can be applied extracellularly (measuring LFPs confined to small areas and thus with a better spatial precision) or intracellularly, where individual spikes can be measured; combinations of different techniques, each having its own advantages, are frequently applied (Buzsaki, 2006; Niedermeyer and Da Silva, 2005).

Combinations of stimulation, lesion techniques and classical electrophysiological recording methods seem promising for more precise and conclusive monitoring and evaluation of cortical network dynamics. Interestingly, with the recent optogenetic approach it now became possible to selectively depolarise or hyperpolarise selected neurons with the application of light and observe their functional roles with high spatio-temporal resolution, which also provides better causality measures (Boyden et al., 2005; Cardin et al., 2009; Zhang et al., 2010). Using specific deep brain stimulation it is now possible to interfere with an ongoing activity in such a way that a focussed oscillatory phase reset could be produced that leads to inter-regional desynchronisation, which enables us to infer the functional role of synchrony, and to observe the outcome of specific synaptic connectivity degradation over time due to disturbance of synchrony (Hauptmann et al., 2009; Hauptmann and Tass, 2009; Tass et al., 2009).

Analytical methods employing complex mathematical and statistical procedures for analysing oscillations have however

[10] Interestingly, this model predicts that intracellular calcium waves disperse along the microtubules. The conductive properties of cytoskeletal filaments and their functional potential are further discussed in Sections 3.2.2 and 3.5.2, respectively.

[11] The full spectrum of EM interactions with biological structures has been extensively reviewed elsewhere (Cifra et al., 2011; Funk et al., 2009).

provided major progress in understanding their complexity by revealing the much more dynamic nature of (de)coupling between particular neurons or assemblies. The higher spatio-temporal precision relating neuronal oscillatory correlates to specific brain functions, and the additional minimisation of possible physical artifacts or statistical biases provided further evidence that synchronisation indeed regulates various cognitive processes and is not merely an epiphenomenon or a reflection. Some of these newer methods are: instantaneous coherence (Schack and Krause, 1995) and event-related coherence (ERCoh) (Andrew and Pfurtscheller, 1996), which allow a high temporal and frequency resolution; dynamic topographic analysis and other methods that employ Hilbert transform to visualise rapid bursts of desynchronisation and phase reset (e.g., Breakspear et al., 2004; Freeman and Rogers, 2003; Thatcher et al., 2009); methods that enable assessment of direction of information transmission, like partial directed coherence (Astolfi et al., 2006) and directed transfer function (Babiloni et al., 2005); the unitary event analysis, which employs complex statistics (Pipa et al., 2007, 2008) and can detect individual events of coincidence firing; spike-field coherence (Fries et al., 2002), which estimates consistent phase relations between the discharges of individual neurons and LFP oscillations; and pairwise phase consistency (Vinck et al., 2010b), which computes how similar the relative phase observed in one trial is to the relative phase observed in another trial, suitable for measuring rhythmic synchronisation for both EEG–EEG, MEG–MEG, spike–LFP, and spike–spike pairs.

2.2. Functional roles in basic cognitive functions

In recent years it has become increasingly clear that neuronal oscillatory coherence correlates with all basic cognitive functions. Coherence mediates not only coupling of distinct brain regions involved in the same function, but also cooperation between different ongoing cognitive processes in different regions, from which unified mental constructs and goal-oriented meaningful behaviour emerge (Başar, 2006; Başar et al., 2001).

2.2.1. Perception/representation and the binding problem

In a pivotal study, Gray et al. (1989) provided strong evidence that highly synchronised spike discharges in the 40–60 Hz gamma frequency range of neurons in the primary visual cortex of anaesthetised cats could serve as a tag for relatedness of different features in a visual field, represented by the selective responses of different neurons or groups of neurons separated in space, thus binding them together into a coherent percept (the dilemma of how the functional coupling is achieved is known as the binding problem). This temporal binding hypothesis, or binding by synchrony[12] (Crick and Koch, 1990a; Eckhorn, 1994; Engel and Singer, 2001; Singer and Gray, 1995; von der Malsburg, 1995; von der Malsburg and Buhmann, 1992) took centre stage in systems neuroscience and has since expanded to include many other cognitive functions. In addition to visual cortex, stimulus induced coherence in the gamma frequency range has been described in other primary neocortical areas, for example in auditory (Brosch et al., 2002) and somatosensory (Bauer et al., 2006) cortices. Odours elicit global oscillatory activity of 20–30 Hz in the insect olfactory antennal lobe, which routes olfactory information to higher areas in the insect brain, as disruption of the synchrony impairs olfactory discrimination (Sivan and Kopell, 2004; Stopfer et al., 1997).

Alongside unimodal processing via neuronal coherence, evidence based on diverse experimental paradigms is emerging that synchronised oscillations within different unimodal regions may synchronise among themselves as well as with higher-order regions to foster multisensory integration and processing. Gamma power and coherence is generally greater when the multisensory inputs are perceptually or semantically congruent (Bauer, 2008; Senkowski et al., 2008). A recent study on humans, which enabled imaging synchronised networks across the entire human brain, has indeed revealed multiple large-scale brain regions that are selectively (depending on individual perception characteristics) synchronised at beta and gamma frequency bands in response to ambiguous audiovisual input (Hipp et al., 2011).

2.2.2. Motor activity and sensori-motor integration

At the simplest level, synchronised firing of neurons drives periodic motor signals for rhythmic movements in a special type of pacemaker network, called the central pattern generator, which is located in the spinal cord and coordinates automatic modes for locomotion, breathing, swallowing, etc. (Marder and Bucher, 2001) and operates in the absence of sensoric feedback, but can be modulated by it and by neuromodulation (Hooper, 2000; Hooper and DiCaprio, 2004; Kiehn, 2006). During voluntary movements, execution of complex action depends on the coordinated action of multiple motor and non-motor cortical areas (Rizzolatti and Luppino, 2001; Roland and Zilles, 1996). Synchronised oscillations function as integrators between such neuronal networks, as measured during spontaneous movements and during bimanual motor learning (Andres and Gerloff, 1999; Andres et al., 1999; Gerloff et al., 1998; Pfurtscheller and Andrew, 1999). Interestingly, oscillations spread like a travelling wave across the motor cortex, reflecting information transfer (Rubino et al., 2006). There also seems to be a direct correlation between physical parameters of specific movements, such as force generation, and the patterns of oscillations (Logar et al., 2008b,c).

In sensory-motor integration, beta-rhythm oscillations become (de)synchronised over a larger scale when motor control, attention or "status quo" maintenance is required (Andrew and Pfurtscheller, 1996, 1999; Engel and Fries, 2010; Kristeva-Feige et al., 2002; Neuper et al., 2006; Pfurtscheller et al., 2003). Theta rhythm and gamma synchrony also seem to be involved in sensori-motor integration and movement preparation (Aoki et al., 1999; Caplan et al., 2003). Such coupling seems logical, as for any goal-directed, purposeful movement or action, the brain has to develop a strategy, a motor programme. For this purpose, premotor and supplementary motor areas (SMA) cooperate with posterior sensory areas and with the primary motor area (Krakauer and Ghez, 2000). In visuomotor control, EEG-coherence increases between visual and motor areas in tasks which require visuomotor integration, in accordance with the concept of synchronisation as a neuronal correlate of increased functional connectivity (Brežan et al., 2007; Classen et al., 1998; Fries, 2005; Roelfsema et al., 1997).

Interestingly, cortico-spinal and cortico-muscular coherence was measured during movement and has direct functional consequences, as elucidated by using the combination of MEG/EEG–EMG (electromyography) (Baker et al., 1997; Mima and Hallett, 1999; Salenius et al., 1997; van Elswijk et al., 2010). It represents another argument for strong direct coding of brain functions by oscillations, also influencing the transfer of relevant signals to the peripheral targets.

2.2.3. Attention

Complex information that is represented at higher stages of processing influences simpler processes occurring at preceding

[12] Critics of this theory argue that oscillatory synchrony cannot explain the organism's ability to identify objects and that spike synchrony could instead provide the relevant information about the stimulus (Jermakowicz and Casagrande, 2007), or that synchrony itself could not be a general mechanism of feature binding because it is too weak (Palanca and DeAngelis, 2005) or due to large trial-to-trial spike timing variability (Shadlen and Movshon, 1999).

stages. The function of any area of the cortex is subject to such a top–down influence of attention, which is dynamically established during ongoing processing (Gilbert and Sigman, 2007). Attentional mechanisms help select the behaviourally relevant stimulus by restructuring cortical activity to sensory inputs, amplifying the influence of neuronal groups conveying behaviourally relevant information, while attenuating the irrelevant ones.

Studies on monkeys and humans generally show that attended uni-or multisensory stimulus triggers stronger oscillatory responses than unattended stimulus, typically in the gamma frequency band (Jensen et al., 2007; Senkowski et al., 2008; Womelsdorf and Fries, 2007; Womelsdorf et al., 2007). The strength of synchronisation, depending on whether it is induced by an attended or unattended stimulus, has been shown to be able to predict the speed of learnt behavioural response, thus having a direct functional relevance for attention (Womelsdorf et al., 2006). It was suggested that biased competition, a hypothetical mechanism for selective attention based on competition between different stimuli corresponding to different neuronal assemblies, and which feed-forwards only the behaviourally relevant ones while suppressing the non-relevant ones (Desimone and Duncan, 1995), operates through enhanced gamma-band synchronisation by ensuring an exclusive communication link between the selected and the higher-order neurons (Fries, 2009). Thus, selective neuronal interactions mediated by synchronisation may underlay selective attention.

2.2.4. Memory

Learning and memory are closely related to attention. Working memory, defined as the capacity to retain and manipulate information that is no longer accessible in the environment (Baddeley, 1992), is based on sustained neuronal activity – the persistent firing of "delay-period" neurons (Funahashi, 2006; Fuster, 2008; Fuster and Alexander, 1971; Goldman-Rakic, 1995) and cooperation among many cortical and subcortical areas (Carpenter et al., 2000; d'Esposito et al., 1998; Veltman et al., 2003). Evidence shows that this persistent firing has an oscillatory character with frequencies in theta and gamma bands, and that firing of individual cells tends to occur at a particular phase of theta oscillation (phase locking) (Lisman, 2010; Rutishauser et al., 2010). Several studies have measured increased theta synchronisation between prefrontal and temporal/parietal cortices during encoding and retrieval, or maintenance of information in working memory (Benchenane et al., 2010; Sederberg et al., 2003). Sustained synchrony enhancement in the beta and gamma frequency bands, as well as phase-locking of higher-frequency (beta, gamma) oscillations to theta oscillations, has also been observed during maintenance of working memory (Fell and Axmacher, 2011; Lisman and Buzsáki, 2008; Sauseng et al., 2010). It was recently confirmed that the strength of coherence could predict memory load and individual working memory capacity, pointing to a causal role of oscillations (Palva et al., 2010).

In a very illustrative model of working memory (Jensen and Lisman, 1998, 2005; Lisman and Idiart, 1995) it is proposed that theta and gamma oscillations interact to form a neuronal code for multiple ensembles to represent an ordered sequence of different memory items in sequentially "nested" gamma cycles at different phases within each theta cycle (each theta contains about 7 gamma cycles, corresponding to a well-known working memory limited capacity buffer) (Sternberg, 1966). The neuronal ensemble was defined as a group of active cells with distinct spatial connectivity pattern, firing within a given temporal window in the gamma band, that represents a particular cognitive construct. Such gamma-coded constructs are temporally offset via afterdepolarisation phenomena at a cell/ensemble level, which causes the same cells to fire again after a delay, sequentially in different gamma cycles. Theta serves as an external drive that resets the start of each serial memory scanning operation during recall after the probe presentation, comparing the probe stimulus to a stored sequence, to provide the temporal frame for maintenance of working memory.

For learning, working or short-term memory must be transferred into long-term memory and neuronal synchronisation plays a role in memory consolidation by modifying synaptic strengths (Section 2.3.3). Human studies show enhanced long-range coherence from delta to gamma frequency range between anterior and posterior brain regions during encoding into, or retrieval from, declarative memory of visually presented objects (Fell and Axmacher, 2011; Jensen et al., 2007). Hippocampus is crucial for the formation of declarative as well as nondeclarative long-term memory – both correlating with an increased synchronisation in broad frequency ranges within the hippocampus and related structures. As the hippocampus has recently been demonstrated to support working memory as well, it is hypothesised that it coordinates the flow of information between both types of memory (Fell and Axmacher, 2011). Cross-frequency synchronisation, especially between the gamma and theta bands also increases, and is thought to support cooperation of both rhythms in the transfer of information maintained in working memory into long-term memory (Canolty et al., 2006; Fell and Axmacher, 2011; Jutras and Buffalo, 2010; Sirota et al., 2008).

2.2.5. Consciousness

Finally, consciousness has been related with neuronal synchrony (Crick and Koch, 1990b; Tononi and Koch, 2008; Uhlhaas et al., 2009). Transient global enhancement of gamma synchrony between occipital, parietal and frontal cortices across the hemispheres has been detected for perceived stimuli, but not for non-perceived, in a human study using brief presentations of words (Melloni et al., 2007). According to the authors, the observed large-scale synchronisation triggers or reflects a cascade of processes, such as perceptual stabilisation, maintenance of working memory, and anticipatory attention, which are plausibly related with perceptual awareness. As consciousness enables access to phenomenal awareness, or subjective experiencing, another paradigm to study correlations between consciousness and neuronal synchrony is the use of physically identical stimuli that lead to different subjective interpretations across trials. Several experiments on humans with various multisensory illusions indeed demonstrate significant changes in gamma synchrony with respect to perceived (illusory or nonillusory) stimuli (Senkowski et al., 2008).

Consciousness might also be studied indirectly, by means of observing and comparing states with lack of consciousness, such as coma, anaesthesia or sleep. During sleep, slow thalamocortical oscillations prevail, as arousal brainstem systems remain silent. Different sleep stages are highly distinct in their oscillatory patterns, regulated by specific circuit and intrinsic mechanisms, modulated by different neuromodulatory effects (Bazhenov et al., 2002; Niedermeyer and Da Silva, 2005; Steriade et al., 1993a). The slow global sleep oscillations may however have an active role: besides reflecting a functional inhibition of sensory input processing via thalamic mechanisms, shutting down the consiousness, they may support memory consolidation by synchronising thalamo-cortical spindles and hippocampal sharp wave-ripples, regulating transfer of re-activated memories between hippocampus and neocortex, where long-term memory is finally stored (Diekelmann and Born, 2010; Steriade and Timofeev, 2003).

2.2.6. Decision making and reward

Decision making on choice alternatives involves defining goals based on preferences/reward and the prediction of expected outcomes, followed by goal-directed actions based on information accumulation, and finally selecting the alternative that is most valuable to us (Pesaran et al., 2008; Wang, 2008). At the neuronal

Plankar M. Koherenca v bioloških sistemih in njene aplikacije v biološke znanosti.
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level, decision processes might depend on neuronal recurrent positive and negative feedback circuits, where strong excitation generates multiple self-sustained stable states of neural populations (attractors) from which categorical choice evolves (Heinzle et al., 2007; Wang, 2008). In "decision neurons", long ramping of individual neural activity over time is primarily correlated with specific decision choice, includes integration of sensory evidence over time, and ends with a winner-take-all competition (Donner et al., 2009; Gold and Shadlen, 2007; Scherberger and Andersen, 2007; Wong and Wang, 2006). Decision choice is made at a certain firing rate threshold of neurons selective for that choice response, where these neurons display stochastic, highly irregular neuronal spiking inherent to neuronal networks. Thus, the source of variability in decisions may not be in the sensory stimuli alone, but also in the neuronal system itself (Brunel and Wang, 2001; Wang, 2008).

