Progress in Biophysics and Molecular Biology 142 (2019) 23–31

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

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

The Singularity of nature

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ARTICLE INFO

Article history:
Received 22 March 2018
Received in revised form
18 July 2018
Accepted 19 July 2018
Available online 1 August 2018

Keywords:
The Singularity
Biology
Physics
Evolution
Central Theory of Biology

ABSTRACT

The feasibility of formulating the Singularity of Nature was enunciated by Einstein's mathematical formula, demonstrating the equivalency of energy and mass ($E = mc^2$). Despite that statement of principle, it has proven impossible to achieve this goal scientifically by directly merging biology and physics into one continuum. More recently, it has been realized that biology can be traced to its origins by reducing evolutionary biology to cell-cell signaling, the unicellular state being seen as a continuum from genotype to phenotype. Mechanistically, Self-referential Self-organization founded on The First Principles of Physiology offers a mechanistic explanation for 'how and why' evolution has transpired, fueled by the ambiguity (Torday and Miller, 2017a) caused by the differential between internal and external cellular entropy. The reduction of biology to cellular networks uniquely gains purchase to the roles of Quantum Mechanics, such as The Pauli Exclusion Principle, The Heisenberg Uncertainty Principle, Non-Localization and Coherence with their homologies in cellular-molecular biology. This opportunity to find the common denominator between physics and biology predicts that consciousness is the denoument of this continuum. As 'proof of principle', the classic dogmatic association of terminal addition with evolution is shown to be due to cell-cell signaling, both developmentally and phylogenetically, as a manifestation of the Singularity. These novel insights offer the opportunity to empirically formulate the basis for the Singularity of Nature for the first time.

1. Introduction

Did you ever wonder why everything in nature appears to mesh together, seamlessly interconnectedly- Man, Nature, Planets, Stars, the Cosmos-spanning human thought from the pre-Socratic Greek philosophers to Aristotle's vitalist concept of *entelechy,* to E.O. Wilson's book Consilience (1998)- the latter formulating the proposition that all knowledge can form one common database by reducing it to 1's and 0's. There have been numerous attempts to determine how and why there appears to be such a continuum, ranging from science (Smolin, 1999) to metaphysics (Lipton, 2016; Sheldrake, 2018) and philosophy (Whitehead, 2010). Up until Einstein's formulation for the equivalency of energy and mass ($E = mc^2$) it was easy to dismiss such ideas out of hand as mere teleologic 'Just So Stories'. But the equivalence of energy and mass spans the entire gamut of reality, described by Einstein in a dream he had as a sixteen year old (Isaacson, 2007), in turn challenging us to determine how biology fits with such a perspective (Smolin, 1999; Torday, 2015a).

1.1. The Singularity

The title of this paper refers to the Singularity of the Big Bang (Hawking and Ellis, 1973), an infinite density and temperature that existed at a finite time calculated to have existed about 13.8 billion years ago. The Singularity is hypothesized to have given rise to the Universe, both inanimate and animate, but how the former gave rise to the latter remains unknown. This paper shows how that may have occurred based on cellular networking for development and phylogeny, emanating from the unicellular prototype, referencing the Singularity as an ambiguity (Torday and Miller, 2017a). Self-referential Self-organization is common to both life and non-life, suggesting a common mechanism giving rise to both. Recent empiric data that Yttrium atoms self-align (Zhang et al., 2017) is the first evidence for this property for matter, and much has been written about this property in biology as well (Mazzocchi, 2012; Matsuno, 2013).

1.2. Physics meets biology as consciousness

Ontologically, the Big Bang provided a point source for the origin of the Universe, first detected as the microwave background that

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https://doi.org/10.1016/j.pbiomolbio.2018.07.013
0079-6107/

echoed the explosion (Singh, 2005). In a recent publication, a homologous point source was identified as the unicellular origin of life (Torday and Miller, 2016a). This is not an analogy or metaphor-the evolution of eukaryotes was catalyzed by the biosynthesis and insertion of cholesterol into the cell membrane (Bloch, 1992), coordinately facilitating vertebrate metabolism, locomotion and respiration, the three foundational traits of vertebrate evolution (Perry and Carrier, 2006). As a result, the cell membrane became more fluid, enabling endo- and exocytosis, allowing for the internalization of environmental factors that would otherwise have killed eukaryotes off long ago-heavy metals, ions, gases-instead compartmentalizing them with endomembranes, rendering them useful for physiologic functions (Torday and Rehan, 2012; Gray, 2017).

Moreover, when the first cell is seen as the origin of niche construction (Laland et al., 1999; Torday and Rehan, 2016a), recursively internalizing the external environment, the image of a complete arc from the origin of life to Gaia (Lovelock, 1972) comes into view. In this way of thinking, from the unicellular state forward, biology interacting with the ever-changing environment, over and over again, the innate continuum of physics and biology becomes self-evident.

As for why cholesterol was utilized at this stage in vertebrate history, it is due to the pre-adaptive exaptations characteristic of the overall process of evolution (Gould and Vrba, 1982), the organism meeting an existential environmental threat by repurposing a genetic trait used earlier in its evolution. In this case, the utility of lipids for the formation of primitive cells, or micelles using the polycyclic hydrocarbons present in the snowball-like asteroids that pelted the atmosphere-less earth to form the oceans (Deamer, 2017) was hypothetically the origin for the subsequent homologous utility of cholesterol at this juncture. And later on yet as an antioxidant (Torday and Rehan, 2016), as lipid rafts for cell-cell signaling (Lingwood and Simons, 2010), and as substrate for the steroid hormones of the endocrine system (Payne and Hales, 2004), all in service to homeostasis, referencing the FPPs.

