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Serial Endosymbiosis Theory: From biology to astronomy and back to the origin of life

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Abstract

Serial Endosymbiosis Theory, or SET, was conceived and developed by Lynn Margulis, to explain the greatest discontinuity in the history of life, the origin of eukaryotic cells. Some predictions of SET, namely the origin of mitochondria and chloroplasts, withstood the test of the most recent evidence from a variety of disciplines including phylogenetics, biochemistry, and cell biology. Even though some other predictions fared less well, SET remains a seminal theory in biology. In this paper, I focus on two aspects of SET. First, using the concept of "universal symbiogenesis", developed by Freeman Dyson to search for commonalities in astronomy and biology, I propose that SET can be extended beyond eukaryogenesis. The extension refers to the possibility that even prokaryotic organisms, themselves subject to the process of symbiogenesis in SET, could have emerged symbiotically. Second, I contrast a recent "viral eukaryogenesis" hypothesis, according to which the nucleus evolved from a complex DNA virus, with a view closer to SET, according to which the nucleus evolved through the interplay of the archaeal host, the eubacterial symbiont, and a non-LTR transposon, or telomerase. Viruses joined in later, through the process of viral endogenization, to shape eukaryotic chromosomes in the process of karyotype evolution. These two proposals based on SET are a testament to its longevity as a scientific theory.

Keywords: Symbiosis, evolution, eukaryogenesis, the origin of life.

In science a bridge is a theory. When bridges are to be built, theoretical scientists may have a useful role to play. Lynn Margulis is one of the chief bridgebuilders in modern biology. She built a bridge between facts of cellular anatomy and the facts of molecular genetics. Her bridge was the idea that parasitism and symbiosis were the driving forces in the evolution of cellular complexity. She did not invent this idea, but she was the most active promoter and systematizer.

Dyson, 1999, p 14.

Biology textbooks define symbiosis anthropocentrically – as mutually helpful relationships or animal benefits, implying social contract or cost-benefit analysis by the partners. This definition is silly – symbiosis is a widespread biological phenomenon that preceded by eons the human world and the invention of money.

Margulis, 1990.

1. Introduction

The biological world is replete with ecological interdependencies. For example, the human body is as much a corporate individual, as it is an ecological collective in which viruses, bacteria, archaea, and fungi of the human microbiome, live in symbiosis with trillions of human cells, themselves products of a symbiotic partnership between archaea and bacteria. These ecological interdependencies that become corporate bodies are known as holobionts (Margulis 1993; Zilber-Rosenberg and Rosenberg, 2008). There is even a recognition that the human genome is a hologenome: three genomes in one, mitochondrial, human, and the genome of the human microbiome (Moran and Sloan, 2015).

In the continental tradition of biology ecological interdependencies have been considered drivers of evolution since the 19th century (reviewed in Carapiço, 2015; Gontier 2007; 2015). Andreas Schimper (1856-1901) and Anton de Barry (1831-1888) in German-speaking countries, and Konstantin Mereschowsky (1855-1921), Andrei Famintsyn (1835-1918) and Boris Kozo-Polyanskiy (1890-1957) in Russia, promoted the idea of a hereditary association between different organisms, that becomes permanent and irreversible. They referred to the origin of eukaryotic cells in which mitochondria and chloroplasts, former bacteria that once lived independently, entered into a permanent and hereditary partnership with larger prokaryotic cells. Paul Portier (1866-1962) in France and Ivan Wallin (1883-1969) in the US developed these ideas further. Despite the enthusiasm of early proponents, symbiosis research was often ridiculed in mainstream academic circles. For example, Ivan Wallin's idea of symbiogenesis was criticised so heavily that he was forced to abandon it. Similarly, Paul Portier was attacked by the French academic community (Margulis 1990).

However, Lynn Margulis synthesized and refined all the relevant evidence in her Serial Endosymbiosis Theory (SET). The starting point was the seminal paper in the *Journal of Theoretical Biology* (as Sagan 1967), followed by further studies (e.g. Margulis 1970, 1991, 1998; Margulis et al. 2006). Margulis argued that the living world is divided into two categories of biological entities, prokaryotes, and eukaryotes. This is the greatest discontinuity in the history of life, according to Margulis. She credited a French biologist, Édouard Chatton (1883-1947), and the Delft School of Microbiology (A.J. Kluver [1888-1956], Cornelius Van Neil [1897-1985] and Roger Stanier [1916-1982]) for this discovery (Margulis 2004). Given that the presence of the nucleus is the key feature that uniquely separates eukaryotes from prokaryotes, the purpose of SET was to describe the origin of nucleated cells.

All eukaryotes evolved by symbiotic mergers, in contrast to prokaryotes. According to SET, the first merger occurred between fermenting thermoplasma-like archaeobacteria and motile spirochete-like eubacteria, leading to the first anaerobe eukaryotic cells. The second merger occurred between the eukaryotic anaerobe cells and oxygen respiring proteobacteria, which turned into mitochondria. This endosymbiotic partnership resulted in the emergence of aerobic protists that evolved into fungi and animals. The third merger occurred when aerobic protists engulfed photosynthesizing cyanobacteria, which evolved into the plant kingdom.

Margulis (2004) defined symbiosis as living together of organisms of different species. For most of their life cycles, endosymbiosis is a form of living in which one prokaryotic partner lives inside another, and this partnership leads to eukaryogenesis. Symbiogenesis, on the other hand, "implies the appearance of new tissues, new organs, physiologies or other new features that result from protracted symbiotic association" (Margulis, 2004).

The 50th anniversary of Margulis' seminal paper was marked by the special issues of the *Journal for Theoretical Biology* (<https://www.sciencedirect.com/journal/journal-of-theoretical-biology/vol/434/suppl/C>). SET was examined critically by experts ranging from geneticists and molecular biologists, to biochemists, ecologists, and theoretical biologists, in light of the most recent evidence including phylogenetics, biochemistry, and ecology. The consensus was that predictions made by SET, concerned with the origin of mitochondria and chloroplasts, have been fully vindicated (see for example Martin 2017; Lopez-Garcia et al. 2017; Lane 2017). However, other predictions of SET fared less well. The heaviest criticism was directed towards the idea of the spirochete symbiont (e.g. Martin 2017; Lane 2017; Sato 2017). Furthermore, SET was thought to be wrong in predicting that the emergence of mitochondria was driven by the heavy presence of oxygen in the atmosphere (Martin 2017; Lane 2017). The key piece of evidence contradicting this aspect of SET was the discovery of anaerobic, H₂ producing hydrogenosomes, and mitosomes, which are forms of mitochondria (reviewed in Embley and Martin 2006). Finally, Martin (2017) and Lane (2017) questioned the type of the host cell for the origin of mitochondria in light of recent phylogenetic evidence.

The aim of this paper is twofold. First, I will argue that SET can be extended beyond events predicted by Margulis, based on the concept of 'Universal symbiogenesis' proposed by Freeman Dyson (1998; 1999) (section 2). [Useful reviews of Dyson's concept can be found in Gontier (2007; 2012; 2015)]. Inspired by Margulis, Dyson argued that symbiogenesis is as much an astronomical phenomenon, as it is a biological one. I will critically examine Dyson's claims and apply them to SET to expand it beyond eukaryogenesis. Second, the processes behind the emergence of the nucleus in the first endosymbiotic event remain neglected. I will outline a new look at the origin of the nucleus and eukaryotic chromosomes that contrasts a recent hypothesis according to which the nucleus has the viral origin (Section 3).

