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STRONG EMERGENCE AND DOWNWARD CAUSATION IN BIOLOGICAL PHYSICS

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ABSTRACT

The methodological lens of physics within the realm of biology creates the interdisciplinary field of Biological Physics: a fruitful one with which to explore the idea of Strong Emergence. Examples of emergent entities are found in: *e.g.* protein assembly within cell membranes, gene expression from external cell signalling, topological interaction of DNA and topoisomerase enzymes. The flow of information (itself determined by constraints) is urged as an indicator for downward causation. Strongly emergent structures carry information at high (larger scale) level that is not constituted by the sum of information at low (smaller scale) levels. Biological physics throws empirical light on the metaphysical question of downward causation without having to broach the additional complexities and contested qualities of the mental.

1. Introduction

The metaphysical discussion of causation and emergence, within the background of polarised views between reductionism and anti-reductionism, has remained unresolved within the last thirty years—the period characterised by the works of the 'new-emergentists' (O'Connor 2015). The primary motivation of the question of causation has historically arisen from the role of the mental in determining the future. Those committed to one interpretation of the results of scientific endeavour to this point in time, referred-to as the 'causal completeness of the physical' (CCP), arrive at the conclusion that mental events (M) cannot be causes of physical events (P) providing that one adds to CCP: (i) the axiom of non-over-determination (OD), and (ii) the assurance that mental events are not identical with physical (this is the assumption of anti-reductionism—AR) (Kim 1998). The contradiction arises because if M and P were both causes of subsequent physical events P', and M-causes are distinct from P-causes, then OD is immediately violated, a logic sometimes referred to as the 'exclusion argument'.

There seems to be much at stake in this conclusion, for if it really implies the relegation of M-events to 'epiphenomena' (phenomena without causal power), there are immediate concerns, among others, that the construction of such arguments themselves, manifestly consisting of M-events, result purely from P-events that carry entirely different significance from the logical argument intended (Fodor 1990), notwithstanding our everyday experience of apparent mental causation. The M/P distinction is just one example of the notion of 'strong emergence'. The idea that high-level entities (clouds, trees, bodies of water, phase transitions, ...) 'emerge' from the concerted and collective behaviour of low-level entities (atoms, molecules, electrons, ...) is not contested. But a reductionist view entails that these penomena are all 'weakly emergent', in the sense that the future evolution of the system is

(and here it seems always necessary to insert an 'in principle') determined by the low-level entities (usually identified as atomic and/or molecular) and their interactions alone. M-causation (and other high-level causation, as I argue here) however, requires more–that there are high-level entities, carrying unique information about the system essential for its future evolution, and whose form and evolution are not determined entirely by the low level entities. Such 'strongly emergent' entities, though high-level, would from a causal perspective be as essential as the low-level variables. A key notion underpinning both weak and strong emergence is that of 'multiple realisability'—that a given state of a high-level variable corresponds to a (typically very large) set of low-level states. This in turn implies a weakening of the idea of 'bridge laws' connecting high and low level descriptions of a system, at first sight a strong challenge to reductionism, and constituting another contested element in the metaphysics of causation (Gillet 2002)

One source of the problematic impasse in deciding on the reality or otherwise of strongly emergence entities is the primary source of the debate—the question of mental causation. However, the mental realm is, at the very least, the most complex emergent physical system science has yet met with. The rather minimal engagement of research programmes in neuroscience with the metaphysical debate on emergence and downward causation is an indicator of the difficulty faced by demonstrating explicit connections between metaphysical notions such as reductionism, or OD with real systems. Yet the questions begged by the simple high-level demonstrations of metaphysics, such as the exclusion argument, invite explicit mechanistic demonstration, rather than its continued postponement with the aspirational use of 'in principle' arguments (Burge 1993, Cartwright 1999).

There is little prospect of satisfying such desirable demonstrations at the multiple levels of the mental in the near future, but, to many scientists, downward causation seems an ubiquitous phenomenon by no means restricted to the mental, and amenable to an interdisciplinary

examination with philosophers within the context of far simpler systems (Ellis 2012). At the very least, a programme of detailed work examining the structure of emergent dynamical processes of change in complex systems for which we do currently possess both experimental measures at multiple scales and theoretical models' predictive capacity, will aid in making more precise the meaning of the deceptively problematic terms 'cause', 'physical' and 'determination'. To take one example: there is a manifest confusion in the literature between 'physical' and 'micro-physical' or 'atomistic', an assumption, in other words, that 'physics' is restricted to one particular level in spatial (or equivalently energetic) scale. Yet as Anderson pointed out long ago (Anderson 1972), physics, and physical processes, are as much concerned with multi-level and inter-level processes, including the emergence of coarse-grained variables that act determinatively, as on microscopic phenomena. A more embracing and less oppositional formulation of emergence that naturally draws from scientific sub-fields other than the mental is the 'contextual emergence' of Silberstein and Bishop (2016).

