On the conditions for mimicking natural selection in chemical systems

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Abstract | The emergence of natural selection, requiring that reproducing entities present variations that may be inherited and passed on, was arguably the most important breakthrough in the self-organization of life. In this Perspective, the assumptions governing biological reproduction are confronted with physico-chemical principles that control the evolution of material systems. In biology, the reproduction of living organisms is never considered to be reversible, whereas microscopic reversibility is an essential principle in the physical description of matter. Here, we show that this discrepancy places constraints on the possibility of finding kinetic processes in the chemical world that are equivalent to natural selection in the biological one. Chemical replicators can behave in a similar fashion to living entities, provided that the reproduction cycle proceeds in a unidirectional way. For this to be the case, kinetic barriers must hinder the reverse process. The system must, thus, be held far from equilibrium and fed with a non-degraded (low-entropy) form of energy. The ensuing constraints must be factored in when proposing scenarios that account for the origin of life at the molecular level.

Since the 1859 publication of *On the Origin of Species*[1], there has been increasing support for the theory of evolution, and it is now overwhelmingly accepted within the scientific community as the only way to account for the past and current living world. Its main tenets lie in the concepts of reproduction with variation and natural selection. It explains that the evolution of inheritable traits is associated with genes in populations of living organisms. None of these concepts was initially related to any specific molecular constitution of living organisms. Indeed, it is truly remarkable that these ideas were put forward almost a century before the molecular basis of genetic heredity was disclosed[2]. Therefore, no theoretical obstacle could a priori prevent the observation of evolutionary processes reminiscent of natural selection in chemical systems and several attempts were made to tackle the questions of the so-called 'chemical Darwinism'[3] or 'molecular Darwinism'[4–10]. The possibility that such behaviour might be observed independently of the current chemical basis of genetic heredity brings into question the factors responsible for the corresponding selection process. An obvious requirement is the availability of inheritable variations. It also suggests that, under certain conditions, the system might undergo an evolutionary process in which selection acts as it does in the living world. The present work aims to emphasize the observation that irreversibility is intimately associated with the essence of life. The birth of a new organism, the death of an old one or, at the cellular scale, divisions and the transitions between the different phases of the cell cycle all correspond to processes that have no possibility of reversal to earlier stages. The basis of irreversibility in these processes lies mostly in the dissipative character and in the growing complexity of living systems. There is, thus, no crucial need for life sciences to question its origin and its consequences, since it is intimately associated with the behaviour expressed at the fundamental level of any living organism. On the contrary, in this work, this issue is claimed to constitute a crucial parameter when considering the possibility of the transition from a physico-chemical system towards the living state. Failing to express explicitly the assumption of an irreversible process is a hindrance to accurate understanding of the problem.

Following a physico-chemical description of matter, any system made of atoms and molecules can be described by establishing an inventory of the species that are present and of the possible chemical transformations occurring between them. According to the principle of microscopic reversibility, any process occurring at the microscopic scale in the system must be considered as reversible, meaning that time inversion leads the motion of particles to unfold in the reverse direction. Indeed, the principle of detailed balance states that, at equilibrium, the flux of reactants in any chemical transformation is identical in the forward and reverse directions[11]. As soon as the system is maintained at some distance from equilibrium, the equality of the forward and reverse fluxes no longer stands. This non-equivalence of fluxes is also involved in non-equilibrium assembly processes[12–15] or in the operation of molecular machines[16], in which kinetics becomes the decisive factor. However, this operation requires conditions that will not occur spontaneously. The second law of thermodynamics states that an isolated system must evolve towards the equilibrium state corresponding to a maximum of thermodynamic stability. By contrast, the existence of a different form of stability has been proposed to account for the direction of biological evolution[17–20]. This form is specific to systems capable of making more of themselves, and has been called dynamic kinetic stability (DKS) in replicating systems[21]. Consequently, kinetic selection can only drive the system towards an increase in DKS. However, to avoid a violation of the second law, it can only apply to systems held in a non-equilibrium state. The concept of DKS and the associated thermodynamic requirements for its observation have been the subject of additional investigations[22–25]. Rather than focusing on the stability issue, we argue here that, in order to properly understand the specificity of biology and the conditions for natural selection, we must consider the actual meaning of irreversibility in the reproduction process and the conditions needed for it to occur at the single-molecule scale. This approach improves the description of the basic features of life and

evolutionary sciences on physico-chemical grounds.

Chemistry and evolutionary principles

Evolutionary concepts have often been employed in chemistry. This is certainly the case for self-assembly processes based on dynamic combinatorial chemistry that enable the identification of supramolecular structures able to bind a guest[26]. Such processes were described as reminiscent of the Darwinian principles of evolution[27]. It has even been suggested that a combinatorial approach might solve chemical problems through the application of evolutionary principles[28]. However, in dynamic combinatorial chemistry, the problem — selecting a convenient solution from a huge number of possibilities — is solved by thermodynamics on the basis of the lock-and-key principle. As such, the identification of a molecular target through its binding properties does not correspond to an open-ended evolutionary process; a solution is found once and for all unless new components are introduced in the combinatorial library. Reproducing the main features of life and especially the observation of an open-ended evolutionary process[29] requires a different approach.