2. SET in the dual context of astronomy and biology

2.1 Dyson's "Universal symbiogenesis"

Freeman Dyson invented many novel concepts in physics and astronomy. His imaginative mind was also intrigued by biology. He applied the concept of symbiogenesis to astronomy.

Symbiosis is as prevalent in the sky as it is in biology. Astronomers are accustomed to talking about symbiotic stars. Dyson 1998, p121.

When symbiosis is extended from biology to astronomy, we end up with what Dyson called 'universal symbiogenesis'. He argued that stars and other astronomical bodies emerge in the dual process: *speciation* followed by *symbiosis*. The term that physicists associate with the process of speciation is the phase transition or symmetry breaking – an abrupt change in the properties of matter caused by cooling or heating. For example, cooling causes precipitation of snowflakes from the water vapour in the atmosphere. Snowflakes are a new species exhibiting a crystalline structure that did not exist in the humid air before cooling. The action of gravity then separates snowflakes from the air and facilitates their fall on Earth.

Phase transitions, like the emergence of snowflakes, exist at all levels of cosmic evolution according to Dyson. In the earliest phase transition, the cosmos split into the phase containing mostly matter, and the phase containing mostly radiation that formed the intergalactic void. The

cosmos lost the original spatial symmetry early in its evolution. Lumps of matter held by their gravitation could radiate gravitational energy into the surrounding void. New phase transitions followed on the successively smaller scales until the galaxies, stars, and planets emerged.

All phase transitions share two features. First, the emergence of a structure that did not exist before (Dyson 1998, p 119). Second, the transfer of the 'newborn' structure into a different region of space (Dyson 1998, p 119). This means that the same process of speciation that characterises the emergence of snowflakes, applies to planets, stars, and galaxies.

Dyson then introduced the second principle of cosmic evolution - symbiosis¹. The lumps of matter that emerged in the act of cosmic speciation – galaxies, stars, planets, and even smaller bodies – were free to merge symbiotically, to produce new and more complex astronomical forms. Dyson was influenced by Lynn Margulis and other pioneers of the original symbiotic theory – in the first act of prokaryotic symbiosis, fermenting thermoplasma-like archaebacteria swallowed smaller bodies of proteobacteria (or archaeal hosts were infected by parasitic bacteria), that continued living inside the hosts. Swallowing of smaller bodies by bigger bodies occurs regularly at the cosmic level.

It happens frequently that big galaxies swallow small galaxies. Nuclei of swallowed galaxies are observed inside the swallower, like mouse bones inside the stomach of a snake. This form of symbiosis is known as galactic cannibalism. Dyson 1998, p122.

The processes behind speciation and symbiosis, which started at the cosmic level, are inherited by the process of life, according to Dyson. For this reason, he used the term 'universal symbiogenesis' – a feature that applies to the entire cosmos, not only to biological evolution. Thus life is just another form of symmetry breaking, or the latest phase transition in the cosmic evolution, followed by symbiosis. However, Dyson went further and proposed another hypothesis, this time concerned with the origin of life.

While for the large majority of thinkers interested in the origin of life, there is only one domain of life, meaning that life on Earth emerged once, Dyson argued that life originated twice. This is known as the 'double origin theory' – life has two domains rather than one. Dyson argued that the first domain of life was primitive cells in which protein chemistry dominated. These cells could reproduce by the process of cell division. However, they could not replicate, or produce exact copies of themselves, because they lacked the genetic apparatus of modern cells such as DNA- or RNA-based structures in charge of cellular memory². This first domain of life can be called *metabolism* (Dyson 1999).

¹ During the review of the paper, an anonymous reviewer asked "Doesn't this apply [universal symbiogenesis; my addition] to all levels of matter and energy and include the formation of all the complex elements?". This is an important question that is beyond the current paper but may be taken up by future research.

² Dyson made a distinction between reproduction and replication. While the process of replication represents a form of precise copying of a sequence of monomers covalently linked into a polymer (e.g. RNA or DNA), the process of reproduction may occur without the presence of polymers such as RNA and DNA. The process of reproduction involves preserving the early information carried in molecular sets, through the catalytic replication of the entire assembly of molecules that form the set. The process of preserving the biological information through RNA/DNA, or replication, is associated with the gene first hypothesis of life origin. The process of preserving biological information through reproduction is associated with the metabolism first hypothesis (for details see Text Box 2).

The second domain of life represented structures that contained RNA and DNA molecules, protected by a biological membrane. These structures were parasitic. They couldn't do anything unless they were swallowed by primitive cells acting as hosts. The second domain of life can be called *information* (Dyson 1999), more precisely the genetic information.

The two domains of life – metabolism (protein-based life) and genetic information (RNA or DNA-based life) – emerged separately, and then merged in the process of symbiosis, leading to the formation of replicating cells. As in the case of galactic cannibalism, or prokaryotic cannibalism, metabolising primitive cells lacking the genetic apparatus, swallowed parasitic structures that contained RNA or DNA, or the parasites containing RNA/DNA infected the hosts. The parasites then found a way to permanently integrate inside the bodies of hosts, by providing the genetic memory through interactions with proteins. In this symbiotic act, a modern replicating cell emerged, in the form of either bacteria or archaea. Here is a relevant quote from Dyson:

*The protein-based life learned to tolerate the RNA-based life. The parasite became a symbiont. And then, very slowly over millions of years, the protein-based life learned to make use of the capacity for exact replication that the chemical structure of RNA provided. The primal symbiosis of protein-based life and parasitic RNA grew gradually into a harmonious unity, the modern genetic apparatus. Dyson 1999. Kindle Locations 245-247. Kindle Edition.*³

2.2 Evidence in support of Dyson's arguments

Dyson was aware that his arguments might have been naïve because his research angle was biased towards physics and astronomy, rather than biology. Nevertheless, he thought he could offer a useful perspective on (i) the origin of life and (ii) similarities between the evolution of the cosmos and biological evolution (Dyson 1998; 1999).

His main argument can be split into two parts. The first part is concerned with the order of events in the origin of life. He argued that the following sequence of events was instrumental in the origin of life: cells first, enzymes second, and genes third. The second part of the argument was that the process of life could not work without the macro-process of homeostasis that orders metabolic processes and facilitates the emergence of a 'quasi-stationary equilibrium deserving the name life'. Let us examine each part of the argument.

2.2.1 The first part of the argument

Dyson was influenced by Oparin's theory of the origin of life when formulating his dictum: cells first, enzymes second, and genes third. He contrasted the above account of events with the view of Manfred Eigen, which is close to the proponents of the RNA world hypothesis, according to which the order of events was: genes first, enzymes second, cells third (Eigen 1996). Dyson developed a mathematical model to quantitate Oparin's theory (a summary of Dyson's mathematical model is presented in Text Box 1).

³ This citation and most citations in section 2.2.2 are from Dyson's book *Origins of Life*, Second Edition, 1999, Cambridge University Press. The quotes are taken from the Kindle edition of the book.

According to Oparin (1955), oily droplets mixed with water tended to form stable mixtures, named coacervates, that persisted in the water solution. The fact that coacervates can be formed as a result of non-biological processes, indicates that this was probably the first form of phase transition required for the origin of life on Earth.