This concept is referred to as the Endosymbiosis Theory (Gray, 2017), which applies to all eukaryotes, from protozoa to Man, and every organism in between. By internalizing the environment, organisms have adapted to it, evolving internal organs over the course of vertebrate evolution (Torday and Rehan, 2017) (Fig. 1). In tandem, their sensing mechanisms, ranging from the unicellular cell membrane to evolved organs of sensing have been vertically integrated, culminating in the nervous systems of more complex organisms (Cook et al., 2014; Torday and Rehan, 2017). The aggregate of this iterative process is consciousness, or mind, as the way in which we intuit our surroundings, which is radically different from conventional ways of thinking about consciousness either as being in our heads (Stapp, 2009; Wigner, 1964; Bohr, 1961) or extending into the environment (Clark, 2008).

1.3. The scientific rationale for consciousness as the aggregate of physiology

A cellular-molecular reduction of physiology has made it clear that biology remains descriptive (Smocovitis, 1996; Torday, 2015a) rather than being a mechanistically scientific (Nicholson, 2012; Moss, 2012), predictive discipline like Alchemy or Astrology, maturing into Chemistry and Physics, respectively, over the course of the last several hundred years beginning during the Renaissance. As a result, biologists continue to compile data in lieu of a framework of founding principles. In an effort to reconcile this problem, a Central Theory of Biology has been formulated (Torday, 2015a), providing a practicable interface between biology, physics and chemistry. As a result, a systems approach to physiologic evolution is finally attainable (Torday and Miller, 2017a,b).

By reducing the developmental and phylogenetic history of the organism to its cellular-molecular common denominator, seen against the backdrop of global environmental epochs, the causal relationships for evolutionary change can finally be understood logically (Torday and Rehan, 2017). This is particularly true when the cellular-molecular mechanisms of physiologic development, phylogeny, homeostasis and dyshomeostasis (pathology) are superimposed on ontogeny and phylogeny (Torday and Rehan, 2007).

Viewing descriptive biology in the forward direction beginning with the unicell, physiology can be understood logically (Torday and Rehan, 2017) instead of being rationalized in retrospect, dogmatically, teleologically and tautologically. By understanding what makes us 'tick' at this fundamental level, we can better realize how we fit into the great scheme of Nature individually, societally, and as a species among species. We could even formulate a Periodic Table of Biology (Torday, 2004), integrating all of the natural sciences as one functionally predictive search engine, classically

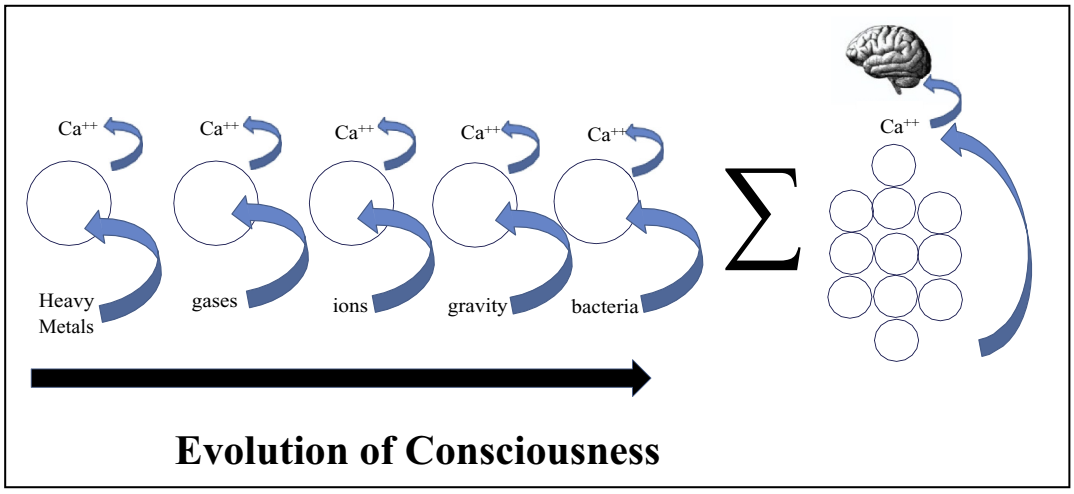

Fig. 1. Evolution of Visceral Organs and the Brain via Endosymbiosis. The internalization of environmental factors and their compartmentalization by endomembranes (from left to right), regulated by homeostatic control of calcium (Ca^{++}) formed the basis for vertebrate evolution. The culmination of that process was the evolution of the brain as the aggregate of the internal organs functionally.

referred to as The Unity of Science (Cat, 2017).

