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RESEARCH ARTICLE

Prebiotic decluttering: the thermodynamic tail-wind to asymmetric autocatalysis

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Abstract

I outline a general thermodynamic condition for the earliest steps in the origin of life based on fluctuation theorems developed in the last two decades. I argue that the exponentially developing loop of asymmetric autocatalysis and thermodynamic tail-wind condition (TTC) in the prebiotic clutter was a key to a particular trajectory of decluttering via a sequence of early symmetry breaking events. Such decluttering was bound to result, most prominently, in homochiral amino acids and homochiral sugars composing nucleotides as the TTC exponentially favoured asymmetric autocatalytic processes over catalytic and symmetric autocatalytic processes in the clutter. I describe the loop's structure, including its chemical and physical properties, and explain that the TTC/asymmetric autocatalysis loop intersected with multiple chemical, geological and climatological feedback loops, thus providing conditions for the propagation of living systems as we know them.

Contents

Introduction

The molecular and chemical diversity and complexity of the prebiotic clutter enables us to hypothesize multiple scenarios that led to its known outcome. What came out of the clutter were the complexes of amino-acids and sugars that formed nucleotides. The clutter also harboured preconditions for speeding up the replication of prebiotic molecular complexes through various forms of catalysis and autocatalysis (Sections 'Molecular components' and 'Emerging catalytic and autocatalytic processes'). One basic universal property common to the product of decluttering and all life is the *homochirality* of amino acids and D-sugars comprising the nucleotides of living systems, while *asymmetric autocatalysis* was an early process behind it.

Because it was a universal property of life very early on, homochirality is perhaps a unique tracker of abiogenetic processes. It also tracks early autocatalytic processes responsible for its emergence (Section 'Homochiral amino acids and D-sugars as the product of decluttering'). Scientists have identified and studied possible mechanisms driving the emergence of homochirality, both theoretically and experimentally (Section 'Reactions'), including relevant thermodynamic conditions (Section 'The entropy rate in the reactions'). Yet there is a crucial piece of the puzzle that we could not have known prior to recent work on fluctuation theorems in stochastic far from equilibrium thermodynamics (Section 'The TTC, homochirality and prebiotic decluttering'). The fluctuation theorems go beyond the results based on the classical Prigogine minimal entropy production principle accounting for the thermodynamics of living states. They provide us with the key general thermodynamic condition that I label the thermodynamic tail-wind condition (TTC), of the relentless increase in dissipation and propagation of symmetry breaking in living systems in the long run.

I argue that if we apply this new understanding as a general condition to the emergence of homochirality in both isolated cases and abiogenesis, it explains the course of events in the most precise and yet generally applicable terms so far. To be more specific, the TTC as the general thermodynamic tendency to exponentially favour irreversible outcomes explains the exponentially flow and outcome of relevant cycles (Section 'The fluctuation theorems and TTC'). In particular, it explains why asymmetric autocatalysis and homochiral molecules as its product won the abiogenetic race. Although the description of individual stages in the energy flow of emerging homochirality is clear enough in the specific experimental and numerical–experimental accounts of asymmetric autocatalysis, the TTC fills a gap in our understanding of the overall maintenance of the cycle, as well as its exponential drive to its final broken symmetry (homochiral) stage.

How exactly the TTC squares with the asymmetric autocatalytic cycle as based on actual experimentally probed cases gives us detailed insight into the nature of this early process (Section 'TTC and asymmetric autocatalysis'). The TTC is a general thermodynamic condition. As such, it had to continuously affect the clutter, including the emergence of catalytic and autocatalytic processes essential to early life and life in general. In general, then, the emergence of homochirality via asymmetric autocatalysis should not be a surprising result given the TTC. When applied to prebiotic decluttering (Section 'TTC and prebiotic decluttering'), the theorems show us that the underlying thermodynamic condition in the prebiotic clutter was such that it *exponentially* favoured the formation of irreversible efficient free energy absorbing/dissipating molecular structures in the clutter.

Prebiotic clutter

The prebiotic[1] molecular clutter was plausibly characterized by an extremely diverse chemical environment, prone to the formation of molecular complexes (Joyce, 2002; Schwartz, 2007). Any attempt at reconstruction of chemical conditions in the clutter deals with 'extremely complex mixture of compounds' (Schwartz, 2007, 656), and reconstructions from organic compounds in meteorites do not fare any better (*ibid*.). Indeed, 'nothing is simple in the prebiotic chemistry' (Schwartz, 2013, 785). But this fact has enabled biologists to postulate multiple plausible scenarios of chemically diverse components and their interactions emerging in such an environment (Luisi, 2016; Marshall, 2020). Biology has also understood possible mechanisms leading to homochirality as a universal property of amino acids and D-sugars as the early product of decluttering, both theoretically and experimentally. This includes general entropy conditions under which such products emerge.

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[1] Infrabiotic rather than prebiotic may be a more precise descriptive characterization of the systems at stake, by designating coupled catalytic and autocatalytic systems. As we will see in the next section, autocatalysis and catalysis take place in the clutter– in part, the clutter forms thanks to them.

Molecular components

A number of plausible hypotheses centre on the content of the prebiotic clutter. Some (Joyce, 2002) focus on identifying individual molecular components, others insist on early proto-metabolic networks in that particular stage of abiogenesis (Dyson, 1999; Kauffman, 2019), and still others try to reconstruct plausible chemical pathways to known outcomes (Schwartz, 2007, 657; Powner *et al*., 2009; Ritson and Sutherland, 2012).

Based on a variety of evidence it is fairly clear that young Earth was rife with diverse organic compounds (Joyce *et al*., 1987; Egholm *et al*., 1993; Bolli *et al*., 1997; Eschenmoser, 1999; Joyce, 2002; Schwartz, 2007). A plausible assumption of the chemical complexity of the clutter presupposes a variety of interacting components, such as amino acids, hydroxy acid, sugars, ribose, phosphates, purines, pyrimidines and fatty acids. Given this complexity, it is likely that various polymers with stereochemistry formed in the clutter, as well as supra-molecular aggregates. Ribose, phosphates, purines and pyrimidines may have combined to form substantial amounts of analogues of nucleotides and small amounts of nucleotides, which, when combined, become polymers.

Even RNA could have plausibly co-existed with similar molecules composed of closely analogous components of similar structures and chemical functions, including threose nucleic acid (TNA), peptide nuclei acid (PNA), glycerol-derived nucleic acid analogue and pyranosyl RNA (Joyce, 2002; Schwartz, 2007). They all harbour similar characteristics that enable replication and autocatalysis crucial to the emergence of life[2].