Decisions are importantly modulated by value signals, such as reward, loss, or risk. Coherent interactions within and between such reward pathways and higher decision making centres in the brain (prefrontal cortex, orbitofrontal cortex, lateral intraparietal area, cortico-striatal loops etc.) could enable parallel processes, such as reward expectation, action value, prediction error and decision choice to communicate between one another and with other relevant contexts (e.g., memory) in reciprocal loops (Fuster, 2008; Miller and Cohen, 2001; Rushworth and Behrens, 2008; Wang, 2008). For example, decision making aspects and its performance correlated with the power of theta oscillations within many different brain regions, with interareal theta coherence (Benchenane et al., 2010; Sederberg et al., 2003; Womelsdorf et al., 2010) and with phase-locking of higher-frequency (beta, gamma) oscillations to theta oscillations (Sauseng et al., 2010). Selective theta synchronisation could reflect selective communication of top–down and bottom–up information (Engel et al., 2001; Womelsdorf and Fries, 2007; Womelsdorf et al., 2007) and may underlie the retrieval of choice-relevant information around decision points (van Wingerden et al., 2010; Womelsdorf et al., 2010). Choice-predictive beta-band oscillations may also reflect decision related processes within and among visual, frontoparietal and motor cortices (Decharms and Zador, 2000; Donner et al., 2009; Engel and Fries, 2010; Wang, 2002), whereas gamma-band synchronisation via attentional networks may mediate attentional selection of the behaviourally relevant visual input (Siegel et al., 2011).

2.2.7. Neurologic and psychiatric pathology

Tremor, epilepsy, schizophrenia, Parkinson disease, dementias, depression and autism, among others, have been strongly connected to dysfunctional neuronal connectivity. Different measures of synchrony were found to be aberrant (Herrmann and Demiralp, 2005; Uhlhaas and Singer, 2010), suggesting a possible explanation of various symptoms. Besides correlations, different focussed therapeutical interventions (e.g., transcranial magnetic stimulation, deep brain stimulation, drugs) may improve symptoms by inducing direct changes to specific, otherwise pathological, oscillatory patterns (Engel and Fries, 2010; Hardesty and Sackeim, 2007; Schnitzler and Gross, 2005; Thut and Pascual-Leone, 2010b; Timmermann et al., 2007). The details are beyond the scope of this article, but it is clear that this line of investigation provides an additional argument for the causal role of synchronised oscillations in functional brain processing.

2.2.8. Synchrony and technology applications: brain–computer interfaces and "mind reading"

Neuronal oscillations can be exploited as a control/input signal for various brain–computer interfaces (BCI) (Andersen et al., 2010; Hatsopoulos and Donoghue, 2009; Kipke et al., 2008; Pfurtscheller et al., 2000). Using different decoding approaches, BCI allows users to control an external device, e.g., by learning to self-change one's own amplitude of oscillatory activity in specific frequency bands (e.g., beta rhythms) at specific regions (a type of neurofeedback learning). For example, beta is inhibited by motor imagery (De Lange et al., 2008), which is exploited in such designs (Bai et al., 2008). New decoding techniques may enable a more precise regulation of BCI by taking into account those oscillations that are naturalistically responsible for coding a certain desired action and by recording with a more precise spatial resolution. On the other hand, similar methods have been used for the intent of "mind reading", for example to be able to decipher one's thoughts, feelings, perceptions, reveal memories, determine truth vs. lies or predict subjects' responses and choices in advance, without the need for subjective reports (Bles and Haynes, 2008; Haynes and Rees, 2006; Haynes et al., 2007).

2.3. Functional roles in information processing

As discussed above, neuronal synchrony clearly correlates with various cognitive processes, and could in some situations even predict behavioural outcome, which implies its functional significance. In recent years, much evidence has accumulated to firmly support its mechanistic role in information coding, neuronal communication and synaptic plasticity.

2.3.1. Information encoding and decoding by oscillatory phase (phase coding)

Information in the brain is thought to be carried by neuronal spikes (AP) and many aspects of firing patterns, e.g., average firing rate, occurrence of specific interspike intervals, bursts, or the degree to which different cells fire in coincidence (Eggermont, 1998; Engel et al., 1992; Lisman, 1997; Rieke et al., 1999) could potentially encode information and therefore represent the "neural code", as reflected by systematic variation of neuronal activity with respect to a behavioural variable. In oscillatory networks, where the timing of spikes is under the combined influence of external inputs and the internal dynamics of the network, the phase at which a neuron fires relative to an oscillatory cycle (LFP) also carries information (Buzsaki, 2006; Hopfield, 1995).

The first evidence for phase coding came from O'Keefe and Recce (1993) where theta phase precession (a gradual phase advance of spikes over time) in hippocampal "place cells" was observed as the rat walks through the receptive field of a recorded pyramidal cell, possibly representing cued 'prospective' recall of the coming positions from long-term memory, where theta provides an absolute phase reference (Jensen and Lisman, 2000; Lisman, 2005; Tsodyks et al., 1996). Specifically, theta and delta oscillations may enable phase coding and temporal segmentation, e.g., as indicated in the theta phase-locked spike output (Jacobs et al., 2007; Klausberger and Somogyi, 2008), conveying specific information beyond the firing rate (Hyman et al., 2010; Jensen and Lisman, 2000; Panzeri et al., 2010). On the other hand, gamma oscillations could mediate content decoding and representation by coupling specific spatial combinations of simultaneously active neurons (Jacobs et al., 2007; Jensen and Lisman, 2005).

Furthermore, the phase precession of spiking relative to depolarising peak of oscillations is a direct measure of input intensity, which enables transformation of rate coding into a temporal code of spike timing in target neuronal groups (Fries et al., 2007; Singer, 2007). As the coupling strength between the neurons reflects the level of depolarising input, it is proportional to the magnitude of phase advancement, which may also be exploited for short-term storage of information (Buzsáki and Draguhn, 2004).

Next, "encoder–decoder" networks in a phase-sensitive detector model (Jensen, 2001) allow different neuronal populations in different regions to integrate firing patterns, if in coherence, and transfer only

specific information dependent on the adjustable phase of the common oscillatory drive input, because of excitability dependent on a depolarising peak phase of the cycle, which can be modulated independently in both regions by among others the theta pacemaker and phase shifting (Jensen and Lisman, 2005; Lisman, 2005).

The phase coding working memory theta-gamma model (Jensen, 2006; Jensen and Lisman, 1998, 2005) predicts that multiple memories held in short-term memory become active at different phases of theta oscillation, supported by evidence that theta oscillations emerge and synchronise in cortex during short-term memory tasks (Gevins et al., 1997; Jensen and Tesche, 2002; Raghavachari et al., 2001; Sarnthein et al., 1998; Sauseng et al., 2004) and that spiking occurs preferentially at a certain theta phase (Lisman and Buzsáki, 2008; Siapas et al., 2005). Interestingly, it was shown that it is possible to decode and predict different states of working memory based on "phase demodulation" processing of EEG signals (Logar et al., 2008a), which also points to a coding potential of the phase content in oscillatory networks.

The phase of theta oscillations also controls long-term potentiation (LTP) or long-term depression (LTD) of the synapse (Hölscher et al., 1997; Huerta and Lisman, 1993; Pavlides et al., 1988). Phase-coding may be used to separate the processes underlying long-term memory encoding and retrieval operating in distinct phases of the ongoing theta (Hasselmo et al., 2002; Judge and Hasselmo, 2004). Phase reset could be a mechanism of neuronal networks to reset their oscillations when they are recruited to process information, e.g., after memory-related stimulus probe (Givens, 1996; Rizzuto et al., 2003). In recognition memory, slow wave (4–12 Hz) phase reset entails serial scanning operations after probe onset (Jensen and Lisman, 1998).

All of the above considerations support a temporal coding hypothesis that may represent a possible general coding scheme in the brain, where oscillations serve as a temporal ordering frame for organising different processes in different phases of an ongoing rhythm (including future probabilities), and hence provide one of the answers as to why the brain oscillates (Buzsáki and Draguhn, 2004; Jensen, 2006; Judge and Hasselmo, 2004; Lisman, 2005). In such a framework, oscillatory synchronisation (coherence) can mediate the exchange of phase-coded information (Fries, 2005; Jensen, 2001; Jensen and Lisman, 2005; Lisman, 2005; Mizuhara and Yamaguchi, 2007; Varela et al., 2001; Womelsdorf et al., 2007).

2.3.2. Neuronal communication

In an attempt to generalise the binding by synchrony hypothesis into a wider theory of communication through coherence, Fries (2005) emphasised that the higher, top–down cognitive control over perception and behaviour – as manifested e.g., through selective attention, or any other fast and efficient cognitive processing – demands flexibility of communicational structure between the neurons that goes beyond the static anatomical connections, appearing fixed on the timescale of cognitive dynamics, and such effective communication could only be achieved through coherently oscillating neuronal assemblies.[13] Phase synchrony of oscillatory signals establishes high functional connectivity, because interacting neurons can exert a stronger impact on one another if they are depolarised at the same time (Fries, 2005; Womelsdorf et al., 2007). A study by Womelsdorf and Fries (2007) gave a strong support to this theory with the finding that the strength of mutual influences among neuronal assemblies oscillating in the gamma frequency band is a direct consequence of the phase relations between them – the strongest interaction being exerted when in phase.

This finding has been supported at the cellular level. Coincidence-sensitive neurons predominantly discharge action potentials if simultaneously activated by multiple presynaptic neurons, defining a narrow time window for activation. Cortical neurons were found to have a dynamic firing threshold that depends on summation of transient depolarisations, enhancing fast and synchronous synaptic inputs, while suppressing slow (low slope) depolarisations (Azouz and Gray, 2003). Moreover, these synchronous inputs can then reliably transform into temporally precise output action potentials by initiating fast local dendritic spikes despite the background synaptic and dendritic noise, thus acting as coincidence detectors (Ariav et al., 2003). These studies suggest that, in addition to passive coincidence detection, which is classically considered to entail communication via synchrony, additional active mechanisms could substantially enhance feed-forwarding of synchronised assemblies. Taken together, neuronal input–output dynamics (e.g., gain modulation), regulated by transmission of synchronised activity could represent a fundamental neuronal mechanism for controlling behaviourally relevant stimuli (Azouz, 2005).

For functional communication between neuronal assemblies, interaction mechanisms must be selective, and hence there must be some general rules for such selectivity. As with all oscillating systems, information is encoded in the phase and the frequency of the oscillation. Because the mechanism of gamma oscillations itself entails frequency-dependent gain modulation, this will have immediate network consequences in the sense that interaction will be enhanced between those assemblies that receive strong input when their synaptic gain is maximum, and suppressed otherwise; the coupling itself will then proceed through the coincidence detection mechanism (Fries, 2009). Interactions could be further refined by the mechanism of phase shifting (Fries et al., 2007): the more excited neurons in a given assembly would fire earlier in an oscillation cycle and thus suppress the less excited ones due to the fast inhibitory system, consequently entraining the phase of an entire assembly and re-defining the phase relations with other assemblies. Recently, the phase shifting mechanism has been experimentally observed in monkey visual cortex (Vinck et al., 2010a). Long-distance functional communication has also been recently elucidated by a study that showed individual local spiking responses modulated by distant phases and LFP phase coupling between multiple regions, in such a way that their distinct patterns translate into corresponding changes in spike rate and correlate with specific functional involvement of a given neuron or an assembly (Canolty et al., 2010).

2.3.3. Neuronal plasticity

Synchronisation of neuronal firing already plays a role during brain development, promoting synaptogenesis and providing efficient anatomic connectivity patterns for later coding via synchrony (Jermakowicz and Casagrande, 2007; Volgushev et al., 1997). Changes in synaptic strength are collectively known as synaptic plasticity, which is considered a fundamental neuronal mechanism modulating neuronal connectivity and thus learning, memory and adaptive behaviour. Spike timing-dependent plasticity (STDP) means dependence of synaptic plasitcity on the temporal order of pre- and postsynaptic spikes within a critical time delay window of tens of milliseconds. When a presynaptic spike precedes a post-synaptic spike within this time window, synapses undergo long term potentiation (LTP), and they undergo long term depression

[13] In terms of graph-theoretical or network modelling, this is the difference between the functional connectivity that emerges from dynamic, moment-to-moment activity fluctuations of an integrated network as a whole – which supports much richer informational processing capabilities as well as being more responsive to perturbations – and structural, or anatomic connectivity (or the network topology) alone, which is primarily modulated by synaptic plasticity (Bullmore and Sporns, 2009).

(LTD) if the situation is reversed (Dan and Poo, 2004; Markram et al., 1997). A diversity of critical time windows for different types of synapses has been discovered recently. Because STDP has been demonstrated on various types of neurons and synapses, and in different animal phyla, it is considered today a generalisation of Hebbian learning (Caporale and Dan, 2008). As mentioned above, correlative functions between neuronal synchrony and long-term memory are already firmly established. In a study by Wespatat et al. (2004) a direct link between gamma neuronal synchrony and STDP was established. It was demonstrated that synapses underwent long term potentiation when presynaptic discharges coincided with the peak of the postsynaptic membrane potential oscillations in the gamma band, and long term depression when coinciding with the trough.

Gamma synchronisation is considered optimal for modifying synaptic plasticity, because it focuses neuronal activity in sufficiently short time windows that coincide with the time windows of STDP (Fell and Axmacher, 2011). However, simple co-firing of presynaptic and postsynaptic neurons within too short time windows would not lead to a systematic STDP (Vinck et al., 2010a). Rather, STDP typically requires that the presynaptic neuron is either leading or lagging the postsynaptic neuron by a few milliseconds, and this might be achieved through the phase shifting mechanism.

To summarise the functional role of neuronal synchrony, neuronal communication and plasticity naturally support each other and coevolve via coherent oscillatory dynamics. Synchronisation between two communicating assemblies will generally enhance communication and strengthen their synaptic connections, whereas desynchronisation will lead to weakening. On the other hand, a pre-existing memory trace may enable a faster synchronisation, processing, and behavioural response (Fell and Axmacher, 2011; Fries, 2009; Singer, 2009; Womelsdorf et al., 2006).

3. Towards the long-range modes of subneuronal information processing

3.1. The need for a dynamic order in brain information processing

Neuronal synchronisation correlates with all basic cognitive processes. Its concomitant impairment in common neurological disorders, and its functional role in neuronal communication and plasticity, imply a generic function in brain information processing. For the same reason, it remains unclear how diverse cognitive functions could emerge from synchronised firing *in se*, as they would interfere among each other, should the relevant information be encoded exclusively on the basis of neuronal oscillations (Fell and Axmacher, 2011). Rather, oscillations in the first place represent the reference timeframe for neuronal communication (Axmacher et al., 2006) and the nervous system likely utilises specific context- and information type-dependent coding strategies (Jermakowicz and Casagrande, 2007), leaving the question of cognitive representation and the "hard" problem of subjective awareness, open to discussion (Cook, 2008; Engel et al., 1999; Koch, 2004; Llinás and Ribary, 2001).

At the processual level, an important issue concerns the problem of the dynamic spatio-temporal modulations of the synchronised oscillations to meet behavioural demands. For example, the basic mechanism of gamma cycle, which is most relevant for encoding representations, is well understood at the systems level in terms of rhythmic inhibition of excitatory neurons via the $GABA_A$ receptor-mediated inhibitory system of fast-spiking interneurons. Strong and fast inhibitory postsynaptic potentials, rapid signal transfer via electrical synapses, and shunting inhibition are important electrophysiological properties of the inhibitory system, responsible for establishing narrow time windows in which the excitatory neurons can generate action potentials (Bartos et al., 2007; Cardin et al., 2009). Realistic models of gamma synchronisation (Bartos et al., 2007; Vida et al., 2006) can successfully explain the robustness of oscillations even in the presence of heterogenous excitatory input, as is the case in cortical networks. Nonetheless, it remains unclear how the neurons undergo very transient episodes of synchrony in the range of tens of milliseconds, as well as the rapid switching between the coherent and incoherent states observed during different cognitive processes such as attention and perceptual awareness (Breakspear et al., 2004; Melloni et al., 2007; Taylor et al., 2005; Uhlhaas et al., 2009), and which in addition may extend orders of magnitude across the spatio-temporal domains in real cortical networks (Freeman, 2003b; Freeman and Vitiello, 2006; Petermann et al., 2009; Van De Ville et al., 2010).

