



**HAL**  
open science

# Evolutionary Abilities of Minimalistic Physicochemical Models of Life Processes

Robert Pascal

► **To cite this version:**

Robert Pascal. Evolutionary Abilities of Minimalistic Physicochemical Models of Life Processes. 2024.  
hal-04569062v1

**HAL Id: hal-04569062**

**<https://amu.hal.science/hal-04569062v1>**

Preprint submitted on 6 May 2024 (v1), last revised 26 Aug 2024 (v2)

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# **Evolutionary Abilities of Minimalistic Physicochemical Models of Life Processes**

Robert Pascal\*

Aix–Marseille Université – CNRS, Institut Origines, PIIM, service 232 -Saint Jérôme - Ave  
Escadrille Normandie Niemen, 13013 Marseille, France Marseille, France

## **Abstract**

The ability of living organisms to persist, grow, evolve and invade environments seemingly challenges physical laws. Emerging Autonomous Systems representing autocatalytic cycles constituted of energized components in a state of Dynamic Kinetic Stability feature some of these properties. These simple theoretical models can grow, can be transferred but need an initiation to emerge and can collapse. Moreover, they can undergo kinetic selection in a way consistent with Darwinian behaviour, though, as a rule, they lack the ability to undergo change. The mere existence of these systems and their open-ended growth potential are proposed to constitute a transmissible factor of a non-coded kind. The onset and selection of epigenetic factors may therefore have preceded that of genetic polymers. Here is addressed the question of how these systems may arise from the diversity exhibited by abiotic organic matter, sometimes associated with intractable mixtures or an asphalt paradox, which may actually be useful in providing initiators. The Darwinian description of evolution may therefore be merged *without critical discontinuity* within an origin scenario. Accordingly, such a theory would rests solely on physicochemical laws beginning with the potential of emerging autonomous systems able to compete and invade the space dimension, and able to further develop along other available dimensions including variability and, possibly, cognition.

## Introduction

There is no widely accepted answer to the question of a driving force for life and its emergence. The Second Law drives the evolution of regular physicochemical systems towards equilibrium. On the other hand, biological evolution is ruled by a theory of evolution involving reproduction with modifications and natural selection. How is it possible to get from the first direction of change to the second? Presently two alternatives are generally considered: either the transition was sharp and occurred by chance through an event that has no possibility of being reproduced [1], in which case science is almost helpless, or, alternatively, an unknown chemical driving force leading to self-organization was at work during the transition [2]. But, rather than relying on unknown and questionable physicochemical principles, undertaking an approach based on established scientific knowledge to account for the process may be wiser.

The proposition of a Principle of Persistence provided a means of reuniting the directives of the Second Law and that of the theory of evolution within a single scheme [3,4], following the views that life constitutes a kinetic state of matter [5]. It was proposed that the evolution of living organisms does have a direction after all – towards increasing Dynamic Kinetic Stability (DKS) in a similar way to isolated chemical systems ruled by the Second Law evolve towards a maximization of entropy [4]. The processes ruled by a drive toward increased DKS are only observed in a context in which an input from an energy source maintains the system away from equilibrium [6]. It is important to take into account that this stability is of a dynamic kind and requires the system to be constantly fed with energy, in the same way as bicycles require motion to ensure stability. Therefore, a transition from non-living systems toward life may be conceived through the intermediacy of a simple replicative DKS system, providing a pathway for a gradual emergence of aliveness [7].

As previously shown [8], some of these systems could behave in a way quite similar to living organisms provided that the components of the reaction network involved in the reproduction cycle are thermodynamically unstable and unable to be formed in any significant amount at equilibrium. These Emerging Autonomous Systems (EASs, Fig. 1) are potentially capable of growing exponentially and can colonize every environment in which a convenient energy source is available to sustain their development. The association of dissipation and of the reproduction of their components, which are intimately coupled in a single process, allows their development to avoid any violation of the Second Law [8–10]. Dissipation is responsible for the irreversibility of the process with the important consequence that evolution proceeds irreversibly [11] provided that minimum conditions regarding the potential of the energy source are met. Most importantly, the components of the chemical network, being thermodynamically unstable, are constantly destroyed and replaced by new ones, a property which is of importance considering the living world is one in which the death of living entities is required in order that evolution can proceed [12]. Moreover, any break in the availability of the energy source will lead all the unstable intermediates to become extinct with limited possibilities of regenerating the preceding state so that not only the components vanish (or expressed in biological terms, die) but the whole system collapses as well.