Now, before we move on to discuss the process driving interactions between the molecular components we specified, we should clarify the nature of *complexity* in the prebiotic clutter more precisely. First, as we have seen, it was characterized by chemical complexity–diversity of molecular compounds and a variety of their interactions that tended to form larger molecular chains (e.g. peptides) and compounds. Second, this implies molecular complexity characterized by various inherent degrees of freedom of these diverse molecular compounds. Third, thermodynamics of the clutter was the key to the pathways through which quantitative complexity could arise and increase[3]. This is the overall concept of complexity and its key aspects we discuss throughout the paper[4,5].

Emerging catalytic and autocatalytic processes

Based on everything we know about living systems and the complexity of the prebiotic clutter, we can assume it harboured initial molecular and environmental preconditions for speeding up the replication of prebiotic molecular complexes through catalysis and autocatalysis, the function that enzymes evolved to perform later in the evolution of life. It is also not surprising that the RNA's autocatalytic potential motivated the dominant 'RNA-first' theory of the origin of life. There are at least four kinds of catalytic and autocatalytic processes that characterize life as we know it. They vary greatly in their efficiency and quality, from simple catalysis to 'product-enhanced' cycles, from ligand-accelerated catalytic cycles to a combination of simple and autocatalytic cycles (von Kiedrwoski, 1986; Zielinski and Orgel, 1987; Bissette and Fletcher, 2013). In this respect, following Bissette and Fletcher's

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[2] It should be noted right away that early replication mechanisms involved entire polymers, not sequences. Only the replication of sequences with variations introduced the Darwinian evolution.

[3] See Schneider and Kay (1994) for a brief historical account.

[4] See Mikhailov and Ertl (2017), Goodby *et al*. (2009) and Charnley and Rodgers (2005).

[5] In general, interrelation between these quantitative and thermodynamic aspects of complexity has been studied in complex systems science and in self-organization of inorganic and organic processes. And various formal accounts of chemical and molecular complexity have been developed, usually based on the information framework (Randić *et al*., 2001; Böttcher, 2016) and increasingly on the Game of Life simulations. Yet our main goal here, once we characterize the prebiotic clutter's molecular components and processes behind its chemical and molecular complexity, is to characterize the key thermodynamic condition behind such pre-biotic complex systems, and crucially, behind autocatalytic processes that drove the specific trajectories via which quantitative chemical and molecular complexity proceeded to known outcomes (homochiral amino-acids and sugars in nucleotides). We will only hint at formal accounts of complexity that may further illuminate this result.

(2013) review, we need to distinguish between induction and the autocatalytic cycle. In the former, the catalytic complex is not reproduced in the outcome but acts as a side component; in the latter, the catalyst self-reproduces[6]. Also, autocatalysis produces an uncontrolled mix of products (e.g. formose) (Schwartz, 2007, 657–658), but replications of biological polymers create controlled template-based autocatalysis.

As far as the prebiotic clutter goes, it has become increasingly clear that it could have harboured very different autocatalytic processes, such as autocatalysis of various proteins and lipids, as well as nucleotides and enzymes (or ribozymes) (Lee *et al*., 1996, 1997; Segré *et al*., 2001; Mossel and Steel, 2005; Hordijk and Steel, 2018). These scenarios have been postulated as plausible mechanisms and modelled under laboratory conditions (Chakrabarti *et al*., 1994; Wick and Luisi, 1996).

Moreover, there is a plausible mechanism by means of which something like reflectively autocatalytic and food-generating sets (RAFs) could have emerged from the clutter's non-catalytic components (Xavier *et al*., 2020, 1). And in numerous experiments, Eigen's hypercycles (Eigen and Schuster, 1978) of mutually catalysing components have been identified as plausible candidates for early autocatalytic networks. Such fairly advanced diverse autocatalytic sets of self-replicating molecules that replicated as wholes were predicated on the existence of a proto-ribosome that could start the autocatalytic process and allow the molecules to compete among each other in the prebiotic environment. These self-replicating molecules were emulated to some extent under laboratory conditions (Lee *et al*., 1996; Lee *et al*., 1997).

Homochiral amino acids and D-sugars as the product of decluttering

Now what came out of such a clutter of molecular complexes, their interactions and their replication sped up by catalytic and autocatalytic mechanisms? In molecular terms, the end products were the complexes of amino-acids and the sugars that formed nucleotides. And one key universal property common to this product of decluttering is the *homochirality* of both amino acids and D-sugars that comprise nucleotides, while *asymmetric autocatalysis* was an early process behind it. It is one of the most basic, universal and early properties, if not the earliest, of the decluttering product. As such, it has to be a key target of any attempt to explain the process of prebiotic decluttering.

Autocatalytic processes producing chiral (handed) molecules can be both symmetric and anti-symmetric. The latter type produces both kinds of chiral structures (enantiomers), whereas the former produces only homochiral (either left or right handed) ones. We say the mirror symmetry (two chiral molecular structures are mirror images of each other) of initial chiral enantiomers is preserved in the former case and broken in the latter. Since all life is composed of basic molecular building blocks that are homochiral, the latter seems to be decisive already in the initial processes relevant to the origin of life (Blackmond, 2004; Bissette and Fletcher, 2013). Understanding asymmetric autocatalysis is thus of special interest to discussions of the origin of biomolecular homochirality (in both amino acids and sugars), and as we will argue, it also played a crucial role in the prebiotic decluttering process in combination with a dominant thermodynamic condition.

Asymmetric autocatalytic processes and homochiral molecules

Reactions

Generally speaking, '[a]symmetric autocatalysis is a process of automultiplication of a chiral compound in which the chiral product acts as a chiral catalyst for its own production' (Soai *et al*., 2000, 382). Autocatalytic processes in crystals, amino acids and RNA have revealed mechanisms behind emergence of homochirality. One prominent instance of such a process is the Soai reaction (Soai *et al*., 2000) and its exhibition of (possibly spontaneous) symmetry breaking to form enantiomers.

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[6] Cross-catalysis between species, whereby species catalyse each other's formation, is widespread.

The homochiral pyrimidyl alcohol is produced in the experiments with various starting components through exponential catalytic cycles of that particular homochiral starting component. The starting homochiral enantiomer eventually takes over as much as 99.5% of the share of all enantiomers in the mix due to its autocatalytic potential. It is the first major reaction of asymmetric autocatalysis to have been studied experimentally in detail, starting some 20 years ago, where the underlying chemical reactions driving asymmetric autocatalysis are fairly well understood.

Understandably, any laboratory reactions resulting in homochirality prompt conclusions on its origin in nature, as it characterizes all known life, leading to considerations of a delicate relationship between conditions in both. We should be wary of the difference between the laboratory context and a complex prebiotic environment, but the results have prompted the following conclusion:

> Experimental studies of the Soai reaction reveal that statistical formation of dimer catalyst species coupled with lower activity of the heterochiral dimer is sufficient to rationalize the evolution of high *ee* from a tiny initial imbalance. This general mechanism could be effective in a world of simple organic molecules such as those likely to have been present in the prebiotic world (Blackmond, 2004, 5736).