A partial explanation of how the brain could achieve such modulatory potential is via stochastic background activity. Individual cortical neurons generally exhibit highly irregular spiking, which contributes a large tonic and only a small sinusoidal component to the network activity, even when engaged in synchronous oscillations (Wang et al., 2010). Stochasticity is inherently generated by the circuit dynamics with balanced synaptic excitation and inhibition even in the absence of external stimuli (Barbieri and Brunel, 2008; Compte et al., 2003; Mattia and Del Giudice, 2004; Renart et al., 2007). It is conjectured that dynamic modulation of excitability through stochastic synaptic bombardment in highly recurrent local and distant networks causes an elevated level of depolarisation that can enhance neuronal responsiveness rapidly and in a multiplicative manner to a variety of inputs (Haider and McCormick, 2009). Balance between excitatory and inhibitory interactions, emerging from such dynamic activity is important for the rapid modulation of functional connectivity and sensitivity to synchronised synaptic inputs, even on a cycle-by-cycle basis (Atallah and Scanziani, 2009; Haider and McCormick, 2009). However, the predominantly stochastic fluctuations of membrane potentials would impose systematic problems to long-distance communication and information encoding based *exclusively* on the oscillatory information (Demir et al., 2000). Without proposing some higher-order organisation of brain activity, the specific information would quickly dissolve in synaptic noise, because stable oscillations are highly sensitive to phase perturbations, and more so the high-frequency oscillations (Wang, 2010), whereas precise and reliable phase relations are considered fundamental for meaningful (de)coding (Section 2.3.1). In summary, the complex balance between oscillatory robustness required for consistent coding and long-range communication, and the flexibility of functional connectivity, must be somehow reconciled for brain information processing to be meaningful.

A more integrative approach is to treat the stochastic background activity as a scale free dynamics that maintains itself close to criticality, as indicated by the power-law distribution ($1/f^{\alpha}$) of power spectral density of oscillations as a function of frequency (Freeman, 2005, 2009). Scale-invariant (fractal) avalanches of neuronal activity – a hallmark of self-organised criticality[14] (Bak et al., 1988) – have been demonstrated in human and animal cortex, and they are considered an important factor allowing for the rapid transitions of cortical activity at multiple spatio-temporal scales (Freeman, 2005; Petermann et al., 2009; Stam and De Bruin, 2004; Thatcher et al., 2009; Van De Ville et al., 2010). Freeman (1990, 2000, 2003b, 2009) has shown that stochastic

[14] A property of complex dynamic systems whereby the system spontaneously maintains itself at the critical border between ordered and chaotic dynamics, with no intrinsic time or length scale (Bak et al., 1988; Kauffman, 2008).

background activity reorganises in response to sensoric stimuli into distinct spatio-temporal structures (The wave packets; section 3.5.1) of cortical activity in different sensory cortices, constrained by a macroscopic order parameter. The wave packet is considered a perceptual carrier, encoded *homogenously* by the (context-dependent) phase- and amplitude-modulated carrier oscillation throughout the whole spatio-temporal domain.

Freeman also observed that the state transitions of different wave packets between basins of attraction occur unusually rapidly, exhibiting a phase velocity that exceeds the group velocity of oscillations, which implies that some long-range neuronal interaction may be required for the transition, independent of synaptic transmission (Freeman et al., 2003; Freeman and Vitiello, 2006). We already mentioned that local neuronal assemblies can also interact by ephaptic (EM) coupling, which could provide very rapid communication between them and contribute to entrainment of neuronal oscillations (Section 2.1.2). In recent years, however, a variety of models of highly cooperative signal propagation and integration have emerged, revealing a potentially even richer level of information processing that may additionally reveal a dynamic order behind the complex spatio-temporal patterns of neuronal oscillations. We shall briefly review those models and then discuss how the cortical dynamics could be functionally modulated through coherent states at different organisational levels.

3.2. The emerging role of neuronal cytoskeleton

The classical role of the cytoskeleton, reduced to structural scaffold supporting cellular shape, growth, motility and the transport of molecular cargo, has been drastically expanded in the last decades. It is established that the cytoskeleton integrates converging signalling pathways, influences the gene expression, coordinates membrane receptors and ionic flows, and localises many cytosolic enzymes and signalling molecules, while at the same time representing an immense catalytic surface for metabolic interactions (Bounoutas et al., 2011; Clegg, 1984; Gardiner et al., 2011; Ingber, 2003; Janmey, 1998; Shepherd, 2006). As the cytoskeletal filaments, most notably the microtubules (MTs) and actin filaments (AFs), have a high net surface charge and density of electric dipoles, they plausibly entail electrically non-trivial biological functions in addition to their structural–mechanical role. Electrical properties of cytoskeletal elements have been the focus of theoretical and experimental research, and are hypothesised to be specifically important for neuronal information processing (Craddock et al., 2010; Jaeken, 2007; Lin and Cantiello, 1993; Priel et al., 2010; Woolf et al., 2009).

The neuronal cytoskeleton is particularly complex and well differentiated. It comprises an integrative intraneuronal network by binding to ion channels and neurotransmitter receptors, scaffolding proteins[15] and their adaptors, motor proteins, microtubule-associated proteins (MAPs), and other linking proteins (Sheng and Pak, 2000; Woolf et al., 2009). AFs and MTs form interconnected networks[16] extending from synaptic spines – where AFs link the ion channels and other postsynaptic proteins – to the MTs in dendritic shafts, which form a network continuum throughout the soma and the axon. Thus, the neuronal cytoskeleton, together with its interconnecting modulatory proteins, such as MAP2 and MAP tau, physically connects ion channels within synapses and synapses throughout the neuron into a structurally and functionally integrated system, or the intraneuronal matrix (Ingber, 2003; Woolf et al., 2009).

3.2.1. Role in neurotransmission and memory

It is increasingly clear that ion channels and receptors of common neurotransmitters and neuromodulators functionally interact with the intraneuronal matrix in a bidirectional way. The matrix functions as a downstream target of neurotransmitters predominantly through calcium signalling, which can modify the matrix stability directly, or via signal transduction pathways by modifying phosphorylation status of binding molecules (e.g., MAP2, CaMKII), which in turn affect its structure and connectivity (Gardiner et al., 2011; Woolf et al., 2009). On the other hand, evidence has accumulated of the matrix exerting a direct control over neurotransmission. Exposure to agents that affect the integrity of various matrix components consistently causes changes in the gating properties of voltage- and ligand-gated ion channels, such as channel conductance variation and desensitisation, where some studies suggest that the function of ion channels could be modulated directly and independently of the filaments' transport role. Channels specific for Na^+, Ca^{2+}, K^+ and Cl^- conductances in neurons and other cell types have been considered (e.g., Janmey, 1998; Mironov and Richter, 1999; Schubert and Akopian, 2004; Shcherbatko et al., 1999; Strege et al., 2003; Sun et al., 2008). Some experiments have suggested that loss of cytoskeletal integrity could directly reduce membrane excitability and propagation of action potentials (Gardiner et al., 2011; Sakai et al., 1985), however without conclusive mechanisms.

The bidirectional interplay between neurotransmission and matrix reorganisation appears to be essential for learning and memory consolidation. Long-term potentiation has been recognised as a surrogate for the cellular processes that encode and consolidate memory, and it is necessarily accomplished by polymerisation and structural reorganisation of actin network in dendritic spines, as reflected in their highly dynamic morphology (Lynch et al., 2008). On the other hand, evidence has accumulated that points to the substantial role of matrix reorganisation in the subsynaptic zones below the synapses for permanent memory storage.[17] Many correlative as well as interventive studies, employing colchicine[18] consistently demonstrated that dendritic MT reorganisation is essential for memory consolidation. Moreover, studies on rats employing different learning paradigms demonstrate that MAP2 is proteolysed at brain regions corresponding to the type of learning, which is thought to promote MT reorganisation as new memories are formed. On the contrary, genetically induced overexpression of MAP tau has been found to impair learning, an effect thought to arise as a consequence of an overstabilised MT network that reduces the potential for reorganisation. For a detailed discussion, see recent reviews (Priel et al., 2010; Woolf et al., 2009).

In addition to MAPs, another layer of stability regulation in the MTs – with possible implications for memory – is represented by the composition of tubulin isoforms and post-translational modifications (Craddock et al., 2010; Woolf et al., 2009). Both types of regulation express most variability in their modifications of the

[15] The proteins attached to the postsynaptic membrane that connect the receptors to the effector proteins responsible for signal transduction cascades, and to the cytoskeleton, e.g., postsynaptic density protein-95 (Sheng and Pak, 2000; Woolf et al., 2009).

[16] There are at least three ways in which AF and MT interact: through direct binding, via cross-linking proteins such as MAP2, and via the signal transduction cascades (Woolf et al., 2009).

[17] Consistently with the fact that synaptic strength itself could not reflect permanent memory storage, because synaptic plasticity must be globally constrained by homeostatic mechanisms in order to maintain long-term system stability and plasticity (Davis, 2006; Turrigiano, 2008).

[18] An MT toxin that completely blocks MT polymerisation and also interferes with their depolymerisation (Vandecandelaere et al., 1997).

C-termini tubulin tails, which have also been hypothesised to participate in intraneuronal electric signalling (Priel et al., 2005). In summary, an intricate balance between stability and instability appears to coordinate the neuronal cytomatrix architecture, which has a role in memory consolidation and in turn it feeds back to modulate neurotransmission.

3.2.2. Electric signalling by actin filaments and microtubules

So far, very little is known about how the intraneuronal matrix modulates neurotransmission. The hypothesised mechanisms are predominantly based on structural interactions imposed by the matrix components that may influence molecular transport, clustering of ion channels, or binding of channel-associated proteins (Casini et al., 2010; Schubert and Akopian, 2004; Sun et al., 2008). While these mechanisms might account for slower neuromodulatory processes whose modifications are dependent on matrix reorganisation, they are insufficient to contribute to dynamic changes of functional neuronal connectivity.

One promising line of research indicates that microtubules and actin filaments act as biological conduction "wires" for charged particles. As negatively charged polyelectrolytes, MTs and AFs condense counterions in the proximity of their surfaces (Wong and Pollack, 2010). The counterions are arranged in ripple-like layers concentrated around charged groups, as directly observed in the case of AFs, and it was demonstrated that they exhibit highly coordinated dynamics (Angelini et al., 2006, 2003). Upon application of a voltage gradient at physiological ionic strength, both types of filaments display conductive capability that depends on the adsorbed counterions (Cantiello et al., 1991; Lin and Cantiello, 1993; Priel et al., 2006a).

In a hypothesised model of electric signalling (Lin and Cantiello, 1993; Priel and Tuszyński, 2008; Priel et al., 2006b; Tuszyński et al., 2004), conductivity is mediated by counterionic propagation along the filaments in the form of nonlinear, soliton-like ionic waves. Molecular modelling indicates that electrostatic perturbations of counterions between adjacent MTs could couple via the MAP2, thus potentially integrating the whole matrix into an electrically coupled network (Priel et al., 2006b, 2005). Since the intraneuronal matrix effectively connects synapses throughout the neuron, the initial electric perturbation (i.e., cations entring the postsynaptic density upon channel opening) would propagate throughout the matrix, and the output signal (resulting from collective input integration by the matrix) may then affect the neuronal response by electrically modulating the activity of voltage-depended ion channels, or by inducing cytoskeletal reorganisation via the signal transduction pathways. Thus synaptic activity could be integrated via the matrix in as many combinations as is mathematically possible. However it might be skewed by the previous memory-dependent structural constraints favouring activation of specific dendrites, or release of specific neurotransmitters and neuromodulators (Priel et al., 2010).

Could the hypothesised intraneuronal electric signal propagation have a role in neuronal synchrony? Priel et al. (2010) indeed suggest that electric signalling may participate in coincidence detection, which is considered fundamental for communication by synchrony because it enables temporal focussing of synaptic inputs (Fell and Axmacher, 2011; Fries, 2009). In this respect, electric signalling can complement current models of adaptive coincidence detection and input integration that are based predominantly on active dendritic conductances through voltage-gated channels (Ariav et al., 2003; Azouz and Gray, 2003). Another possible implication of electric signalling is its interaction with endogenous EM fields. The "strategic" position of counterions at the filamentous surfaces suggests antennae-like properties which could enhance the susceptibility of, and amplify the physiological response to, EM fields of exo- or endogenous origin (Funk et al., 2009; Gartzke and Lange, 2002). As described in the next sections, the emerging concept of molecular coherence could afford this system the required long-range coordination.

3.3. Overview of molecular coherence

As an integrated part of a living organism, the brain must ultimately obey the same organisational principles that apply to biological systems. We already pointed out that synchronisation is one of the mechanisms of self-organisation harnessed by organisms to boost their efficiency. Since Schrödinger (1944), one of the founders of quantum physics, pointed out that statistical mechanics alone is not sufficient to explain the remarkable efficiency of living organisms, the idea of a long-range order in biological systems that "escapes" the dictum of Brownian (statistical) molecular motion, has gradually expanded. The phenomenon of spontaneous synchronisation of weakly coupled oscillators with random frequency distribution has been mathematically proven by Winfree (1967). Fröhlich (1968) has shown for the first time how spontaneous synchronisation could be established within biological macromolecules by modelling them as a system of thermally driven electro-mechanically coupled dipole oscillators. At some critical level of energy input, a phase transition occurs whereby thermally distributed excitation energies are funnelled into a single (coherent) oscillation mode, resulting from the phase synchronisation of electric dipole oscillations. Fröhlich (1978, 1975) has further predicted that such a system would have important implications for molecular dynamics, allowing highly selective molecular recognition and long-range interactions based on resonant frequency coupling.

Fröhlich's model of molecular coherence has been further elaborated within the framework of quantum field theory, which provides the most fundamental physical description of condensed matter currently available (Del Giudice et al., 2005; Del Giudice et al., 1985; Del Giudice et al., 1988; Preparata, 1995; Vitiello, 2001, 2009). This theory can describe several well-known macroscopic quantum systems which display high stability despite their orderliness (and which is not the case in classical systems where order requires energy expenditure), such as crystals, ferromagnets, lasers, etc. The coherent state is described in terms of spontaneous symmetry breaking – that is, *ordering* – of specific molecular degrees of freedom due to their dynamic interaction with the long-range correlation quanta that mediate coherent condensation. For example, dipole wave quanta mediate breaking of rotational symmetry of dipole oscillations and hence their phase synchronisation. A peculiar property of the theory is that it can describe phase transitions and the coexistence of multiple inequivalent phases of a coherent system, making it directly applicable to biological systems (see Vitiello (2001) for a qualitative discussion). The theory has been specifically applied to model the two-phase liquid state of water (Arani et al., 1995) and later extended to the dissipative dynamics of biochemical cycles (Del Giudice et al., 2005; Del Giudice et al., 2010; Del Giudice and Tedeschi, 2009). Its application to neurobiology was pioneered by Ricciardi and Umezawa (1967) and later further elaborated by Jibu and Yasue (1995) and Vitiello (Section 3.5.1).