This approach was made considering kinetic features of life only, neglecting the issue of variability that is an obvious requirement for natural selection to yield an evolutionary process. Here are addressed the questions of how this kind of replicative DKS systems made of unstable entities could arise, compete with other systems of the same kind and how they could be coupled to other sub-systems allowing for instance genetic variations capable of enhancing the DKS of the super-system as a whole.

### **The unique behaviour of EASs**

The formation of a dissipative autocatalytic cycle made only of thermodynamically unstable intermediates gives rise to a process that shares an important feature in common with the behaviour of living organisms (Fig. 1), namely, a DKS state that is transmissible and that can become extinct as a result of a shortage in energy and/or material supply. Its autocatalytic character means that it can grow exponentially when resources are not limited. Ideally, this state is a network property shared by all the intermediates and it is not that of an individual molecule or coded into any structure. When considered apart from the context of the EAS model depicted in Fig. 1B that includes a source of energy feeding the system, all the individual intermediates (as  $R^*$ ,  $I_1^*$  and  $I_2^*$ ) should undergo irreversible decay and be doomed to extinction. An inventory of the components is therefore unable to encompass the unique nature of the system. The possibility of feeding the EAS model with reactants and energy together with its autocatalytic nature give rise to its specific behaviour making it autonomous and dynamically stable. It is worth emphasizing that the EAS of Fig 1B could therefore be considered as a kind of minimalistic physicochemical model rather relevant to the processual perspective on life advocated by Dupré and co-workers [13], and contrary to a ‘metaphysics of things’. Moreover, autocatalytic networks constituted only of activated and unstable intermediates are not unrelated to biochemistry as shown by the cycle through which high-energy ATP is produced and recycled from ADP (another unstable anhydride) in cells, even though the realization of this process requires the presence of enzymes (Fig. 1C). However, because an extinction following a shortage in energy can persist (at least for systems in which the components of the cycle are totally unstable), two different states could be stable, namely the one in which the system is present and the one in which it is not. This alternative means that *the very presence of such a system in an environment presenting a given thermodynamic disequilibrium determines the resulting kinetic state among any number of different options*. Notice, no encoding is needed for any one of these alternative kinetic

states to exist. The presence of the system would manifest a heritable phenotypic trait, whose transmission through an initiation process in a native environment proceeds in the same way as the transmission of an epigenetic factor, one that would have preceded the utilization of coded information.

This analysis shows that a replicative DKS state of a metabolic nature, which contributes to self-organization by coupling development with dissipation [8], can be considered as autonomous and distinct to the genetically encoded features of life that allow for variation and evolution. But reaching this thermodynamically unstable but kinetically stable state can be considered as a sign of viability for a selection process based on an increase in DKS. Indeed, a competition of two systems of this kind for a limited common resource would lead the less efficient to become extinct precisely because they present autocatalytic features [14]. This observation validates the approach of considering the kinetic features of systems evolving towards life independently of the issue of variability and evolvability [8]. This does not mean that the presence of a metabolic process was sufficient for life to emerge since the contributions of different sub-systems are obviously needed to bring about compartmentalization and genetic variability. However, it already suggests that when a living organism gives birth to another one, it does not only transfer its genome but also a non-genetically encoded factor associated with its replicative DKS state. What is signalled by this heritable phenotypic factor is a property universally found in populations of living organisms: the ability to be driven towards increased DKS as an evolutionary directive. The model described here shows that this factor can be present in virtual fashion in a rudimentary model even though the system in itself possesses no or few variation possibilities [15,16].