Text Box 1

A summary of Dyson's mathematical model

Dyson aimed to convert Oparin's theory to a mathematically precise form. He achieved this in two stages. Stage one was a formal description of molecular populations within a bounded environment (Oparin's coacervates) in the manner of classical dynamical systems. Dyson used precise classical dynamics equations, but the laws that govern the interactions between molecular populations were set to be completely general. In stage two, this general theory was converted into a mathematical toy model governed by a simple and arbitrary rule for the probability of molecular interactions. Thus, Dyson's model represents the quantitative model of homeostasis, which allows the self-replication of molecular assemblies in the absence of genomes. In brief, molecular assemblies enclosed in bounded environments (Oparin's coacervates) consist of catalytically active and catalytically inactive monomers. The active monomers are capable of turning the inactive counterparts into active states resulting in the phenomenon of autocatalysis. Autocatalysis usually leads to an explosion of catalytically active molecules. However, Dyson's model includes a backward step, namely that some active molecules will become inactivated, thus preventing the exponential growth. The result is that steady states, typical of homeostasis, are reached in certain circumstances. Dyson's model shows that the organized metabolism will eventually emerge from the mixture of catalytically active and inactive monomers within a bounded environment. The average time required for the metabolism to emerge is the function of the monomer type and the ability of an active molecule to activate the inactive counterpart, combined with the total number of monomers. Dyson's model has been interpreted in great detail by Segré and Lancet (1999) and Segré et al., (2000). These authors praised the model and compared it against other models of homeostasis including that of Stuart Kauffman's (1995) and their model (Segré and Lancet 1999).

Life began when coacervates started to be filled with molecular populations, some of which led to the emergence of molecules that could catalyze chemical reactions within coacervates (Text Box 1).

These molecules, or enzymes, started organizing other molecular populations into metabolic cycles (Text Box 1), some of which persisted or become self-sustainable. Metabolically active coacervates gained the capacity to reproduce without the accuracy of replication that we see in modern cells. Dyson calls this "the garbage bag world" – coacervates collect all sorts of molecular material available in the environment. This garbage bag world of protocells that reproduce, will, with the help of natural selection, produce rare cells with the capacity to replicate, in the manner of the modern cell. The replication process is mediated by the integration of DNA or RNA molecules into the already existing metabolic pathways within the protocells, an event that

turns protocells into fully functioning, replicating cells. In life's later history these replicating cells, all prokaryotes, started merging symbiotically, to produce eukaryotes. Further symbiotic events occurred that lead to the formation of multi-cell organisms (King 2004; Woznica et al. 2016), ecological populations (Zilber-Rosenberg and Rosenberg 2008), and even human culture (Gontier 2007).

Interestingly, Dyson's theory is largely ignored by biologists, but it is taken up by chemists (e.g. Segré and Lancet 1999; Segré et al., 2000). More recently, Spitzer et al. (2015) offered a view of life origin from the perspective of physical chemistry remarkably similar to Dyson's account. The sources of energy on early Earth, including the solar diurnal disequilibria, and energies of chemical gradients at hydrothermal vents, induced repeated colloidal phase-separations that resulted in the emergence of 'micro-spaces' (Spitzer et al. 2015) – semi-permeable lipid-protein bags, similar to Dyson's 'garbage bags'. Spitzer et al. (2015) interpreted micro-spaces as 'enclosures of future cells'. The primitive micro-spaces turned into open thermodynamic systems – self-sustainable chemical units that could use the material and energy from the environment to grow and divide. The key to micro-spaces becoming open thermodynamic systems was the process termed 'molecular crowding' (Spitzer et al. 2015). The molecules involved in this process included macromolecules, ions, and electrolytes. The term 'molecular crowding' describes the cytological force that keeps molecules close to each other, so that "the non-covalent forces act over a commensurate distance of about one nanometer" (Spitzer et al. 2015). 'Molecular crowding' is impossible outside 'micro-spaces'. The process of molecular crowding diversified with time, leading to the emergence of catalyst molecules (enzymes) that organized groups of molecules into metabolic cycles. This prompted further chemical complexification inside the micro-spaces through the process of self-organization. The key things here are that the processes of 'molecular crowding' and molecular recognition required for self-organization cannot occur outside the confined spaces or 'micro-spaces'. Molecules with information storage capacity emerged (DNA and RNA) and this enabled the merger between the metabolic and informational processes. The chemistry of life was further refined by the process of homeostasis – a macro-scale series of events that unified numerous autonomous thermodynamic systems (cells) and stabilised their interactions with each other and the environment through feedback loops (Spitzer et al. 2015).

2.2.2 The second part of the argument

The second side of Dyson's arguments is related to the concept of homeostasis. He defined homeostasis in the following way:

Homeostasis is the machinery of chemical controls and feedback cycles that make sure that each molecular species in a cell is produced in the right proportion, not too much and not too little. Without homeostasis, there can be no ordered metabolism and no quasi-stationary equilibrium deserving the name of life. Dyson 1999, Kindle Locations 913-914, Kindle Edition.

Dyson's support for homeostasis as an important regulator of life processes highlighted two important things. First, Dyson thought that homeostasis research should become the central point of research in biology.

Half a century ago, Erwin Schrodinger suggested to biologists that they should investigate experimentally the molecular structure of the gene. That suggestion turned out to be timely. I am now suggesting that biologists investigate experimentally the population structure of homeostatic systems of molecules. If I am lucky, this suggestion may also turn out to be timely. Kindle Locations 965-967, Kindle Edition.

Second, placing a high value on the concept of homeostasis in the biology of the future, indicated that the gene-centric view (Dawkins 1976), in particular the concept of Modern Synthesis, should be re-evaluated.

The replicators were never as firmly in control as Dawkins imagined. In my version, the history of life is counterpoint music, a two-part invention with two voices, the voice of the replicators attempting to impose their selfish purposes upon the whole network and the voice of homeostasis tending to maximize the diversity of structure and flexibility of function. The tyranny of the replicators was always mitigated by the more ancient cooperative structure of homeostasis that was inherent in every organism. The rule of the genes was like the government of the old Hapsburg Empire: Despotism us gemildert durch Schlamperei, or "despotism tempered by sloppiness." Kindle Locations 1116-1117, Kindle Edition.

If we accept Dyson's view that regulators of life processes are not only genes but also the more ancient process of homeostasis, a new picture of the biological world opens up. In this new picture, the tyranny of replicators is in the background. What dominates the picture is symbiosis as a wide-ranging phenomenon universally present in the "quasi-stationary equilibrium deserving the name of life".

The Margulis picture of evolution converts the nucleic acids from their original status as indigestible by-products of ATP metabolism to disease agents, from disease agents to parasites, from parasites to symbionts, and finally from symbionts to fully integrated organs of the cell. Kindle Locations 1037-1039. Kindle Edition.

Finally, the concept of homeostasis in Dyson's interpretation always goes together with the concept of symbiogenesis. If symbiogenesis is a universal feature in the history of life, the same is true of homeostasis as a wide-ranging regulatory process. In other words, evolutionary echoes of homeostasis visible in primitive cells should also be visible in more complex biological processes including ecological relationships and the evolution of culture.