The recent groundbreaking experiments on photosynthetic systems (Collini et al., 2010; Engel et al., 2007; Lee et al., 2007) represent a proof-of-principle that macroscopic molecular coherent states exist in "warm and noisy" biological environment and exert a biologically meaningful function. Oscillations of light-induced electronic excitation energy in these systems preserve stable phase relationships throughout the whole molecular complex – composed of several proteins and light pigments – for

a short, but sufficient period to allow simultaneous sampling of an entire energy phase space to find the most effective sink for excitation transfer to the reaction centre. As the energy is shared among the excited molecules, this mechanism is fundamentally different from the semi-classical "hopping" through which the electronic excitation would move stepwise between different excited states, dissipating energy at each step, and where only one state could be occupied at any one time (Engel et al., 2007).

Apart from photosynthetic systems, strong indications of macroscopic quantum phenomena have been observed in various animal sensory systems, such as avian navigation (Gauger et al., 2011), odour recognition (Brookes et al., 2007; Franco et al., 2011) and vision (Prokhorenko et al., 2006). Other non-trivial (i.e., of biological significance) coherent phenomena include resonant vibrational energy transfer in proteins and water (Kobus et al., 2011; Woutersen and Bakker, 1999; Yang and Skinner, 2010), hydrogen tunnelling in enzyme catalysis (Nagel and Klinman, 2009), and long-range transport of electrons in proteins (Bandyopadhyay, 2010; Sahu et al., 2011; Skourtis et al., 2011). These findings initiated a general interest in "quantum biology" and in the role of coherence in various aspects of life (Abbott et al., 2008; Arndt et al., 2009; Bischof, 2008; Fleming et al., 2011; Lloyd, 2011; Plankar et al., 2011; Trevors and Masson, 2011; Tuszyński, 2006). The theoretical frameworks under which they are interpreted remain, however, disputed.[19]

3.4. Coherence and the intraneuronal matrix

3.4.1. Coherent electromagnetic fields

As already pointed out, actin filaments and microtubules are polyelectrolytes with high polarisation density. In the MTs, electric dipoles are arranged into helical tubular lattice composed of tubulin heterodimers. MTs exhibit interesting biophysical properties, such as ferroelectricity (spontaneous dipole alignment upon transient application of an external electric field) and piezoelectricity (mechano-electrical coupling), which implies their potential for electrodynamic interactions (Mavromatos et al., 2002; Mershin et al., 2006; Tuszyński et al., 1997, 2008).

Theoretical analyses of electro-mechanical dipole oscillations in MTs indeed predict a wide range of longitudinal coherent modes with frequencies ranging from the kHz to the THz (Cifra et al., 2010; Pokorný, 2004; Pokorný et al., 1997). Coherent oscillations collectively produce a dynamic electromagnetic field with a complex spatial geometry around the filament and of sufficient strength to influence the motion of charged or polarisable neutral (via dielectrophoretic force) particles in their vicinity (Cifra et al., 2010). Evidence of endogenous coherent EM fields has been obtained by examining the externally induced frequency-dependent growth rate of bacteria, by studying dielectrophoretic behaviour of particles around cells, and by direct measurements of EM fields emanating from different cells, with some studies indicating MTs as the field generators (e.g., Cifra et al., 2011; Giladi et al., 2008; Grundler and Kaiser, 1992; Hölzel, 2001; Kirson et al., 2007; Pokorný et al., 2001).

Coherent EM field produced by the longitudinal dipole oscillations in the MTs could exert biological effects through a plethora of biophysical mechanisms, in much a similar manner as externally applied EM fields (Cifra et al., 2011; Funk et al., 2009), by adding a non-Brownian (directional) term to particles' kinetics (Pokorný et al., 2005). Resonant interaction of the field with condensed counterions surrounding the filaments is plausibly one of the most direct consequences (Gartzke and Lange, 2002), suggesting a modulatory effect of the coherent field on voltage-dependent ion channels (Sections 3.2.2 and 3.5.2).

3.4.2. Microtubule as an information processing device

Tubulin dimers can exist in at least two stable conformational states, which differ in the alignment of electric dipoles depending in part on conformational constraints of neighbour tubulins in the filament and partly on GTP hydrolysis (Mershin et al., 2006; Woolf et al., 2009). The idea that an MT could act as an information processing nanostructure by switching conformational states was proposed almost forty years ago (Atema, 1973) and further elaborated upon by many research groups. In one model, electromagnetic interactions between the dipoles of adjacent tubulins occur as input-sensitive two-dimensional lattice of evolving conformational states, analogous to cellular automata. The "output" state of such processing is hypothesised to modulate binding of MAPs and thus influence the structural properties of MTs (Hameroff, 2006; Smith et al., 1984). Another model of dipole interactions predicts the propagation of waves of transient conformational changes along the filaments coupled to the energy of GTP hydrolysis, either as dipole "flip" waves (Mershin et al., 2006) or kink-like solitonic excitations (Satarić and Tuszyński, 2003), that are hypothesised to influence the MTs' conductive properties and mediate long-distance transfer of energy (Priel et al., 2010).

Assuming sufficient thermal isolation, some models predict that tubulin conformational states may sustain quantum mechanical superposition for a sufficient period to support the long-range information processing along the whole MT filament (Hameroff and Penrose, 1996; Mershin et al., 2006). Although such macroscopic coherence is generally considered implausible (McKemmish et al., 2009; Reimers et al., 2009) it received experimental support by the recent detection of ballistic electron conductance at physiological temperature – with temperature and filament length-independent resistance as a direct indication of coherent transport (Bandyopadhyay, 2010, 2011; Sahu et al., 2011). Hameroff (2006) argues that the coupled chains of polarisable electron clouds in tubulin hydrophobic pockets, and not the whole dimers, are sufficiently isolated from thermal noise and balanced by molecular forces to support long-range pathways of coherent interactions across the filament. Preliminary experiments indicate that these pathways may take the form of topological qubits, which are stable against temperature fluctuations and could allow efficient information transfer and processing (Bandyopadhyay, 2010; Bonderson and Lutchyn, 2011; Das Sarma et al., 2005).

In their orchestrated objective reduction theory, Hameroff and Penrose (1996) further hypothesise that upon quantum state reduction, the collapsed state would act as molecular "lever" governing the conformational state of an entire tubulin dimer, thus conveying the output of information processing to the MT exterior. Periodic switching between the classical (incoherent) and quantum (coherent) states is thus inherent to this theory, and its rate is hypothesised to coincide with that of gamma frequency oscillations. However, while the recent experimental progress may have weakened to some extent the usual criticism regarding the relevance of macroscopic quantum phenomena for cognition (Koch and Hepp, 2006), this and other theories of the "quantum mind" (Stapp, 2009) that exploit the measurement problem to explain consciousness (or even qualia as the "units" of subjective experience), face the difficulty of how the proposed mechanism of the wave function collapse might be reconciled with the well-

[19] The vast majority of research on coherent phenomena is interpreted quantum mechanically. However, important distinctions between quantum mechanics and quantum field theory have been pointed out and suggested that the latter is exclusively applicable to organisms, because it can describe complex systems exhibiting phase transitions, which is not the case in quantum mechanics (see Vitiello (2001) and Del Giudice et al. (2010) for a discussion).

established mechanisms of neuronal oscillations (Sections 2.1 and 3.1); we assert that this criticism may be even more important than the mere (im)plausibility of macroscopic quantum states.

Finally, the MT lumen has been speculated to represent another layer of information processing – optical signalling – by acting as a quantum optical cavity (Jibu et al., 1994; Mavromatos et al., 2002; Vitiello, 2001). Modelled in the framework of quantum field theory, water dipole oscillations in the lumen are predicted to be sufficiently thermally isolated to sustain a highly polarised, electret-like state due to tubulin surface charge. Such ordering could allow highly synchronised interactions with the quantised electromagnetic field entering the filament, and a consequent propagation of coherent excitations along the cavity without energy dissipation (the phenomenon of self-induced transparency), implying a potential for signal integration with an immense capacity. Optical signalling remains the least experimentally tested hypothesis of coherence-based communication along the MT, although indirect support for it is provided by the spectroscopic studies of resonant intermolecular transfer of vibrational energy in liquid water (Woutersen and Bakker, 1999; Yang and Skinner, 2010), and by the observed optical conductance along sensory and motor nerve roots, obtained by *in situ* biophoton autography (Sun et al., 2010).

3.5. Coherence as a generic property of information processing in the brain

So far, we have addressed the neuronal and molecular coherent oscillations separately. Jibu et al. (1994) have already remarked that both types of coherent dynamics might be related. Only recently, however, a synthetic approach to both levels of brain information processing has been elaborated within the dissipative brain dynamics theory, proposed by Freeman and Vitiello (2006, 2008, 2009).

3.5.1. Dissipative brain dynamics

Using high-density electrocorticography on animals trained to specific sensory stimuli, Freeman (1990, 2003b, 2005, 2009) observed distinct spatio-temporal patterns of synchronised neuronal oscillations emerging from the background cortical activity in the sensory cortices of animals responding to conditioned stimuli. Individual stable patterns, or the wave packets, exhibit distinct phase- and amplitude-modulation of specific carrier frequency in the beta and gamma ranges throughout the electrode array, and they appear in a sequential manner that resemble cinematographic frames. The frames remain stable from milliseconds to a second and can span from under a millimetre to an entire hemisphere – conforming to the self-organised criticality of cortical activity (Section 3.1). The size and discernibility of the frames correlate with the state of subject arousal; clearly discernible frames are only observed in subjects fully engaged with the environment, indicating their correlation with perception and meaning (Freeman, 2003a; Freeman and Vitiello, 2006). Related concepts of dynamic spatio-temporal patterns of synchronised activity as the "units" of cognition have been termed transients (Friston, 2000), microstates (Van De Ville et al., 2010), and dynamic cell assemblies (Breakspear et al., 2004).

A specific characteristic of the wave packet is that the border between different frames is marked by a rapid and transient decrease in the order parameter (measured as a decrease of the analytic signal power and a concomitant increase of analytic frequency and phase variances), manifested in the transition of neuronal activity into chaotic (non-synchronised) oscillations, a phenomenon referred to as the null spike (Freeman, 2009; Freeman and Vitiello, 2009). The most elusive property of this transitory instability is an almost instantaneous phase reset (the phase slip) across the entire electrode array which, in a study on humans, spanned up to 19 cm in less than 5 ms, implying a global state transition of cortical activity occurring with a phase velocity of over 40 m/s (Freeman et al., 2003). A similar phenomenon was observed in the rabbit olfactory bulb, where phase velocity during the state transition was demonstrated to be independent of the group velocity of synaptic propagation (Freeman, 1990, 2000). Such a long-range correlation of neuronal activity and rapid subsequent onset of a new wave packet is difficult to explain exclusively by serial synaptic transmission due to continuous variations (stochasticity) in transmission frequencies (Freeman and Vitiello (2006); see also Section 3.1). Neither can it be sufficiently explained by ephaptic transmission, because electric field emerging from synaptic inputs and postsynaptic potentials is considered inadequate to exert the *long-range* modulatory effects on dynamic synchronisation patterns because of its relatively rapid decay with distance and dependance on relevant geometric restraints (Canolty et al., 2010; Freeman and Vitiello, 2006).

Dissipative brain dynamics theory explains this seemingly instantaneous phase correlation by a spontaneous breakdown of the electric dipole rotational symmetry which entails the state transition of cortical dynamics from a microscopic (Hebbian) assembly to the macroscopic ordered pattern. Spontaneous symmetry breaking is ascribed in the quantum field theoretical approach (Preparata, 1995; Vitiello, 2001) to macroscopic coherent condensation of the long-range correlation quanta, i.e., dipole wave quanta, into synchronised electric dipole oscillations within densely polarised media. It is postulated that the coherent state utilises the transitory oscillatory instability by imposing to the cortex a macroscopic order parameter which initiates the rapid neocortical phase transition propagating radially from localised regions (forming distinct phase modulation patterns, or phase cones[20]), and settles the cortical dynamics into a new emergent pattern-attractor, or a frame. As a specific coherent state represents only one of the many possible physically inequivalent ground states (states with minimum energy), the theory also accounts for the experimentally observed state transitions in the same cortical region between many different modulation patterns with distinct carrier frequencies (Freeman and Vitiello, 2006; Vitiello, 2009). In summary, the role of spontaneous symmetry breaking and the concomitant phase transitions between different coherent states is to subtly "steer" the functional network connectivity and thus enable the rapid spatio-temporal transitions of macroscopic oscillatory cortical activity between different basins of attraction in response to external perturbations, by utilising the high cortical sensitivity maintained through self-organised criticality.

3.5.2. Connecting the levels of coherence?

Dissipative brain dynamics provides the first integrative framework for brain information processing based on the principle of coherence that incorporates both neuronal synchronisation and coherence of molecular dynamics. As shown mathematically by Vitiello (2009), the fractal, scale-free nature of coherent states is inherent to this theory. However, it does not explicitly address the mechanistic relationship between both levels of coherent dynamics (see also Uzan, 2011). Biological polymers and the polarised water molecules with which they are endowed generally meet the temperature and polarisation density criteria determined by quantum electrodynamics theory to represent plausible carriers of

[20] As the precise location and phase orientation of the phase cones seems to be randomly determined by the system's internal dynamics, it is unlikely that the synchrony can be ascribed to entrainment by an external pacemaker or a central relaying hub, such as the thalamus (Freeman, 2003b).

the coherent states (Arani et al., 1995; Del Giudice et al., 2005, 1988, 2010; Vitiello, 2001).

In order to modulate local and long-range neuronal firing and the patterns of neuronal synchronisation, coherent molecular states would have to interact with the membrane potential. Based on discussion in previous sections, it is reasonable to hypothesise that dynamic pathways of energy and information transfer along the intraneuronal matrix filaments may be involved in such an interaction within a neuron. As this system is immersed in an ionic atmosphere with a vast surface (Section 3.2.2), the presumed intraneuronal mechanism of membrane potential modulation is by regulating voltage-dependent ion channels in the dendrites and at the axon initial segment via the gradients of electric potential induced by ionic waves (Pereira and Furlan, 2010; Priel et al., 2006b, 2010).[21] We thus predict that endogenously generated electric dipole oscillations in the matrix are strong enough to exert an electrodynamic modulation of the counterions – causing their oscillatory movement around a fixed position or net translational movement, coordinating their dynamics according to the frequency and geometry of the electric field – which can be tested by theoretical modelling and experimentally on isolated filaments.

Components of the brain extracellular matrix[22] are, however, also negatively charged polyelectrolytes that bind water and condense counterions at their surfaces. The counterions are presumed to act as a buffering system controlling for the availability of cations for generating action potentials (Brückner et al., 1993; Dityatev et al., 2007; Härtig et al., 1999). Assuming that the cations are periodically perturbed, either by an external EM source or by endogenously generated coherent dipole oscillations, their electrostatic interactions could likewise be modulated in a frequency-dependent manner and thus may, if sufficiently excited (depending on the ion mobility, their vicinity to the EM source and frequency of the field), cause interference with the membrane potential fluctuations. Recent observations of the frequency entrainment of a whole oscillating neuronal assembly to an externally applied frequency of *weak* electric field, i.e., within physiological range, indeed provide a proof-of-principle that similar modulatory role of EM oscillations at the local network level is possible, although much lower frequencies were employed (Section 2.1.2). The highly localised endogenously generated coherent oscillations may provide yet a greater focus on modulating the membrane excitability by acting on ion channels.

The recent experiments also confirm that the loss of structural integrity of perineuronal nets – lattice-like differentiations of extracellular matrix that ensheath specific types of neurons – directly affects the function of voltage-dependent calcium channels (Kochlamazashvili et al., 2010) and excitability of fast-spiking basket interneurons (Dityatev et al., 2007) in hippocampal cultures. As this type of interneuron substantially contributes to establishing synchronised high-frequency neuronal oscillations (Section 3.1), it can be assumed that perineuronal nets are functionally involved in modulating neuronal synchrony (Dityatev et al., 2007). Abnormal oscillations in the gamma and theta frequency band have indeed been observed in the hippocampus of mice deficient in specific glycoprotein *in vivo* (Dityatev et al., 2007; Gurevicius et al., 2009).