A promising field in which to operate with such approaches is the relatively newly-defined field of 'biological physics'. The term marks the latest historical manifestation of a recurrent phenomenon—the profound engagement of biology and physics to mutual and transformational benefit. Earlier examples are well-documented: the role of Neils Bohr's laboratory in the introduction of radio-labelling in physiology (Morange and Cobb 1998), the introduction of counter-factual thinking into biology by Schrödinger in his early foray *What is Life?* (Schrödinger 1944) and, most notably, the development of X-ray crystallography in biomolecular structure determination (Morange and Cobb 1998).

The latest phase of interdisciplinary engagement has been driven from a collective phenomenon within the discipline of physics itself—the emergence of 'soft matter physics' (McLeish 2017). If quantum mechanics furnishes the underpinning theoretical paradigm of 'solid

state' materials physics for which the correlation of electron wave-functions is the dominant feature (so applying metals, semiconductors, superconductors etc.), then statistical mechanics provides the natural paradigm for 'soft' materials in which (approximate) thermal equilibrium is the dominant paradigm (exemplified by gels, rubbers, polymers, colloidal fluids, liquid crystals, polymers, self-assembled membranes, surfactants, emulsions etc.). Soon after a common frame and research programme had been established–one that unified the previously disparate sub-fields of 'colloid physics' and 'polymer physics', for example, several research groups within soft matter physics, especially in Europe and the USA, began to work intensively on biological systems. For, if the structures of living systems are largely based, at the mesoscopic level, on polymers (DNA, proteins, RNA, polysaccharides, ...) and membranes (cell membrane lipid bilayers, nuclear membranes, the Golgi apparatus, ...) then the methods and insights from the soft matter physics of such structures might have something to say about at least the physical constraints under which they must work in biological contexts. On the other hand, it is also perfectly possible that the highly evolved and specific nature of biological macromolecules, together with the strongly non-equilibrium environment within which they function, might moderate these hopes substantially.

In any case, a strong commonality enjoyed by all soft matter systems is the emergence (at least in the weak sense) of coarse-grained structures that act causally, both in empirical experimental investigation and within mathematical theories constructed to model them. Most theory for soft matter systems, including biological ones, does not choose the atomic level at which to write down its fundamental description. In this way they become helpful arenas in which to examine how well the high-level metaphysical apparatus stands up to a mechanistic examination in practice. By virtue of the apparent efficacy of high-level variables, they are also candidates for examining the definition of strong emergence within the context of detailed examples. The promise of a fruitful set of

exemplars is even more persuasive in the biological cases, for here evolution and organism function has directed the emergence of systems in which causal flows seem to cross levels of coarse-graining all the time.

In this paper, after a more detailed overview of the structure of soft matter principles, we will examine three examples of biological soft matter systems: (i) self-assembly of and within membranes, (ii) aspects of signalling in gene-expression, and (iii) the role of enzymes that interact with the topology of DNA (the 'topoisoperases'). Each case will offer itself as a candidate-system combining the notions of strong emergence, top-down causation and multiple-realisability. Finally we conclude by revisiting the metaphysical questions in the light of the new science.

2. Soft matter and biological physics

It is difficult to present an exact description of systems that belong to the class of 'soft condensed matter'. However, there is agreement on five characteristic features that commonly arise.

First, the energy scale of internal interactions in soft matter is comparable to the scale of thermal energy, $k_B T$ (the product of Boltzmann's constant and the absolute temperature). So, in contrast to systems whose physics is dominated by quantum mechanics, thermal transitions between microscopic energy levels are frequent, and quantum coherence is (usually) negligible. Classical statistical mechanics furnishes, in consequence, the appropriate set of tools to model and calculate with. Fluctuations in structure are large (in a dimensionless sense), and local equilibrium is the dominant paradigm.