The concept of homeostasis can be transferred without difficulty from a molecular context to ecological, economic, and cultural contexts. In each area, we have the unexplained fact that complicated homeostatic mechanisms are more prevalent and seem to be more effective than simple ones. This is most spectacularly true in the domain of ecology, where a typical stable community, for example, a few acres of woodland or a few square feet of grassland, comprises thousands of diverse species with highly specialized and interdependent functions. But a similar phenomenon is visible in economic life and cultural

evolution. The open market economy and the culturally open society, notwithstanding all their failures and deficiencies, seem to possess robustness that centrally planned economies and culturally closed societies lack. Kindle Locations 1065-1072, Kindle Edition.

Dyson's views of homeostasis have not been taken up by biologists who remain, by and large, influenced by the gene-centric view of life processes (for the difference between the gene-centric view and homeostasis, see Text Box 2).

Text Box 2

Explaining life origin: homeostasis versus genes?

There are two major schools of thought concerned with the origin of life. The school that enjoys the greatest support stems from the notion of the "RNA world", or the genome first hypothesis (Gilbert 1986; Gesteland et al. 1999; Joyce 2002; Higgs and Lehman 2015), dubbed here the gene-centric school (GCS). The alternative school is based on the concepts from statistical chemistry, known variously as the "lipid world", metabolism-first hypothesis, or autocatalysis (Kauffman 1995; Dyson 1999; Segré and Lancet 1999; Segré et al. 2000; Lancet et al. 2018), dubbed here the homeostasis school (HS).

The key difference between the two schools is how they understand the concept of biological memory. Biological memory can be broadly defined as the transmission and preservation of biological information, from one generation of proto-cells/functional cells to the next.

GCS narrowly interprets biological memory. The biological information is transmitted and preserved exclusively through the genetic code. However, GCS fails to appreciate that molecules not covered by the genetic code – e.g. lipids and polysaccharides – contribute to the transmission of biological information in the equal measure as RNA and DNA (Segré and Lancet 1999; 2000; Lancet et al. 2018). For example, how do cells "determine" the amount of lipids required to complete the process of cell division? If there is no "lipid code" the genetic code would not work.

HS interprets biological memory more inclusively. The biological information is not only stored in RNA and DNA, but also in the metabolic composition (Kauffman 1995; Dyson 1999). Homeostatic growth models show that genome-free self-replication is possible through preserving compositional information – through "memorizing" relationships within molecular sets enclosed inside spontaneously assembled vesicles, such as Oparin's coacervates (Dyson 1999; Segré and Lancet 1999; Segré et al. 2000; Lancet et al. 2018). The genome-free self-replicating molecular sets, enclosed within coacervates, become enriched with nucleic-acid polymers, such as RNA and DNA (Segré and Lancet 1999; Segré et al. 2000; Lancet et al. 2018). Thus, HW integrates genetic information with metabolic information.

However, the outlook is changing. In a recent book, Turner (2017) presented a view of homeostasis that is remarkably similar to Dyson's. Turner was not shy to criticise the gene-centric view of biology.

Now, homeostasis does not derive from natural selection; it is homeostasis that drives selection, and there is nothing natural about it. What drives the course of evolution is not the soulless lottery of the gene pool, but life's striving for persistence. The striving is driven not by the luck of the lottery, but by the cognitive sense of self, even down to the smallest bacterium, even preceding, as I have argued, the emergence of life itself. Turner (2017) p292.

Similarly, Noble (2012) argued strongly in favour of homeostasis as the key regulator of biological processes:

So, how has mainstream biology tended to ignore it [homeostasis, my addition], as has physiology also with some exceptions, for example, Guyton's modelling of the circulation? I think the main culprit here has been neo-Darwinism and particularly the popularizations of this theory as a purely gene-centric view.

2.3 Extending SET with the help of "Universal symbiogenesis"

When Dyson's concept of "universal symbiogenesis" is applied to SET, an interesting possibility emerges – SET may go beyond eukaryogenesis. SET was concerned with the emergence of nucleated cells – composite cells formed by mergers of prokaryotic cells that once lived independently. However, Dyson's account suggests that even prokaryotic cells could have emerged through the process of symbiosis. This possibility was acknowledged by Segré and Lancet (1999) in their reviews of Dyson's mathematical model (see below). If we accept this possibility then SET can be extended as shown in Figure 1.

Let me outline the extension of SET. In the SET merger 1, there are two independent organisms, in merger 2 three organisms, and in merger 3 four organisms (Figure 1). All these prokaryotic organisms, when examined separately, before symbiotic mergers, can be considered autonomous natural agents because they are open thermodynamic systems, capable of exchanging energy, matter, and information with the environment (Slijepcevic 2018; 2019; 2020). The prokaryotic organisms, the simplest known cells, can also be considered cognitive agents because they are capable of sensing and interpreting information coming from the environment and exchanging the processed information with the environment (Lyon 2015; 2017; Slijepcevic 2019; 2020). When the four types of prokaryotes merge symbiotically, the result is the three types of composite cognitive agents, single-cell eukaryotic organisms (anaerobic prototists, aerobic prototists, and aerobic prototists with chloroplasts), from which multi-cellular natural agents emerge with evolutionary time, including fungi, plants, and animals (Figure 1).