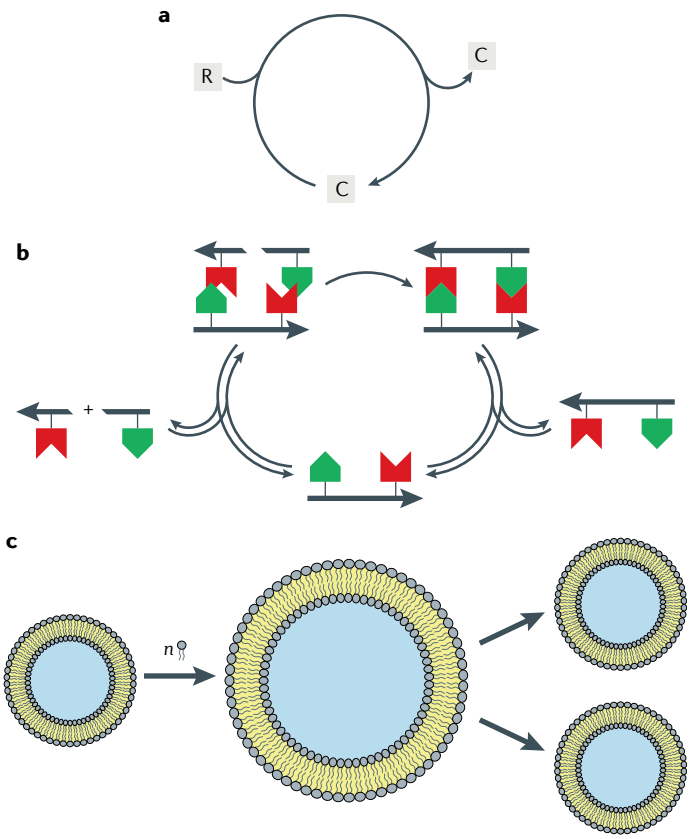
Natural selection and kinetic selection

Darwin's theory of evolution states that all species evolve through the natural selection of inherited variations that present an advantage for their survival and their ability to reproduce. It, therefore, requires populations of organisms with inheritable variations. As a result of producing more numerous offspring, better-adapted organisms with a set of mutations that present an advantage in a given environment will tend to prevail, independent of their initial abundance in the population. That Darwin developed these views almost a century before the molecular mechanisms of heredity were discovered strongly suggests that the corresponding laws can be accounted for without considering our extant knowledge of molecular biology. It may be better considered as a kinetic issue that translates to a mathematical solution for the growth of a given population. This is consistent with Lotka's description of 'natural selection as a physical principle'[30]. Although the concept is defined within a biological context, no theoretical obstacle prevents natural selection from having an equivalent in non-living systems. Indeed, populations of RNA have been shown to evolve in test tubes under the effect of stress[31]. This observation clearly demonstrated that a kinetic selection process reminiscent of natural selection can work in a chemical system, provided that the system involves reproducible entities with some possibilities for variation (BOX 1). This result opened the way for both experimental[32] and theoretical[33,34] developments on artificial evolutionary processes involving nucleic acids. Szathmáry and Gladkih[35] analysed the requirements for the strand survival as a function of replication rate using a simple model of autocatalysis (FIG. 1a). In a population of autocatalysts, X_i, the sum of concentrations of autocatalysts can be maintained ($\Sigma[X_i] = \text{constant}$) by simulating an outflow.

The term $k_i\,[X_i]^n\,[R]$ in the rate law describes the autocatalysis: the rate of formation of the autocatalyst is dependent