Second, 'mesoscopic' structure (at the length-scale of several (tens of) nanometers) is almost ubiquitous in soft matter systems. For example, colloids are suspensions of particles at this scale suspended in a solvent—stabilised because the thermal energy is large compared to their typical gravitational potential energy in the bulk fluid. To give some other

examples: polymers are long-chain molecules of very high molecular weight, whose random configurations in solutions or in melts are such that the macromolecular coils are typically several tens of nanometers in scale. The dominance of this structural, 'mesoscopic' length scale (neither macroscopic—mm to m, nor truly microscopic at the atomic dimension of sub-nanometer) is also responsible for the epithet 'soft', for the existence of a typical structural length l, together with the condition of strong thermal dominance, leads to a natural estimate of the elastic modulus $G \approx (k_B T/l^3) \approx 10^6$ Pa, a thousand times smaller than the modulus of metals or ceramics

Third, the dynamics of soft matter systems is often very rich, and contains one or more 'slow variables'—coordinates that due to constraints or internal energy barriers, return to equilibrium on much longer relaxation timescales than the typical intermolecular ballistic trajectory time (at 300K) of ≈10ps (Larson 1999). An example is the set of very slow viscoelastic relaxations in solutions and melts of polymers (Doi and Edwards 1986). These are generated from the multiple topological interactions between polymer chains, which typically (for chemically formed polymers) cannot cross each other.

A fourth characteristic of soft matter is the thermodynamic (and emergent—Ellis 2012) property of multiple realisations at lower levels than the operative structure. For example, even when states of a colloidal or polymeric system are characterised by specific configuration of colloidal particles, or entire polymer chains (at suitable small-scale resolution) there are many configurations of solvent molecules, and/or of subchain states, that correspond to the same 'meso-state'. For many purposes (e.g. the analysis of scattering experiments, or the measurement of osmotic pressure) even coarser variables, such as local mean density averaged over a mesoscopic volume, are sufficient, and hyper-exponentially more multiply-realised in microstates. The techniques of statistical mechanics can therefore be applied even to these mesoscopic structural volumes.

Fifth, and consequent on the other four, the variety of soft materials and their phases exhibit a high degree of 'universality'. Essentially the same emergent material arises from different underlying chemistries. With a rescaling of a few coarse-grained parameters, the mapping may be essentially exact. So, for example, the linear elastic modulus of a polymeric gel is dependent on the density and distribution of the cross-links between its constituent polymer chains, not on the chemistry of the chains themselves. The similarity may persist into even non-linear response.

The interdisciplinary nature of the (multiple) sub-discipline of soft matter is remarkably broad. The nature of the materials required in each of the exemplars listed above frequently implies just as significant challenges to synthetic chemistry in their fabrication as it does to theoretical and experimental physics in explanation and characterisation. The more recent application of soft matter science to the analysis of biological and bio-inspired phenomena (Nelson 2004) increases the interdisciplinary palette even further. The consequences are as yet hard to predict, but already two promising directions for research have been generated by the confluence of biology and the statistical physics of soft matter. The first sheds new light on the physical basis of biological phenomena; the second draws inspiration from biology to define new research programmes in physics. Examples in this paper are now drawn from the first of these classes.

3. Three cases of emergence and top-down causation in biological physics

3.1 Membrane and intra-membrane self-assembly

As Max Delbrück pointed out long ago (Adam and Delbrück 1968), the ubiquity of two-dimensional structures in biology is not surprising. Not only do they constitute partitions between (*e.g.* cellular) domains that require the maintenance of different conditions inside and outside, but they also provide low dimensional spaces within which diffusive searches are efficient. This latter point is subtle: the processes of life require the constant meeting of two or more different molecular species to assemble or react. Examples are protein sub-domains that need to self-assemble into multi-domain and quaternary protein structures such as the bacterial flagellar motors, or proton pumps within membrane pore-complexes (see figure 1). Although many dynamic processes in biology are directed, this requires the concerted and organised action of molecular motors, as well as the consumption of biomolecular fuel (the most common is ATP, itself synthesised within a membrane protein, ATP-Synthase, of extraordinary complexity and dynamics). In consequence, where free diffusion is able to generate mutual contact between components (at which point the specific interactions of charged, hydrogen-bonds or hydrophobic sites complete the local assembly) then it will commonly do so.

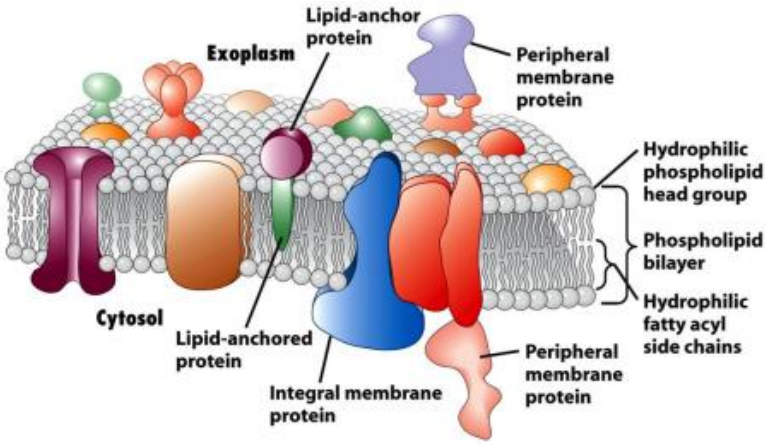

Figure 1: Schematic of a portion of lipid membrane containing different types of membrane proteins. (from http://www.creative-proteomics.com/ services/ membrane-proteomics.htm)

