Available online at www.sciencedirect.com

ScienceDirect

Physics of Life Reviews 24 (2018) 32–36

PHYSICS of LIFE reviews

www.elsevier.com/locate/plrev

Comment

Embodying Markov blankets
Comment on "Answering Schrödinger's question: A free-energy formulation" by Maxwell James Désormeau Ramstead et al.

Giovanni Pezzulo [a,*], Michael Levin [b]

[a] *Institute of Cognitive Sciences and Technologies, National Research Council, Rome, Italy*
[b] *Allen Discovery Center at Tufts University, Medford, MA, United States*

Received 22 November 2017; accepted 23 November 2017
Available online 24 November 2017
Communicated by J. Fontanari

The free-energy principle (FEP) has been initially proposed as a theory of brain structure and function [1], but its scope is rapidly extending to explain biological phenomena at multiple levels of complexity, from simple life forms and their morphology [2] to complex societal and cultural dynamics [3].

Appealing to the same principles to explain "the mind" and "the biological world at large" may appears bizarre from a biological perspective, which recognizes a risk in applying some concepts that are typical of the mental world – such as teleology and intentionality – to the realm of biology. However, it is becoming increasingly recognized that neural tissues (the accepted seat of intentionality) did not invent their powers *de novo* but rather optimized fundamental capabilities already present in their evolutionary ancestors [4,5]. Unicellular creatures and non-neural metazoan tissues were already solving problems, maintaining physiological and anatomical homeostasis, and constantly trying to improve their lot in life – long before nervous systems evolved [6–8]. Even more fundamentally, the formal ground of this idea emerges clearly if one considers that all living systems must self-preserve their integrity and avoid dissipation; or in other words, counteract the third law of thermodynamics [9–11]. As this self-preservation imperative applies at all levels of complexity and organization that life assumes, one can attempt to use similar principles to explain, for example, how cells, schools of fish, countries or cultures maintain their (internal) identity and identity while shielding themselves by (external) disturbances, thus counteracting at their best dissipative dynamics. All the examples above – cells, schools of fish, countries, cultures – entail some form of separation between what is "inside" (e.g., organelles of a cell, citizens of a country) and what is "outside". What is inside tends to be rather stable over time – or changes more slowly than the external perturbations. Furthermore, there is some form of separation or barrier between the inner and the outer, which is sometimes physically realized (e.g., cell membrane, country boundaries) and sometimes more fuzzy (e.g., separations between cultures). The boundary of the "self" has very practical implications, for example in the biomedicine of cancer, where individual cells revert back to unicellular programs that treat the rest of the body as the external environment [12].

DOI of original article: https://doi.org/10.1016/j.plrev.2017.09.001.
* Corresponding author.
E-mail address: giovanni.pezzulo@istc.cnr.it (G. Pezzulo).

https://doi.org/10.1016/j.plrev.2017.11.020
1571-0645/

The appeal of the FEP is that it suggests a way to cast this sort of metaphorical thinking into a formal specification of "what is needed to be (and to remain) alive" [9–11]. To address this challenge, an appealing starting point is the statistical construct of a Markov blanket, which essentially formalizes the separation between an "inner" and an "outer" environment, in terms of conditional independence between inner states of a generative model and outer states, whose reciprocal influences are mediated by intermediate (sensory and active) states of the generative model [10]. Metaphorically speaking, the intermediate states of a Markov blanket "shield" inner states from the direct influence of outer states. Protected within this barrier, inner states can then preserve their integrity over long time periods, thus avoiding the usual fate (dissipation) of non-living entities. Crucially, to do this, internal variables need to develop (or become) models of the outer environment, thus being able to select adaptive actions (via the intermediate states) that both probe external dynamics (to learn them) and reciprocate their dissipative influences. This formulation is both fascinating – it seems to allude to stories of medieval fortifications and sieges – and useful, as it clarifies that the teleology intrinsic in the reciprocal inner–outer exchanges does not imply and dangerous biological finalism (e.g., the belief that there is a final cause in evolution). Rather, it appeals to more reassuring and mechanistic principles of cybernetic control [13–16], autopoiesis and self-organization [17–19].