Interestingly, close association between the perineuronal nets and astrocytic processes was also described (Derouiche et al., 1996). The modulatory potential of astrocytes in neuronal synchronisation has been already discussed (Section 2.1.2) and could, in the context of perineural nets, contribute to another layer of neuro-glial interactions based on coherence. We may speculate that the "quantum-like macro coherent process" Pereira and Furlan (2010) envision as a requirement for the collective integration of calcium waves into the astroglial network is embodied in the long-range coherent states within intra- and intercellular matrix filaments.

Taken collectively, theoretical considerations, together with the recently emerging experimental evidence, support the role of filamentous networks of intra- and extracellular matrices in dynamic modulation of functional neuronal connectivity. At the network scale, the long-range interactions within these matrices could help explain – e.g., via resonant coupling with the membrane potential fluctuations and network oscillatory entrainment – the experimentally observed rapid transitions of the phase and the carrier frequency, defining distinct patterns of synchronised neuronal oscillations, which have as yet not been conclusively explained by the classical models of functional connectivity.

4. Conclusions

Throughout this review, we have explored mechanisms of dynamic order in brain information processing at different organisational levels and from a variety of research disciplines, whose one common denominator is the principle of coherence, or synchronisation. Knowledge from neuronal oscillations and long-range molecular dynamics, together with their potential modulatory interactions, e.g., via electric signalling along the cytoskeletal filaments, ephaptic coupling, or neuroglial interactions, is for the first time collectively discussed in the context of dynamic emergent order, epitomised by coherence. Coherence may represent a dynamic operational principle capable of modulating functional network connectivity, upon which a succession of rapidly arising and transforming neuronal activity patterns could emerge that mediate integration of interneuronal and subneuronal information processing (i.e., its local and long-distance transfer, encoding and storage) into a unified ongoing cognitive synthesis.

Coherent neuronal oscillations have become acknowledged as a fundamental mode of interneuronal information processing and could represent one of the principal neuronal correlates of cognition. Yet, the basic operational principles behind them remain unclear. As Uhlhaas et al. (2009) remind us, there currently exists no satisfying explanation of "how different percepts dynamically map into different states, and how the system dynamically selects subsets of neuronal responses for conscious representation". We have tackled this problem from a multidisciplinary perspective, taking into additional consideration the integrative approach of the dissipative brain dynamics theory, and the so far much neglected properties of filamentous matrices that pervade the brain inside and outside the neurons, endowing it with an immense catalytic and electrically active surface. Because of their information processing potential, the intra- and extraneuronal matrices may represent an integrative functional system, complementing synaptic interactions.

An important intracellular component of this system are the microtubules, supramolecular nanostructures hypothesised to support coherent transport of energy and information at various layers: in their ionic exterior, within the protein filaments themselves, and in their aqueous interior. It remains to be determined

[21] Tsong and co-workers have demonstrated that periodic electric potentials of low and medium intensity, ranging widely in optimal frequency (from 10 Hz to 1 MHz), can induce conversion of electric field energy into chemical potential energy in the tested membrane proteins (see reviews by Tsong (1992) and Cifra et al. (2011) and references therein).

[22] The extracellular matrix of the brain consists of large molecular aggregates of proteins and carbohydrates, of which the main components are hyaluronic acid, proteoglycans and glycoproteins. It forms a network continuum with the intracellular matrix of neurons and glia by binding to various transmembrane proteins, which participate in signal transduction pathways that modulate synaptic plasticity (for a detailed discussion, see the recent review by Dityatev and Rusakov (2011)).

which of these layers could actually interact with the synaptic (or non-synaptic) input and contribute to signal integration and neuronal response. Some of the proposed mechanisms demand treatment of biological structures as macroscopic quantum systems, a topic that deserves to be approached with caution and upon which we did not here elaborate.

The structures of the extracellular matrix, on the other hand, represent an analogous extracellular system that could additionally establish and modulate long-range interactions between the neurons. Conspicuous structures of the perineuronal nets, connecting specific types of neurons and glia, as well as their functional significance in modulating ionic currents, certainly support such a dynamic role. However, their electrodynamic properties are much less known and need further investigation. It will have to be established whether they are capable of rapid local and long-distance information transfer and what are the underlying carriers of such information. It will also have to be determined how the filamentous matrices are capable of modulating the membrane potential, e.g., by the generation and modulation of ionic waves, or by some other means of acting on charge transport, and finally how such processing will affect the neuronal response. Selectively disturbing and manipulating the coherent states to establish their causal role in generating real-time changes on the membrane and network level will undoubtedly represent a great methodological challenge. Nevertheless the ordered filamentous matrices within and between the brain cells may likely provide, in addition to membranes and synapses as the principle substrates, the structural basis for the emerging theoretical framework required for a systems understanding of the dynamic oscillatory behaviour of the brain; coherence can provide its functional basis.

Acknowledgements

This work was in part financed by the European Union, European Social Fund and was implemented in the framework of the Operational Programme for Human Resources Development for the period 2007–2013, Priority axis 1: Promoting entrepreneurship and adaptability, Main type of activity 1.1.: Experts and researchers for competitive enterprises.

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3 RAZPRAVA IN SKLEPI

3.1 BIOLOŠKA KOHERENCA KOT SAMOORGANIZACIJA

Kljub temu da hipoteze o samoorganizaciji v objavljenih člankih nismo obravnavali kot osrednje teme, je iz njih pa tudi iz uvodnega poglavja razvidno, da jo lahko potrdimo. Koherenca je konvergentna lastnost dinamičnih sistemov, saj ni odvisna od specifične fizikalno-kemijske narave sistema, iz katerega vznika (emergira). Lahko jo opišemo v matematičnih (Pikovsky in sod., 2001) ali pa v različnih snovnih sistemih, v fizikalnih sistemih na primer kot kvantno koherenco, v bioloških sistemih pa na primer kot koherenco nevronskih oscilacij (Razdelek 1.2).

Koherenca je oblika samoorganizacije; če je samoorganizacija opredeljena kot spontano povečanje organiziranosti sistema zaradi zmanjšanja prostostnih stopenj njegovih sestavnih elementov – brez dejavnikov, ki bi vsiljevali organizacijo po kakšnem zunanjem načrtu – potem je tudi sinhronizacija v matematičnem smislu oziroma koherenca v fizikalnem smislu vrsta samoorganizacije, saj nastane zaradi prav takšnega spontanega in notranje pogojenega zmanjšanja prostostnih stopenj oscilirajočih elementov na račun večje organiziranosti sistema. V matematičnem pojmovanju sinhronizacije oziroma koherence je zmanjšanje prostostnih stopenj posledica specifičnosti mrežne topologije, ki določa povezljivost elementov sistema in posledično dinamiko njihovih interakcij (Arenas in sod., 2008); v termodinamičnih sistemih pa je posledica notranjih energijskih preprek, kar omejuje pretok energije oziroma vzpostavlja heterogenost energijskega tóka, ki določa dinamiko interakcij med elementi (Kauffman, 2008). Koncept molekulske koherence po Fröhlichovi teoriji kot tudi teoriji italijanske skupine ne krši načela disipativnosti, saj je za vzpostavitev koherence nujen pogoj odprtost sistema, ki za povečanje reda porablja energijo sistemove okolice, navzven pa izvaža termično energijo (Marchettini in sod., 2010; Šrobár, 2009).

Emergentnost koherence pa se v kaže v tem, da ima koherentno stanje nove lastnosti, ki jih posamezni deli koherentnega sistema, pa tudi nekoherentno stanje, iz katerega koherenca izhaja, nimajo (Gregorčič, 2010). Nove lastnosti nastanejo zaradi usklajenosti izhodnih stanj posameznih elementov, ki imajo šele kot celota dovolj veliko moč, da omogočajo kolektivno odzivanje sistema na zunanje dejavnike. V klasičnem sistemu sinhronih oscilatorjev, kjer je koherentno stanje posledica zgolj seštevka izhodnih stanj, je

emergenca šibka, saj je koherentno stanje načeloma izpeljivo iz lastnosti posameznih elementov navkljub nelinearnosti njihovih interakcij; v kvantno koherentnem sistemu pa je emergenca močna, saj se lastnosti elementov, ko so ti del koherentnega sistema, izrazito spremenijo in pravzaprav niti ne moremo več govoriti o posameznih elementih kot avtonomnih sestavnih delih sistema. Močna koherenca v tem primeru pomeni, da dobi sistem novo valovno funckijo, ki je ne moremo povzeti s faktorizacijo valovnih funkcij sestavnih delov (Gregorčič, 2010). Ne glede na vrsto emergence pa ima v obeh primerih koherentni sistem prav zaradi novih lastnosti, tj. moči usklajenosti sistema kot celote, lastno vzročno moč in lahko po načelu spuščajoče se vzročnosti določa vedenje svojih sestavnih delov, na primer ojača njihovo stabilnost zaradi robustnosti, ali pa prav zaradi močnih interakcij z zunanjimi sistemi povzroči spremembo njihovega vedenja, na primer razpad koherentnega stanja ali pa prehod v drugo stabilno stanje. Seveda pa koherenten sistem kot entiteta z lastno vzročno močjo vpliva tudi na višjeravenske procese po načelu dvigajoče se vzročnosti.

Te lastnosti pomenijo, da je koherenca značilna lastnost kompleksnih sistemov in torej njeno teoretično preučevanje sodi pod teorijo kompleksnosti (Arenas in sod., 2008). To pa hkrati tudi pomeni, da koherentni pojavi, v kolikor jih preučujemo v bioloških sistemih, spadajo v področje sistemske biologije, ne glede na to ali gre za molekulsko koherenco ali pa za druge biološke ritme z značilnostmi sinhronizacije. Kot biološko koherenco lahko načeloma pojmujemo vse koherentne pojave v bioloških sistemih, ki imajo netrivialno biološko funkcijo. V ožjem pomenu pa biološka koherenca označuje molekulsko koherenco (Gregorčič, 2010).

3.2 APLIKACIJA KONCEPTA MOLEKULSKE KOHERENCE V BIOLOGIJO RAKA

Rak je kompleksna bolezen, za katero je značilna nenormalna celična rast in tkivna organizacija. Kompleksnost raka je v veliki meri posledica dejstva, da je to sistemska bolezen, ki se sočasno razvija na več med seboj prepletenih organizacijskih ravneh – genetski, metabolični, celični, tkivni in celo organizemski – od katerih ima vsaka raven svoje značilnosti in razlagalno moč. Kljub temu da je ena najintenzivneje raziskovanih bolezni, osnovni vzroki za razvoj raka niso pojasnjeni v taki meri, da bi bilo možno njegovo sistematično obvladovanje. Pri tem imamo v mislih zlasti genetiko raka, ki od odkritja prvih onkogenov v retrovirusih (Huebner in Todaro, 1969) velja za prevladujočo, na genskem determinizmu utemeljeno paradigmo, ki pa ni dala dokončnih odgovorov o izvoru te bolezni. Zato tudi ne preseneča navidezni paradoks, da se v zadnjih nekaj letih pojavlja ali pa zgolj obuja vedno več teorij o izvoru raka navkljub dejstvu, da se splošno

razumevanje molekularnih mehanizmov, ki spremljajo njegov razvoj, povečuje. V objavljenih člankih s področja sistemske biologije raka smo analizirali etiologijo raka z različnih zornih kotov ter na različnih organizacijskih ravneh, predvsem pa v smislu vzvodov, ki so ključni za njegovo sistemsko, emergentno naravo in vplivajo na pretok informacij in energije ter s tem na dinamiko biološke organizacije. Koncept molekulske koherence, kot ga pojmujejo zlasti Fröhlichova teorija in teorija t.i. italijanske skupine, neposredno vpliva prav na dinamiko pretoka energije in informacij v bioloških procesih, zato ima lahko izguba koherence lahko določeno vlogo pri razvoju raka, kar je naše osnovno raziskovalno vodilo in izhodišče.

Lahko bi rekli, da razumevanje raka v zadnjih letih dejansko na paradigmatskem razpotju (Baker in sod., 2010). Vse več raziskovalcev je mnenja, da je rak sistemska bolezen, o čemer med drugim pričajo tudi številne tematske izdaje revij, ki se osredotočajo prav na sistemsko biologijo raka (Cell, Science, Seminars in Cancer Biology ter Progress in Biophysics & Molecular Biology, v okviru katere je izšel tudi naš prispevek). Skupni imenovalec vseh pristopov in smeri znotraj sistemske biologije raka je, da rak ni enoznačno z genetskimi mutacijami določena bolezen, pač pa se razvija skozi dinamično množico interakcij med različnimi molekulskimi sistemi znotraj pa tudi med različnimi organizacijskimi ravnmi, ki imajo kompleksen in izrazito variabilen vpliv na fenotip. Tudi v sistemski biologiji raka pa imamo t.i. pragmatično (redukcionistično) smer, ki pojmuje raka še vedno kot načeloma genetsko določeno bolezen, a upošteva kompleksnost signalno-regulatornih in metaboličnih omrežij, ki vodijo v izrazito nelinearno določenost fenotipskih lastnosti od izražanja genov (Kreeger in Lauffenburger, 2010), ter t.i. sistemsko teoretično smer, ki poleg kompleksnosti molekulskih mrež (pa tudi višjih organizacijskih ravni) priznava tudi njihovo lastno vzročno moč oziroma sposobnost organizacijske celovitosti teh ravni na določanje lastnosti svojih sestavnih delov po načelu spuščajoče se oziroma krožne vzročnosti, kjer so vse organizacijske ravni medseboj sodoločujoče (Saetzler in sod., 2011). Tako niti ne moremo več govoriti o kaki privilegirani organizacijski ravni, ki bi imela ekskluzivno vzročno in razlagalno moč, pač pa pravzaprav le o različnih prostorsko-časovnih merilih, pri katerih lahko opazujemo in razlagamo dani sistem (Noble, 2010).

Navkljub temu konceptualnemu premiku rak v splošnem še vedno velja za genetsko determinirano bolezen, katere razvoj bistveno določajo genetske mutacije. Genetske teorije raka, ki jih lahko ločimo na genske in genomske, pojmujejo mutacije kot osnovni materialni vzrok nepovratnih sprememb določenih stopenj specifičnih signalnih in metaboličnih poti, ki napovedljivo določajo fenotip, kot lahko ponazorimo z linearnim molekularnim diagramom (Stratton, 2011; Vogelstein in Kinzler, 2004). Kopičenje

somatskih mutacij postopoma osvobaja celice homeostatskih kontrolnih mehanizmov, kar povzroči klonsko ekspanzijo celic, katerih mutacijski spekter je najbolje prilagojen fiziološkim razmeram oziroma selekcijskim pritiskom, ter postopen pojav osnovnih fenotipskih značilnosti raka[5]. Medtem ko se genske teorije osredotočajo zlasti na točkovne mutacije, ki bodisi aktivirajo ali pa zavirajo izražanje specifičnih tumorskih genov, tj. onkogenov, tumor supresorskih genov in stabilnostnih (ang. caretaker) genov, pa genomske teorije poudarjajo pomen sistemske genomske nestabilnosti in genomskih mutacij, ki na različne načine destabilizirajo genom kot integrativno celoto, s tem pa nespecifično spremenijo izražanje mnogih genov in posledično povzročijo deregulacijo mnogih celičnih procesov (Duesberg in sod., 2005; Heng in sod., 2010; Upender in sod., 2004). Ob tem je pomembno poudariti, da genomska nestabilnost ni le posledica mutiranih stabilnostnih genov (Negrini in sod., 2010), pač pa mnogih, povsem različnih dejavnikov, in lahko odraža splošno patološko stanje oziroma nezmožnost celice za vzdrževanje homeostaze (Baverstock in Karotki, 2011).