The subtlety is found in the effective dimension of the search, determined in turn by the topology of membrane and protein (Von Heijne 2006). There is a qualitative difference in the dependence of the mean search (collision) time and the size of the searched domain, between domains of low and high dimension. In one or two dimensional spaces (on curves or on surfaces) the mean search time grows as the square of the domain size, but in all higher dimensions the domain size is raised to the power of the number of dimensions. This soon renders search times impossibly (exponentially) long unless the search spaces are structured in very specific ways (this is the case, for example, in protein folding, which can be conceived as a search in a space whose dimensionality grows as the number of amino acids in the protein—so commonly several hundred (McLeish 2005)). In this way the self-assembly of the quaternary complexes of proteins, frequently found within the lipid membranes, is enhanced and accelerated by many orders of magnitude with respect to a complex of similar sophistication within the bulk interior of the cell. Examples are G-protein coupled receptors,

and the rotary motor of ATP-synthase. One should note that this is not simply a reduction of three-dimensional diffusion to two: in order for a protein unit successfully to diffuse and combine with a complex it must be present both at the correct position (3 degrees of freedom) and in the correct orientation (a further 3 degrees of freedom). By locating the protein sub-units within a two-dimensional membrane, one spatial and one rotational degree of freedom are immediately controlled, so that the diffusive search compresses from a 6 to a 3-dimensional general space. Assemblies of n proteins multiply the effective dimension of their mutual search space by n, so that the dimensional reduction achieved by the emergent space of the membrane is $2n$.

The protein subunits co-localise and assemble because of and in response to the presence and structure of the lipid membrane—itself an object at a higher level of description than the complexes or subunits. Furthermore, the extended topology of the membrane (cell boundaries of genus 1) is definable only globally, and not locally. One of the examples of the complexes just mentioned, the ATP-synthase, functions in response to a protein concentration difference maintained between the interior and exterior of the cell. This is only possible if the global topology of the membrane is closed. So the diachronic structuring and consequent functioning of these protein complexes is more than made possible—it is caused—by the presence and structure of higher level objects, the membranes. These possess essential structure both at a higher spatial coarse-graining and a non-local and topological level.

Intriguingly, the lipid membrane is itself a self-assembling object: the chemical structure of the lipid molecules comprising its double-layer structure codes for the local stability, elasticity and curvature of the extended sheet. The mutual attraction of the polar heads, and hydrocarbon tails, of the lipids, as well as the dominant attraction of the former, and repulsion of the latter to water, results in the formation of the well-known double layer. Furthermore, it is the hydrophobic interior of the lipid membrane that allows the possibility of specific membrane-

bound proteins, for these contain hydrophobic molecular sidegroups at the surface of their 'trans-membrane domain' that anchor them within it.

A plausible causative and explicative chain for the assembly of a membrane protein complex therefore begins with the assembly of the membrane itself, implicitly coded in the lipid molecular structure, yet contingent on the context of the organism manufacturing the lipids in sufficient local concentration to assemble. The emergent structure of the membrane then acts both geometrically (in a coarse-grained sense) and topologically (in a non-local sense) to determine the assembly of trans-membrane complexes as well as the timescale on which they achieve their full structure.

A final point pertinent to theorising emergence is the strong multiple realisability implicit in the biophysics of membrane proteins. The long-ranged elastic properties of the cell membranes themselves are renormalized (Ami and Kleinert 1987) by the incorporation of statistical fluctuations of the membrane at all scales, in much the same way that effective polymer elasticity arises from the thermal fluctuations in chain configuration. So multiple-realisability at finer-grained levels is at the heart of the coarse-grained physics. At another level of multiple pathways, there are multiple routes by which protein domains may diffuse together and self-assemble, but once the constraining high level structures of membrane and subunits are there, the formation and function of the final complex is determined.