Ever since the Golden Age of Greece there have been those who have expressed the atomistic idea of the 'Singularity', from Anaximander to Anaximenes, Parmenides, Heraclitus and Aristotle (entelechy). In the modern age, there have also been those who have considered the possibility of such a unity, such as L.L. Whyte (1949), and more recently E.O. Wilson, in his book "Consilience" (1998). Whyte merely reasoned that there must be inherent common principles that form the basis for the Singularity, whereas Wilson proffered that since the world's knowledge is being reduced to 1's and 0's, that there is opportunity to form a common universal database. These unifying ideas about biology and physics are countered by the attempts of Prigogine and Stengers (1984), and Polanyi (1968), who all concluded that biology was too complicated to understand.

There is a systematic error in assuming that the solution to the Singularity problem can be achieved based on logic (Bohm, 1982), which itself is the result of our lack of understanding of the underlying principles by which life has evolved, particularly we hominins, given that we are the species that purports to be able to conceive of the continuum. The solution to the question of The Singularity lies in understanding the First Principles of Physiology (FPPs) as a unity (Torday and Rehan, 2012), which in turn are derived from the physical environment (Deamer, 2017), providing for the effective merging of life and non-life based on sound scientific principles (Torday, 2018). Only then will we be able to formulate the much-vaunted Singularity.

1.4. Mechanicism and biologic evolution

Nicholson (2012) defines biologic mechanism in three ways: "It may refer to a philosophical thesis about the nature of life and biology ('mechanicism'), to the internal workings of a machine-like structure ('machine mechanism'), or to the causal explanation of a particular phenomenon ('causal mechanism')." A series of publications have addressed the first aspect by looking at evolution from its unicellular origins (Torday and Rehan 2012, 2017), culminating in a novel perspective on Evolutionary Biology. By starting from the beginning of life, both ontogenetically and phylogenetically based on cellular-molecular principles, the mechanism by which biology has perpetuated itself in the face of environmental stress can be elucidated (Torday, 2015b). The establishment of the FPPs – namely negentropy, chemiosmosis and homeostasis-provide the initial conditions for evolution, and homeostasis (Torday and Rehan, 2012), gaining insight to how and why organisms have evolved.

In the field of developmental physiology one sees the overt singular nature of biology recurring throughout the life cycle of the organism, transiting from the unicellular to the multicellular state and back again, iteratively. Up until recently, it was assumed that this was merely the life cycle, the organism having to go through all of those stages in order to replace members of the species lost through attrition, or gained through evolutionary success (Darwin, 1859). But with the formulation of the cell as the first niche construction (Torday, 2016a), gaining new knowledge of its surroundings through its epigenetic phenotypic agency (Torday and Miller, 2016b), the function of the life cycle can now be seen in a totally different light as an active means to an end rather than as an end in itself (Torday, 2016b; Torday and Miller, 2016c).

It had long been thought that the epigenetic marks gathered during the life cycle were expunged during meiosis, only to learn that there is a specific mechanism for sorting such marks out during meiosis (Schaefer and Nadeau, 2015), embryogenesis (Cheedipudi et al., 2014) and the life cycle itself (Zhang and Ho, 2011). The latter is affected by epigenetics since the endocrine system is also under its influence (Anway and Skinner, 2008), determining the length and depth of any given stage of the life cycle-maternal bonding, crawling, toddling, adolescence, teenhood, adulthood and senescence/aging. In contrast to the conventional way of thinking of the life cycle descriptively as just a passive series of stages, this view is actively mechanistically tied to the environment through the process of niche construction (Torday, 2016a).

With the advent of the wide acceptance of epigenetic inheritance, the perspective on the life cycle had to be retooled. For example, it has long been known that exposure of the conceptus and newborn to cigarette smoke is strongly associated with the development of childhood asthma (Zacharasiewicz, 2016). This relationship really gained interest when the 'freeway' epidemiology group at The University of Southern California showed that it was actually whether your grandmother smoked that was the biggest risk factor for childhood asthma more so than whether your mother or father smoked (Gilliland et al., 2000), inferring a transgenerational effect of cigarette smoke on the upper airway of the infant, both before and after birth (Gilliland et al., 2001). Our research group decided to study the heritable effects of nicotine, one of the 3000 constituents of cigarette smoke, largely because it crosses the placenta and is stored in fatty tissue in the fetus (McEvoy and Spindel, 2017). Experimentally, treating mother rats with nicotine causes asthma in the offspring for several generations (Rehan et al., 2013).

Epigenetic agents cause chemical changes in DNA transcription-methylation, ribosylation, ubiquitination, etc. Nicotine induces such 'marks' in the upper airways of rat offspring; perhaps even more importantly, it induces the same marks in the germ line cells-sperm and egg-which is how the nicotine effect is transferred from one generation to the next.

1.5. Paracrine mechanisms of embryonic pattern formation

The impetus for our insights into the fundament of physiology (Torday and Rehan, 2012) has exclusively been derived from experimental evidence, starting with the realization that the cortisol effect on lung development, specifically on lung surfactant production, was paracrine in nature (Smith, 1979). The glucocorticoid receptor was localized to the interstitial fibroblasts of the alveolar wall, stimulating the maturation of connective tissue fibroblasts to produce Fibroblast Pneumonocyte Factor (Smith, 1979). This empiric discovery ran contrary to the conventional wisdom that the effect would be directly on the alveolar type II pneumocyte, the origin of lung surfactant production (Goss et al., 2013). The realization that the development of the lung was dependent on cell-cell communication was consistent with Grobstein's earlier discovery that the process of lung development was mediated by low molecular weight soluble growth factors Grobstein (1953). Moreover, when epithelial cells of the lung (Lwebuga-Mukasa et al., 1986) or liver (Michalopoulos et al., 1979) were cultured in isolation they lost their differentiated structure and function unless supplied with factors from their normal physiologic cellular environment, providing important clues to the fundamental nature of their development, homeostasis and repair (Warburton et al., 2010). In the ensuing decades, the paracrine regulation of many tissues and organs has been determined, beginning with the cross talk between the animal and vegetal poles of the zygote (Gurdon et al., 1997).