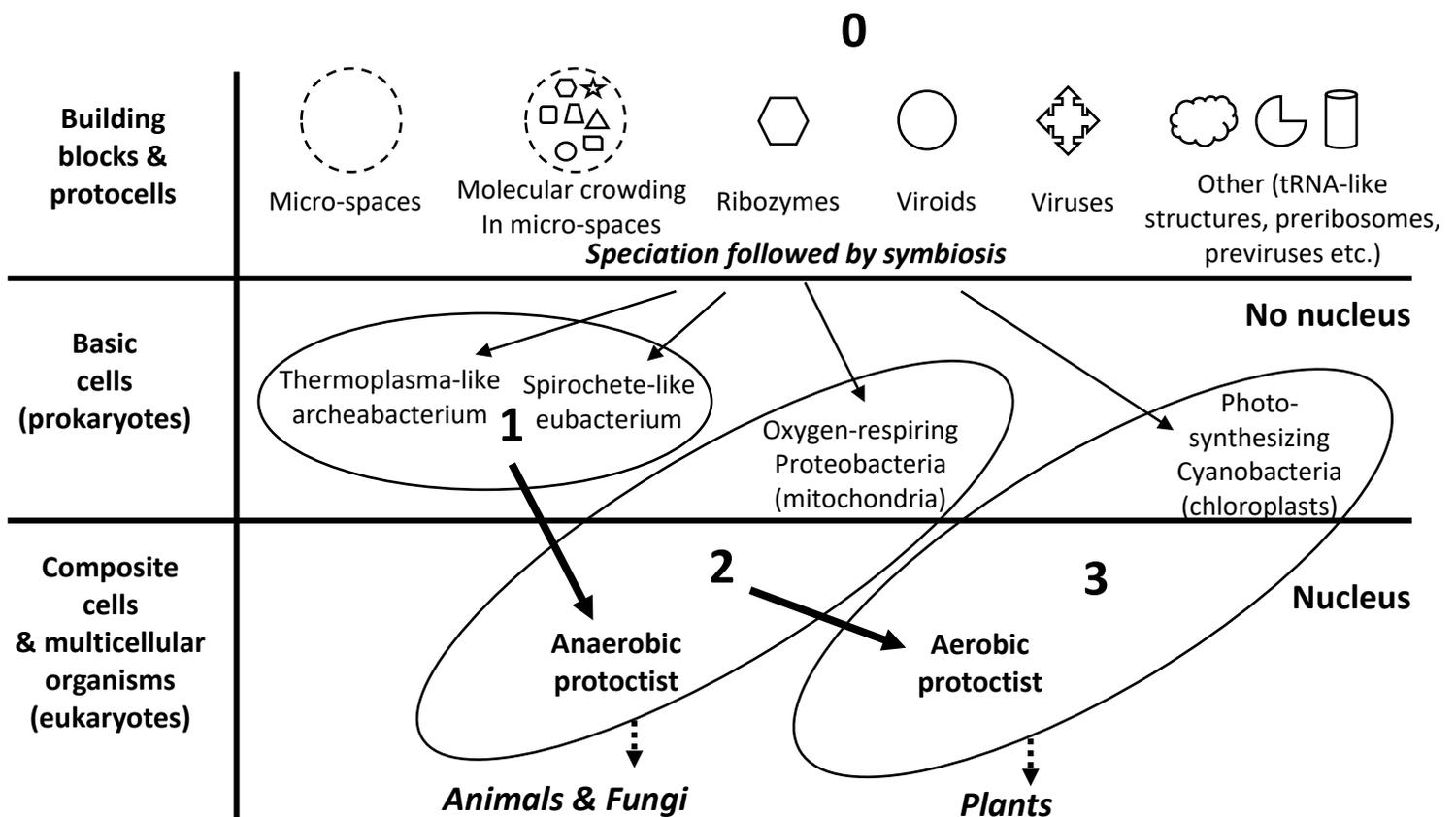


Figure 1. Extension of SET through introducing stage 0 (zero). The remaining stages (1-3) are already defined in SET. For details see the text.

The question that becomes apparent when we take account of Dyson's concept of universal symbiogenesis, is the following one. Was the process that led to the emergence of the simplest known cells, prokaryotes that include bacteria and archaea, also symbiotic? I would like to suggest that the answer is affirmative. This is in line with Dyson's interpretation of universal symbiogenesis: *speciation* followed by *symbiosis* (see also Figure 1; Text Boxes 1 and 2). Before prokaryotic cells emerged as autonomous and fully functioning natural agents, they must have been preceded by primitive proto-cells and their building blocks. This stage of cellular evolution, when we extend SET, is labelled stage 0 (zero) (Figure 1). Therefore, in the extended version of SET, stage 0 consists of (i) speciation, or the emergence of building blocks of cells, including micro-spaces that represent enclosures of future cells (Spitzer et al. 2015), macromolecules, and supramolecular biogenic structures such as ribozymes, viruses, viroids, and other structures such as tRNA (Dyson 1999), etc. and (ii) symbiosis, or the merger of building blocks in a specific order, starting with the molecular crowding of micro-spaces by macromolecules (Spitzer et al. 2015), the emergence of catalytic molecules or enzymes, that drive metabolic pathways within evolving micro-spaces that gradually become proto-cells (Dyson 1999; Segré and Lancet 1999; Segré et al. 2000; Lancet et al. 2018), combined with the emergence of supramolecular structures such as

viroids, viruses, ribozymes, etc, until fully functioning cells emerge in the form of bacteria and archaea that represent autonomous natural agents (Figure 1; Text Box 2).

The whole process, from the colloidal phase separation that yielded micro-spaces, and other forms of phase separation that yielded basic macromolecules, to the emergence of supramolecular structures that exist as parasites (e.g. viruses), is driven by solar energy and the energy of hydrothermal vents and regulated by the macro-process of homeostasis (Dyson 1999; Segré and Lancet 1999; Segré et al. 2000; Spitzer et al. 2015).

There is some evidence in support of the extended SET. First, amphiphilic vesicles, known variously as coacervate particles (Oparin 1955), proteinoid microspheres (Fox 1991), garbage bags (Dyson 1998), lipid vesicles (Luisi et al. 1999), micelles (Segré and Lancet 1999) and micro-spaces (Spitzer et al. 2015), which presumably emerged spontaneously and prebiotically, are considered cell precursors. These amphiphilic vesicles may be a *conditio sine qua non* for symbiotic events required for eukaryogenesis (Figure 1). For example, Segré and Lancet (1999) argued that amphiphilic vesicles can undergo fusion events that facilitate symbiosis. Therefore, the proposed stage 0 in extended SET (Figure 1) is essential because it identifies the prebiotic precursor required for all later symbiotic or fusion events in SET.

Second, the capacity of amphiphilic vesicles to promote symbiosis is demonstrated through the concept of a "compositional genome" (Segré et al. 2000; Segré and Lancet 1999). This concept provides an argument in support of the idea "[t]hat in a mixture of relatively simple chemicals, the array of relevant concentrations may be viewed as a vehicle for information storage." (Segré and Lancet 1999; see also Text Box 2). Thus, amphiphilic vesicles populated by simple chemicals already have the information transmission potential through metabolic information (Text Box 2). The information transmission potential becomes more sophisticated when polymers, such as RNA and DNA, integrate with the metabolising amphiphilic vesicles, generating the source of genetic information (Text Box 2). Integration of nucleic acid polymers with cell precursors is already a symbiotic event as shown in stage 0 (figure 1) because it entails the fusion between genome-free micro-spaces that contain a set of metabolising biomolecules and parasites that may contain nucleic-acid polymers.

It is important to stress that stage 0 in the extended SET probably contradicts the view, often expressed by Margulis, that symbiosis occurs exclusively between living beings. Indeed biogenic structures associated with stage 0, such as micro-spaces, ribozymes, viroids, viruses, and other elements (see Figure 1), cannot be characterized as living beings. For example, viruses are not considered alive by some authors because they cannot replicate without a cellular host (see for example Lopez-Garcia 2012). However, Koonin and Starokadomskyy (2016) argued that the process of life may be interpreted as the coevolution between hosts (living beings from bacteria to multicellular organisms) and parasites (e.g. selfish genetic elements such as viruses), in which parasites drive the evolution of complexity. Therefore, one of the purposes of stage 0 in SET is to (i) integrate viruses into the process of life and (ii) acknowledge the possibility that these parasitic genetic elements may become symbionts.

Nevertheless, stage 0 of extended SET is a testable hypothesis, meaning that future research should examine the validity of the above claims. One way of testing the extended SET is to employ already existing theoretical models. For example, Segré and Lancet (1999) and Segré et al. (2000) have generated the GARD (Graded Autocatalysis Replication Domain) model, that integrates Dyson's model (see Text Box 1) and the autocatalysis model of Stuart Kauffman (1995).

A further modification of the model, the Amphiphile GARD model (Segré and Lancet 1999), can be used to test whether the amphiphilic vesicles are indeed essential for all stages in SET, from 0 to 3 (Figure 1). The extended SET can also be tested experimentally. The most suitable experimental approach would be that used by Pier Luigi Luisi (e.g. Luisi et al. 1999; Capra and Luisi 2014, p 227-233). This would involve using amphiphilic particles, such as lipid vesicles, to populate them with various biomolecules to test (i) whether the molecular sets within vesicles can become autocatalytic and (ii) the symbiotic potential of metabolising vesicles, for example, whether they can take up nucleic-acid polymers to generate the merger between metabolic and genetic information.