Box 1 | **Chemical systems able to multiply**

A mandatory condition for observing a kinetic selection process reminiscent of natural selection in chemical systems is that entities are able to multiply themselves. Notable examples include: autocatalysis, in which a catalyst C is reproduced through a cycle from a reactant R (more than one stoichiometric equivalent of catalyst C should be released after the cycle is completed) (see the figure, part **a**); template replication of polymers, in which monomers or segments can be ligated into longer strands after binding to a template (the earlier, non-covalent association of short segments to the template ensures fidelity in copying sequences) (part **b**); molecular assemblies like micelles or (as depicted) vesicles able to grow and divide by accretion of monomers (part **c**). However, biological evolution cannot be considered independently of the presence of genes (irrespective of their chemical nature). Mutations of these genes enable the corresponding characters (phenotypes) to be selected (or driven to extinction), as a result of the ability of the corresponding organisms to give birth to an offspring in a given environment. The propensity of any chemical system to accommodate for variations would, therefore, constitute a key factor in enabling evolution. Thus, not all chemical systems with the ability to multiply would be equivalent with respect to their ability to undergo a kinetic selection process reminiscent of natural selection. For instance, autocatalytic processes involving simple chemicals (part **a**) are, at best, likely to accommodate only a limited number of variations and, in the general case, will, therefore, not be able to generate an open-ended evolutionary process[29,68,69]. In this way, templated replication has been shown experimentally to suffer from the limitation that the higher affinity of the ligated product for the template compared with that of shorter segments will induce kinetic inhibition by the product[36]. This limitation to exponential growth makes the system unable to achieve a process of kinetic selection reminiscent of natural selection[35]. Lastly, although compositional genomes based on assemblies of different surfactants have been proposed as early genetic systems[70], this idea has been challenged[68,69]. Moreover, the exchange of ligands between different aggregates is likely to be limited by diffusion processes, which is in contradiction with the emphasis on kinetic barriers involved in our approach. To overcome these drawbacks in origin-of-life studies, super-systems made of combinations of autocatalytic systems, templates and assemblies have been proposed through a systems-chemistry approach[41].



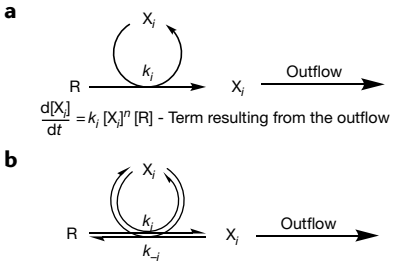


Fig. 1 | **Accounting for strand survival with models of autocatalysis. a** | The model of autocatalysis[35], in which an overall constant population ($\Sigma[X_i]$ = constant) of m autocatalyst variants X_i (with $i = 1$ to m) is maintained by an outflow. **b** | Autocatalytic system as above but modified to take into account the occurrence of a reverse process for autocatalysis.

on its own concentration. In this situation, Darwinian behaviour will only be observed[35] if $n = 1$, corresponding to classical autocatalysis and exponential growth[34]. This analysis provided understanding for the observed lack of evolvability of systems involving templated nucleic-acid ligation. The ligation product is more tightly bound to the template than the shorter fragments. This inhibits further replication, leading to parabolic growth with $n = 1/2$ in the rate equation[36]. In their analysis of conditions for effective selection, Szathmáry and Gladkih considered an irreversible process for replication[35]. This being the standard approach in biology, the assumption was not explicitly stated. Our approach is a more general one, consistent with the aforementioned importance of irreversibility, and considers a state closer to equilibrium in which the reverse reactions are included (FIG. 1b). The process can select variants for which the kinetic constants k_i increase as well. Note, however, that, for any catalytic process, the rates of both the forward (k_i) and reverse (k_{-i}) reactions must increase at the same time. Therefore, the selection of the variants replicating faster will eventually lead to those for which the kinetic term k_{-i} $[X_i]$ is no longer negligible compared with the breakdown process simulated by the outflow.

As a result, the system no longer behaves like one far from equilibrium. It reaches a state in which the concentration of species tends to be determined by the equilibrium constant k_i/k_{-i} rather than by kinetics and, therefore, becomes independent of the catalytic efficiency. Kinetic selection is no longer efficient. This conclusion is consistent with the view that the evolution of a system close to equilibrium can be understood through a macroscopic description using thermodynamic quantities without knowledge of the microscopic processes[37]. The corollary of this is that, a far-from-equilibrium state and the occurrence of autocatalysis are required for fluctuations occurring at the microscopic scale to become prevalent, such that complex behaviours (for example, oscillations or chaos) can be observed[37]. For microscopic events like mutations to prevail in a population of replicating entities, these events must be independent of macroscopic thermodynamic quantities and, thus, a close-to-equilibrium situation must be avoided. Reactant fluxes corresponding to the replication cycle of the autocatalyst must remain unidirectional (FIG. 1a) and involve strongly exergonic processes. If not, selection of the kinetically most efficient autocatalyst would no longer be observed. Autocatalysts with lower efficiency would not be driven to extinction and, instead, their concentration would be ruled by thermodynamics. Close to equilibrium, a simple replicator corresponding to an autocatalytic cycle involving a possibility of variation of the reproduced entity[38] cannot, therefore, evolve in an open-ended fashion, which is an essential feature of life[29]. This assumption raises the question of the quantitative characterization of far-from-equilibrium states favourable to the emergence of an equivalent of natural selection in chemical systems. An approach to solve this question is presented in the following sections.