V objavljenih člankih smo zavzeli kritično stališče zlasti do genocentričnega pojmovanja raka. Kljub izrazitemu dolgoletnemu prizadevanju namreč konsistentni vzorci genskih mutacij za večino vrst rakov niso znani, kar govori proti njegovi genski določenosti (s potencialno izjemo nekaterih hematoloških tumorjev in nekaterih dednih tumorjev z visoko penetrantnimi prirojenimi mutacijami). Raziskave genomov tumorskih celic, katerih prvotni namen je bil izluščiti prav tovrstne ponovljive vzorce mutacij iz »šuma« mutiranih genov, so v nasprotju s pričakovanji še dodatno potrdile in utrdile spoznanje, da so genske mutacije pri veliki večini kliničnih tumorjev, tudi znotraj iste skupine, izredno heterogene in nespecifične (Bell, 2010; Fox in sod., 2009; Gerlinger in sod., 2012; Wood in sod., 2007). Dodaten argument proti genski določenosti raka pa predstavlja močan pomen tkivne organizacije oziroma tkivnega konteksta na izražanje fenotipskih značilnosti raka in reverzibilnost le-teh (Bissell in Hines, 2011; Bizzarri in sod., 2011; Hochedlinger in sod., 2004; Ingber, 2008; Maffini in sod., 2004; Rubin, 2006; Sonnenschein in Soto, 2011).

V skladu s sistemsko naravo raka smo zagovarjali stališče, da je rak predvsem razvojno-organizacijska motnja, ki ima svoj sistemski vzrok v nespecifični deregulaciji pretoka metabolične energije in torej na fenotipski ravni. Razvojno-organizacijski vidik te predpostavke je konceptualno podprt s teorijo rakastih atraktorjev Sui Huanga in

[5] Hanahan in Weinberg (2000) jih opredelita kot samozadostnost rastnih signalov, izogibanje programirani celični smrti (apoptozi), neomejen celični delitveni potencial, vzdrževana tvorba žilja (angiogeneza), sposobnost vraščanja v okolno tkivo ter sposobnost zasevanja (metastaziranja) v druga tkiva.

sodelavcev (Huang, 2011; Huang in sod., 2009; Huang in Ingber, 2007), vidik pretoka metabolične energije pa s teorijo kompleksnosti in zlasti s konceptom disipativnih sistemov (Nicolis in Prigogine, 1977), v okviru katerega nekateri pojmujejo raka celo kot poseben disipativni sistem (Bizzarri in sod., 2011; Davies in sod., 2011; Hauptmann, 2002; Klimek, 2001). Argumente v prid tej predpostavki smo črpali tako iz genetike kot tudi različnih negenetskih vidikov karcinogeneze: tumorjevega mikrookolja oziroma tkivne organizacije, epigenetike in energijskega metabolizma. Analiza teh vidikov kaže, da je njihova skupna značilnost splošna destabilizacija fenotipa in genotipa, ki je nespecifična in se na različnih ravneh odraža kot izguba funkcionalne tkivne organizacije, globalna in nespecifična deregulacija epigenotipa (epigenoma), sistemska genomska nestabilnost, nespecifična okvara oksidativne fosforilacije, dediferenciacija in izražanje nekaterih značilnosti matičnih celic ter splošno povečanje informacijske entropije (Plankar in sod., 2012; Plankar in sod., 2011).

Tovrstna postopna (samo-)dezorganizacija (Clark, 1995) je načeloma skladna s konceptom daljnosežnega reda, kot ga predvideva molekulska koherenca. Koherenca je namreč predvsem mehanizem prenosa metabolične energije, kar potrjujejo dosedanji dokazi na fotosistemih in drugih molekulskih kompleksih. Zato smo v skladu z emergentno naravo koherence postavili koherenčno hipotezo raka, ki pravi, da v kolikor pride do okvare koherentnega prenosa metabolične enegije na določeni organizacijski ravni, lahko takšna okvara povzroči nespecifično deregulacijo bioloških procesov. Koherenčna hipoteza raka združuje do sedaj v znanstveni literaturi ločeno predpostavljene vloge molekulske koherence pri razvoju raka v enoten konceptualni okvir in jih tu le na kratko povzemamo.

Fröhlich (1978; Hyland, 2009) je predpostavil, da t.i. globalna koherentna elektromagnetna ekscitacija, katere valovna dolžina presega celico in lahko nastane v večjih molekulskih kompleksih z zadostno polarizacijsko gostoto, vzpostavlja privlačne sile med celicami in jih na ta način stabilizira v tkivu. Kadar pa takšna koherentna ekscitacija iz kakršnegakoli razloga preneha obstajati, celice niso več podvržene tkivni stabilizaciji in pričnо izražati svoj naravni delitveni potencial. Ta, sicer precej splošna predpostavka, je vsaj načeloma podprta z nekaterimi eksperimenti, ki potrjujejo, da nekemijska (elektromagnetna) komunikacija med celicami lahko vpliva na njihovo razmnoževanje in morfologijo (Cifra in sod., 2011; Rossi in sod., 2011). Obenem pa je skladna z osnovnima predpostavkama teorije tkivnega organizacijskega polja (ang. tissue organization field theory), po kateri je za razvoj raka najpomembnejša tkivna organizacijska raven in po kateri je razmnoževanje privzeto celično stanje (Rubin, 2006; Sonnenschein in Soto, 2011; Soto in Sonnenschein, 2011).

Pokornýev model (2009; 2011), ki izhaja iz Fröhlichove teorije, predpostavlja obstoj celičnega elektromagnetnega polja z visokim organizacijskim potencialom, ki ga generirajo koherentne oscilacije električnih dipolov v mikrotubulih (Cifra in sod., 2011; Cifra in sod., 2010) pod pogojem, da funcionalni mitohondriji z oksidativno fosforilacijo ustvarjajo dovolj močno statično električno polje, ki je potrebno za vzbujanje koherentnih oscilacij. V kolikor pride do okvare oksidativne fosforilacije, celično koherentno polje upade, posledično pa se zmanjša njen organizacijski potencial. Ta hipoteza je skladna s t.i. bioenergetskim vidikom raka (Ortega in sod., 2009), po katerem ima vsaj 97% pogostih človeških tumorjev okvarjeno oksidativno fosforilacijo. Po drugi strani pa je podprta z eksperimenti, ki posredno ali pa neposredno potrjujejo koherentna elektromagnetna polja v celicah (Cifra in sod., 2011; Grundler in Kaiser, 1992; Hölzel, 2001; Kirson in sod., 2007; Pokorný, 2001) ter z vlogo mikrotubulov oziroma citomatriksa pri organizaciji bioloških procesov (Clegg, 1984; Gardiner in sod., 2011; Ingber, 2003; Jaeken, 2007; Janmey, 1998; Kurakin, 2011; Shepherd, 2006).

Hameroff (2004) je opozoril na problem pravilne ločitve kromatid med mitozo, katerega mehanizem še ni dokončno pojasnjen, in predpostavil kvantno koherentno superpozicijo stanj celotnega delitvenega vretena kot možno razlago. Komunikacijo med kromatidami naj bi omogočali centrioli zaradi njihovih domnevnih lastnosti valovnih vodnikov za vidno in infrardečo svetlobo, kot je poročal Albrecht-Buehler (1992). V kolikor bi prišlo do okvare takega koherentnega stanja celotnega delitvenega vretena, bi lahko prišlo do napačne ločitve kromatid in posledično anevploidije ali drugih oblik genomske nestabilnosti. Razen omenjenih indikacij o s centrioli posredovanemu zaznavanju svetlobe ta hipoteza nima druge eksperimentalne podpore, zato jo obravnavamo kot manj pomembno.

V članku (2.2) smo predpostavili tudi potencialno vlogo koherence za razvoj raka po teoriji kvantne elektrodinamike, ki predvideva pomembno vlogo celične vode pri organizaciji bioloških procesov zaradi koherentne dinamike dipolov vodnih molekul, ki v celicah obdajajo biološke makromolekule ter omogočajo izmenjavo metabolične energije med njimi. Vitiello (2009) je pokazal, da imajo lahko t.i. razširjene koherentne domene gnezdeno (fraktalno) strukturo zaradi širokega spektra frekvenc elektromagnetnega polja, ki ga lahko absorbirajo. Teorija predvideva, da prebitek energije, ki presega t.i. energijsko vrzel, razliko med osnovnim koherentnim in nekoherentnim stanjem, izniči (termalizira) koherentni režim, saj je koherentno stanje osnovno energijsko stanje sistema. Zato smo predpostavili, da ob tovrstni prekoračitvi dotoka metabolične energije pride do postopne termalizacije razširjene koherentne domene s posledično zmanjšanim potencialom za prenos metabolične energije. Kot poseben primer tega mehanizma smo navedli primer

koherentnih plazemskih oscilacij na površini koloidnih kristalov kot modelnih celic, ki povzročijo privlak med njimi (Larsen in Grier, 1997), dokler polarizacijska gostota plazme ostane pod kritičnim pragom. V kolikor pa je ta prag presežen, koherenčni režim izgine in stabilizacijske privlačne sile popustijo. Ta predpostavka je skladna z nekaterimi eksperimenti, ki potrjujejo nasičenje celičnega površinskega naboja pri tumorskih celicah (Dobrzyńska in sod., 2005; Pethig in Kell, 1987).

Potrditev zastavljene hipoteze o raku ima dva pogoja. Če naj ima koherenca kot emergentna lastnost, ki vpliva na dinamiko pretoka energije in informacij, kakršenkoli pomen pri razvoju raka, je nujno, da tudi raka pojmujemo kot emergentno in dinamično lastnost biološke organizacije, ki ni absolutno določena z lastnostmi oziroma informacijami na specifični organizacijski ravni. Sistemski vidik raka, katerega preučevanje poleg genomov, transkriptomov in drugih molekulskih sistemov vključuje tudi tkivno organizacijo, energijski metabolizem ter druge negenetske vidika, potrjuje veljavnost tega pogoja. Drugi pogoj za potrditev hipoteze o raku pa je, da je molekulska koherenca dovolj močan oziroma razširjen mehanizem pretoka metabolične energije, da lahko zaznamuje biološko samoorganizacijo bodisi na tkivni, celični ali metabolični ravni. Ta pogoj je seveda le deloma izpolnjen, saj je funkcionalna vloga koherenca do sedaj bila dokazana samo na nekaj molekulskih sistemih. Vendar pa trenutno niso znane omejitve, zaradi katerih njena vloga ne bi mogla biti potrjena tudi na mnogih drugih molekulskih in supramolekulskih sistemih, saj se po svoji kemijski zgradbi in biofizikalnih lastnostih ne razlikujejo od dokazano koherentnih sistemov. Glede na omenjene ugotovitve sklepamo, da ima hipoteza o raku močno teoretično podporo, a je glede na trenutno poznavanje molekulske koherence ne moremo dokončno potrditi. Pokazali smo, da je umestitev molekulske koherence v etiologijo raka konceptualno možna, s čemer smo jo v luči obeh prispevkov pravzaprav šele znanstveno utemeljili. Vsekakor pa bodo šele nadaljnje raziskave s področja koherentnega prenosa metabolične energije pokazale jasnejšo sliko o splošni razširjenosti koherence v bioloških sistemih, ki bodo dale tudi odgovor o njeni domnevni vlogi pri razvoju raka.

3.3 KOHERENCA KOT ORGANIZACIJSKI PRINCIP KOGNICIJE

Kognicija je skupen pojmovni okvir za višje duševne procese kot so zaznava in vezava čutilnih dražljajev, pozornost, spomin, zavest, odločanje in predvidevanje, pa tudi emocionalna stanja, in zajema kortikalne in subkortikalne predele centralnega živčnega sistema (Pessoa). Ena temeljnih dinamičnih značilnosti kortikalnih in subkortikalnih predelov možganov so periodične spremembe jakosti lokalnega električnega polja, ki so

posledica sinhronizacije ritmičnih nihanj membranskega potenciala med mnogimi nevroni in spadajo med najznačilnejše fiziološke ritme (Buzsáki in Draguhn, 2004). Koherenca nevronskih oscilacij ali nevronska sinhronizacija je postala osrednje raziskovalno področje sistemske nevroznanosti[6] v začetku devetdesetih let, ko so Singer, Gray, Eckhorn in drugi eksperimentalno podprli hipotezo, da sinhronizacija v gama frekvenčnem področju omogoča vezavo posameznih lastnosti vizualnega dražljaja v enoten kognitivni konstrukt[7] (Fries, 2009). Danes so na razpolago številni dokazi o povezavah nevronske sinhronizacije s praktično vsemi kognitivnimi funkcijami, vključno z zavestjo, pa tudi o njeni funkcionalni vlogi pri lokalni in globalni komunikaciji med nevroni in sinaptični plastičnosti, zato jo mnogi raziskovalci pojmujejo za enega temeljnih mehanizmov informacijskega procesiranja v možganih (Bartos in sod., 2007; Fell in Axmacher, 2011; Fries, 2009; Fries in sod., 2007; Jensen in sod., 2007; Senkowski in sod., 2008; Singer, 2009; Singer in Gray, 1995; Uhlhaas in sod., 2009; Wang, 2010). Po drugi raziskovalni liniji pa mnogi teoretični modeli molekulske dinamike zlasti na citoskeletnih filamentih predvidevajo obstoj kolektivnih vzbujenih stanj z značilnostmi koherence, ki lahko omogočajo povsem nove načine prenosa in procesiranja informacij v nevronih (Cifra in sod., 2010; Jibu in sod., 1994; Mershin in sod., 2006; Priel in sod., 2006; Priel in sod., 2010; Tuszyński in sod., 1997; Woolf in sod., 2009). Glede na to da so se pred kratkim pojavili tudi prvi eksperimentali dokazi o obstoju tovrstnih kolektivnih vzbujenih stanj (Bandyopadhyay, 2010; Sahu in sod., 2013), se upravičeno zastavlja vprašanje, ali so koherentni procesi na obeh organizacijskih ravneh lahko med seboj tudi funkcionalno povezani, česar potrditev bi obenem pomenila tudi potrditev zastavljene hipoteze o kogniciji.

V objavljenem članku s področja sistemske nevroznanosti smo predstavili splošen pomen nevronske koherence za kognicijo. Mnogi raziskovalci so mnenja, da prav časovni odnosi med aktivnostjo nevronov in nevronskih skupnosti, ali natančneje njihove ritmične (oscilatorne) značilnosti, učinkovito dopolnjujejo manj prožno in počasnejše informacijsko procesiranje na osnovi stopnje proženja akcijskih potencialov in hierarhije nevronov (Senkowski in sod., 2008; Singer, 2009; Uhlhaas in sod., 2009). Podali smo osnovni pregled splošnih značilnosti nevronskih oscilacij, mehanizmov njihovega nastanka in dejavnikov njihove modulacije. Povzeli smo mnoge raziskave, ki pričajo o sistematični korelaciji različnih (frekvenčnih, faznih, amplitudnih) parametrov in meritvenih kazalcev (odvisno od uporabljenih metod) nevronskih oscilacij z vsemi osnovnimi kognitivnimi funkcijami: z vezavo čutilnih dražljajev (znotraj določene in med različnimi čutilnimi

[6] Sistemska nevroznanost po analogiji s sistemsko biologijo uporablja konceptualna in metodološka orodja teorije kompleksnosti na področju nevroznanosti.
[7] Hipoteza je v angleščini znana kot »binding by synchrony« in je ena osrednjih nevroznanstvenih hipotez.

modalnostmi), senzorimotorično integracijo, pozornostjo, kratkoročnim in dolgoročnim spominom, zavestjo, odločanjem, pa tudi z različnimi nevrološkimi motnjami. Da koherenca nevronskih oscilacij nima zgolj korelativne funkcije – kot epifenomen usklajene aktivnosti nevronov, povzročene z zunanjimi dražljaji – potrjujejo dokazi o njeni funkcionalni vlogi pri informacijskem procesiranju: pri faznem kodiranju, npr. z mehanizmom fazne precesije (O'Keefe in Recce, 1993); pri prenosu informacij (komunikaciji) med nevroni, npr. z mehanizmi koincidenčne detekcije (Ariav in sod., 2003; Azouz in Gray, 2003); ter pri uravnavanju sinaptične moči, ki ga podpirajo raziskave sinaptične plastičnosti v časovni odvisnosti depolarizacije med pred- in postsinaptičnimi nevroni (ang. spike timing-dependent synaptic plasticity) (Wespatat in sod., 2004).