As soon as the system is in the replicative DKS state of Fig. 1B, it is transmissible, as for instance, by the transfer of an aliquot portion of the system in a new favourable

environment. The process carries with it the possibility of settling in any environment in which the source of energy is available to feed growth (a property related to the lack of limits to exponential growth). This possibility corresponds to an anticipation of the capability of invading all the free space even if this goal is not yet realized, in other words ability for *open-ended* growth. Indeed, this projection in the future manifests a teleonomic feature [17] corresponding to the potential completion of growth. This observation confirms that the roots of many of the non-material features of life can be identified in chemical systems provided that they share the property of becoming stable in a replicative DKS state [18–21].

However, even though this system is transmissible, it is not easily able to undergo change because of the intrinsic lack of evolvability of metabolic replicators [15,16]. But, owing to its non-material nature, the non-genetically transmissible factor is in principle independent of the encoded ones usually associated with information stored within the sequence of nucleic acids in extant forms of life. The former factor is therefore likely to be established at a different stage that can would likely be earlier than the latter ones, therefore introducing a step forward in the emergence process (Fig. 2). A system of this kind is therefore viable even if it lacks possibilities of evolution. Additional features of heterogeneity that will not be considered here might be present due to diffusion since EASs are likely to arise as a result of stochastic events in the environment. The onset of EASs would however represent a step forward in evolution because the introduction of any alternative behaving in a similar way would mechanically lead to a selection process based on kinetic efficiency according to the directive of evolution toward an increase in DKS. Nothing in this scheme excludes the early association with other features of self-organization like compartmentalization that may be helpful in gathering the energy gradient (concentration of activated species) or by connecting metabolic and genetic subsystems into a supersystem.

## **Emergence of EASs**

In the preceding section, systems made of intermediates that are totally unstable with respect to inactivated reagents were considered. In reality, the Gibbs free energy potential corresponding to the activated species should correspond to finite values. In that event, equilibrium concentrations of the activated states should correspond to very low, but non-zero values (Fig. 3). The fate of the system would then depend on a stochastic factor related to the number of individual molecules in the activated state  $\mathbf{R}^*$ . A consequence of the autocatalytic nature of the process is that a single molecule of one of the less activated intermediates of the cycle (as  $\mathbf{R}^*$  in Fig. 1B) may in principle be sufficient for initiation so that the autocatalytic process may be ignited by a scarce number of molecules present at equilibrium and therefore the system may not totally collapse as a result of a shortage in the source of energy. This situation could take place if the energy of the excited state does not exceed a threshold corresponding to a value related to the number of molecules present in the macroscopic system (typically of the order of magnitude of the Avogadro constant,  $\Delta G = -RT \ln 1/N_A = 136 \text{ kJ mol}^{-1}$ ). Above this threshold, equilibrium concentration corresponds to less than 1 molecule of  $\mathbf{R}^*$ , then a delay would be required before the initiation of the system, which would rather result from kinetics than from thermodynamics. This delay could also be associated with a low abundance of the proper reactants (as  $\mathbf{R}$  in Fig. 3) among the organic matter of abiotic origin that is indeed known to present a high diversity [22,23]. The non-activated reactant  $\mathbf{R}$  may for instance be present in a picomolar rather than a molar range leading to a much lower requirement for thermodynamic instability ( $\Delta G = 67 \text{ kJ mol}^{-1}$ ). It may additionally result from very slow kinetic of formation of  $\mathbf{R}^*$  involving a high kinetic barrier and/or a bimolecular reaction of reactants having both a low abundance. Reaction networks that are more complicated than a simple autocatalytic cycle may also introduce a delay in the emergence [24]. Very different situations are likely to be found depending on the probability of obtaining systems of this kind. In the more favourable situations, several