3.2 Allosteric Signalling in Gene Expression

The transcription of genes from DNA into RNA by the enzyme RNA Polymerase, and thence into proteins in the ribosome, is contextually switched for any cell and organism. Even once the restriction of possible gene-transcription is made by cell-differentiation, the biochemical, thermal and mechanical environment is sensed continually (involving the transmembrane protein complexes discussed above). Which genes

are transcribed at which moments depends on the local concentration of families of signalling molecules whose synthesis is responsive to these contextual conditions.

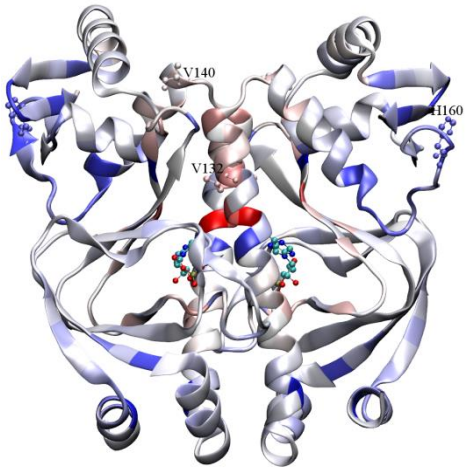

Figure 2: 'Ribbon' structure of an allosteric protein (CAP) implicated in the metabolism of the bacterium *E. Coli*. The binding of the two effector cAMP molecules (shown as small 'ball-and-stick' representations) is co-operative by thermal fluctuation

The route by which signalling molecule concentration controls expression is typically through allosteric binding to transcription factors. RNA polymerase binds to the DNA at a control sequence 'upstream' of a gene when also bound by a transcription factors, or are prevented from binding there if the site is occupied by a repressor. Both transcription factors and repressors bind, not only to the DNA, but also to small signalling molecules at other binding sites. The intra-protein transfer of information, so that the binding properties of one of the two binding sites are dependent on the bound state of the other, is known as 'allosteric' binding (Nussinov 2016).

There are two classes of mechanism underpinning allosteric signalling, according to our current understanding. The first, advanced by Monod, Wyman and Changeux (1965) invokes a conformational switch on binding the signalling molecule. In this picture, allosteric proteins possess two potentially stable globular states, and the binding event

controls which one dominates. Only one of these states actively binds the other substrate (usually DNA), so through this chain the binding of the signalling molecule controls binding of the protein to DNA. A second mechanism is more subtle, and has come to light more recently. Rather than alter the mean conformation of the protein, the binding event changes the rigidity of the molecule locally, and so affects the thermally-activated fluctuations of protein structure around its mean (McLeish *et al.* 2013). Since these structural fluctuations may be correlated at long-range, even spanning the entire protein, changes in the pattern of fluctuation can alter binding properties (specifically the binding free-energy, through the entropic channel) at other sites. This mechanism avoids the exposure of new surface and other disadvantageous consequences of the switching of mean structure.

The salient point of this mechanism is that the thermal fluctuations of the complex of protein, substrate and DNA are not incidental, let alone deleterious, to the function of information flow, binding and subsequent control of gene expression. Rather they, and the multiple realisations of the fine-grained atomistic structures that they represent, are integral to the process. However, the focussing of correlated fluctuation necessary to the allosteric relation between the two binding sites seems to be an exquisitely-tuned function of the elastic geometry of the folded protein (Rogers *et al.* 2013). This structure is a property of the coarse-grained topology of the protein, and not of its atomistic-level description. The causal interplay of local binding events and non-local structures supporting multiply-realised fluctuations generate a global flow of information (at least a 1-bit quantum of data that indicates whether a binding site is occupied or not).

3.3 Entangled DNA and Topoisomerases

A remarkable application of polymer physics came to light in the theoretical examination of bacterial cell-division. Since the early work of de Gennes, Doi and Edwards (Doi and Edwards 1986) motivated by the

phenomenon of viscoelasticity in concentrated polymer solutions and melts, we have understood that the principle underlying physics is that of the *topology* of strings in random, fluid configurations. Rather than attractive or repulsive interactions between molecules, it is the uncrossability of two 1-dimensional objects embedded in a 3-dimensional space that endows the system with very slow dynamics. For in order that the coarse-grained fluid composed of many overlapping polymer molecules may flow, the molecular chains must themselves repeatedly reconfigure themselves, adopting new neighbours and leaving old ones. This process cannot be achieved by simple convection with the flow as the molecular chains cannot pass through each other.