The take-home message from this experience was the realization that the smallest functional unit of biology is the cell (Torday and Rehan, 2012), as had been concluded by Schleiden and Schwann in the mid-nineteenth century (Tavassoli, 1980). The reason for the long hiatus between the top-down and bottom-up approaches to development was the prevailing 'machine' concept

of the organism (Nicholson, 2012; Moss, 2012), i.e. that the whole is equal to the sum of its parts. That perception persists in biology today, DNA-RNA-protein being the "central dogma" for molecular biology and the Modern Evolutionary Synthesis alike (Crick, 1970).

The irony is that the cellular evolutionary principle is predictive (Torday, 2015a), whereas the molecular biologic approach is not. On the one hand, the cell-cell communication model predicts the maturation of the lung after a cortisol challenge (Torday and Rehan, 2007); the molecular model cannot predict whether someone will develop a specific disease, only that there is an association or correlation (Ioannidis, 2005). In the steps leading up to the publication of the Human Genome, it was hypothesized that hominins would have at least 100,000 genes based on the analogy to other so-called simpler organisms. As it turns out, we hominins have fewer genes than a carrot (19,000 vs 40,000). One would think that this would challenge the existing paradigm, but nothing has changed in the interim.

1.6. The first principles of physiology

When the lipids in the primordial oceans coalesced to form micelles (Deamer, 2017) they naturally separated the internal milieu of the cell (Deamer, 2017) from the external environment. In doing so, they fostered negative entropy (Schrodinger, 1944), defying the Second Law of Thermodynamics, fueled by chemiosmosis and sustained and perpetuated by homeostasis. These are the FPPs (Torday and Rehan, 2012). The organism complies with these FPPs by monitoring the environment using homeostasis as its detection method. There is an evolved range that homeostasis can tolerate, beyond which molecular mechanisms cause remodeling of the cellular niches formed by developmental mechanisms (Storr et al., 2013). It is such so-called auto-engineering that underlies the process of evolution (Varela et al., 1974; Shapiro, 2011; Torday and Rehan 2012, 2017).

The FPPs must be adhered to for survival of the species, making it deterministic. On the other hand, homeostasis is the mechanism by which the organism monitors its environment, providing freedom to vary about its optimally evolved set point. If the limits of homeostatic control are breeched, the organism will remodel itself by defaulting to its earlier phylogenetic regulatory state to maintain homeostasis. As a result, the cells involved in the process of physiologic homeostasis can either regenerate the evolved homeostatic state, or revert to an earlier form (Bacallao and Fine, 1989; Torday, 2016b).

1.7. Ambiguity at the inception of life as the driving force behind biology

The partitioning of life from non-life was due to the lipid membrane delineating the protocell, forming negative entropy sustained by chemiosmosis, and controlled by homeostasis, or the FPPs (Torday and Rehan, 2017). The differential between the internal negentropy and the external entropy generated an ambiguity (Torday and Miller, 2017a) that is the life force that propels organisms to solve the problems presented by an ever-changing environment. We hominins recognize that ambiguity as 'original sin' or Karma in religious terms, as the life force biologically, or as consciousness psychologically. Nevertheless, it can now be understood as the consequence of the Faustian pact that life has made with the Laws of Physics, circumventing the Second Law of Thermodynamics. Traditionally, we have coped with the ambiguity using religion, myth, art, music, and literature. It is only over the course of the last five hundred years that we have employed science to systematically push back the curtain of fear created by the ambiguity, gaining insight to our origins as a species and how we have evolved. Darwin (1859) freed us from the Great Chain of Being, but did not provide us with a way of doing testable and refutable science, instead invoking Natural Selection as the metaphoric 'mechanism' of evolution. However, the cellular-molecular approach to evolution does provide such a Popper (2002) testable and refutable means.

1.8. Biology, evolution and physics are scale-free

Seen from its unicellular origins, biology and evolution are scale-free, based on cell-cell interactions mediated by soluble growth factors and their cognate receptors at every level of physiology. By contrast, physics appears to be scalar, requiring different math at the micro- and macro levels, inferring a fundamental difference between them. However, Kafatos et al. (2005) have resolved these differences of scale, allowing for biology being self-referential and self-organizational based on physical principles for its own ends after all (Varela et al., 1974). By internalizing the environment to formulate physiology, biology has authored its own set of FPPs (Torday and Rehan, 2012), functioning between the boundaries of determinism and Free Will. As such, it is autonomous, having to comply with the Laws of Physics, not in a direct manner, but as a pseudo-physical construct. This relationship between biology and physics has been made possible by internalizing and assimilating physical factors like heavy metals, ions and gases, making them work for the perpetuation of negentropy (Schrodinger, 1944). In turn, biology has been able to invent such circumventions as simple and compound machines, aerodynamic foils and gravity-feed toilets.