autocatalytic systems could be initially present, they would grow according to their own capacities and compete until they are able to deplete the energy source or other reactants or resources with the consequence that the less efficient of them would be suppressed and the more efficient one would be conserved according to their relative dynamic kinetic stabilities. In the less favourable situations, no such activated species may initially be present and the initiation of the system would depend on the probability of the formation of an intermediate like  $\mathbf{R}^*$  involved in an EAS and therefore of the time needed for a single microscopic occurrence of this event to take place, which can span over a large range and might extend to geological times. The microscopic event responsible for the emergence is required to be highly improbable for this situation to be observed so that the activated intermediate  $\mathbf{R}^*$  should correspond to a substantial degree of instability, but its formation would more certainly require to be limited by kinetics as a result of high kinetic barriers (Fig. 3). Independently of this requirement, and in a way consistent with the existence of a decay threshold [25], the intermediate  $\mathbf{R}^*$  must also be protected from deactivation by a kinetic barrier in order that the autocatalytic cycle is viable (that the turnover can produce more than one stoichiometric amount of  $\mathbf{R}^*$  and, therefore, that the lifetime of  $\mathbf{R}^*$  is longer than the turnover time). Establishing or sustaining these systems therefore needs high-energy potentials that have earlier been estimated to correspond to the ranges that can be provided by visible or UV photons or by electric discharges [11, 26]. These properties associated with long initiation delays are the consequence of the magnitude of rate constants, therefore emphasizing the importance of kinetics in establishing qualitative thresholds.

Compared to an origin of life based on a single unlikely event, the process involving first the emergence of an autocatalytic system made of unstable intermediates offers several advantages. First, extending the existence of autocatalytic processes to systems in which none of the intermediates is thermodynamically stable is likely to significantly widen the chemical

space of available possibilities for leading to the origin of life. This statement indicates that there is no ground for discarding systems involving thermodynamically highly unstable intermediates. Looking for means to stabilize these species by using protecting groups as usually made in synthetic organic chemistry should not be considered as scientifically founded in an origin of life perspective. A strategy considering kinetic stability in a range compatible with the timescale of replication may be wiser. Second, it turns out that any evolutionary process also depends on the possibility that the initial poorly efficient systems could be replaced by better ones and driven to extinction. Extinction is likely to be less likely for autocatalytic reaction cycles involving even a single thermodynamically stable intermediate, which may therefore hardly be able to evolve further. Therefore, evolutionary considerations also support the involvement of systems made of thermodynamically unstable intermediates only [8].

## **Breakdown of EASs**

A break in energy feeding would lead unstable EASs to collapse in a way that may be reminiscent of the death of living organisms. However, the latter generally die rapidly after their energized character vanishes due to an interruption of the feedback processes and an exhaustion of stocks of energy currencies and chemical gradients maintaining the autopoietic state of cells. By contrast, the collapse of EASs following a shortage in the energy source feeding them would correspond to the simple first-order kinetics corresponding to the decay of the less unstable intermediate (as  $R^*$  in Fig. 1B). Furthermore, as the emergence of EASs requires several tens of generations before reaching macroscopic abundance, their decay would similarly require tens of half-lives, which must independently exceed the generation time [8], for reaching total disappearance at the molecular scale. This stage corresponds to a threshold of less than one molecule in the environment below which the system would not be

able to recover spontaneously once an energy source is reinstated. However, from an evolutionary point of view analysed subsequently, the slow decay of the intermediate  $R^*$  is independent of the reproduction kinetics (Fig. 3) that would be responsible for selection. Therefore, the difference is not likely to hinder the selection process against another replicator competing for the same source of energy. On the contrary, a decay involving long periods of time may not be detrimental in the absence of additional processes allowing an active maintenance of a non-equilibrium state. This longer period of time required for collapsing may lead EASs to be able to survive long periods of feeding shortage, which may additionally be favourable in an origin of life process occurring in an environment that very probably underwent contingent changes.