Crucially, to explain the living at different levels of complexity and organization, one can apply the concept of a Markov blanket recursively – hence realizing a nesting of Markov blankets within Markov blankets. This nesting propagates the statistical (in)dependencies between inner, intermediate and outer variables across levels, thus providing a suitable formal model to address biological phenomena at increasing complexity e.g., from cells to individuals to societies and beyond – thus motivating a variational neuroethology that spans all these levels [10]. In sum, the formal framework of FEP and the concept of (nested) Markov blankets offers formal tools to understand "the realm of the living" at multiple levels of complexity, while also addressing the reciprocal influences between all these levels – an interesting avenue for future research.

Here we discuss the application of FEP and the concept of (nested) Markov blankets to a key construct of living beings: the body. If one considers where the FEP originates from – explaining brain and mind [1,20–26] – it may seem utterly bizarre to appeal to the same constructs to also explain bodies, at least for those who believe that the immaterial mind and the material body are two irreconcilable kinds of substances [27]. However, there are very strong – and in some cases even surprising – similarities between the ways brains and body are organized. The conservation of mechanisms is perhaps inevitable given their inescapable evolutionary histories; the conservation of algorithms by which they operate is, on the other hand, a remarkable finding with many deep implications for understanding causation [28,29] and goal-directedness [30] in a range of living and synthetic systems. These similarities can be understood at both functional and mechanistic levels.

At the functional level, one can identify analogies in the ways individual neurons located in different brain structures form functional networks (e.g., a fronto-parietal attention network [31]) and individual cells form complex organs and body parts during morphogenesis [32,33]. The formal analogies between these processes can be understood by appealing to the concept of nested Markov blankets. In the brain, individual neurons, small neural networks and big functional networks (e.g., the whole fronto-parietal circuit) represent three nested levels of organization, in which the functional interactions (and conditional independences) can be understood by appealing to (nested) Markov blankets, e.g., by considering that some "nodes" of the network play the role of intermediate states, mediating "input–output" dynamics. In the body, one can identify nested levels of organization in cells, organs and the whole body, and appeal to the same principles of (nested) Markov blankets to explain them. Clearly, brain processes are highly plastic, with rapid shifts between functional networks; whereas bodily processes are apparently less plastic at a macrolevel (e.g., organs do not change so rapidly). However, there are some cases in which plasticity is very high, such as for example during morphogenesis and regeneration, as well in relation to some diseases such as cancer [33]. An important avenue for future research is identifying formal methods permitting to treat these bodily phenomena in the same way neuronal dynamics or functional networks are understood in computational and systems neuroscience [32–34].

Intriguingly, in the case of bodies, some functional aspects of the Markov blankets become – so to say – embodied into the structure of the organism. This is the case, for example, of our sensory epithelia, whose cells play the functional role of intermediate (sensory) states of a Markov blanket, but they also actually, physically separate the body from the outside world and protect its integrity. In this case, the morphogenetic process of separation between cells that become parts of internal organs and cells that become parts of sensory epithelia actually embodies the functional separation between inner and intermediate states of Markov blankets. If one extends this idea to increasingly higher levels of complexity, one can trace similar phenomena (for example) in schools of fish or storms, where some animals actually become temporarily part of the periphery or the soft borders of the school or the storm. Moving in the other direction, the same kinds of strategies could be applied to the origin of multicellularity, to ask about the perception space and motivation of single cells, alone and when combined into (real or synthetic) multicellular organisms [35–39].