The extent to which mechanisms in these reactions were applicable to the real-world interactions and conditions surrounding them that led to the homochirality of amino-acids and sugars composing life was certainly immediately questionable, but it was a major encouragement to such theorizing. And Soai reactions were only the beginning of experimental study of such sorts of reactions. Another major step in understanding the mechanisms behind asymmetric autocatalysis was taken by Viedma (2005). This experiment achieved a surprising 100% homochirality of the crystals of sodium chlorate, starting from an equal proportion of both enantiomers (L and D crystals), thus demonstrating that the initial seeding of a prevailing enantiomer is not necessary. The energetic stirring in a glass flask seems instrumental in achieving such a result, enabling the process of so-called secondary nucleation (Cartwright *et al*., 2004; Viedma, 2005). In the process, the abrasion transfers mechanical energy to chemical energy; in this process, chiral molecules are constantly broken into smaller non-chiral constituents until they all bind into a homochiral form of the crystal that eventually prevails. This process and the model behind it offer a tangible model of the actual early natural formation of homochirality at the molecular level, with the 100% homochiral result adding to the model's plausibility.

The homochirality of amino acids has been modelled via Soai and Mannich mechanisms (Xu and Lu, 2008). The former demonstrated the occurrence of asymmetric autocatalysis and its amplification after the initial dis-balancing of chiral components. Even *spontaneous* symmetry breaking was reported, without initial 'chiral impurities', which may lead to the conclusion that homochirality is essentially a statistical 'force'. It is important to point out that Soai's mechanism presupposes unrealistic prebiotic conditions, in contrast to Mannich's mechanism (Mauksch *et al*., 2007, 2010). The latter, however, has been a subject of some controversy. Blackmond claims the proposed mechanism violates reversibility at the micro level, a claim other researchers have denied (Bissette and Fletcher, 2013).

What about the mechanism that results in D-sugars' homochirality built into RNA and all other natural nucleic acids? Currently D-ribose in RNA determines the L-chirality of amino acids. Yet we do not have straightforward proposed mechanisms as we do for amino acids, although proposals on plausible chemical pathways to D-sugars in the clutter exist (Ritson and Sutherland, 2012) and can be a useful first step. It may also be a result of early nucleotides, including pre-chiral RNA, and amino acids interacting in the clutter (Sandars, 2005). It is possible that pre-chiral RNA could not have turned homochiral on its own, but only as a result of interactions with already homochiral amino acids. Or primordial mini-helices (tRNA) could have developed homochirality through non-enzymatic aminoacylation (Tamura, 2009). And under laboratory conditions, the stirring process makes a chiral crystal of achiral cytosine an initiator of the homochiral formation of cytosine (Kawasaki *et al*., 2008). Generally speaking, it is quite plausible that nucleotides, amino acids and lipids co-emerged from the clutter, as evidence from systems chemistry (Kindermann *et al*., 2005) and the study of meteorites (Martins *et al*., 2008) suggests.

Although this research is clearly work in progress, it offers a number of key insightful glimpses of molecular mechanisms behind asymmetric autocatalytic emergence of homochirality from which abiogenetic process can be extrapolated.

The entropy rate in the reactions

In general, numerical experiments analysing the entropy rate in autocatalytic systems that result in symmetry breaking and chirality suggest that the increase is stable at far from equilibrium values – up to a point. At the critical distance from equilibrium, the entropy rate jumps sharply due to the greater activity of the autocatalytic segments of the process than the catalytic ones. This abruptly drives the system into the asymmetric autocatalytic stage. The system finally settles down in this novel state, at an increased level of minimum entropy production.

Kondepudi and Kapcha (2008, 528) tracked entropy production during the chirality formation process. They modelled it using a common modification of the Frank model. The Frank model (Frank, 1953) is a system of rate equations modelling the exchange of chiral catalysts that result in homochirality. Certain assumptions of the model, like unlimited flow of components, are typically varied when the model is used as a starting point. The modelled reaction of the system, the in-flow of substances, includes catalytic and autocatalytic steps. In the experiment, the rate of entropy rises steadily when the system is being removed from equilibrium. More precisely, the continuous values of the non-equilibrium constraint (λ), which measures how far the system is from equilibrium, rise steadily. At a critical point of λ, that is, at a certain distance from equilibrium, the entropy production rate starts rising exponentially and the system exhibits behaviour analogous to second-order phase transitions. Crucially, this jump is caused by the increase in the autocatalytic steps in the reaction, not the catalytic ones. Thus, at a certain critical distance from equilibrium, the amplified autocatalysis of the system results in a highly asymmetric irreversible state; the process exhibits irreversible homochirality as the amplified autocatalytic levels take it to a sharply increased entropy production rate where it eventually settles down.

Blanco and Hochberg (2011) reached a similar conclusion, calculating the entropy production per unit volume, when the onset of increase occurs with the symmetry breaking. Tsogoeva and collaborators (Mauksch *et al*., 2010, 2007) used the same model of chirality formation, with some modifications. They found entropy sharply increases, peaking once the symmetry breaking takes place and then decreasing.

Especially interesting is an account of the thermodynamics behind the Viedma reaction. Viedma (2005) refers to the state described by the Gibbs–Thomson equation, notably its prediction of a small concentration gradient between smaller and larger crystal particles due to the greater solubility of the former. This effect is enhanced by the stirring, i.e. abrasion in the glass flask through secondary nucleation, and leads to the 100% homochiral molecules. Now, a numerical simulation model (Cartwright *et al*., 2004) required initial fluctuation analogous to the seeding of a homochiral state that will prevail, but another more detailed simulation (Saito and Hyuga, 2004) that added a feedback mechanism analogous to the secondary nucleation process due to abrasion against the glass flask resulted in an exponential jump in homochirality and a quick and complete breakup of mirror symmetry because the competition was extinguished. An initial small excess of one enantiomer can be overcome by another due to the intensified break-down into achiral parts and reassembly into enantiomers. The exponential growth of homochirality and a critical non-equilibrium value of enantiomers' concentration seem inherently related to the rates of disassembly and assembly, irrespective of seeding.