1.9. Deception in biology

The FPPs have permitted the cell to circumvent the Second Law of Thermodynamics. The success of this initiating deception has permeated all of life (Trivers, 2011). In seeking to sustain this condition in order to maintain homeostatic status, living systems must confront a constant stream of ambiguous information. Cells cope with this constant flux through epigenetic accommodations (Cheedipudi et al., 2014) and niche construction (Torday, 2016a), the organism generating its own immediate environment. The cellular response to metabolic demands and external environmental stresses through self-organizing, self-referential adaptations, therefore represents the crux of evolutionary development. When considered within this perspective, many dogmatic aspects of selection-biased evolution can be re-appraised as a continuum of self-referential cells solving external environmental problems by remodeling their internal milieus. Despite flexible temporary adjustments to transient stresses, the eukaryotic cellular form remains permanently anchored within cellular First Principles extending ever-forward without substantial deviation from its unicellular origins (Torday and Rehan, 2012).

1.10. Terminal addition as 'proof of principle' for the unity

Terminal Addition is one of the classic dogmas of biology, citing the fact that as new traits appear they are added at the end of evolutionary sequences, both developmentally and phylogenetically. However, when seen as a manifestation of the evolutionary communication between cells for embryologic development (Torday and Miller, 2017b), homeostasis and phylogeny (Torday and Rehan, 2012), the fundament of The Singularity is revealed.

These interrelationships are best exemplified by the cellular-molecular mechanisms that evolved during the water-land transition (Torday and Insel, 2013). Three gene duplications occurred during that era. They were all for receptor genes-namely,

Parathyroid Hormone-related Protein (PTHrP), βAdrenergic, and glucocorticoid. It is probably not a coincidence that all three duplications were for receptors rather than their ligands because the receptor-mediated pathways evolved by terminal addition (Torday and Miller, 2017b), the down-stream ligand-receptor-mediated cell-cell interactions having evolved to provide homeostatic stability iteratively over the course of phylogeny and ontogeny. Amplification of the receptor component is far more bioenergetically efficient than augmenting its ligand, the receptor having an innate multiplier effect. The gross structural homologs of these signaling pathways are what are usually focused on in describing terminal addition. However, it is actually the underlying cellular-molecular components that are being selected. The growth factor ligands are elaborated by one cell-type, whereas the growth factor receptors are elaborated by a neighboring cell-type from a different embryonic germ layer. The receptor then elaborates a so-called 'second messenger' that ultimately communicates to the nucleus of the cell through a series of intermediate steps, binding to DNA polymerase to synthesize RNA, which then stimulates the biosynthesis of a peptide that facilitates the metabolic function of the pathway involved.

It is instructive to compare and contrast the consequences of the above-mentioned receptor gene duplications that occurred during the water-land transition to those that affected structural proteins such as the type IV collagen isotype involved in Goodpasture's Disease (MacDonald et al., 2006). The Goodpasture's Disease Type IV collagen isotype prevents water and electrolyte loss across the alveolar and glomerular walls because it has several amino acid substitutions that are hydrophobic. The other examples are the isotypes of hemoglobin (Natarajan et al., 2016) that facilitated oxygen carrying capacity over evolutionary time. In the case of the receptor duplications, there is minimal evidence for them causing disease (Dorn, 2010). However, in the case of the type IV collagen isomer, Goodpasture's Disease due to said type IV collagen isotype can cause respiratory and kidney failure, resulting in death (Greco et al., 2015); as for the hemoglobin polymorphisms, they are well-known to cause specific genetic diseases (Smith and Orkin, 2016). The difference between the receptor mutations and those of the Type IV Collagen and hemoglobins is that in the case of the former they were terminal additions that had to conform evolutionarily with the up-stream earlier metabolic signaling cascades, whereas in the case of the latter they were ad hoc measures that did not comply with atavistic evolutionary constraints.

1.11. Proximate and ultimate aspects of evolution No more

To solidify the nature of evolution, Ernst Mayr published a landmark paper in 1952 stating that there was a fundamental difference between the biologic traits underpinning evolution and the mechanism of evolution itself, which he referred to as the proximate and ultimate aspects of the overall process of evolution (Mayr, 1961). The example he used was that of migratory birds. In the interim, we have learned a great deal about the reproductive physiology of birds, particularly how the wavelength of ambient light affects the pineal gland (Nishiwaki-Ohkawa and Yoshimura, 2016) to change reproductive physiology. Such data offer a seamless continuum from environmental light to the reproductive physiology of birds that explain how and why birds migrate. Many other cellular-molecular physiologic properties of vertebrates are now known that offer an understanding of evolution, ranging from the lung to the kidney, skin and brain.