What did cells "think about" before they became brains? The amazing plasticity of body patterning processes, as observed in regulative embryogenesis and regeneration, suggests an answer: they thought about the body's anatomical structure [33]. Most living organisms, with all of their body complexity, self-assemble from the progeny of a single fertilized egg cell – a process in which geometric complexity grows by many orders of magnitude. However, this process is usually not hardwired: in some species, embryos can be cut in half and each half goes on to make a fully normal organism. Many species, as adults, can regenerate entire complex structures (salamanders regenerate whole legs, eyes, jaws, tails, etc.), or remodel inappropriately patterned structures upon ectopic transplantation [40]. What underlies all these phenomena is fundamental anatomical homeostasis – cells grow, move, die, or proliferate as needed to form the correct target morphology of the organism, and they *stop when a structure of the precisely correct shape, size, and position has been achieved*: these systems are able to execute a dynamic loop which continuously minimizes the error (difference) between the body's current pattern and an anatomical goal state. Concepts from cybernetics, closed loop control or the FEP can help us understand these phenomena [2,33].

During the appearance of metazoan life, unicellular creature transitioned from managing metabolic and behavioural homeostasis of single cells to the maintenance of *large-scale* goals. We know that brains represent goal states via the activity of an electric network. How do bodies carry out this task? Recent data have revealed that somatic tissues of all types use precisely the same trick, exploiting bioelectric signaling to regulate individual cell behaviors toward large-scale anatomical repair and patterning [41]. The precisely same ion channels, neurotransmitters, and electrical synapse molecules are involved, as befits the ancient origin of this ubiquitous control system. Recent data have demonstrated proof-of-principle of "neural decoding" applied to non-neural bioelectric prepatterns during development [42]. Even more exciting, modulating ion channel-dependent circuits has enabled re-writing (editing) of target morphologies in living tissues to induce predictable, drastic, rational changes of anatomy – reprogramming cell groups to make eyes, heads, and other structures that differ drastically from the species-specific genome-default bodyplan [43]. All these examples highlight fundamental similarities between brain and bodily (e.g., developmental) processes at the mechanistic and not just the functional level. Beyond regenerative medicine, these fundamental parallels between neuroscience and developmental biology suggest research programs into "somatic psychiatry" to extend not only the tools [32] but also the deep concepts of cognitive science to the control of living growth and form.

In sum, here we have shortly discussed how to apply FEP and the concept of (nested) Markov blankets to understand bodily processes, such as morphogenesis and regeneration, and shed new light on the evolution of life and cognition. Our discussion highlights several similarities between neuronal and bodily processes, which suggest the possibility of using concepts from computational and systems neuroscience (such as FEP) to understand morphological processes and epigenesis. Furthermore, our discussion highlighted the intriguing fact that in bodily processes, some functional aspects of Markov blankets may become physically realized; for example, the case of cells that compose the sensory epithelia and physically realize the segregation or factorization between inner and outer states. These examples illustrate the heuristic appeal of using FEP to explain the biological world – providing that this idea itself becomes well nested within a Markov blanket, to survive the perturbations of scientific debate.

Acknowledgements

M. L. is supported by the Allen Discovery Center program through The Paul G. Allen Frontiers Group (12171). In addition, M.L. gratefully acknowledges support of the G. Harold and Leila Y. Mathers Charitable Foundation (TFU141) and the Templeton World Charity Foundation (TWCF0089/AB55 and TWCF0140).

References

[1] Friston K. The free-energy principle: a unified brain theory?. Nat Rev Neurosci 2010;11:127–38. https://doi.org/10.1038/nrn2787.

[2] Friston K, Levin M, Sengupta B, Pezzulo G. Knowing one's place: a free-energy approach to pattern regulation. J R Soc Interface 2015;12:20141383. https://doi.org/10.1098/rsif.2014.1383.

[3] Clark A. Surfing uncertainty: prediction, action, and the embodied mind. Oxford University Press, Incorporated. ISBN 978-0-19-021701-3, 2015.