Unidirectional reactant flux

The spontaneous emergence of a chemical system capable of meeting the condition for being considered alive is assumed to be highly improbable. The most likely scenario presumes that chemical determinism[39,40], including the kinetic selection of chemical systems capable of reproducing themselves, has been present since the very early stages of chemical evolution[24], driven by an increase in replicative DKS[19]. This process requires first, the production of chemical entities that can replicate, and second, that variations are possible that will result in selective growth of a replicating system that reproduces faster. These chemical entities may be based on polymers that replicate through base pairing (such as nucleic acids), vesicles or metabolic networks, each of which has its drawbacks (BOX 1). More likely is that they should be constituted by cooperation in a systems-chemistry approach that overcomes the drawbacks of any one subsystem in isolation[41]. Independent of their actual composition, it is possible to represent the reproduction process of growth and division with the input of food, thereby mimicking the reproduction cycle of simple living organisms like bacteria (FIG. 2). The reproduction cycle is unidirectional, which means, for example, in the case of a bacterial reproduction cycle (FIG. 2a), that unfolding the cycle in the reverse direction is virtually impossible. Such an unfolding process would not only require cells to merge but also the ordered cleavage of biopolymers, the reconstitution of energy carriers and many other transformations with negative entropy values. In order to account for this essential irreversibility, a comparison is made in FIG. 2 with two different chemical cycles. First, an autocatalytic cycle working close to equilibrium is considered (FIG. 2b). Second, a source of energy is coupled to the reproduction process to maintain a far-from-equilibrium state (FIG. 2c), restoring a situation similar to that of bacterial division (FIG. 2a).

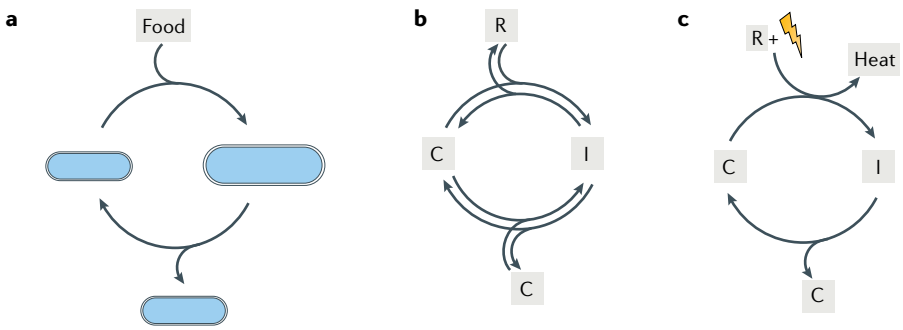


Fig. 2 | **Reproduction cycles. a** | Cell cycle: feeding bacteria induces bacterial growth and cell division. Irreversibility is expressed at the scale of a single (usually microscopic) entity through unidirectional transformations, in contrast with microscopic reversibility that rules the motion of particles in physics. **b** | Thermodynamic control: autocatalytic cycle at equilibrium. The composition of the medium is determined by the difference in free energy of reactants (R) and other species (intermediate I and catalyst/product C). Equilibrium concentrations are independent of the occurrence of autocatalysis. **c** | Kinetic control: an autocatalytic cycle taking into account the need for irreversibility as a consequence of the dissipation of energy (generating heat and producing entropy).

At equilibrium, no specific behaviour is expected from a replicating system (FIG. 2b); the concentrations of the different species are determined by thermodynamics. The concentrations of reactants, intermediates and products should be independent of the occurrence of an autocatalytic architecture. In the case of FIG. 2c, the replicating system (represented by a simple autocatalytic cycle) is fuelled by an energy input. It becomes irreversible and can now reproduce the kinetic behaviour of living organisms and, possibly, the ability to undergo a self-organizing evolutionary process driven by an equivalent of natural selection. Some free-energy potential provided by the energy source must be dissipated (for example, converted into heat) to induce self-organization work. The reverse process must be prevented on the timescale of reproduction (i.e. the period of time separating two generations) by the kinetic barriers and this enables an assessment of the energy that must be dissipated[23,42] (FIG. 3). If we take the length of one generation of most living organisms as being in the range 1 s–100 years, then this leads to an estimate of 74–129 kJ mol^{-1} (an order of magnitude of 100 kJ mol^{-1}) for the minimum kinetic barrier at 300 K. An input of free energy is, therefore, needed for a replicating chemical system to undergo a kinetically irreversible process of reproduction that can pave the way for natural selection and ensuing possibilities of self-organization. Our estimate of 100 kJ mol^{-1} can be compared with the thermodynamic potential required to produce chemical work in biology. The free energy of hydrolysis of ATP under standard conditions is −31 kJ mol^{-1} at pH 7 (REF.[43]) (though it can exceed this value by several tens of kJ mol^{-1} under the non-equilibrium conditions of the cell). Thus, the free-energy requirement for the origin of life is not only attributable to prebiotic polymer assembly or other forms of work needed to build chemical components but with the inescapable production of entropy (for example, by the dissipation of energy as heat in the environment). In other words, triggering an equivalent of natural selection in chemical systems requires that they be fed with free energy, not only to build material components or to drive polymerization but mostly for the system to become irreversible (which is generally equivalent to dissipating energy as heat). Irreversibility must reach a degree such that reactant fluxes become unidirectional, meaning that the system no longer corresponds to the situation in FIG. 2b but to that in FIG. 2c. The role of energy in the origin of life is, therefore, mainly that of making a system work so that self-organization is produced at the same time as variations are selected. It is worth emphasizing that the energy dissipated as heat to make the reproduction cycle irreversible cannot be used for any other function and must be 'wasted' (as the source of self-organization and evolution). Provided that this condition is met and that a non-limited domain of variations is accessible — for instance, through the mutations of an information carrier — the system might then evolve, driven by the imperative of reaching higher degrees of replicative DKS[19,22]. This process can include not only the improvement of catalytic abilities but also the emergence of new functions and complex forms of organization[44]. In the context of this work, the evolutionary process itself becomes irreversible because it is inherent to the concept of stability[17,19,22]: in a given environment, there is no possibility of a spontaneous reversal of its direction, leading to the selection of replicators with lower DKS. Environmental changes or stochastic/historical events may mitigate the latter conclusion, since the kinetic stability of replicators in intrinsically open systems depends on many external factors.