1.12. Comparing apples with apples

Reduction of vertebrate evolution to the cellular-molecular level offers the means of effectively interfacing biology with the physical environment (Torday and Miller, 2016a). Although there is no direct evidence for the molecular origins of life, subsequent steps in vertebrate evolution are well documented. Konrad Bloch (1992) hypothesized that cholesterol was a 'molecular fossil' since it took 11 atoms of oxygen to synthesize one molecule of cholesterol. Cholesterol subsequently provided the structural basis for lipid rafts, which form physical the base for cell surface receptors for cell-cell signaling (Head et al., 2014). Accumulation of carbon dioxide during the early phase of unicellular vertebrate evolution led to increased calcium in the water due to the formation of carbonic acid. Excess calcium caused endoplasmic reticulum stress, which was met by the evolution of the peroxisome (De Duve, 1969). The 'greenhouse' effect subsequently caused rising atmospheric temperatures, drying up bodies of water (Romer, 1949), driving some vertebrates out of the water on to land. The skeletal changes during the adaptation to land were well documented and widely accepted (Clack, 2012), but the effect on the visceral organs was overlooked. It was the experimental deletion of the PTHrP gene that highlighted the role of this bone calcium regulatory hormone in the lung (Rubin et al., 2004), kidney (Hochane et al., 2013), skin (Philbrick, 1998) and brain (Gu et al., 2012). That, in combination with evidence that the PTHrP Receptor gene duplicated during the water-land transition offered the opportunity to invoke an evolutionary mechanism (Pinheiro et al., 2012). The consequences of the adaptation to land can be seen in the physiologic stresses on cell-cell communication in various organs-lung, kidney, skin, bone, brain-allowing for the cell-molecular changes that mediated these tissue-level changes for land adaptations. Direct effects of such environmental factors as oxygen (Berner et al., 2007) and gravity (Torday, 2003) on morphologic changes allowed for connections between the physical and biologic environments that constituted evolution. This was the first time that evolutionary changes were directly attributed to known sequential geophysical changes in the environment (Torday and Rehan, 2011).

1.13. The mechanism of epigenetic inheritance infers the primacy of the unicellular state

Lamarck invoked epigenetic inheritance in the 18th Century, but was unable to provide scientific evidence to support his hypothesis. It was not until recently that direct inheritance of epigenetic 'marks' from the environment was shown (Skinner, 2015). Such so-called marks appear in the gonadocytes of both males and females, and are passed on to the offspring during reproduction. During meiosis a yet to be determined mechanism sorts out which epigenetic marks are retained or discarded (Schaefer and Nadeau, 2015). Nevertheless, the evidence is that the gametes determine the epigenetics of the offspring not the adults as dictated by Darwinian evolution.

1.14. Pauli exclusion principle and the first principles of physiology

As mentioned in the Introduction, Mendeleev was successful in formulating a Periodic Table of Elements because he identified atomic number as a 'common denominator' that normalized the data. Beyond that, it was Quantum Mechanics that provided the explanation for this phenomenon. As expressed by Harold Morowitz in his book "The Emergence of Everything" (2004), when the primordial 'soup' generated by the Big Bang finally cooled the particles, electrons and photons came together and matter emerged. The determining factor is that electrons interact with nuclei in certain quantum states designated as orbits. The interaction of an electron with a nucleus is characterized by four quantum numbers-n, the principal quantum number, ℓ, the angular

momentum quantum number, m_ℓ, the magnetic quantum number, and m_s, the spin quantum number. The quantum mechanical solutions are the interaction rules, which yield probability distributions for the distribution of the electrons around the nucleus. The Pauli Exclusion Principle demands that no two electrons in an atom or molecule can have the same four quantum numbers, three in space and one in time.

The Pauli Exclusion Principle (PEP) led to the arrangement of electrons and nuclei that resulted in the Periodic Table of the Elements, chemical bonding and the different states of matter. This property of matter begins to explain how and why the whole is not equal to the sum of its parts, given that the PEP dictates the behavior of two or more electrons, not one electron in isolation. And the fact that the quantum state of the first electron determines that of the second electron confers a noetic character, or logic to the Universe.

"Similarly, the FPPs - negentropy, chemiosmosis and homeostasis-act to both determine the constraints on biology and the capacity of homeostasis to confer 'Free Will'. Moreover, physics has a 'non-localization' or 'action at a distance' aspect to it that renders it holistic (Bohm and Hiley, 1975). The same holds true for biology in the form of pleiotropy (Torday, 2015b) - the distribution of the same gene in different structures and functions throughout the organism, reflecting the capacity to invent novelty holistically. The evolutionary distribution of such pleiotropic genes is founded on the pre-adaptive exaptations (Gould and Vrba, 1982) that facilitate the repurposing of the same gene under the pressure of new existential threats. Mechanistically, pleiotropic genes are selected for based on the FPPs, and under physiologic stress, such pleiotropic genes will act synergistically as a functional network, forming an electrochemical field to maintain allostasis (Torday, 2018)."

1.15. Non-localization in physics and biology

The notion of non-localization has been discussed at length by Bohm and Hiley (1975). They highlight the fact that the essential new quality implied by the quantum theory is non-locality; i.e., that a system cannot be analyzed into parts whose basic properties do not depend on the state of the whole system. They show that this approach implies a new universal type of description, in which the standard or canonical form is always supersystem-system-subsystem; and this leads to the radically new notion of unbroken wholeness of the entire Universe.