Plasson and Brandeburg (2010, 6) accurately parse thermodynamic cycle of Viedma reactions into phases, albeit descriptively, stating the following: 'This is an irreversible process, consuming the excess of energy initially present in the system, characterized by an excess of less stable small crystals. Simultaneously, the grinding process is an uphill process, consuming the energy given by the mechanical grinding.… This is not an equilibrium state, as unstable compounds (small crystals) are maintained by a continuous input of energy (the grinding)'. The eventual emergence of global homochirality in the cycle – when all individual emerging systems turn homochiral – occurs due to inhibition of the other chiral structure and the co-opting of every new unstable complex into the homochiral strain. *Crucially, maintaining this state requires continuous energy input to break the tendency to slide into the entropically stable state of racemization*. The process requires autocatalytic self-amplification of the chiral structure and inhibition of the other chiral structure, as well as the continuous flow of external and free energy (Plasson and Brandenburg, 2010). The thermodynamic effect of stirring, abrasion and resulting secondary nucleation seems to be crucial for both an exponential turn of events and the complete purity of the product.

The stages of the cycle and its thermodynamic flow in Viedma reactions are pretty precisely parsed. It is also clear from these and other previously outlined experiments that, when compared to catalytic, inductive and symmetric autocatalytic processes, asymmetric autocatalysis does an extremely efficient job of turning the mixed chiral 'puddles' into a global homochiral state. Moreover, Ribó and Hochberg (2020) simulated entropy flow, as it depends on the extent of the autocatalytic order and the matter exchange flow, starting from various initial chiral compositions. A wide range of initial chiral compositions will result in stable or unstable non-equilibrium stationary states (NESS)[7] – all in agreement with the minimal entropy production principle (*ibid*., 5) – and these will either go back to an initial NESS state or bifurcate further[8].

Yet with all this in mind, it is not exactly clear why the cycle that drives autocatalysis to win is maintained in the first place. Is there a unifying principle behind it at all, and if so, what is it? That there is a missing piece of the puzzle is also apparent in the general argument put forward by Crusats *et al*. (2006, 7780) that the homochiral state may be thermodynamically more stable than the racemic mixtures. The authors state that 'a principal objective to the study of the emergence of homochirality in critical phenomena is to know the structural reasons why in some compounds the homochiral interactions in aggregated phases are more favourable than the heterochiral'. Similarly Sandars (2005) states that 'one must try to explain not just the symmetry-breaking initiation of the asymmetry but its amplification to total single handedness, followed by its maintenance in a racemizing world', adding that 'it is not clear that a world of relatively simple but dirty prebiotic chemistry in an open and chaotic environment could produce such a chirally amplifying process' (*ibid*. 53). This is part of a larger worry about achieving 'chemical homogeneity' from the clutter (Schwartz, 2007, 662).

We submit that this challenge can be met once we specify the key thermodynamic factor and its exact role in producing the actual outcomes. The emergence of homochirality, as well as the process of decluttering in general, will remain well beyond the reach of existing theories of the origin of life (Avetisov, 1999) without this additional factor.

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[7] The processes that seem to us to be at equilibrium under laboratory conditions may not be so. Recent fluctuation theorems (Roldán, 2014, Ch. 6) show that we can distinguish between a genuine equilibrium state and a NESS that appears to be at equilibrium. Given this, the kinetic push that does not require an overall far from equilibrium state and thus the irreversibility that some authors (Danger *et al*., 2020) argue is the main state of propagation of living systems may not be occurring in systems in the equilibrium state at all, but rather in the systems in the NESS.

[8] General bifurcation theory (Chaikin *et al*., 1995) explores the bifurcation of properties and transitions and, as such, can shed useful light on the details of the autocatalytic processes, especially asymmetric transitions. In particular, along with the central Hopf bifurcation where the mixing of two communities is taken over by one community over time, represented as a fork in the distribution of the units, a number of other transitional bistability states (most relevant for us is the 'saddle' state) occur during the transitional period. These are especially pertinent in asymmetric bifurcation periods before the system settles into the new asymmetric phase (Skardal, 2019). This sort of modelling can provide a more detailed account of how exactly symmetry breaking occurs over time, especially during intermediate transitional phases of bistable partial synchronization (to borrow the terms of bifurcation analysis of coupled oscillators). Such models can also provide relevant results for real finite systems (*ibid*.). This is especially important if larger systems are modelled. This sort of analysis is applicable to the early and most obvious symmetry breaking in infra-biotic systems, that of molecular chirality and also to all subsequent symmetry breakings.

The TTC, homochirality and prebiotic decluttering

A crucial piece of the puzzle that we could not have known prior to recent work on fluctuation theorems in stochastic far from equilibrium thermodynamics explains the course of events of emerging homochirality in studied reactions and in the prebiotic clutter as well. To put it simply, the asymmetric autocatalysis is exponentially driven by TTC to win the race, and homochiral basic molecular blocks are its end result (Fig. 1).

The fluctuation theorems and TTC

In the last two decades, researchers have taken another shot at understanding the connection between dissipation of energy and irreversibility in living systems. The previous major step in that direction was the work of Prigogine (1978) and his collaborators. They focused on self-organizing systems far from equilibrium, studying the convergence of the macro-parameters of a living system on a steady state producing minimum entropy and the related phase changes the system undergoes. Prigogine's minimum entropy production principle accounts for the conditions at which a living system stabilizes at a minimum entropy production rate when a continuous influx of heat is steadily dissipated in the surroundings.

Living systems are mostly nonlinear far from equilibrium systems; thus, applying Prigogine's kind of analysis was very difficult until fairly recent improvements in the power of computer simulations. Moreover, in the field of non-equilibrium statistical dynamics, until recently, most studied relations have been applicable not only to linear but also to near-equilibrium regimes. In contrast, some relatively recent work has focused on *far from equilibrium states*. And, crucially, as England (2015,