[4] Baluška F, Levin M. On having no head: cognition throughout biological systems. Front Psychol 2016;7. https://doi.org/10.3389/fpsyg.2016.00902.
[5] Keijzer F, van Duijn M, Lyon P. What nervous systems do: early evolution, input–output, and the skin brain thesis. Adapt Behav 2013;21:67–85. https://doi.org/10.1177/1059712312465330.
[6] Calvo P, Baluška F. Conditions for minimal intelligence across eukaryota: a cognitive science perspective. Front Psychol 2015;6. https://doi.org/10.3389/fpsyg.2015.01329.
[7] Ford BJ. Cellular intelligence: microphenomenology and the realities of being. Prog Biophys Mol Biol 2017. https://doi.org/10.1016/j.pbiomolbio.2017.08.012.
[8] Lyon P. The biogenic approach to cognition. Cogn Process 2006;7:11–29. https://doi.org/10.1007/s10339-005-0016-8.
[9] Schrodinger E. What is life?. reprinted Cambridge University Press; 1992. p. 87. 1995.
[10] Ramstead MJD, Badcock PB, Friston KJ. Answering Schrödinger's question: a free-energy formulation. Phys Life Rev 2018;24:1–16 [in this issue].
[11] Friston K. Life as we know it. J R Soc Interface 2013:10. https://doi.org/10.1098/rsif.2013.0475.
[12] Moore D, Walker SI, Levin M. Cancer as a disorder of patterning information: computational and biophysical perspectives on the cancer problem. Converg Sci Phys Oncol 2017;(3):043001. https://doi.org/10.1088/2057-1739/aa8548.
[13] Ashby WR. Design for a brain. Oxford, England: Wiley; 1952. Vol. ix.
[14] Powers WT. Behavior: the control of perception. Hawthorne, NY: Aldine; 1973.
[15] Wiener N. Cybernetics, or, control and communication in the animal and the machine. 2d ed. New York: MIT Press; 1961.
[16] Pezzulo G, Cisek P. Navigating the affordance landscape: feedback control as a process model of behavior and cognition. Trends Cogn Sci 2016;20:414–24. https://doi.org/10.1016/j.tics.2016.03.013.
[17] Allen M, Friston KJ. From cognitivism to autopoiesis: towards a computational framework for the embodied mind. Synthese 2016:1–24.
[18] Maturana HR, Varela FJ. Autopoiesis and cognition: the realization of living. Dordrecht, Holland: D. Reidel Pub.; 1980.
[19] Haken H. Advanced synergetics: instability hierarchies of self-organizing systems and devices. Springer Series in Synergetics. Berlin, New York: Springer-Verlag. ISBN 0387121625, 1983.
[20] Friston K, Rigoli F, Ognibene D, Mathys C, Fitzgerald T, Pezzulo G. Active inference and epistemic value. J Cogn Neurosci 2015:1–28. https://doi.org/10.1080/17588928.2015.1020053.
[21] Friston K, FitzGerald T, Rigoli F, Schwartenbeck P, O'Doherty J, Pezzulo G. Active inference and learning. Neurosci Biobehav Rev 2016;68:862–79. https://doi.org/10.1016/j.neubiorev.2016.06.022.
[22] Friston K, FitzGerald T, Rigoli F, Schwartenbeck P, Pezzulo G. Active inference: a process theory. Neural Comput 2016;29:1–49. https://doi.org/10.1162/NECO_a_00912.
[23] Pezzulo G, Rigoli F, Friston KJ. Active inference, homeostatic regulation and adaptive behavioural control. Prog Neurobiol 2015;136:17–35.
[24] Pezzulo G, Cartoni E, Rigoli F, Pio-Lopez L, Friston K. Active inference, epistemic value, and vicarious trial and error. Learn Mem 2016;23:322–38. https://doi.org/10.1101/lm.041780.116.
[25] Donnarumma F, Costantini M, Ambrosini E, Friston K, Pezzulo G. Action perception as hypothesis testing. Cortex 2017. https://doi.org/10.1016/j.cortex.2017.01.016.