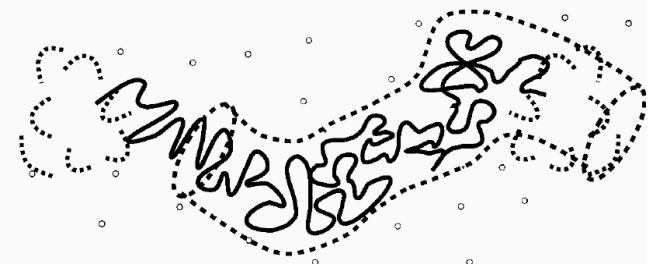

Figure 3: Schematic of the reptation of a polymer chain (solid curve) entangled with neighbours (dots intersecting the plane) and moving in an effective tube (dashed lines)

In synthetic polymeric fluids, the dominant diffusive process is the only one not inhibited by these topological constraints: the diffusion and convection of chains along their own contours. It is the chain ends, not subject to the same topological constraints as the inner chain segments, which allow new configurations to be adopted. This one-dimensional contour diffusion was termed *reptation* by De Gennes, who was reminded of a snake-like crawling. He showed, since confirmed by many experiments, that the timescale for reconfiguring a single polymer molecule by the reptation process scales as the third power of its molecular weight. Since macromolecular chains can reach very high

molecular weights, these times can become (in molecular terms) extremely long, even seconds or minutes.

This topological slowing down of the dynamics of diffusion and flow appears in biological contexts as well. The most extreme example is the requirement of the separation of daughter strands of bacterial DNA into the two new daughter cells. In bacteria, DNA is not confined to the ordered structures of chromosomes, but is much more randomly distributed through the organism. So when it divides into two strands prior to cell-division, the two macromolecules thus created are in a highly entangled state. If they were to disentangle by reptation, or even by forced diffusion along the contour length determined by the topological uncrossability constraints, the timescale for cell-division would be astronomically long. Instead, one of a family of enyzymes known as topoisomerases (Roca 1995) performs local breaking and recombination of DNA strands at points at which two strands meet together with the enzyme. During the process, the unbroken strand is passed though the nick in the other strand, before the break is healed and the enzyme releases from the two strands. The action of the topoisomerase is to change the mutual topological state of the strands.

Among many remarkable aspects of this near-miraculous example of evolved molecular engineering is that a small fleet of topoisomerase II molecules are able to resolve the topological constraints that would otherwise inhibit DNA segregation on cell division. This is all the more surprising since the crossing-over events are local, but need to respond to a direction of topological complexity (the strands need to move from higher degrees of entanglement to lower in order to separate) which is defined only globally. It is not, for example, possible to decide whether two loops of string are knotted by examining them locally, but only from their global configurations. The current hypothesis for the mechanism of communication from the global topology to the local activity of the enzyme draws on statistical mechanics. There small bias in thermal fluctuations that will tend to explore less constrained states slightly

more frequently than more. So if the complex of topoisomerase and the two strands of DNA is sensitive to the bias in these fluctuations, represented as an attempt frequency to cross or to escape, after many such encounters, there will be a drift in the very high dimensional space of DNA topologies toward simpler entangled states.

The 'top-down' causative role of long-range topology in the physics of string-like structures has been checked in the synthetic case of ring polymers (Sakaue 2012). Here, the two extreme states in which no ring molecule is linked with any other, and in which they all are, constitute an emergent liquid and solid respectively. This is true in spite of the fact that all local physics is identical in the two cases. Intermediate topological states tune continuously between the liquid and solid states *via* an unusual type of percolation transition. Usually for any liquid to solid transition, this is second-order, not first-order, in the control parameter (the mean linking number of the ring molecules).

Topology is defined in all these systems only globally, and in terms of the coarse-grained variables of the complete molecular paths. Furthermore it furnishes an additional set of state-variables themselves undefined at atomistic level, yet which are highly determinative of the future evolution and macroscopic properties of the systems.

4. Discussion: Consequences for ontological emergence

Drawing together consequences from the exemplars in biological physics that we have briefly considered, there are a number of salient contributions to the discussion of strong emergence. In particular these include: (i) a critique of the meaning of 'physics' in 'causal completeness of physics'; (ii) the need to distinguish between the 'long-range' and 'coarse-grained' aspects of high-level descriptions; (iii) the role of contextual constraints in general and of topological ones in particular in

causal chains; (iv) the active role played by multiple realisations in the emergence of high-level properties and their challenge to a simplistic conception of 'bridge-laws'. We briefly expand on these in the following.