Energy quantum for life's emergence

In the above, we identified that a reproduction cycle having a dissipative character is a necessary condition to endow a chemical system with abilities similar to natural selection. This observation then raises the question of how energy can feed the system. Is a single quantum of energy needed for this purpose or is it possible to assemble contributions from different carriers? Whatever the solution, the analysis presented above shows that dissipation must be present because heat, the most degraded form of energy at a given temperature, must be produced from a less degraded form. The second law of thermodynamics prevents the reconstitution of higher-quality forms of energy from degraded ones without compensating for the difference in entropy. Any process involving the addition of multiple energy quanta to overcome the irreversibility constraints would, therefore, need to be coupled with energy dissipation through an appropriate mechanism (BOX 2). These processes are not impossible, as has been shown by molecular machines that are able to drive systems far from equilibrium through oscillations in environmental parameters[16,45] or by combining thermal convection and the Soret effect[46], and possibly through other mechanisms[47]. However, at the surface of the early Earth, quanta of energy meeting the conditions required to feed an irreversible reproduction loop were abundant, owing to solar radiation (see development in the next section). Provided that reaction pathways are available, coupling photochemical energy to the autocatalytic cycle should constitute a spontaneous (and, therefore, thermodynamically favourable) process. Redox gradients present on the surface of the early Earth have also been proposed as providing a strong potential[48]. However, the processes by which electron transfer might be coupled to the generation of high-energy metabolic intermediates remains questionable. Using more degraded forms of energy would not be required. It should even be considered less probable than the straightforward use of a suitable photochemical energy source and would, in addition, require a mechanism to increase the entropy in the environment (BOX 2).

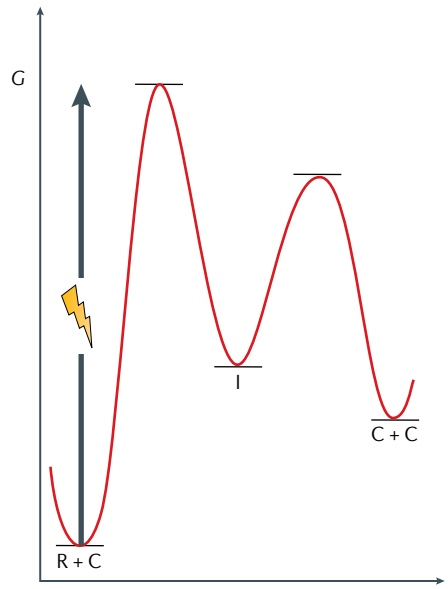
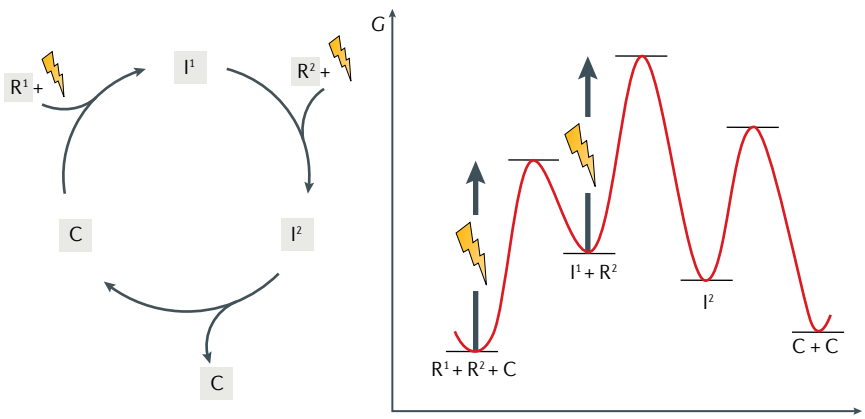