3. Symbiotic eukaryogenesis

The title of this section is inspired by the 'viral eukaryogenesis' hypothesis (Bell 2001; 2020; Forterre, 2006). According to this hypothesis, the nucleus in eukaryotes evolved from the complex DNA virus (Bell 2001). The most recent version of the hypothesis suggests that unique features of the nucleus, including the uncoupling transcription from translation, are viral in origin, rather than cellular (Bell 2020). This contradicts SET's elaboration of the merger 1 (Figure 1), which explicitly argued that the process of eukaryogenesis included the interplay between two prokaryotic organisms, in particular the combinatorics between their genomes, without the influence of viruses. In this section, I will argue that the 'viral eukaryogenesis' hypothesis is difficult to accept given (i) more recent arguments (Koonin and Yutin, 2018; Krupovic et al. 2019) and (ii) a hypothesis that supports SET's elaboration of eukaryogenesis (Villasante et al. 2007). My alternative to the 'viral eukaryogenesis' hypothesis is named 'symbiotic eukaryogenesis', for the reasons that will become clear below.

The discovery of giant viruses sparked several speculations relevant to the early events in evolution. One of the most radical speculations was that giant viruses are the transitional form between viruses and bacteria (Moelling and Broecker, 2019). This speculation is supported by the analysis of the genome size and the physical size of giant viruses and bacteria. According to this view giant viruses accumulated enough molecular and supramolecular structures to turn them from parasites incapable of independent living, into fully functioning autonomous natural agents, not different from bacteria.

However, this hypothesis has recently been challenged (Koonin and Yutin, 2018; Krupovic et al. 2019). Instead of the 'virus first' hypothesis, according to which viruses do not belong to any of the three known domains of life (archaea, bacteria, and eukaryotes), and should have its fourth domain (Forterre 2006), the 'chimeric' scenario of the viral origin seems more likely. According to this scenario, viruses emerged from primordial selfish replicons and then re-emerged at all evolutionary stages (Krupovic et al. 2019), while giant viruses originated many times from smaller viruses and thus are not qualitatively different from the other virosphere members (Koonin and Yutin 2018). This also means that there is no continuity between viruses and bacteria. In other words, viruses remain cellular parasites, while giant viruses could not be a transitional form between viruses and cells.

When arguments presented by Krupovic et al. (2019) and Koonin and Yutin (2018) are contrasted with the arguments behind the 'viral eukaryogenesis' hypothesis, it turns out that it is difficult to accept the scenario in which a complex DNA virus was solely responsible for the emergence of the nucleus. It seems more likely that viruses played a role in the nuclear evolution,

but not the central role. For example, the emergence of the nucleus is primarily a co-adaption between the archaeal host and the bacterial endosymbiont, including combinatorics between their genomes (Speijer 2020) in which virus-like mobile genetic elements play an auxiliary role (Villasante et al. 2007).

In line with this argument, proponents of the 'viral eukaryogenesis' hypothesis use telomerase and telomeres, the essential parts of eukaryotic chromosomes, as evidence for their hypothesis, but ignore other essential elements of eukaryotic chromosomes such as centromeres. According to Nakamura and Cech (1998), phylogenetic analysis places telomerase in the group of parasitic genetic elements that belong to the class of non-LTR retrotransposons. Thus it seems unlikely that telomerase is a former virus, although it is evolutionarily related to retroviruses. This does not contradict the 'viral eukaryogenesis' hypothesis directly, because the hypothetical complex virus from which the nucleus evolved could have acquired telomerase. However, the 'viral eukaryogenesis' hypothesis fails to appreciate the complexities of eukaryotic chromosomes which could not evolve solely from the viral DNA. For example, proteins that dominate in eukaryotic chromosomes are histone proteins, not found in viral and bacterial genomes (Witzany 2008), but are present in archaeal genomes in the simpler form (Mattioroli et al. 2017). The question that remains unanswered is how the virus could have contributed to the transition from the simpler archaeal histones to the more complex eukaryotic histones. Furthermore, gene regulations in eukaryotes are influenced by epigenetic mechanisms, emanating from the chromatin organisation and the presence of histone protein chemical modifications. On the other hand epigenetic mechanisms, as seen in eukaryotes, are largely absent from viral, bacterial, and archaeal genomes. Finally, the main weakness of the 'viral eukaryogenesis' hypothesis is the separation of the eukaryotic cell structure into the archaeal cytoplasm, the viral nucleus, and the bacterial mitochondrion (Bell 2020). This possibility ignores the co-adaptation between the three biogenic structures (Speijer 2020) that may lead to (i) the emergent new forms in the proto-eukaryotic cell and (ii) the implausibility that the strict structure separation brought about by the symbionts is retained by the new emergent forms.

These findings argue that the nucleus is a complex and composite structure, that evolved through the process in which genomes of the archaeal host and the bacterial symbiont combined (Villasante et al. 2007). These combinatorics were enriched by additional independent elements such as retrotransposons, viruses, and other mobile elements. For example, telomerase, a non-LTR retrotransposon, was essential for the stabilization of linear chromosomes. For this reason, I would like to contrast the term 'viral eukaryogenesis', which singles out a complex DNA virus as the sole originator of the nucleus, with the term 'symbiotic eukaryogenesis', which recognises symbiosis of at least three biogenic elements (genomes of two prokaryotes and an array of mobile genetic elements including viruses) and their combinatorics in the evolution of the nucleus (Figure 2). I would also like to suggest that once the nucleus emerged, viruses were free to integrate further into eukaryotic chromosomes by infecting eukaryotic organisms, a process known as endogenization of viruses (Moelling and Broecker 2019) (Figure 2). Therefore, eukaryotic genomes are composite symbiotic structures, the same way that the eukaryotic cells are composite symbiotic structures.

Here is a scenario for the evolution of the nucleus and eukaryotic chromosomes compatible with the 'symbiotic eukaryogenesis' hypothesis (Figure 2 B). According to the consensus view based on seven different models including SET (Embley and Martin 2006), the