4.1 Where 'Physics' is to be found

As we reviewed in the introduction, the uniqueness of causal powers is commonly connected with the difficulty of any conception that laws from special sciences might need to be added to those of 'physics'. There might be epistemological advantages in holding both a high level and a low level description of events together (such as a molecular fine-grained description, perhaps a simulation, of a fluid flow as well as a coarse-grained one solving the Navier-Stokes equations in terms of a local velocity field), however in this example there is no ontological extra causal power at the level of the coarse-grained variables. However, our soft matter/biological physics examples have pointed us to more complex cases in which it is important to differentiate the notion of 'physics' from the notion of fine-grained variables, be they atomistic, nuclear, quantum mechanical or quantum-field. 'Physics', as represented by the most salient, quantitatively and mathematically explanatory structures underlying a phenomenon, may be found at any spatial level of coarse-graining, and should not be confined to any one level, such as the 'atomistic', or 'nuclear'.

In particular, these examples (as others in soft matter and chemical physics) challenge the assumption that the 'physics' of a phenomenon lies at a lower level to that of the special sciences, such as chemistry. In polymer physics more generally, for example, and in biological physics specifically, the 'physics' of the problem lies at a *higher* level of coarse-graining than the chemistry (or biochemistry). So the physical, quantifiable, and predictive (including statistically predictive) processes of membranes and bio-macromolecules emerge from the continuity, flexibility, curvature and elasticity, not from their local molecular constituents, over which the membrane properties *qua* membrane, are

universal. The effective elasticity of a macromolecular chain is observed at its coarse-grained level, not at the level of chemical bonds. Furthermore, the embedding of these objects within thermal ensembles is essential to the emergence of their physics. This takes the mathematical form of the large sum-over-states known as the 'partition-function' (whose logarithm generates the system's free energy). We examine this special, 'active' case of multiple realisations in (iv) below further.

So, without challenging CCP, we may conclude that the set of fundamental variables in our models, corresponding to structures with causal powers in the world, that together constitute the deterministic structure of 'physics', may include (strongly) emergent, high-level, degrees of freedom as well as the set of fine-grained variables. Examples are the membrane structures of cells, the elasto-dynamic structure of allosteric proteins, and the topological states of DNA. Furthermore, such high-level variables exert demonstrable causal powers both at their own level of coarse-graining and at lower levels. So, for example, protein subdomains at the molecular level self-assemble through causally-determined (if still statistical) spatio-temporal pathways constructed by the high-level membrane variables.

4.2 Long-range vs. Coarse-grained

Our examples also urge a nuanced discussion of terms used to describe higher-level entities against lower-level. The strong examples of top-down causation that we claim represent high-level 'physics' required to complement the (incomplete) set of low-level 'physics' variables are not only, and not strictly 'coarse-grained'. They are self-emergent and 'long-range'. Pure coarse-graining in the sense of renormalisation (Batterman 2013), singular limits and asymptotic approximation is not the issue here. Rather the 'strongly emergent' variables are super-additive to, rather than renormalised from, the local fine-grained ones. Another way of

saying this is that they are 'long-ranged' rather than simply 'coarse-grained'.

Our three examples (and many others we could have chosen) illustrate the distinguishing features of long-ranged emergent structures and their concomitant variables. The essential feature of the lipid membranes in our first example is not that they are locally coarse-grained correlations of orientation and position of lipids, but that they constitute an entire two-dimensional manifold (of topological genus-1) that operates downward on the diffusion of the protein subdomains that it contains. The entirety and the topology of the structures are essentially long-ranged in character and not 'renormalisable' from the fine-grained coordinates. Further to the trans-membrane function of the protein complexes whose formation we discussed, the overall topology of the membranes is essential in maintaining the gradients of protons and ions across their local geometry. So, functionally, the long-range topology is also quite distinct from their local geometry (which is indeed renormalisable from the local molecular variables).

Similarly, the function of the topoisomerase proteins is consequent on the globally-defined topological state of the bacterial DNA. The mechanism by which the long-range topology is communicated to the local activity of an enzyme, currently bound to the contingency of two DNA candidate strands for re-crossing, is a fascinating one. The statistical fluctuations in which the long-range information is coded themselves constitute an example of the way multiple realisations at microstructural level create meso- and macro-scopic structures–in this case an information pathway. A similar pathway for information through thermal fluctuations is found in the case of allosteric proteins, where the long-range geometry in protein structure creates emergent pathways by which the occupation of binding sites can be signalled to other, distant regions.

Causally-active high-level variables are strongly-emergent in this long-range sense, rather than being simply coarse-grained from finer-

scaled variables. That property would in any case be a necessary condition for their 'physics' to complement, rather than over-determine the 'physics' of the finer-grained, but incomplete, set of variables.