Fig. 3 | **Free-energy diagram representing an autocatalytic cycle fuelled by an energy input corresponding to** FIG. 2c. Scales are not intended to be quantitative. In principle, any kind of energy input (yellow lightning symbol) could be used to fuel the process, provided that it allows the reactant R and catalyst C to be converted into the intermediate I. Irreversibility is ensured by the kinetic barrier of the reverse reactions, which should be such that thermal activation is not sufficient for the process to unfold spontaneously in the reverse direction (reverting C and R from I) at the timescale of the reproduction cycle. Figure is adapted from REF.[24], CC BY 3.0 (https://creativecommons.org/licenses/by/3.0/).

Box 2 | **Using degraded energy quanta to induce irreversibility**

A putative autocatalytic cycle involving two activation steps in order to feed the system with energy and allow it to work irreversibly is considered in the scheme (see the figure). Intermediate I^1 is maintained in a non-equilibrium steady state from reactants R^1 and C by absorption of an energy quantum representing half the value needed for the reproduction cycle to work irreversibly. The kinetic barrier of the reaction spontaneously reverting I^1 into R^1 and C cannot be very different from ca. 50 kJ mol^{-1} (half the value required for the process involving a single activation event, as in FIG. 3). This barrier corresponds to a ca. 50 µs order of magnitude for the lifetime of intermediate I^1 at 300 K, through an estimate made from transition-state theory by using the Eyring equation, as in the corresponding earlier work[23,42]. Therefore, any process that could yield intermediate I^2 from I^1 must be the result of a kinetically very fast reaction competing with the spontaneous breakdown in order to avoid intermediate I^1 from reverting to the reactants. This process is, therefore, considered to be highly unlikely for a rudimentary, non-enzymatic prebiotic process. Otherwise, the yield of I^2 would be strongly limited and the system would dissipate the large majority of energy into a degraded form (e.g. heat) in a non-productive way (which, most importantly, includes the purpose of making the cycle irreversible).

The fact that an autocatalytic cycle depicted above is unlikely does not, however, rule out the initial role of weak energy quanta. But, in order to become efficient, such possibilities should involve additional features. This is the case, for instance, in recent investigations carried out by Otto's group, which suggest that irreversibility might be achieved through a self-assembly process in which fibres are built by stacking cyclic oligomer units maintained in a dynamic out-of-equilibrium state[47]. As stacking occurs only at the extremities and the inner units are chemically non-reactive and, thus, protected from solution reagents, the process becomes irreversible and growth is provoked by stirring that breaks fibres. The potential of such systems requires a detailed analysis because the inner units of the fibres cannot be reproduced. It does show that the kinetic barrier protecting the covalent system from being broken back to reactants can also be strengthened indirectly through the formation of a molecular assembly. The elongation of a polymer by the formation of covalent bonds with building blocks at its two extremities might yield a similar result, provided that intrachain units are protected from breakdown. However, this possibility does not apply to the origin of a putative RNA world. The presence of the 2′-OH group in the backbone avoids most possibilities of stabilization within the polymer structure. Processes like alternation of wet and dry environments[71–73], in which polymers could be formed thanks to a thermodynamically favourable reaction under concentrated hot conditions, could not easily overcome this limitation. Indeed, notwithstanding the issue of non-covalent recognition being less favourable, the high temperatures favouring the addition of monomers at the extremities would also be responsible for breaking the strand at inner positions.



The use of degraded forms of energy should, therefore, require an analysis of the specific advantages and disadvantages of the mechanism through which they overcome the entropy barrier associated with the formation of quanta of energy meeting the requirement (BOX 2).

A statistical-physics approach has claimed that the amount of heat produced during replication could be a driver for self-organization[49]. Such an approach is reminiscent of the so-called principle of maximum entropy production[50], another theory that has raised strong criticism[25,51]. Our present analysis points instead towards the importance of the quality of the energy provided to the system, rather than the quantity of heat released by the replication process. In other words, it focuses on the importance of a single energy quantum necessary to drive the system in a unidirectional fashion at the microscopic scale, rather than on the macroscopic amount of heat produced by replication[49]. Considering that dissipation of the energy coming from several carriers can work in an equivalent way overlooks the difficulty associated with upgrading energy quanta. It would be unable to induce replication to proceed irreversibly unless a very specific mechanism able to compensate for the entropy loss is available.