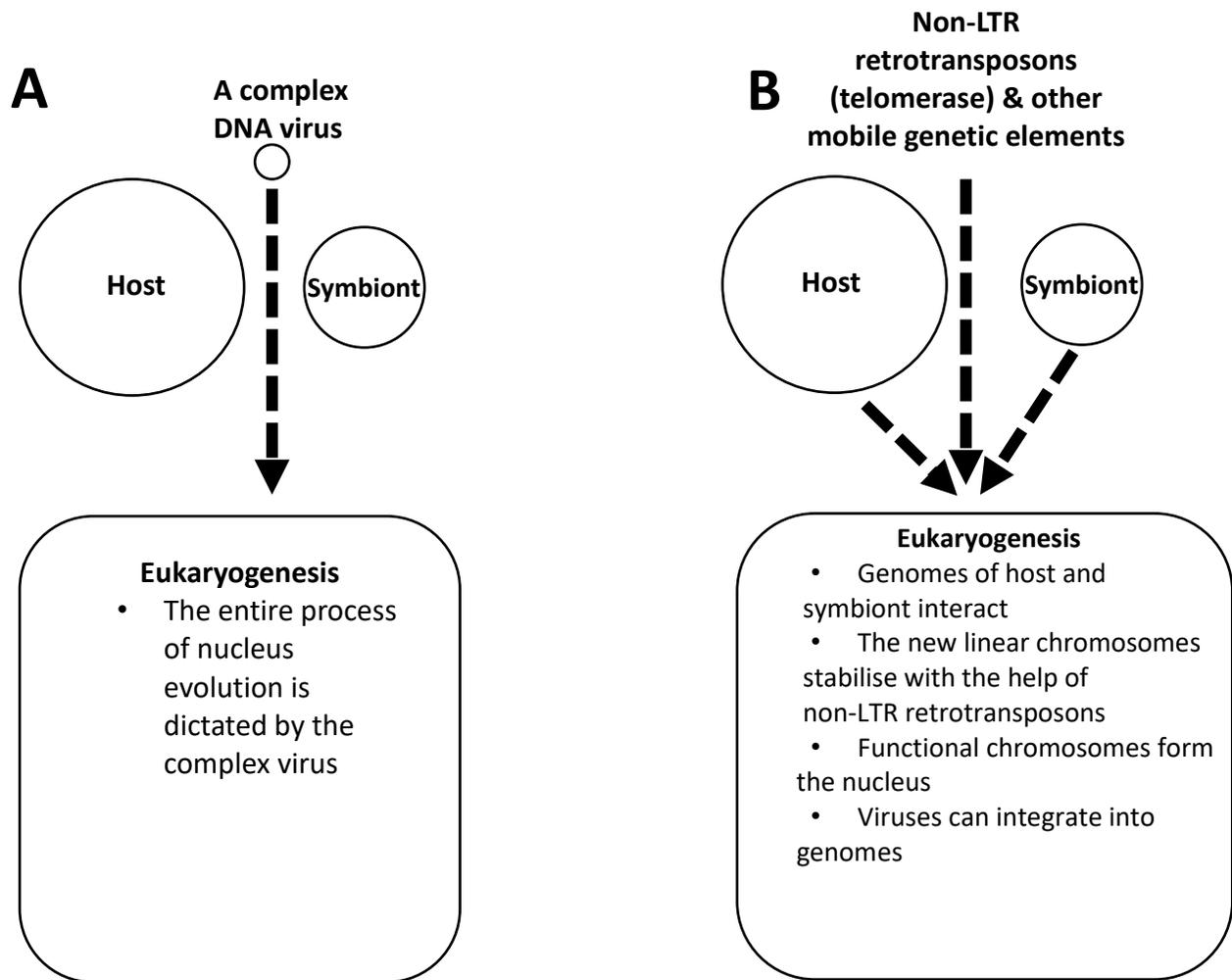


Figure 2. Contrasting the “viral eukaryogenesis” hypothesis (A) with the “symbiotic eukaryogenesis” hypothesis (B). For details of events in (B), see the text and also the following two references, Villasante et al. (2007) and Slijepcevic (2016).

process of eukaryogenesis started when an archaeal host (a thermoplasma-like archaeobacterium according to SET) swallowed an α -proteobacterium (a motile spirochete-like eubacterium according to SET). This triggered the adaptive responses of the symbiont eubacterium and its archaeal host to the new conditions (Villasante et al. 2007; Slijepcevic 2016). The result was a massive invasion of mobile group II introns from the symbiont’s genome into the host’s genome, leading to the disintegration of the circular genome of the host into multiple linear fragments (for details of this process see Villasante et al. 2007). These linear fragments were initially unstable. However, the fragments eventually stabilized with the help of non-LTR retrotransposons, a process that resulted in the emergence of prototelomeres (Villasante et al. 2007). Sequences immediately next to prototelomeres were recognised as the new cargo by the tubulin-based cytoskeleton, a process that turned subtelomeric regions into proto-centromeres (for details see Villasante et al. 2007). A temporary genomic instability ensued until it was resolved by the emergence of functional telomeres and centromeres. Other processes occurred in parallel, including the emergence of the nuclear membrane, which separated the new fragmented genome from the

rest of the cell. This model implies that centromeres and telomeres are key functional elements of eukaryotic chromosomes, absent in viruses, bacteria, and archaea. Telomeres and centromeres can functionally inter-change during the evolution of eukaryotic chromosomes and it seems likely that the first eukaryotic chromosomes were telocentric [for details behind these mechanisms see (Slijepcevic 2016)]. It is also likely that the viruses joined in, through the process of viral endogenization, to shape further eukaryotic chromosomes in the process of karyotype evolution.

4. Concluding remarks

The evolution of the nucleus and the process of eukaryogenesis remain contested topics – there is no consensus among biologists about the origin of eukaryotes. Yet SET still offers a valuable insight into the processes behind eukaryogenesis. Some authors argued that Margulis was right to interpret symbiosis as an important evolutionary mechanism, but at the same time stated that perhaps "she had a pinch too much symbiosis in her theory" (Martin 2017). However, other authors emphasized the importance of symbiosis in evolution and attempted to universalize it (e.g. Gontier 2012; 2015). Freeman Dyson universalised symbiogenesis from the angle of astronomy and offered a unique perspective on the history of life. In this paper, I used some of Dyson's arguments to extend SET. The result is that the origin of prokaryotes could also be interpreted as a process driven by symbiogenesis and regulated by the macro-process of homeostasis. I have also argued that the evolution of the nucleus was symbiogenetic, in contrast to a recent hypothesis that singled out the complex DNA virus as the driving force. Future research, theoretical and experimental (see above), should provide critical tests for some of the above arguments.

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References

- Bell, P.J., 2001. Viral eukaryogenesis": was the ancestor of the nucleus a complex DNA virus? *J. Mol. Evol.* 53, 251-256.
- Bell, P.J., 2020. Evidence supporting a viral origin of the eukaryotic nucleus. *Virus Research* 289, 198168.
- Capra, F., Luisi, P.L., 2014. *The systems view of life*. Cambridge University Press.
- Carrapiço, F., 2015. Can we understand evolution without symbiogenesis?" In Gontier, N., (Ed.), *Reticulate Evolution, Interdisciplinary Evolution Research*, Vol 3. Springer, Cham. pp, 81–105.
- Dawkins, R., (1976). *The selfish gene*. Oxford: Oxford University Press.
- Dyson, F., 1999. *Origins of Life*. Cambridge University Press, Cambridge.
- Dyson, F., 1998. *The Evolution of Science*. In Fabian, A.C., (Ed.), *Evolution: Society, Science and the Universe*. Cambridge University Press, Cambridge, pp, 118-135.
- Embley, T.M., Martin, W., 2006. Eukaryotic evolution, changes and challenges. *Nature* 440, 623-630.
- Eigen, M., 1996. *Steps towards life: A perspective on evolution*. New York: Oxford University Press.