Biology ascribes to the same principle. It is not apparent when seen from a synchronic, descriptive vantage point, but when understood from a diachronic perspective, transcending space and time, it can be understood in the same terms used by Bohm and Hiley for quantum physics. This way of thinking about biology in cellular-molecular terms is exemplified by re-examining pleiotropy (Torday, 2015b). In contrast to the stochastic way of conventionally thinking about pleiotropy as the random expression of genes throughout the organism to generate more than one distinct phenotypic trait, it is actually a deterministic consequence of the evolution of complex physiology based on The FPPs in the unicellular state. Pleiotropisms emerge through recombinations and permutations of cell-cell communication established during meiosis based on the history of the organism, both developmentally and phylogenetically, in service to the present and future existential needs of the organism. Functional homologies ranging from the lung to the kidney, skin, brain, thyroid and pituitary exemplify the evolutionary mechanistic strategy of pleiotropy. The power of this perspective is exemplified by the resolution, for example, of evolutionary gradualism (Darwin, 1859) and punctuated equilibrium (Eldredge et al., 1972) in much the same way that Niels Bohr resolved the paradoxical wave-particle duality of light as Complementarity (Selleri, 2012). Hence, seen in this way, biology and physics are both non-localized, acting at all scales to form and maintain their integrated entirety.

1.16. Life as fractals

As a disclaimer, the following concept of physiology as fractal is not descriptive "turtles all the way down", it is founded on adherence to the FPPs, starting with unicellular organisms, all the way up to complex physiology (Torday and Rehan, 2012). This way of understanding the evolution of physiology comes from an understanding of the ecological niche in which we evolved and how our bodies responded, through cell-cell communication, and physiological regulation of genes, to the signals provided by the environment (Torday, 2016a). At the root of this approach is an appreciation for the fractal nature of physiology, founded on the ubiquity of the cell membrane (Torday and Rehan, 2017), facilitating oxygenation, metabolism and locomotion from the insertion of cholesterol into the cell membrane (Bloch, 1992). The self-similarity of physiology at different scales is important because it demonstrates the universality of the underlying self-referential, self-organizing principle involved.

The on-going discovery of deep homologies in the physiological systems of widely disparate taxa underscores the fractal nature of physiological processes. To start, a fractal is a mathematical pattern—it is the math that underlies the dynamics of natural systems—and it drives the evolution of phenomena via a basic function that repeats itself across all scales of time and space, producing self-similarity on all levels of inspection. The similarity of ontogeny and phylogeny are not being claimed to have resulted from selection acting independently on different processes (development of a trait versus the evolution of traits). Instead, it is being claimed that the processes of ontogeny and phylogeny are one and the same, operating at different time scales. Upon inspection of molecular traits, ontogenetically (within an individual across time) and phylogenetically (across generations of individuals), they appear in specific sequences on both time scales. The genes expressed earliest in ontogeny (i.e., immediately following conception) are those that are phylogenetically most ancient. Genes expressed late in development are those that evolved more recently and have a much narrower phylogenetic distribution (Roux and Robinson-Rechavi, 2008).

When physiologic traits are 'stressed', they can recall the cell-cell interactive signaling patterns for the trajectory that they followed in the forward direction developmentally and phylogenetically, only now in the reverse direction, suggesting that there is a common zygotic origin for all evolved traits, iteratively referring all the way back to the unicellular state. Conversely, if physiologic traits were due to Darwinian random mutations there would be no such pathways leading back to the FPPs, like a blueprint, only dead ends, literally. Organismally, this means that the dynamics playing out at the molecular level during chronic diseases are mediated by ligand-receptor signaling mechanisms at the cellular level, which can scale up during the regenerative process to produce both organ and organ system level allostatic interactions that culminate holistically in integrated physiology.

These fractal interrelationships may reflect the mechanism for the evolution of the internal cellular environment, or physiology, in adaptation to the external environment (Torday and Rehan, 2012). The external environment was formed from the Singularity/Big Bang (Singh, 2005), which we now have evidence for empirically because the Universe references that event through the phenomenon of the background radiation referred to as the Redshift, providing a 'point source' for the origin of the Universe. In contrast to this, physiology mimics the external Universe to form its own

internal environment, or milieu interieur (Bernard, 1957), homeostasis being its iterative, self-referential, self-organizational framework as an emerging concept in evolution theory (Torday and Rehan, 2012). The cause for the self-referential self-organizational properties of both the inanimate and animate may derive from the action caused by the Big Bang, generating an equal and opposite reaction based on Newton's Third Law of Motion.

This pattern is shared by all living beings. For example, Brad Davidson has shown that developmentally, the stem cells for the heart in the tunicate *Ciona intestinalis* are derived from the tail, suggesting that the beating of the tail for locomotion has been exapted for heartbeat (Davidson, 2007). Unicellular organisms do not require a heart or a circulatory system, suggesting that the heart evolved in support of fundamental biologic traits like respiration, metabolism, and locomotion in multicellular organisms. That is, the heart is derivative. Exaptations such as the evolution of the middle ear bones in vertebrates from the jaw bones of early fishes, have generally provided powerful clues to the ancestry of structures, and reveal the repeating process of evolution through innovation from preexisting conditions (Tucker et al., 2004; Downs et al., 2008). Similarly, the brain may have a history in response to the demand for central control of the evolving viscera organ systems for respiration, digestion, barrier function, and movement (Bronner and Le Douarin, 2012; Obermayr et al., 2013).