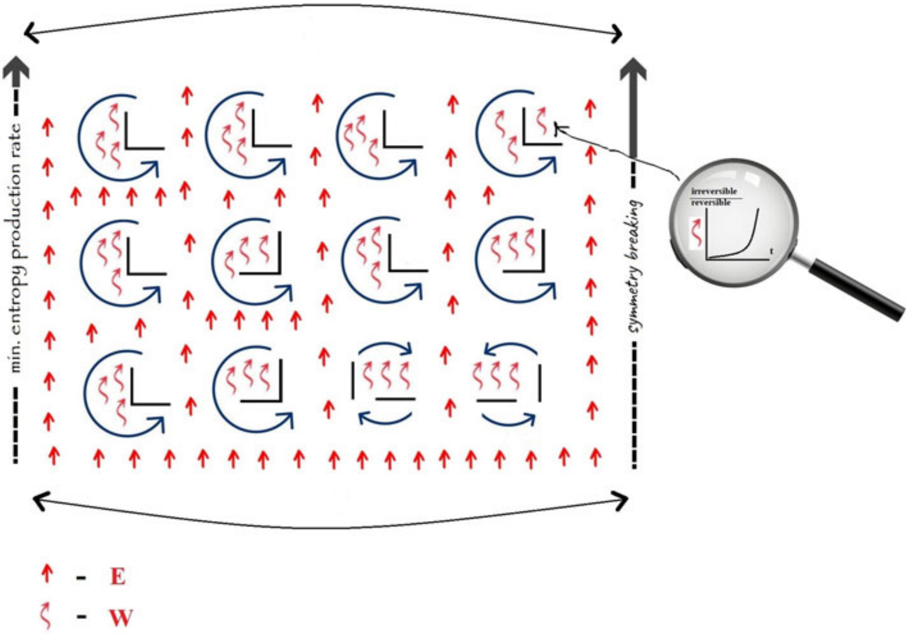

Fig. 1. *Thermodynamic flow (energy (E) turns into work (W) within the molecular complex) exponentially favours irreversible over reversible trajectories. Such flow is coupled with catalytic and autocatalytic mechanisms of basic molecular structures. This coupling sequentially increases the level of total minimum entropy production via the sequence of the structures' symmetry breaking: it steadily pushes the differentiation of autocatalytic over catalytic and asymmetric autocatalytic over symmetric autocatalytic structures.*

919–920) noted, it has *compared trajectories of relevant systems* instead of focusing on the development of the thermodynamic properties of an individual local state, as in the Prigogine principle-based analysis. This approach produced entropy production fluctuation theorems (Evans *et al*., 1993; Evans and Searles, 1994; Jarzynski, 1997; Cohen and Gallavotti, 1999; Crooks, 1999). With the use of numerical experiments, these authors have explored statistical properties of the fluctuations in far from equilibrium systems. One set of these experiments (Evans and Searles, 1994) analysed the trajectory segments of finite duration in many-particle systems and calculated the probability of observing an entropy production rate over a trajectory of t in arbitrarily perturbed systems. Another set of the experiments (Evans *et al*., 1993) looked at an average phase-space contraction rate near phase-space point x. The result to which these experiments converged is the *logarithmic probability* of shear stress reversing the sign. In other words, increased *irreversibility*, that is, an increase in the entropy rate of the trajectory or the phase-space contraction states, becomes *exponentially more likely than reversibility* (Cohen and Gallavotti, 1999).

Jarzynski (1997) and Crooks (1999) went a step further by analysing the thermodynamics of such fluctuations in relation to the work (W) in the system. They calculated the difference in free energies of two equilibrium ensembles and the amount of work expended in switching between the ensembles. England (2015, 920) succinctly summarized their result: ‘[a] microtrajectory is more likely than its time-reversed movie by an exponential factor of the positive amount of the heat that is released into the surrounding thermal reservoir while the forward path is being traversed’[9].

Based on these results, England (2015, 2013) formulated a general account of the statistical physics of self-replication and the dissipative adaptation in the self-assembly of the systems driven by free energy. In terms of the general properties of thermodynamic systems far from equilibrium, ‘the more statistically irreversible a spontaneous process is … the greater the minimum amount of total entropy increase required’ (England, 2015, 920–922). This is expressed by the following formula (*ibid*.):

$$\langle W\rangle_{X\rightarrow X'} - \langle \Delta E\rangle_{X\rightarrow X'} + T\Delta S_{\mathrm{int}} \geq k_{\mathrm{B}} T \ln\left[\pi_\tau(X\rightarrow X')/\pi^{*}_{\tau}(X'\rightarrow X)\right]$$

The formula includes the work applied to switching the states and internal entropy, minus dissipated energy, on the one side, and the logarithmic ratio of probabilities of the system going into a forward over a reversed state on the other. The ‘greater irreversibility must be powered by more of the work done on the system being dissipated rather than stored in the system’ (*ibid*., 921). In other words, reliable high work absorption/dissipation configurations that inevitably increase irreversibility are exponentially more sustainable. This, as England argues, quite obviously includes living systems.

As we will see, the relevance of this process for life is dependent on the physical scale and the size of the systems at stake, that is, on their degrees of freedom. The ease with which this relationship achieves the conditions favourable for the emergence of life thus varies across scales, while its intricacies are crucial for the individuation (and thus actual size) of living and early prebiotic processes. Yet, generally speaking ‘Nature will not do anything unless we entice her into it with the promise of higher entropy’ (Goodstein, 2015, 74). Thus, the round-about way the absorbers/dissipaters increase the minimum entropy level in jumps of symmetry breaking (irreversible states) while preserving the structure (with modifications) is a key manifestation of this principle. They successfully dissipate energy while changing the structure in a suitable way, through symmetry breaking jumps.

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[9] It should be noted that two notions of irreversibility related to energy dissipation are at play here. The first is a more classical thermo-physical notion: the classical characterization of a system in an energy bath that extracts and deposits heat through currents and flows with an appropriate amount of work. The notion makes use of the Gibbs partition function. The second notion defines the relationship between dissipation and the probability of forward and backward trajectories or the contraction of density of the phase-space volume. In fact, the fluctuation theorems of the far from equilibrium thermodynamics we outlined above are derived in both of these frameworks of understanding irreversibility in relation to energy dissipation and work, and they have been insightfully combined as well.

Thus, since irreversible phase-changes are exponentially more likely in far from equilibrium processes, everything else being equal, the accumulation of symmetry breakings should be exponentially more likely than their symmetrical counterpart processes. When it comes to prebiotic and biotic processes, then, this exponential drive to symmetry breaking must start with basic ones like emergence of the homochirality of amino acids and sugars in early prebiotic molecular evolution, before moving to cell division at the level of development and beyond.

As we mentioned earlier, under a variety of initial chiral compositions, non-equilibrium stationary states will undergo bifurcating or exponential transformations as tracked by the minimal entropy production principle (Ribó and Hochberg, 2020). Yet the recent fluctuation theorems we discussed above characterize a global propensity of life that represents the next step in the cycle: *through symmetry breaking, life has a general tendency to persistently raise the stakes by raising the minimal entropy production level at which this temporary stasis happens*. That is what makes life likely to continue existing once it starts, thermodynamically speaking, and this is what pushes its relentless propagation (Fig. 1). This process continuously creates symmetry breaking locally and globally, thus increasing both chemical and molecular quantitative bio-complexity (see Section 'Molecular components') through specific thermodynamic increases in the energy flux, dissipation and the extent of symmetry breaking (SB)[10].

TTC and asymmetric autocatalysis

A recent study (Seara *et al*., 2018) offered a more direct experimental insight into the thermodynamic condition defined by these outlined results by tracing dissipation and structural changes in actomyosin filaments. The calculation of average total energy dissipated per unit filament length over time t revealed three major phase-changes whereby 'entropy production rate is highest in non-contractile (stable) actomyosin' (*ibid*., 6). That is, the system stabilizes after a jump in dissipation rate, resulting in the irreversible (asymmetric) structure of filaments.