[26] Friston KJ, Lin M, Frith CD, Pezzulo G, Hobson JA, Ondobaka S. Active inference, curiosity and insight. Neural Comput 2017:1–51. https://doi.org/10.1162/neco_a_00999.
[27] Descartes R. Meditations on first philosophy 1641/1993.
[28] Hoel EP. When the map is better than the territory. Entropy 2017;19:188. https://doi.org/10.3390/e19050188.
[29] Hoel EP, Albantakis L, Marshall W, Tononi G. Can the macro beat the micro? Integrated information across spatiotemporal scales. Neurosci Conscious 2016:2016. https://doi.org/10.1093/nc/niw012.
[30] Nechansky H. Elements of a cybernetic epistemology: decisions, control and principles of societal organization. Kybernetes 2008;37:83–93. https://doi.org/10.1108/03684920810851005.
[31] Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002;3:201–15.
[32] Pezzulo G, Levin M. Top-down models in biology: explanation and control of complex living systems above the molecular level. J R Soc Interface 2016:13. https://doi.org/10.1098/rsif.2016.0555.
[33] Pezzulo G, Levin M. Re-membering the body: applications of computational neuroscience to the top-down control of regeneration of limbs and other complex organs. Integr Biol 2015;7:1487–517. https://doi.org/10.1039/c5ib00221d.
[34] Levin M, Pezzulo G, Finkelstein JM. Endogenous bioelectric signaling networks: exploiting voltage gradients for control of growth and form. Annu Rev Biomed Eng 2017;19. https://doi.org/10.1146/annurev-bioeng-071114-040647.
[35] Bugaj LJ, O'Donoghue GP, Lim WA. Interrogating cellular perception and decision making with optogenetic tools. J Cell Biol 2017;216:25–8. https://doi.org/10.1083/jcb.201612094.
[36] Fields C, Levin M. Multiscale memory and bioelectric error correction in the cytoplasm-cytoskeleton-membrane system: multiscale memory and bioelectric error correction. Wiley Interdiscip Rev, Syst Biol Med 2017;e1410. https://doi.org/10.1002/wsbm.1410.
[37] Ollé-Vila A, Duran-Nebreda S, Conde-Pueyo N, Montañez R, Solé R. A morphospace for synthetic organs and organoids: the possible and the actual. Integr Biol 2016;8:485–503. https://doi.org/10.1039/C5IB00324E.
[38] Solé R, Amor DR, Duran-Nebreda S, Conde-Pueyo N, Carbonell-Ballestero M, Montañez R. Synthetic collective intelligence. Biosystems 2016;148:47–61. https://doi.org/10.1016/j.biosystems.2016.01.002.
[39] Sole RV, Munteanu A, Rodriguez-Caso C, Macia J. Synthetic protocell biology: from reproduction to computation. Philos Trans R Soc Lond B, Biol Sci 2007;362:1727–39. https://doi.org/10.1098/rstb.2007.2065.
[40] Mustard J, Levin M. Bioelectrical mechanisms for programming growth and form: taming physiological networks for soft body robotics. Soft Robotics 2014;1:169–91. https://doi.org/10.1089/soro.2014.0011.

[41] Sullivan KG, Emmons-Bell M, Levin M. Physiological inputs regulate species-specific anatomy during embryogenesis and regeneration. Commun Integr Biol 2016;9:e1192733. https://doi.org/10.1080/19420889.2016.1192733.

[42] Levin M, Martyniuk CJ. The bioelectric code: an ancient computational medium for dynamic control of growth and form. Biosystems 2017. https://doi.org/10.1016/j.biosystems.2017.08.009.

[43] Durant F, Morokuma J, Fields C, Williams K, Adams DS, Levin M. Long-term, stochastic editing of regenerative anatomy via targeting endogenous bioelectric gradients. Biophys J 2017;112:2231–43. https://doi.org/10.1016/j.bpj.2017.04.011.