Reaching further into the past, the evolution of semi-permeable cell membranes provides an informative example of how fractal processes influence human beings' nutritional needs in the modern day. The following thoughts may be helpful in thinking about fractal physiology and nutrition. Biology entrained energy via semi-permeable membranes, promoting the reduction in entropy that is the 'metabolic driver' for evolution as a way of perpetuating that mechanism (Torday and Rehan, 2012). For example, the entraining of cholesterol in the plasma membrane facilitated both endocytosis and exocytosis by eukaryotes, and aerobic respiration by thinning out the membrane, making it more permeable for gas exchange. Another process in this context is chemiosmosis, the theory that forming semi-permeable membranes allowed for the creation of ionic gradients that are fundamental to generating the 'vital force' of life. The entropy and chemiosmosis mechanisms are complementary in their mutual dependence on the existence of a semi-permeable membrane. As these processes evolved, they had to cope with thermodynamics in a hierarchical manner. Cholesterol subsequently was exapted to facilitate the formation of lipid rafts, which are the structural basis for cell-cell signaling, ultimately culminating in the synthesis of steroid hormones to form the endocrine system. That interrelationship has been serially reiterated in evolution, particularly as vertebrates emerged from water to land (Bridgham et al., 2006; Torday and Rehan, 2011), tracing the arc of physiologic evolution fractally from unicellular to multicellular organisms, from simple to complex physiology.

2. Consciousness, the Epitome of the continuum from inanimate to animate

As indicated above, the case can be made for the interrelationship between the physical and biologic realms based on the 'logic' of each. The consideration of consciousness as the interface between the two (Torday and Miller, 2016b) forms the conduit for the flow of information between the inanimate and animate. This is what is referred to in the literature as the 'hard' problem, the very nature of what consciousness is, which has been debated for thousands of years. By providing a level playing field between the atom and the cell (Torday and Miller, 2016a), in combination with such concepts and the non-locality of both, the bigger venue of consciousness has become soluble.

3. Discussion

Recognition of the continuum of biology is way overdue, both because it must be a predictive science on par with chemistry and physics (Birks, 1962), and in order to effectively utilize all of the 'omics' now available to biology and medicine. It appears that the constraint on realizing this has largely been historic, due to the overarching of cell biology by genetics (Smocovitis, 1996). Even with the newly recognized relevance of developmental biology to evolution, or EvoDevo (Hall, 2003) as 'all of biology' (Dobzhansky, 1973), cell biology, which is the fundament of embryology (Slack, 2014) has been absent until now. With the recognition of the centrality of cell-cell communication in evolution (Torday and Rehan 2007, 2012, 2017), many dogmas of biology have been redefined in mechanistic terms (Torday 2015a, 2015b, 2015c, 2016c), offering transparency for biology that was untenable in the descriptive, dogmatic convention. As a result, the language of biology changes, constituting a paradigm shift according to Thomas Kuhn (1962) in his classic book "The Structure of Scientific Revolutions". Importantly, this enlightened view of biology has led to the novel recognition of the FPPs (Torday and Rehan, 2012) and A Central Theory of Biology (Torday, 2015b) predicting the advent of endothermy based on developmental and phylogenetic physiologic principles instead of ex post facto rationalization (Bennett and Ruben, 1979). Such insights are on par with Heliocentrism, the recognition that the Sun is the center of the Solar System. Like that event, the displacement of hominins from the center of the biosphere offers a new vista for understanding our place in the biologic 'universe'. This realization is critically important to a world of Climate Change, Artificial Intelligence and genetic engineering (CRISPER). There is great danger in misjudging the significance in the case of the former, and application in the case of the latter phenomena at this critical phase of hominin existence, tagged as the Anthropocene (Edwards, 2015; Steffen et al., 2011). Moreover, by understanding the principles of biology, we can formulate ways of affecting the arc of our evolution based on commensurate ethical principles rather than blindly invoking technological change, and then having to play 'catch up'. We can only hope that 'cooler heads' will prevail.

3.1. Conclusion

To read the works of Plato, Whyte (1949), Morowitz (2004) and Capra (2016), there is a continuous, on-going process in Nature that accounts for all that we see, from rocks to life, from flora to fauna. We are encouraged in this way of thinking by the ability, for example, to equate mass and energy, or to conceptualize the merging of all of knowledge as Consilience (Wilson, 1998). Yet the great physical scientists Polanyi (1968) and Prigogine and Stengers (1984) concluded that the relationship between physics and biology is just too complicated. The truth lies between these two realms. When confronted with this question, scientists have invariably sought the answer in mysticism and metaphysics. However, the key to the scientific approach is exemplified by the way that Mendeleev configured his version of the Periodic Table, identifying atomic number as the 'lowest common denominator'. There were others who attempted this feat, but failed to find the organizing principle behind the properties of the elements.

In a review article regarding the cellular-molecular perspective on evolution (Torday and Miller, 2016a), it was suggested that there are homologies between the atom and the cell that provide such a common denominator. For example, both the atom and the cell exhibit properties that are dependent on homeostasis, the electron in balance with the nucleus (Smolin, 1999), on the one hand, and the FPPs in balance with one another, on the other hand (Torday

and Miller, 2016a). That insight was gained by the reduction of biology to the unicell, communicating with its surroundings, both inanimate and animate, to foster life on Earth (Torday and Miller, 2016c), fulfilling the 'One' seen by the Greek Atomists such as Heraclitus and Anaximander. The power of this concept is in the empiric basis for it (Torday and Rehan 2012, 2017), offering a scientific means of exploiting the Information explosion occurring all around us.

Acknowledgement

NIH Grant HL055268.

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