More laboratory and numerical experimentation will provide more detailed insights into the working of the TTC, but as it is a general condition applicable across far from equilibrium systems, we can expect to recognize the pattern of its activity across the existing laboratory and numerical experiments with homochirality and asymmetric autocatalysis in a manner similar to the above-mentioned experiment with protein filaments. Although, as we have seen, the description of individual stages and energy flow is clear enough in these experimental and numerical–experimental accounts, the TTC fills a gap in our understanding of the overall maintenance of the cycle, as well as its exponential drive to its final homochiral stage.

Thus, in Viedma reactions, the continuous cycle of abrasion, secondary nucleation and homochiral assembly unfolds as a thermodynamically irreversible process wherein consumption of energy is needed to break larger crystals into smaller ones that exponentially approach homochiral state. Similarly, the flow of components into the formation of the chiral molecule (Kondepudi and Kapcha, 2008, 526) means the entropy rate (σ) is gradually increased, up to the critical value of λ, at which point the entropy value rate exponentially jumps and the homochiral state is achieved. In both cases, at the critical distance from equilibrium, the corresponding entropy rate jump occurs as symmetry breaking results in homochirality[11]. *The general thermodynamic tendency to exponentially*

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[10] An information-based measure of molecular complexity that includes molecular symmetries (Randić *et al*., 2001) can be helpful in quantifying and assessing this process.

[11] 'The parameter λ is a nonequilibrium constraint on the system; it may be considered as a measure of how far the system is from thermodynamic equilibrium. Hence, as λ increases, the rate of entropy production, σ, increases but when $\lambda > \lambda_c$, the slope of σ changes' (*ibid*., 528). And this occurs due to increased autocatalysis. Thus, the sufficient efficiency of autocatalysis at a critical distance from equilibrium enables the SB jump. In effect, the decluttering threshold reached a certain distance from equilibrium.

favour irreversible outcomes in such cycles explains why the cycles exponentially flow in that direction in the first place.

Thus, the TTC and the asymmetric autocatalysis processes are inherently tied to a reinforcing loop. Autocatalytic symmetry-breaking processes are exponentially more likely to take over in a molecular complex than symmetric autocatalytic and catalytic processes, because of their looping with the TTC. Given the general nature of the TTC, this applies equally to isolated experimental cases and the prebiotic clutter environment.

Now even if we try to argue that the overall thermodynamic structure of such processes is no more than a suggestive analogy to the TTC under experimental conditions, it is much harder to make such an argument in the case of early Earth. The unique explanatory power of the TTC cannot be emphasized enough in early natural processes, such as abiogenesis, that took place over much longer time-scales and in much larger and chemically diverse environments than the laboratory permits. The time-scales and environments enabled a long-term differentiation of relevant states, and the principle had a chance to deliver long-lasting outcomes where both abrasion and seeding could have been plausible factors. Indeed, the minimum entropy production principle is preserved in far from equilibrium systems and NESS states (Ribó and Hochberg, 2020), but the effects of TTC kick in during a long-term differentiation that has to be modelled accordingly. This is why abiogenesis, as well as the level of biosphere, should be a prime target for assessing such a general principle with the help of laboratory and numerical experimentation.

In fact, we cannot fully understand either in isolation. Interesting outcomes from early Earth conditions in laboratory work and simulations are, generally speaking, frequently intractable (Schwartz, 2007, 656; Schwartz, 2013, 787). And as far as limitations of laboratory glimpses go, in this case, as we have seen, the simple stirring (vortices) and abrasion of the molecular complexes under laboratory conditions may crucially contribute to the emergence of homochirality (Ribó *et al.*, 2001; Kawasaki *et al.*, 2008; Luisi, 2016, 99).

Interrelated defining features of the loop are apparent in isolated cases of emergence of homochirality and also across abiogenetic scenarios.

An efficient autocatalyst absorbs exponentially more energy and thus increases entropy by dissipating that energy, gradually achieving asymmetry in individuals (homochiral polymers from monomers), eliminating (by inhibition relation) or co-opting the opposite processes and individuals more efficiently[12]. Thus, the entropy jump leading to SB at the global level in such a complex is predicated on increased absorption of energy by autocatalysis[13]. As a result, the minimal (steady state) entropy production jumps due to SB. The system becomes irreversible with respect to its defining property such as chirality. Due to the TTC, the probability of (long-term) differentiation of such (SB-autocatalytic) processes exponentially increases over reversible ones with no or less SB amplification. Exponentially more energy and matter will go into this asymmetric autocatalytic process at the expense of vanishing, catalytic and less SB-prone autocatalytic processes in the global complex.

Note that symmetric autocatalytic systems will turn both ways, forward and backward; for example, they will contain both enantiomers. The system's chances of reaching either state are equal. But a system that has undergone an asymmetric autocatalytic transition will be exponentially less likely to go to its previous state. Thus, some catalytic and symmetric catalytic elements will be co-opted by the asymmetric autocatalytic system, but never the other way around. The more degrees of freedom and the larger the complex, the faster the transition driven by exponential tail-wind to the irreversible state will be. In fact, the timeline will depend on the size and the degrees of freedom characterizing the complex, as we discuss in the next section.

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[12] Yet is more efficient (faster) autocatalysis inevitably more complex? A tiny extra-component or chemical property improves its chances over others (e.g. flexibility in RNA versus TNA).

[13] This may explain why SB as global is delayed in the numeric experiments (Blanco and Hochberg, 2011): individuals increasingly absorb energy.

TTC and prebiotic decluttering

The process

In general, then, it is plausible that, driven by the TTC the prebiotic autocatalytic and catalytic complex entered a string of symmetry breaking occurrences after reaching a critical distance from equilibrium (λ_c). Due to the increased autocatalysis the global state grew at the expense of other catalytic or less refined (e.g. inductive and symmetric) autocatalytic states. The result is the emergence of asymmetric states (SB) with enhanced absorption and dissipation potential; along with a jump in the entropy rate, with eventual stabilization at the new minimal entropy level when a global homochiral state has been achieved.

The prebiotic molecular complex that establishes autocatalytic activity first, even by a small margin, could have won quickly (close to the exponential value) the local autocatalytic battle due to the TTC. We know RNA won the race. TNA could have achieved this perhaps, if it got there first, even if it was not as efficient in autocatalysis. The autocatalytic structure does not have to be more efficient in TTC terms than others, but this certainly helps.