- Forterre, P., 2006. Three RNA cells for ribosomal lineages and three DNA viruses to replicate their genomes: A hypothesis for the origin of cellular domain. *Proc. Natl. Acad. Sci. USA* 103, 3369-3374.
- Fox, S.W., 1991. Synthesis of life in the lab? Defining a protoliving system. *Q. Rev. Biol.* 66, 181–185.
- Gesteland, R.F., Cech, T.R., Atkins, J.F., 1999. *The RNA World*. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.
- Gilbert, W., 1986. The RNA world. *Nature*, 319, 618.
- Gontier, N., 2007. Universal symbiogenesis: An alternative to universal selectionist accounts of evolution. *Symbiosis*, 44, 167-181.
- Gontier, N., 2012. Introducing universal symbiogenesis. In Pombo, O., et al. (eds.), *Special Sciences and the Unity of Science, Logic, Epistemology*, 89 and the *Unity of Science 24*, Springer ScienceCBusiness Media B.V., pp 89-111.
- Gontier, N., 2015. Reticulate evolution everywhere. In Gontier, N., (Ed.), *Reticulate Evolution, Interdisciplinary Evolution Research 3*. Springer International Publishing Switzerland, pp 1-40.
- Higgs, P., Lehman, N., 2015. The RNA World: molecular cooperation at the origins of life. *Nat Rev Genet* 16, 7–17.
- Joyce, G., 2002. The antiquity of RNA-based evolution. *Nature* 418, 214–221.
- Kauffman, S. 1995. *At Home in the Universe*; Oxford University Press.
- King, N., 2004. The unicellular ancestry of animal development. *Cell* 7, 313–325.
- Koonin, E.V., Starokadomskyy, P., 2016. Are viruses alive? The replicator paradigm sheds decisive light on an old but misguided question. *Stud. Hist. Philos. Biol. Biomed. Sci.* 59, 125–134.
- Koonin, E.V., Yutin, N., 2018. Multiple evolutionary origins of giant viruses [version 1; referees: 4 approved]. *F1000Research*, 7, 1840.
- Krupovic, M., Dolja, V.D., Koonin, E.V., 2019. Origin of viruses: primordial replicators recruiting capsids from hosts. *Nat. Rev. Microbiol.*, 17, 449-458.
- Lancet, D., Zidovetzki, R., Markovitch, O., 2018. Systems protobiology: origin of life in lipid catalytic networks. *J. R. Soc. Interface* 15, 20180159.
- Lane, N., 2017. Serial endosymbiosis or singular event at the origin of eukaryotes? *J. Theor. Biol.* 434, 58-67.
- Lopez-Garcia, P., 2012. The place of viruses in biology in light of the metabolism-versus -replication-first debate. *Hist. Philos. Life. Sci.* 34, 391–406.
- Lopez-Garcia, P., Eme, L., Moreira, D., 2017. Symbiosis in eukaryotic evolution. *J. Theor. Biol.* 434, 20-33.
- Lyon, P., 2015. The cognitive cell: bacterial behavior reconsidered. *Front. Microbiol.* 6, 264.
- Lyon, P., 2017. Environmental complexity, adaptability and bacterial cognition: Godfrey-Smith's hypothesis under the microscope. *Biol. Philos.* 32, 443–465.
- Luisi, P.L., Walde, P., Oberholzer, T., 1999. Lipid vesicles as possible intermediates in the origin of life. *Current Opinion in Colloid & Interface Science*, 4:33-39
- Margulis, L., 1970. *Origin of Eukaryotic Cells*. New Haven, CT: Yale University Press.
- Margulis, L., 1990. Words as Battle Cries: Symbiogenesis and the New Field of Endocytobiology. *BioScience* 9, 673-677.
- Margulis, L., 1991. Symbiogenesis and symbiointicism. In: Margulis, L., Fester, R. (Eds.), *Symbiosis*

- as a Source of Evolutionary Innovation. Cambridge: The MIT Press, pp. 1–14.
- Margulis, L., 1993. *Symbiosis in Cell Evolution: Microbial Communities in the Archean and Proterozoic Eons*, 2nd ed. W.H. Freeman and Co., New York.
- Margulis, L., 1998. *The Symbiotic Planet: A New Look at Evolution*. London: Weidenfeld & Nicolson.
- Margulis, L., 2004. Serial endosymbiotic theory (SET) and composite individuality: transition from bacterial to eukaryotic genomes. *Microbiol. Today* 31, 172–174.
- Margulis, L., Chapman, M., Guerrero, R., Hall, J., 2006. The last eukaryotic common ancestor (LECA): Acquisition of cytoskeletal motility from aerotolerant spirochetes in the Proterozoic Eon. *Proc. Natl. Acad. Sci. USA* 103, 13080–13085.
- Martin, W.F., 2017. Physiology, anaerobes, and the origin of mitosing cells 50 years on. *J. Theor. Biol.* 434, 2-10.
- Mattiroli, F., Bhattacharyya, S., Dyer, P.N., White, A.E., Sandman, K., Burkhart, B.W., Byrne, K.R., Lee, T., Ahn, N.G., Santangelo, T.J., Reeve, J.N., Luger, K., 2017. Structure of histone-based chromatin in Archaea. *Science* 357, 609-612.
- Moelling, K., Broecker, F., 2019. Viruses and evolution - viruses first? A personal perspective. *Frontiers in Microbiology*, 10, 523.
- Moran, N.A., Sloan, D.B., 2015. The hologenome concept: Helpful or hollow. *PLOS Biol.* 13(12): e1002311.
- Nakamura, T.M., Cech, T. R., 1998. Reversing time: origin of telomerase. *Cell* 92, 587-590.
- Noble, D., 2012. A theory of biological relativity: no privileged level of causation. *Interface Focus* 2, 55-64.
- Oparin, A. 1955. *L'origine de la vie*. Moscou: Editions en langues étranges.
- Sagan, L., 1967. On the origin of mitosing cells. *J. Theor. Biol.* 3, 225-274.
- Segré, D., Lancet, D. 1999. A Statistical Chemistry Approach to the Origin of Life. *Chemtracts -Biochemistry and Molecular Biology* 12:382-397.
- Segré, D., Ben-Eli, D., Lancet, D. 2000. Compositional genomes: Prebiotic information transfer in mutually catalytic noncovalent assemblies. *Proc. Natl. Acad. Sci. USA*, 97, 4112-4117.
- Sato, N., 2017. Revisiting the theoretical basis of the endosymbiotic origin of plastids in the original context of Lynn Margulis on the origin of mitosing, eukaryotic cells. *J. Theor. Biol.* 434, 104-113.
- Slijepcevic, P., 2016. Mechanisms of the Evolutionary Chromosome Plasticity: Integrating the 'Centromere-from- Telomere' Hypothesis with Telomere Length Regulation. *Cytogenet. Genome Res.* 148:268–278.
- Slijepcevic, P., 2018. Evolutionary epistemology: Reviewing and reviving with new data the research programme for distributed biological intelligence. *BioSystems* 163, 23-35.
- Slijepcevic, P., 2019. Principles of Information Processing and Natural Learning in Biological Systems. *J. Gen. Philos. Sci.* <https://doi.org/10.1007/s10838-019-09471-9>.
- Slijepcevic, P., 2020. Natural intelligence and anthropic reasoning. *Biosemiotics* 13, 285-307.
- Spitzer, J., Pielak, G.J., Poolman, B., 2015. Emergence of life: Physical chemistry changes the paradigm. *10:33*.
- Turner, J.S., 2017. *Purpose and Desire: What makes something “alive” and why modern Darwinism has failed to explain it*. HarperCollins, New York.
- Villasante, A., Abad, J.P., Mendez-Logo, M., 2007. Centromeres were derived from telomeres

- during the evolution of the eukaryotic chromosome. *Proc. Natl. Acad. Sci. USA*, 104, 10542–10547.
- Witzany, G., 2008. The viral origins of telomeres and telomerase and their important role in eukaryogenesis and genome maintenance. *Biosemiotics* 1, 191-2016.
- Woznica, A., Cantley, A.M., Beemelmans, C., Freinkman, E., Clardy, J., King, N., 2016. Bacterial lipids activate, synergize, and inhibit a developmental switch in choanoflagellates. *Proc. Natl. Acad. Sci. U. S. A.* 113, 7894–7899.
- Zilber-Rosenberg, I., Rosenberg, E., 2008. Role of microorganisms in the evolution of animals and plants: the hologenome theory of evolution. *FEMS Microbiol. Rev.* 32, 723–735.