Zaradi splošne prisotnosti nevronske sinhronizacije pri kodiranju in procesiranju kognitivnih funkcij ter njihovega prepletanja v različnih predelih možganov se zastavlja vprašanje, kako so različne kognitivne funkcije ločene med seboj, oziroma ali so nevronske oscilacije že same po sebi lahko elektrofiziološki korelat kognicije. Zdi se, da oscilacije bolj kot kognitivne procese kot take predstavljajo predvsem referenčni časovni okvir za procesiranje informacij (Axmacher in sod., 2006; Fell in Axmacher, 2011). Po drugi strani pa se zastavlja problem njihove dinamične modulacije, ki mora biti izredno hitra, da zadosti zahtevnim vedenjskim potrebam. Realistični modeli sinhronizacije višjih frekvenc, ki so najbolj relevantne za obdelavo čutilnih dražljajev, sicer lahko pojasnijo robustnost oscilacij kljub heterogenosti vhodnih stanj (Bartos in sod., 2007; Vida in sod., 2006), ne razložijo pa izredno hitrih sprememb oscilatorne dinamike, npr. prehodov med koherentnim in nekoherentnim stanjem (Uhlhaas in sod., 2009), ki se razen tega lahko raztezajo preko več velikostnih razredov v času in prostoru (Freeman, 2003). Tudi t.i. šum ozadja, ki izhaja iz sinaptičnega šuma in stohastičnega proženja akcijskih potencialov ter v splošnem povečuje odzivnost in prožnost nevronskih mrež (Haider in McCormick, 2009), po drugi strani zmanjšuje konsistenco faznih odnosov in posledično stabilnost kodiranja in prenašanja informacij zlasti pri komunikaciji dolgega dosega (Wang, 2010). Kaže se torej, da je eden osnovnih problemov sistemske nevroznanosti, kako uskladiti kompleksno ravnotežje med oscilatorno robustnostjo, potrebno za stabilnost informacijskega procesiranja na eni ter prožnostjo funkcionalne povezljivosti nevronskih mrež na drugi strani.

Kot možna rešitev tega problema se ponujajo pristopi, ki obravnavajo dinamiko možganske aktivnosti na bolj sistemski oziroma fizikalen način. Več raziskovalcev poroča o stabilnih vzorcih koherentne oscilatorne dinamike spontane ali z zunanjimi dražljaji pogojene aktivnosti nevronskih skupnosti, ki ima značilnosti samoorganizirane kritičnosti in se torej razteza preko mnogih časovno-prostorskih skal ter lahko zajema tudi

makroskopske predele možganske skorje (Breakspear in sod., 2004; Freeman, 2005; Petermann in sod., 2009; Stam in De Bruin, 2004; Thatcher in sod., 2009; Van De Ville in sod., 2010). Po mnenju avtorjev prav tovrstni, izrazito dinamični vzorci stabilne aktivnosti, predstavljajo osnovne enote višjeravenskega informacijskega procesiranja. Spontana aktivnost ozadja pri tem zagotavlja temeljno, notranje določeno (endogeno) možgansko dinamiko, ki jo zunanji dražljaji le šibko modulirajo (Fiser in sod., 2004). Walter Freeman, eden najprodornejših raziskovalcev s področja sistemske nevroznanosti, tovrstna – v njegovih poskusih s pogojnimi dražljaji povzročena in merjena z metodo elektrokortikografije – stabilna stanja imenuje valovni paketi, saj imajo lastno nosilno frekvenco z značilno fazno in amplidudno modulacijo, ki je stabilna skozi celotno trajanje valovnega paketa (Freeman, 2003). Osnovna značilnost valovnih paketov je, da se oblikujejo iz predhodno stohastične aktivnosti ozadja izredno hitro in jih ni mogoče enostavno pojasniti z modeli sinaptičnega prenosa, zato jih najustrezneje opišemo fizikalno kot fazne prehode (Freeman in sod., 2003; Freeman in Vitiello, 2006). Pogojnemu dražljaju navadno v sosledju sledi več zaporednih valovnih paketov s specifičnimi nosilnimi frekvencami in njihovimi modulacijami, pri čemer se red med zaporednimi valovnimi paketi vselej popolnoma izniči in se kratkotrajno obnovi stohastična (nekoherentna) aktivnost, ki ima izrazito manjšo analitično amplitudo in spominja na navzdol obrnjen vrh, t.i. ničelni potencial (ang. null spike), ki mu sledi ponovna nenadna obnovitev reda v sledečem valovnem paketu.

Za fizikalno razlago dinamike valovnih paketov Freeman in Vitiello (2006; 2008; 2009) razvijata teorijo, ki uporablja matematično formalizacijo kvantne teorije polja in tovrstne fazne prehode pojmuje kot spontani zlom rotacijske simetrije, katere predpostavljeni nosilci so električni dipoli v polarizacijsko gostem mediju. Zlom simetrije pomeni kondenzacijo dipolnih ekscitacij iz neurejenega (izotropnega) stanja v koherentno (anizotropno) stanje, ki zaznamuje fazni prehod nevronske aktivnosti iz mikroskopske ravni lokalne, s čutilnimi dražljaji vzbujene nevronske skupnosti v kolektivno polje makroskopske možganske dinamike, kot ga opisuje valovni paket. Teorija predvideva, da prehod nevronske aktivnosti med organizacijskima ravnema izkorišča zlom simetrije v času ničelnega potenciala, ki lokalni skupnosti vsiljuje makroskopski red in sproži prehod aktivnosti skorje v območje privlaka stabilnega stanja (atraktorja). Koherentna kondenzacija torej po tej teoriji deluje kot nekakšen daljnosežni usmerjevalnik funkcionalne povezljivosti nevronov, ki izkorišča visoko občutljivost spontane možganske aktivnosti na zunanje dražljaje in narekuje prehode koherentnih nevronskih oscilacij med mnoštvom stabilnih stanj. Po mnenju avtorjev je ta proces, gledano v celoti od transdukcije čutilnih dražljajev do makroskopskega valovnega paketa, osnovni mehanizem, s katerim možgani osmišljajo zunanji svet.

Poleg omenjene razlage dinamike makroskopskih vzorcev koherentnih nevronskih oscilacij je teorija Freemana in Vitiella trenutno edina, ki celovito združuje princip koherence kot organizacijskega principa na nevronski in molekulski ravni v skupen konceptualni okvir. Pomanjkljivost teorije pa je, da je preveč splošna, saj implicitno predpostavlja funkcionalno povezanost obeh ravni koherentne dinamike, ne ponuja pa konkretnih odgovorov o naravi te povezave. Z ozirom na dejstvo, da so nevronske oscilacije sklopljene in sinhronizirane preko oscilacij membranskega potenciala (Bartos in sod., 2007; Vida in sod., 2006), je jasno, da morajo domnevne koherentne oscilacije električnih dipolov imeti modulatorni učinek na membranski potencial nevronov, v kolikor imajo kakršnokoli vlogo pri usmerjanju makroskopske dinamike nevronskih oscilacij; dinamika valovnih paketov pa kaže, da mora biti ta učinek daljnosežen in verjetno tudi vsaj deloma neodvisen od sinaptičnega prenosa.

Predpostavili smo, da bi tovrstno interakcijo znotraj nevrona lahko posredoval intranevronski matriks[8], saj tvori električno aktivno omrežje, ki se lahko odziva na elektromagnetna polja in prevaja električne signale (Cantiello in sod., 1991; Funk in sod., 2009; Gartzke in Lange, 2002; Lin in Cantiello, 1993; Priel in Tuszyński, 2008; Priel in sod., 2010; Tuszyński in sod., 2004; Woolf in sod., 2009). Oscilatorna dinamika ionov (t.i. električna signalizacija), ki so elektrostatično vezani na površino aktinskih filamentov in mikrotubulov zaradi njihovega negativnega naboja, lahko načeloma modulira napetostno odvisne ionske kanale in s tem membranski potencial (Priel in sod., 2010), podobno kot pri dokazanem vplivu nihajočega električnega polja na aktivnost membranskih ionskih črpalk v poskusih Tsongaja in sodelavcev (1992). Predpostavljeni nosilci koherentnih dipolnih oscilacij so citoskeletni filamenti, katerih teoretično modeliranje molekulske dinamike zlasti na mikrotubulih nakazuje, da lahko generirajo koherentne oscilacije in posledično oddajajo elektromagnetno polje širokega frekvenčnega spektra v skladu s Fröhlichovo teorijo (Cifra in sod., 2010). To potrjujejo tudi nedavne meritve balistične prevodnosti elektronov pri fiziološki temperaturi kot neposreden dokaz koherentnega prenosa energije vzdolž filamenta (Bandyopadhyay, 2010; 2011; Sahu in sod., 2013). Vsekakor pa bodo potrebne nadaljne zlasti kvantitativne raziskave, ki bodo dale neposreden odgovor, v kolikšni meri lahko tovrstna endogena elektromagnetna polja vplivajo na vzdražnost nevronov in njihov sinhronizacijski potencial.

[8] Omrežje citoskeletnih filamentov in povezovalnih beljakovin, ki je pri nevronih še posebej izrazito in povezuje ionske kanale oziroma sprejemnike živčnih prenašalcev ter sinapse v nevronu v enovit funkcionalen sistem (Woolf in sod., 2009).

Med nevroni pa bi se predpostavljeni zlom rotacijske simetrije lahko širil preko zunajceličnega matriksa, katerega osnovne komponente, proteoglikani, so tako kot citoskeletni filamenti negativno nabiti polielektroliti, ki zaradi elektrostatičnega privlaka vežejo katione (Brückner in sod., 1993; Härtig in sod., 1999), zato bi lahko igrali podobno vlogo prenosa električnih signalov kot citoskeletni filamenti. V skladu s to domnevo je nedavna potrditev ephaptičnih (tj. vzbujenih s šibkim elektromagnetnim poljem, ki ne presega jakosti fizioloških polj) učinkov na čas proženja akcijskega potenciala posameznih nevronov (Anastassiou in sod., 2011) ter na spremembe oscilatorne dinamike nevronskih mrež (Deans in sod., 2007; Fröhlich in McCormick, 2010; Ozen in sod., 2010). Te raziskave potrjujejo hipotezo, da nesinaptična komunikacija lahko vpliva na makroskopsko dinamiko nevronskih skupnosti. Po drugi strani pa nekatere raziskave kažejo, da izguba strukturne integritete perinevronskih mrež – mrežastih diferenciacij zunajceličnega matriksa, ki obdajajo nekatere vrste nevronov – zmanjša aktivnost določenih napetostno odvisnih ionskih kanalov (Kochlamazashvili in sod., 2010) ter vzdražnost košarastih internevronov (Dityatev in sod., 2007), ki pomembno sodelujejo pri nevronski sinhronizaciji višjih frekvenc, kar nakazuje na možno specifično vlogo zunajceličnega matriksa tudi pri modulaciji nevronske koherence (Dityatev in sod., 2007; Gurevicius in sod., 2009). Gledano v celoti ta opažanja nakazujejo, da zunajcelični matriks morda igra pomembnejšo vlogo pri modulaciji nevronske aktivnosti, kot je bilo predpostavljeno do sedaj, zato si vsekakor zasluži večjo pozornost raziskovalcev (Dityatev in Rusakov, 2011); z ozirom na zelo verjetno strukturno povezanost z intranevronskim matriksom pa se zastavlja tudi vprašanje, ali zunaj- in znotrajcelični matriks lahko tvorita enovit funkcionalni sistem, ki vpliva na mednevronsko komunikacijo.

Z našim prispevkom smo hipotezi o kogniciji dali močno konceptualno podporo. Kljub temu da trenutno še ni eksperimentov, ki bi neposredno dokazovali funkcionalno povezavo koherentne molekulske dinamike in koherentnih nevronskih oscilacij, pa obstaja mnogo posrednih znamenj in okoliščin, ki so skladni s hipotezo. V tem smislu smo hipotezo s sintetičnim pristopom, ki združuje nevrofiziologijo nevronskih oscilacij z uveljavljajočimi se biofizikalnimi modeli prenosa in procesiranja informacij v nevronih, umestili v nevroznanstveni kontekst. Z ozirom na temeljno vlogo nevronske koherence pri organizaciji kognitivnih procesov in predpostavljeno vlogo molekulske koherence pri organizaciji nižjeravenskih procesov, sklepamo, v kolikor bo ta vloga seveda tudi neposredno dokazana, da je princip koherence lahko eden najbolj splošnih organizacijskih principov kognicije.

3.4 SKLEPI

V tem razdelku najprej povzemamo izvirne novosti predloženih člankov, ki po našem védenju doslej še niso bile objavljene v znanstveni literaturi, v nadaljevanju pa skupne sklepe doktorske disertacije.

Članek On the origin of cancer: can we ignore coherence? (razdelek 2.1):

- Prispeva izvirno opredelitev raka kot nespecifično progresivno destabilizacijo mnogih interaktivnih omrežij v okviru celičnih in medceličnih bioloških procesov kot skupni imenovalec genetike in epigenetike raka ter teorije rakastih atraktorjev.

- Na novo definira biološko koherenco kot sinhrono dinamiko sklopljenih elementov v biološkem sistemu, ki je lahko kvantnega ali elektromagnetnega izvora in ima funkcionalen (netrivialen) biološki pomen.

- Na novo izpostavlja možnost vzročne povezave med okrnjeno koherentno molekulsko dinamiko in razvojem raka, po kateri zunanje motnje v obliki mnogih nespecifičnih okoljskih in notranjih dejavnikov ojačajo vzajemno povratno zvezo med energijskim in informacijskim tokom ter okrnjeno koherentno dinamiko znotraj celice ali med celicami, kar v zadostni meri lahko povzroči splošno destabilizacijo mnogih molekulskih signalnih poti, genskih regulatornih mrež in genoma.

Članek The role of coherence in a systems view of cancer development (razdelek 2.2):

- Prispeva izvirno sistematično razvrstitev teorij in raziskovalnih pogledov o izvoru in razvoju raka. Osnovna delitev pogledov na etiologijo raka je na genetske in negenetske; genetski se delijo na genske in genomske, negenetski pa na integriteto tkivne organizacije, energijski metabolizem raka, epigenetiko raka, sistemsko-teoretični vidik oz. teorijo rakastih atraktorjev in termodinamični oz. entropični vidik.

- Opredeli sistemski vzrok raka kot motnjo v pretoku energije in informacij skozi organizem, ki destabilizira samoorganizacijski potencial celic in tkiv ter se manifestira v genetskih in negenetskih vidikih razvoja raka.

- Na novo opredeli koncept biološke (molekulske *s.str.*) koherence kot pomemben in potencialno splošno razširjen način pretoka energije in informacij v bioloških sistemih,

ki kot tak predstavlja pomemben dejavnik biološke samoorganizacije, skladen s teorijo disipativnih sistemov.