Also, each structure always competes against utter dissipation (dissolution); it has to 'go along' with the irreversibility increase by dissipating while guarding against its own dissolution. In general, not only in the case of homochirality but other key symmetry breaking that followed, differentiation at the critical value is a long-term process. In this respect, decluttering in combination with a decisive atmosphere penetration by asymmetric autocatalysis may eventually bring atmosphere to a new stable/minimum entropy state (Paltridge, 1975) by reinforcing prebiotic negative feedback. This would be a long-term win against dissolution through crucial long-term regulation of greenhouse gases and albedo (Chopra and Lineweaver, 2016) and other opportunities of that sort. Indeed, the TTC and symmetry breaking via an autocatalysis feedback mechanism may be the key mechanisms enabling such regulation. And once life emerges and avoids annihilating catastrophes, the long-term biospheric global system may be inevitable (Janković *et al*., 2022), precisely due to the TTC.

It is not clear whether the initial amplification is contingent, and the critical value takes off because of the symmetry breaking. Or whether amplification occurs gradually due to the thermodynamic condition but before the critical value is reached. In other words, does the process leading to the autocatalytic symmetry breaking conspire with, or is it driven by the thermodynamic condition? Is amplification of autocatalysis part of the process? Again, the answer may be simply who gets there first and picks up the thermodynamic tail-wind, but small differences in properties of molecules will amplify over time and determine whether autocatalysis will amplify and to what extent (i.e. whether λ_c is reached or not). For instance, rotational freedom in nucleotides and their analogues or impurities (*ee* in amino acids), slightly more efficient monochiral structures and so on may be decisive. Alternatively, topological and thermodynamic properties of an actual loop may matter. Moreover, boundary conditions may affect or even shape the spatial and temporal size of the basic systems, a possibility we discuss in the next sub-section.

The amplification of certain properties and their eventual takeover, and the cascading symmetry breaking of that sort in autocatalytic molecular systems will inevitably lead to the escalating narrowing of chemical constraints; there will be less and less variety to draw on in the clutter itself. The cascading symmetry breakings, one after another, will eventually co-opt many of the basic molecular components in the clutter and thus continue to increase the dissipation of energy by more and more streamlined processes that keep narrowing the chemical variety. The TTC is the best candidate to be the main driver behind the structuring of chemical constraints, something Montévil and Mossio (2015) identified as a major sign of living systems[14]. The chemical constraints will streamline the free energy into work, as well as entropy increases (Kauffman, 2019, 21). The TTC explains how this happens over time and why it favours autocatalysis. Understanding constraints *per se* and the closure of systems into

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[14] Perhaps a more adequate notion than the 'constraint closure' these authors suggest is the 'constraint cycle' or 'open constraint cycle', given the relentless propagation and evolution of the infra-biotic and biotic systems.

self-referential catalysis (Farmer *et al*., 1986), although plausible, does not explain a key factor of their narrowing over time, that is, decluttering, or offer an account of the relentless propagation of very special systems (asymmetric autocatalytic ones), that is, the push to replication and, later on, reproduction. Nor does it clarify their special defining properties like homochirality.

The basic units

Given the TTC as defining feature, what is a plausible characterization of the early prebiotic systems that broke through and took over the clutter? What were their molecular structures and their sizes? Finally, why is life of the sort we know not as expansive elsewhere given a physically and chemically fairly straightforward trajectory to early life? In a closed thermodynamic system of a proto-biosphere, which is energy-flux rich and thus continuously stirred, the homochiral outcome is exponentially more likely due to the reinforcing of the TTC and autocatalysis. Yet how closed could this system have been? What other crucial factors could have interfered?

It is not easy to unambiguously delineate prebiotic systems (Bruylants *et al*., 2011), or even biotic ones, for that matter. As we pointed out earlier, the molecular components of the clutter consisted of early amino acids and nucleotides, perhaps even lipids, and likely molecules like TNA or PNA. Yet in the decluttering process, the local and then global autocatalytic processes became the most relevant properties of relevant systems, as autocatalysis was the most pronounced process in the decluttering and co-opted the basic molecules. The autocatalytic symmetry breaking eventually led to identifiable complexes of homochiral amino acids and nucleotides composed of D-sugars that could be treated as basic units of living systems, but the units in the processes leading to it are not as easily identifiable. Although we could argue in favour of various criteria for cutting autocatalytic complexes into units, a key property of such complexes in early decluttering was provided by the process of asymmetric autocatalysis, or more precisely, by the size of the phase-space of its contraction.

In more concrete terms, L-2 and D-sugars came out of the clutter. The homochirality of amino acids composing all life, as well as that of D-sugars in RNA, was a result of asymmetric symmetry breaking. The TTC will loop with any of these potential mechanisms, as it is a very general condition. It is a missing link between limited models of decluttering that churn out the clear winners in the form of amino acids and RNA on the one hand, and the reality of the chemical complexity of the prebiotic clutter.

Could TNA, PNA and other molecules structurally and potentially functionally analogous to RNA develop the needed level of autocatalysis, especially symmetry breaking, and synthesize with amino acids in analogous ways? It is commonly understood that the prebiotic decluttering that resulted in the dominance of RNA was based on ‘a series of biased syntheses, fractionations and other enrichment processes’ (Joyce, 2002, 215). The TTC, in combination with autocatalytic processes and local circumstances (especially ‘who got there first’), was the driving force behind these ‘biases’. One question is whether they could take advantage of TTC the same way the RNA/amino acids complex did. And how exactly could they have done so given their molecular and autocatalytic properties? Could the poor rotational freedom of TNA prevented this and offered an advantage to RNA? More specifically, these complexes do not have adequate self-replicating molecules characterized by a satisfying level of autocatalysis. If they could only have achieved induction, and not full autocatalysis, no major and decisive symmetry breaking would have been possible, and they could not have won over RNA. If this were the case, these complexes would have remained within the clutter and perhaps served as a precursor (Hein *et al*., 2011, Sczepanski and Joyce 2014) but not a full-blown alternative to RNA (Banfalvi, 2006).

In another plausible scenario, the first step in decluttering is the formation of *autocatalytic networks*, simple replications that only the thermodynamic tail-wind selects. A more sophisticated reproduction may have occurred early, as some authors suggest, such as metabolic networks (Dyson, 1999; Schwartz, 2007, 660; Kauffman, 2019), but the TTC acting on asymmetric autocatalysis explains why simple molecular replication is not less plausible as the first step in the process. The emergence of asymmetric autocatalysis and symmetry breaking is necessary for replication, and this process may be possible in early metabolic reproductive systems. But this possibility does not position symmetry breaking as the key to decluttering. At any rate, it is certainly not as pronounced as in the case of simpler molecules, so it is not clear what exactly would drive decluttering in the metabolism-first world. Various proto-metabolic complexes could thrive, and no actual chiral streamlining of amino acids and sugars would necessarily take place. The complex and proto-metabolic clutter could have been there first, before the self-replicating molecules like RNA. But eventually, the initial metabolic clutter had to turn into more reduced and more streamlined molecules like homochiral amino acids and RNA with homochiral D-sugars via symmetry breakings and after that, development into the more complex metabolism we see today[15]. So a plausible trajectory starts with an early messy proto-metabolism followed by symmetry breaking(s) and formation of homochiral autocatalytic molecules making the clutter much more streamlined, followed finally by the emergence of novel metabolic complexes.