Implications for early life

The present analysis concludes that non-degraded energy quanta are essential for processes equivalent to natural selection to emerge. This conclusion suggests that carriers or intermediates having a high content in energy would have been essential to the origin-of-life process and that their imprint might remain in biology. Here, for example, it is worth noting that amino-acid adenylates constitute one of the most activated families of biological intermediates (the free energy of hydrolysis $\Delta G^{\circ\prime}$ is ca. −70 kJ mol^{-1} at pH 7)[52], a value that significantly exceeds the energy required for peptide-bond formation. These intermediates are involved in both the ribosomal translation process and certain non-ribosomal peptide-synthesis pathways and are, therefore, among the most ancient chemical species universally present in cells. Energy-rich metabolites were, therefore, likely present at early stages and peptide formation was associated with waste of energy rather than being energy efficient. The process by which aminoacyl-tRNA synthetases ensure the fidelity of the translation process through energy dissipation[53] may also support the idea that early life was 'wasting' energy. It may have involved highly activated intermediates rather than those with chemical potentials matching the thermodynamic requirements of a given reaction. This idea is consistent with the hypothesis that life initially made use of directly available forms of energy and that further improvements led living organisms to harness less powerful sources of energy. Accordingly, the generation of ATP (now considered as the universal energy currency for intracellular processes) from the conversion of proton gradients[54] by proton ATPases may be considered a later development[55]. Proton ATPases are, indeed, a typical example of molecular machines capable of reaching upgraded energy quanta (ATP) from degraded forms (proton gradients)[56]. They are unlikely to have emerged early because of their huge complexity, such that they should have been preceded by energy metabolic

pathways involving carriers associated with non-degraded energy quanta.

Approaches to the origin of life that focus only on the formation of biochemicals and the claim that the origin of life is possible from the occurrence of nucleotides, peptides or metabolic cycles overlook the main barrier hindering the process, that is, the emergence of the kinetic selection of replicators as a self-organization principle. The thermodynamic potential of a free-energy source adapted to the emergence of life must, therefore, provide both the amount of energy needed to build the biochemicals and that required to drive it in an irreversible fashion. A value exceeding 150 kJ mol^{-1} has been proposed to this aim[23,42]. At the molecular scale, this value corresponds to a minimum quantum of energy of 1.55 eV per microscopic event or to a photon having a wavelength shorter than 800 nm. This assessment points towards the visible region of the electromagnetic spectrum and, thus, the maximum flux of the solar spectrum received at the surface of the Earth. The most abundant source of energy available at the surface of early Earth therefore matches the condition needed for kinetic selection to become efficient. This fact may not be fortuitous and should be considered thoroughly by researchers involved in the origin-of-life field. At this point, it should be emphasized that the main spontaneous thermodynamic transformation occurring at the surface of the Earth consists in the overall conversion of photons coming from the Sun into ca. 20 times more photons of longer wavelengths emitted into space from the Earth's surface[57]. Therefore, alternative hypotheses for the origin of life involving a reassembly of quanta of energy from degraded forms do not satisfy the maximum-parsimony (Occam's razor) criterion. Following this same line of thought, the origin of life at a higher temperature is less likely because the kinetic barriers would need to be correspondingly higher to ensure irreversibility (raising the temperature to 400 K would require an increase of ca. 40 kJ mol^{-1} in the kinetic barrier)[42,58,59]. Indications such as these that arise from a physico-chemical approach to the origin of natural selection might, therefore, prove highly valuable in identifying environments favourable to the origin of life. The analyses developed here point towards those that benefit from possibilities of photochemistry (or processes capable of delivering an equivalent energy potential, such as lightning or electromagnetic radiation with wavelength shorter than visible light). The lower range of temperatures compatible with the presence of water in the liquid state is also considered as more favourable in order to take advantage of its properties inducing, for instance, the formation of aggregates driven by the hydrophobic effect.

If chemists consider that the origin of life is mainly a question of synthesis of building blocks and subsequent polymerization, then they underestimate the importance of energy, and its intrinsic quantum nature, in the process. On the other hand, top-down approaches derived from the analysis of biological pathways emphasize the importance of electron transfers and on pathways from which ATP is produced in the cell thanks to chemiosmosis[60]. These latter approaches have trouble with the complexity of the molecular machines needed to assemble energy quanta from degraded forms. Thus, it would be preferable to choose an alternative route that avoids the misconceptions coming from both synthetic-chemistry (bottom-up) and top-down approaches.