4.3 Contextual Constraints

The delicate exploitation of self-assembled matter that processes information and energy in directed ways that constitute the physical manifestation of living processes richly illustrate the ideas of 'contextual emergence' advocated by Bishop and Silberstein. Bishop (2016) defines 'epistemological contextual emergence' (ECE) as applying to systems whose

> ...description at a particular descriptive level (including its laws) offers some necessary but no sufficient conditions to derive the description of properties at a higher level.

So the high-level and long range structures that we have exemplified (membranes, protein elasticity, DNA topology) act in the sense of ECE as *contextual constraints* on the lower-level variables, without which their own level of description is incomplete. In this way, for example, proteins are constrained to diffuse in the cell membrane. Likewise, the thermal fluctuations of allosteric proteins are, in fine-grained description, no less than the vibrations of local polypeptide backbone and side-group atoms, but become more than this through the non-local elastic geometry of the globular structure that the entire protein had formed. The function of topoisomerase II is constrained by the global topological constraints of the DNA that it reconfigures.

All three of these systems (and many others we could have chosen) possess a property in addition to the definition of ECE above–for in these cases the description at the lower level does not even include sufficient conditions for completeness. It requires knowledge of variables at the higher level in order to become so. It would be tempting to define an

'Ontological Contextual Emergence' (OCE) to describe systems such as these. In that sense our examples, especially the third, although classical, share the same essential features as the long-range topological constraints discussed in the context of the quantum system of the 'fractional quantum hall effect' by Lancaster and Pexton (2015).

4.4 Bridge Laws and Constitutive Multiple Realisation

A persistent observation in the philosophy of emergence is that the (large) reduction in the number of degrees of freedom (Wilson 2010) when bridging from low level to high level descriptions implies the multiple realisation at the lower level of single states at the higher level. The biophysical, and more generally, soft matter, examples we have considered provide rich illustrations of this (so that, for example, the topological state of a given set of DNA strands is multiply realised by *any* geometric transformation of their configuration that does not violate an uncrossability constraint). Weakly emergent (epistemological rather than ontological) emergence has been characterised by the connections between high and low level descriptions by adding 'bridge laws' to the two sets of variables (these describe functionally a many-to-one mapping when proceeding from lower to higher level descriptions). Thought by early critiques of reductionism to be inimical to it, the threat posed by multiple realisation was mitigated by careful construction of such bridge laws. For example, Butterfield (2011) describes a set-theoretic formalism by which the higher level of description can be constructed as a subset of the lower, providing that one adds bridge laws to the lower-level physics.

However, the multiple realisations discussed in our biophysical examples, as has already appeared in (i) above, have a significance far beyond that of lower-level states taken in many-to-one mappings onto higher level descriptions. Within the statistical mechanical phenomena we have discussed, it is *multiple realisability itself* which provides the higher-level property or law. The sum over states that constitutes the partition function, and hence the free energy (particularly controlling its

entropic part) is the element of formalism in statistical mechanics that represents explicitly the 'bridge law' from multiple realisations of lower level descriptions (microstates) onto high level descriptions (macrostates). But in these cases there are two important additional quality to the mapping: (i) the salient physical properties at the high level are entirely absent from the lower level and arise though the multiple realisation; (ii) there are direct causal constraints operating on the lower level variables from the emergent properties at high level that come into being through multiple realisation.

So the lipid molecules themselves, as well as the self-assembling membrane proteins, possess dynamics which respond to their long-range elastic environment, which is in turn the high-level emergent elasticity and fluidity of the membrane they constitute. In these cases bridge laws exist, but they do not 'bridge' in one direction of epistemological flow only; they also allow the incompleteness of the physics at the lower level to be completed by higher level variables that act upon them.

5. Conclusion

The potential for strongly emergent physics within soft matter seems to be recruited by biological systems ubiquitously. Perhaps this is not surprising, given our prior experience of candidates for top-down causation within living organisms. What may be more surprising is the relatively low level at which examples are already multiple- far removed from considerations of mind and cognition.

The three examples have allowed us to follow in detail the way that long-range (e.g. topological) physics is differentiated from the merely coarse-grained, and leads to strong, rather than weak notions of emergence. Similarly the phenomenon of multiple-realisability served to earth a strongly-emergent ontology for realised material form and

function, in addition to the weak coarse-graining of low-level descriptions.

The approach of taking a physical perspective onto biological matter additionally illustrates the unboundedness of physics from any special scale of length or energy. Rather it locates the 'physical' at the set of fundamentally causal variables, which themselves may simultaneously occupy multiple length scales (and in biology unvaryingly do). The future of interdisciplinary conversations between philosophers, biologists and physicists promises to be a fruitful one.

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