Finally, if early autocatalytic hypercycles of Eigen's sort dominated, their replication had to move towards ever more irreversibility – as much as that of any winner in the clutter. The TTC was behind this tendency. More precisely, the key to their success was ever more precise replication, and this gave them the edge over competing complexes. The TTC leading to simplifying units by accumulating asymmetries, e.g. homochirality, conceivably increased this precision, as it effectively streamlined the hypercycles.

Other general conditions of the exponential growth of replicating homochiral molecules

The global environment may be conducive to the formation of homochiral processes (e.g. a favourable molecular chemical surface and/or ubiquitous vortices), or neutral to it. We should keep in mind that some natural selection conditions applicable to self-replication and autocatalysis exist already in the prebiotic environment. Thus, an exponential growth is necessary for the symmetry breaking due to asymmetric autocatalysis to take place, as sub-exponential growth inevitably leads to the co-existence of opposed units (Szathmáry and Gladkih, 1989) and systems with limited growth (Eigen and Schuster, 1978). In the latter case, various oligonucleotides, that is, short sequence nucleotides, can co-exist without mutual inhibition (Szathmáry, 1991), and various catalytic and autocatalytic processes do not inhibit each other to a substantial extent. Thus, in clutter-replicating molecular (mutualistic) hypercycles, hyperbolic growth will result in the survival of the already common cycle, while parabolic growth will lead to the survival of all cycles (Eigen and Schuster, 1978; Szathmáry, 2006), and decluttering will not occur. This demonstrates the importance of exponential growth for decluttering, although it obtains under rather idealized kinetic conditions. It is worth mentioning that due to stochastic conditions and the invasion of uncommon but more efficient autocatalytic cycles, in a more realistic assumption of prebiotic clutter, the takeover will look more complicated (Szathmáry, 2006, 1766).

In any case, the role of exponential growth indicates the need to take evolutionary factors into account as relevant, along with the kinetic factor in the context of vortices and kinetic control of homochirality (Luisi, 2016, 99) and the key thermodynamic factor.

In terms of the origin of autocatalytic processes, RAFs are autocatalytic networks in which the molecules produced in them do the autocatalytic work but can be produced from simple 'food'. Their emergence is gradual, as they move from non-catalytic to catalytic cycles. Although, theoretically, RAFs 'can emerge spontaneously and proliferate via constraints imposed by substrates, catalysts, or thermodynamics' (Xavier *et al.*, 2020, 1), we know of such autocatalytic networks only in those complexes where the autocatalytic function is performed by enzymes.[16] Yet RAFs are quite advanced

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[15] Similarly, it is not clear whether and how asymmetric autocatalysis could have occurred in the postulated early lipid world (Segré *et al.*, 2001), especially given the lower reactivity of such autocatalytic systems. Once we understand the role of the thermodynamic tail-wind, it seems more plausible that early replication in autocatalytic processes formed a bottleneck of sorts where more complex systems reproducing with code-like mechanisms emerged as more efficient energy absorbers/dissipaters than early replicators and relatively quickly co-opted or took over through a series of symmetry breaking events.

[16] See Olasagasti *et al.* 2011 for a possible alternative.

metabolic catalytic processes, compared to simpler ones lacking a mechanism of repair via enzymes, as such damage is the key obstacle to the survival of the autocatalytic cycle (Szathmáry, 2006, 1763).

As we have pointed out, differentiation at the critical value is a long-term process. It happens in a very diverse geochemical interconnected 'milieus' (Schwartz, 2007, 659). In such an environment, decluttering and decisive atmosphere penetration by autocatalysis and symmetry-breaking feedback may bring atmosphere to a new stable minimum entropy state (Paltridge, 1975, Kasting 2014) by reinforcing prebiotic negative feedback. This would constitute a long-term win against dissolution due to minimum entropy increase. The boundary conditions related to planetary dynamics, starting with the emergence of the core, crust and other layers and continuing into atmosphere formation, may be much harder conditions for the emergence of life to achieve than those at the level of molecular structures. In fact, symmetry breaking plays a role even in the formation of planetary structure as dissipation of entropy is steadily 'compensated' through the formation of planetary layers. But at such large physical scales, symmetry breaking cannot produce as much variety as it can at the molecular level once the prebiotic clutter is formed. The symmetry breaking sequences in the clutter will quickly select stable autocatalytic processes that will increase in complexity, but the planetary condition will not be as easily obtained. Chopra and Lineweaver (2016) argued that life has to evolve quickly in order to start regulating the key atmospheric conditions (greenhouse gas emissions and albedo and, hence, presence of liquid water). This results in a bottleneck in the emergence of life; as a rule, life will emerge but not co-opt planetary conditions to its advantage. They also pointed out that life's management of the planetary conditions broadens the environment, especially in terms of catalytic and feedback processes (*ibid*., 10). Yet, on its own this seems a less convincing explanation than if the thermodynamic tail-wind is an additional key factor, as it explains the almost uncanny persistent stability of a biosphere after it reaches the critical value.

One potentially contentious argument can be made against our view. Is the occurrence of homochirality in ice, at low temperatures, or at low flux prebiotically plausible at all? The crucial initial asymmetric autocatalysis of amino acids may have occurred in the state of equilibrium. Blackmond (see Klussmann *et al*., 2006) suggested this possibility under laboratory conditions. These are a far cry from the conditions of the actual prebiotic clutter, but Blackmond's proposition is a possibility worth considering. What about the minimum entropy increase in such a case? When does it kick in, and what is its role, if any? Must such a far from equilibrium state necessarily be an accident? It is possible that amino acids transitioned to homochirality close to equilibrium, but the interaction with the nucleotides and subsequent symmetry breaking occurred far from equilibrium, and the interaction was the point at which the TTC kicked in as the major factor.

Finally, in a way, the overall picture has a tangible experimental potential to create artificial clutter and a decluttering recipe, in effect, an artificial early stage biosphere. This would include recreating early infra-biotic conditions characterized first and foremost by favourable temperature and negative feedback, with fairly simple and diverse components enabling polymerization and the chemical environment favouring catalysis, autocatalysis and crucially, the chains of symmetry breaking. The system must move sufficiently far from equilibrium – up to the critical flow of the components – to generate asymmetric autocatalytic processes as irreversible cascading; and at some point, it has to substantially penetrate and co-opt the atmosphere.

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