The energy-barrier requirements, however, indicate that chemistry does matter. The importance of these barriers for holding a system in a far-from-equilibrium state has already been emphasized[58,61,62] but it relies not on the presence of inactivated building blocks or polymers but on the properties of activated species. Activated intermediates involved in the process must, therefore, share both thermodynamic instability and sufficient kinetic stability that impedes their reversion to non-activated precursors. Indeed, these properties have been identified as essential in understanding the role of ATP[63]. The lifetime of the activated intermediates must allow room for catalysis without limiting the number of sequential downstream steps. Such processes should be effective, provided that none of the steps involves a transition state higher in energy than that providing kinetic stability to the activated precursors (i.e. these steps do not become rate-determining in the activation process). From the perspective of self-organization, kinetic selection would favour the occurrence of specific autocatalytic processes. Multiple covalent bonds are one type of molecular entity that fulfil these criteria. The hydrolysis of such bonds releases a significant amount of energy but they are kinetically quite stable. The best examples are nitriles or alkynes and related species. They often react sluggishly but specific paths have been disclosed through which they may be involved in prebiotic catalytic processes[64,65] or lead directly to polymers[65]. Nitriles and related species have also been shown to give rise to rich synthetic pathways yielding a variety of biochemicals through a highly versatile photoredox cycle reduction involving sulfides[66]. Nitriles are found in interplanetary bodies, could be formed by high-energy impacts or photochemistry in the upper layers of a reducing atmosphere and their kinetic stability enables them to move into an environment remote from the location in which they are formed. Finally, it is worth mentioning that biochemistry involves many cycles other than reproduction, but there is no specific need for them to proceed irreversibly from the perspective of natural selection. Some of them involve the coupling of an endergonic reaction with the hydrolysis of ATP. They are rendered irreversible because cells are maintained in a disequilibrium state reflected by the ratio of ATP to ADP concentrations.

The chemistry that is envisioned above is quite different from the energy metabolism of present-day living organisms. Most extent biochemical pathways rely on redox chemistry. Evolution has built a highly sophisticated system in which redox gradients are converted into the free energy of hydrolysis of ATP. It is subsequently used to provide energy for synthetic, endergonic reactions. It seems most probable that there was a long evolutionary pathway between the chemistry considered above and the biochemistry in which a wide range of redox gradients can be converted into proton gradients through an electron-transfer cascade and, ultimately, into the synthesis of ATP. These processes require the availability of many cofactors, enzymes and, most importantly, the ATPases responsible for the synthesis of ATP. The sophisticated processes involving molecular machines therefore allowed life to overcome the energy constraints obstructing its emergence. Less potent forms of energy that were not initially fit to induce the emergence of life processes could later become the main energy source of the owners of such machines. It is worth noting in this context that the value of 1.55 eV per microscopic event characterizing the energy quanta translates into a redox potential of 1.55 V for the transfer of one electron and 0.77 V for the transfer of two electrons in a single event. Strong reducing or oxidizing agents alone might bring about irreversibility and activation in a putative self-organization of replicating entities driven by redox gradients.

Conclusions

Delving into the nature of the living state and the thermodynamic and kinetic requirements for open-ended evolution has enabled the identification of irreversibility in the reproduction cycle as the key factor that characterizes the advent of a living entity. Fulfilling this condition would allow kinetic selection to play a role in the emergence of self-replicating entities having an increased kinetic stability. Evolution would then have led living entities to develop new functions and to grow in diversified environments thanks to a more complex metabolism. Eventually, they could present self-maintenance abilities and, thus, become less dependent on changes in the environment. Directions for experimental research can be deduced from this approach. A special focus should be placed on the search for processes capable of harnessing the main sources of energy present on the early Earth that might serve to feed entities able to reproduce themselves in a dynamic kinetic state[19]. Entities involving such processes could not be considered as fully living, in the biological sense of the term, but on a pathway leading to the emergence of life. The claim that physical principles need to be amended to account for the living state has been reiterated recently[67]. Nonetheless, the analyses presented here support the views that there is no 'mystery' in life's physical basis, except the fact that its emergence is associated with the low probabilities of structures having a high degree of functional organization. Physics and chemistry can, therefore, account for the main features of the living state without needing any additional principles. Life might eventually be considered a logical consequence of the association of irreversibility and replication in order that replicators having a non-limited range of variations[38] can undergo selection and evolution. Considering the possibility that life processes like reproduction could be reversible defies common sense and implies that any theory of life should be built upon elucidating the means that the system uses to avoid it. This approach constitutes a new step in the endeavour to unify the physical and life sciences, whereas it has often been the case that the former has been built by considering ideal reversible processes that are fatal to the latter. It should be noted that irreversibility is used here not with its thermodynamic meaning associated with processes moved a short distance from equilibrium and that produce entropy along their return path. Its meaning is more radical. Rather than being a consequence of statistics at the macroscopic scale, it must also be expressed at the scale of each unique entity that is reproduced. The flux of reactants involved in the process should become unidirectional, fuelled by strongly exergonic processes. This situation gives rise to the realm in which the process of reproduction drives evolution. The non-linearity in the growth of the number of replicating entities is fully expressed as a consequence of autocatalysis. In this situation, the system would eventually behave in a way similar to extant living beings in which irreversibility reaches an extreme degree such that not a single entity in the biosphere can be conceived to undergo the exact reverse of reproduction.

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