- Izrecno opredeli koherenčno hipotezo o izvoru raka, ki pravi, da v kolikor pride do okrnjene ali nepravilne koherentne molekulske dinamike na določeni organizacijski ravni, lahko takšna okvara zmanjša biološki samoorganizacijski potencial; tako zastavljena hipoteza združuje do sedaj predpostavljene fizikalne modele, ki povezujejo razvoj raka z okrnjeno koherenco v skupen konceptualni okvir biološke samoorganizacije.

- Prispeva izviren fizikalni model o izvoru raka, ki temelji na aplikaciji teorije kvantne elektrodinamike na vodo in pravi, da ob prekoračitvi dotoka metabolične energije v razširjeno koherentno domeno pride do njene postopne termalizacije z zmanjšanim potencialom za prenos metabolične energije in posledično samoorganizacijskim potencialom. Kot primer tega mehanizma je naveden primer koherentnih plazemskih oscilacij na površini koloidnih kristalov kot modelnih celic.

Članek The principle of coherence in multi-level brain information processing (razdelek 2.3):

- Kot celota predstavlja in utemeljuje izvirno hipotezo, da koherenca predstavlja pomembno načelo organizacije informacijskega procesiranja v možganih na več organizacijskih ravneh.

- Vsebuje na osnovi sistematičnega pregleda literature s področja nevronskih oscilacij izpeljano dognanje, da smiselno informacijsko procesiranje v možganih zahteva uskladitev kompleksnega ravnovesja med oscilatorno robustnostjo na eni strani, ki je potrebna za konsistentno kodiranje informacij in komunikacijo dolgega dosega, ter na drugi strani prožnostjo funkcionalne povezljivosti nevronov, ki je potrebna za hitre modulacije nevronskih oscilacij; zelo verjetno je, da takšno uskladitev omogoča dinamična višjeravenska organizacija možganske aktivnosti.

- Vsebuje izvirno kritiko teorij, ki za razlago delovanja možgansko-duševnega kompleksa uporabljajo spoznanja kvantne fizike. Te teorije morajo za smiselno integracijo z nevrofiziološkimi dognanji razložiti zlasti in predvsem mehanizem interakcije kvantnih procesov z membranskim potencialom, obenem pa morajo biti njihove napovedi tudi skladne z do sedaj dobro raziskanimi in utemeljenimi mehanizmi nevronskih oscilacij ter njihovimi modulacijami.

- V kontekstu omenjene kritike ter na osnovi pregleda literature izpostavlja možnost, da elektrostatično vezani ioni v kombinaciji s koherentnimi elektromagnetnimi

oscilacijami filamentov intranevronskega in zunajceličnega matriksa lahko prispevajo k modulaciji membranskega potenciala nevronov in posledično vplivajo na dinamiko nevronskih oscilacij. Posebej je izpostavljena morebitna vloga zunajceličnega matriksa pri takšni modulaciji, ki je bila do sedaj v biofizikalnih modelih premalo upoštevana.

Glede na analizo zastavljenih hipotez in problematike, na katere se nanašajo, lahko sklenemo naslednje sklepne ugotovitve doktorskega dela:

- Sinhronizacija je oblika samoorganizacije, saj se pojavi spontano ob določenih pogojih in povzroči večjo urejenost sistema ali koherenco.
- Koherenca je konvergentna lastnost, saj ni odvisna od specifične fizikalno-kemijske zgradbe sistema, iz katerega vznika.
- Koherenca je emergentna lastnost kompleksnih sistemov, saj ima nove značilnosti, ki niso zvedljive na lastnosti posameznih elementov in dajejo koherentnemu sistemu lastno vzročno moč. Kot emergentna lastnost je koherenca predmet preučevanja v sistemski biologiji in v teoriji kompleksnih sistemov, v kolikor se nanaša na biološke sisteme.
- Biološki pomen koherence je večja učinkovitost in organiziranost bioloških procesov.
- Molekulska koherenca v bioloških sistemih (biološka koherenca v ožjem pomenu) ima dokazan funkcionalni pomen pri organizaciji nekaterih molekulskih procesov kot dejavnik, ki usmerja pretok energije, ki se porablja za biološke procese.
- Rak je sistemska bolezen, za katero je značilna nespecifična deregulacija bioloških procesov na mnogih organizacijskih ravneh.
- Konceptualna umestitev molekulske koherence v biologijo raka je možna in smiselna.
- Koherenčna hipoteza raka pravi, da v kolikor pride do okvare koherentnega prenosa metabolične enegije na določeni organizacijski ravni, lahko takšna okvara povzroči nespecifično deregulacijo bioloških procesov. Koherenčna hipoteza združuje do sedaj v znanstveni literaturi ločeno predpostavljene povezave med okrnjeno biološko koherenco in razvojem raka.
- Koherenca nevronskih oscilacij je eden temeljnih mehanizmov informacijskega procesiranja v možganih, saj korelira z vsemi osnovnimi kognitivnimi funkcijami in

ima funkcionalno vlogo pri kodiranju informacij, mednevronski komunikaciji in sinaptični plastičnosti.

- Intranevronski matriks strukturno povezuje sinapse v nevronih, sodeluje pri signalizaciji živčnih prenašalcev in podpira visoko kooperativne načine prenosa informacij, ki lahko prispevajo k modulaciji nevronske aktivnosti.

- Koherenca lahko predstavlja enega temeljnih organizacijskih principov možganskega informacijskega procesiranja, kjer se koherenca nevronskih oscilacij in molekulska koherenca funkcionalno dopolnjujeta.

4 POVZETEK (SUMMARY)

4.1 POVZETEK

Samoorganizacija je ena temeljnih značilnosti organizacije bioloških sistemov in predmet preučevanja teorije kompleksnosti. Sinhronizacija je vrsta samoorganizacije in pomeni fazno in frekvenčno uskladitev notranjih ritmov oscilirajočih elementov. Koherenca (skladnost, ubranost) kot emergentna lastnost sinhronizacije v snovnih sistemih omogoča večji pretok energije skozi sistem, komunikacijo med različnimi sistemi in informacijsko kodiranje.

Biološke ritme z značilnostmi koherence najdemo na vseh nivojih biološke organizacije. Med najbolj znanimi so na primer metabolični cikli pri kvasovkah, cirkadiani ritmi, koherentne nevronske oscilacije, pa tudi različne vrste usklajenega delovanja med različnimi organizmi. V bioloških znanostih pa se vse bolj uveljavlja tudi koherenca molekulske dinamike, saj je bilo nedavno dokazano, da usmerja pretok energije v nekaterih fotosintetskih in čutilnih sistemih. Biološki pomen molekulske koherence je teoretično napovedal Herbert Fröhlich leta 1968. Njegova teorija koherentnih ekscitacij je vplivala na mnoge fizike, ki so razvijali lastne modele koherentnega prenosa metabolične energije v različnih molekulskih sistemih. Kljub teoretičnemu in eksperimentalnemu napredku pa še ni splošno sprejete fizikalne teorije in prav tako ni znano, kakšen je splošen obseg in pomen molekulske koherence za organizme.

V delu smo se osredotočali predvsem na biološki pomen molekulske koherence kot teoretičnega koncepta, ki omogoča učinkovit prenos metabolične energije in organizacijo bioloških procesov. V ta namen smo analizirali, prvič, ali lahko molekulsko koherenco umestimo v biologijo raka kot dejavnik, ki vpliva na njegov razvoj; in drugič, ali lahko molekulska koherenca funkcionalno dopolnjuje koherenco nevronskih oscilacij in na ta način prispeva k informacijskemu procesiranju v možganih.

Pokazali smo, da lahko koncept molekulske koherence umestimo v sistemsko biologijo raka, saj je rak bolezen, ki se sočasno razvija na mnogih, med seboj sodoločujočih se organizacijskih ravneh. Sistemski vidik raka ni skladen s klasično doktrino, ki pravi, da so mutacije specifičnih genov osnovni vzrok za njegov razvoj; kljub izrazitim prizadevanjem namreč niso poznani značilni in konsistentni vzorci genskih mutacij, na podlagi katerih bi

bilo moč diagnosticirati pa tudi zdraviti večino tumorjev. Različni negenetski vidiki raka kažejo, da je ena njegovih najbolj splošnih značilnosti nespecifična destabilizacija fenotipa in genotipa na mnogih organizacijskih ravneh, ki se kaže kot izguba funkcionalne tkivne organizacije, globalna in nespecifična deregulacija epigenoma, sistemska genomska nestabilnost, nespecifična deregulacija oksidativne fosforilacije, dediferenciacija in izražanje nekaterih značilnosti matičnih celic ter splošno povečanje informacijske entropije. Tovrstna (samo-)dezorganizacija je skladna s pojmovanjem raka kot sistemske organizacijske motnje ter s konceptom molekulske koeherence kot načinom prenosa metabolične energije. Koherenčna hipoteza raka pravi, da v kolikor pride do okvare koherentnega prenosa metabolične enegije na določeni organizacijski ravni, lahko takšna okvara povzroči nespecifično deregulacijo bioloških procesov. Hipoteza pod skupnim teoretičnim okvirom združuje do sedaj v znanstveni literaturi predpostavljene vloge molekulske koherence pri razvoju raka; odgovor nanjo pa lahko dajo šele podrobne eksperimentalne raziskave molekulske koherence, ki bodo dokončno pokazale, kakšen je njen splošen pomen za biološko samoorganizacijo.

Na področju kognitivne nevroznanosti smo podali celovit pregled koncepta koherence kot organizacijskega principa pri modulaciji nevronskih oscilacij. Pokazali smo, da koherentne oscilacije nevronov korelirajo z vsemi osnovnimi kognitivnimi funkcijami: percepcijo čutilnih dražljajev, pozornostjo, spominom, zavestjo in odločanjem. Poleg korelativne vloge ima nevronska sinhronizacija funkcionalen pomen pri informacijskem kodiranju, mednevronski komunikaciji in uravnavanju sinaptične plastičnosti. Kljub temu da mnogi nevrologi smatrajo nevronsko koherenco kot enega temeljnih načinov informacijskega procesiranja v možganih, pa narava nekaterih izjemno hitrih časovno-prostorskih modulacij makroskopskih razsežnosti, ni dokončno pojasnjena. Zato nekateri raziskovalci napovedujejo obstoj molekulskih interakcij dolgega dosega, ki jih domnevno posredujejo koherentne oscilacije molekulskih dipolov in imajo vlogo pri usmerjanju nevronske povezljivosti. Vse več raziskav kaže na intranevronski matriks kot nosilca tovrstnih interakcij. Intranevronski matriks strukturno povezuje nevronske sinapse in sodeluje pri signalizaciji živčnih prenašalcev, konsolidaciji spomina in t.i. električni signalizaciji. Teoretično modeliranje molekulske dinamike nakazuje, da lahko mikrotubuli generirajo koherentne ekscitacije električnih dipolov, kar je v skladu z nedavnimi meritvami koherentnega prenosa elektronov dolge razdalje vzdolž filamentov. Nadaljne raziskave bodo lahko dale jasnejše odgovore, ali lahko tovrstni mehanizmi interakcij dolgega dosega dejansko modulirajo membranski potencial in na ta način funkcionalno dopolnjujejo koherentne nevronske oscilacije ter prispevajo k informacijskemu procesiranju v možganih.

4.2 SUMMARY

Self-organisation is a fundamental charasteristic of biological organisation and it is the subject of complexity theory. Synchronisation is a form of self-organisation and referes to phase and frequency coupling of oscillating units. Coherence is an emergent property of synchronisation in material systems, which maximises energy flow through the system, as well as enables information coding and communication between different oscillating systems.

Coherent biological rhythms are found at all basic levels of biological organisation. Some of the most typical biological rhythms include metabolic cycles in yeast, circadian rhythms, coherent neuronal oscillations, and also synchronous behaviour among different organisms. Recently, however, coherence of molecular dynamics was also confirmed to have a biological function by guiding the flow of metabolic energy in certain photosynthetic and sensory systems. Biological meaning of molecular coherence was already predicted by Herbert Fröhlich in 1968. Fröhlich's theory of coherent excitations has influenced many physicists who developed various models predicting coherent transfer of metabolic energy in different molecular systems. Despite the recent theoretical and experimental breakthrough, however, there is currently no general consensus regarding the underlying physics of coherence, and neither is it clear to what extent does this phenomenon generally apply in organisms.

In the present work we have focussed at the biological meaning of molecular coherence as a theoretical concept allowing efficient transfer of metabolic energy in therefore biological organisation. We have analysed whether the concept of molecular coherence could be applied to cancer biology as an active factor contributing to cancer development; and whether the concept of molecular coherence could functionally complement neuronal synchronisation, thus contributing to brain information processing.

We have shown that molecular coherence could be conceptually applied to systems biology of cancer that consideres cancer as a systems disease developing simultaneously at multiple organisational levels. The systems view of cancer development is not consistent with the current doctrine, which ascribes the primary cause of cancer to mutations at specific genes. Despite intensive efforts, no consistent mutational patterns definitive of specific tumours were found. Various nongenetic aspects of cancer indicate that one of the most general charasteristics of cancer development is nonspecific deregulation of fenotypic and genotypic traits, manifesting as the loss of functional tissue organisation, global and

unspecific epigenetic deregulation, systemic genomic instability, nonspecific malfunction of oxidative phosphorylation, dediferentiation and manifestation of stem cell properties, and a general increase of informational entropy. Such (self-)disorganisation is consistent with cancer being a systems organisational disorder, as well as with the concept of molecular coherence as a means of metabolic energy flow. The coherence hypothesis of cancer predicts that a dysfunctional coherent dynamics at any organisational level can lead to unspecific deregulation of biological processes. The coherence hypothesis unites under a common conceptional framework hypotheses introduced so far in the scientific literature that predict specific roles of the loss of coherence contributing to cancer initiation. However, careful experimental investigations shall provide a final answer to this hypothesis.

In the field of systems neuroscience, we reviewed the concept of coherence in modulating neuronal oscillatory activity. We showed that coherent neuronal oscillations correlate with all basic cognitive functions: sensory perception, attention, memory, consciousness, and decision making. In addition to their correlative role, neuronal synchronisation participates in information encoding and decoding, it guides communication between neuronal assemblies, and it modulates neuronal plasticity. Despite being acknowledged by many neurologists as one of the fundamental mechanisms of information processing in the brain, it is currently not clear how the very transient large-scale spatio-temporal modulations of synchronous neuronal firing could reconcile with the well-established synaptic mechanisms. Some researchers propose that long-range molecular interactions mediated by coherent electric dipole oscillations may have a role in guiding functional neuronal connectivity. Research indicates that the intraneuronal matrix may act as a carrier of such long-range interactions. Intraneuronal matrix structurally connects synapses within neurons as well as mediates neurotransmission, memory consolidation, and electric signalling. Theoretical modelling of molecular dynamics indicates that the microtubules may can generate coherent electric dipole oscillations, consistently with the recent measurements of long-range coherent transfer of electrons along the filaments. Further experiments shall reveal whether such modes of long-range interactions may indeed modulate the membrane potential, hence complementing coherent neuronal oscillations and contributing to information processing in the brain.

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ZAHVALA

Zahvaljujem se vsem soavtorjem člankov, ki so s svojimi prispevki sooblikovali doktorsko delo; posebej se zahvaljujem mentorju Igorju Jermanu, ki mi je omogočil svobodo raziskovanja. Zahvaljujem se vsem bivšim sodelavcem Inštituta Bion za inspirativno sodelovanje. In hvala, Petra, za vse ostalo.

Izdelavo doktorske disertacije je delno financirala Evropska unija iz Evropskega socialnega sklada.