## **Evolvability**

It can be conceived that different dissipative EASs may compete for the same energy source. Selection should take place by the elimination of the ones corresponding to a lower DKS. This criterion is independent of the probability of the emergence of such systems, which could take either place through an independent activation process or through a single microscopic event that would be related to the distance from equilibrium of the most accessible intermediate. This observation is related to the fact that the initiation of the autocatalytic process and its DKS state are governed by fully independent factors (they depend on the free energies of different transition states as shown in Fig. 3). At first sight, an EAS made of unstable intermediates having a low molecular weight should have no or very few possibilities of evolution. However, the almost infinite possibilities of structures provided by organic chemistry, even further extended to those that could exist in an energized state, suggests that *no preexisting autocatalytic system of this kind can be considered as definitely stable since it will never be possible to exclude the fortuitous late emergence of an alternative*

*system characterized by improved DKS. Such reasoning establishes the possibility of evolution as an unavoidable feature of a chemical environment involving a sufficiently far from equilibrium state.* A preliminary possibility of evolutionary process may then be triggered by the slow kinetics of emergence of alternative EASs having an improved efficiency and that could replace a predated one at any time, as suggested above. Indeed, the emergence of a primordial system does not exclude the possibility that other ones might appear subsequently because they could be based on even less stable or less probable intermediates. The selective behaviour implies that the more efficient one will grow, deplete the source and will thus be conserved on kinetic grounds. Selectivity is independent of emergence and only related to the kinetics of the reproduction cycle. Therefore, an evolutionary process may take place in the direction of improved DKS and in an irreversible manner as long as the environmental conditions do not change. It is worth noting that this process does not mandatorily need support for information storage and that selection may take place among highly reactive systems initiated by chance. On the contrary, it could be based on a low probability of emergence of an EAS in a far-from-equilibrium environment. There is then no reason for excluding such a kind of evolutionary process involving highly unstable entities without a genetically encoded basis though it must be emphasized that the different EASs do not need to be genealogically linked to each other and that they are on the contrary likely to result from totally unrelated emergence events. Incidentally, the fact that this possibility relies on the huge diversity of abiotic organic matter offering a wide space for selection thereby gives the beginning of an answer to the so-called asphalt paradox [27] by suggesting that chemical diversity may have an evolutionary utility. However, the picture may be more complex since different autocatalytic processes may not compete for the same source of energy so that different systems may coexist and interact possibly giving rise to an intricate network [24].

It can also be conceived that an improvement could take place through the association of this kind of metabolic replicators with a reproducible system prone to variability like a biopolymer that grows through template replication (e.g. a nucleic acid like RNA) giving rise to a kind of symbiosis similar to the one recently proposed from a biological perspective and involving reproducers and genetic replicators [28]. This association might involve a covalent bond provided that the process of replication of this structure can establish a chemical bond or a functional connection with the intermediates of the EAS. But the question of the association of different subsystems more generally raises the issue of compartmentalization, which has been a topic of wide interest in origins of life studies [29–31]. Therefore, the association of subsystems can take place within molecular assemblies or aggregates (vesicles or coacervates) so that the advantage of association and the evolutionary features are physically linked ensuring a connection of the phenotype with the genotype [32,33]. The conjugate involving the biopolymer may therefore present improved capabilities so that it can grow faster than the preceding one. Having reached a much higher efficiency, it might at a certain stage become able to deplete the energy source in a more effective way, therefore rendering the less efficient forerunners non-viable. Though this suggestion would need further support, the hypothesis that an association of a metabolic replicating system with a genetic polymer may therefore provide a solution to the problem of how to overcome the intrinsic limitations of template replicators. It is indeed well-known that the reproduction of these systems is limited by product inhibition resulting from the stronger pairing association of a covalent conjugate compared to that of shorter segments [34], which yields coexistence rather than Darwinian behaviour [35]. Associating these polymers with a metabolic replicator may avoid their limitations since the burden of exponential growth in the merged system would not be borne by the genetic component but by the metabolism. A similar comment may be made about overcoming the error threshold associated with the reproduction of genetic polymers

[36] since errors that do not affect the capacity of the metabolic sub-system to self-reproduce and therefore its viability would not be immediately deleterious and, on the contrary, any tiny advantage displayed by imperfectly reproduced short oligomers might even be beneficial for the whole system.

The formation of a single thermodynamically unstable molecule is an improbable event but one that may by itself generate a full autocatalytic cycle. This event should however be much less improbable than the emergence by chance of a whole system endowed with both metabolic and genetic properties. Moreover, it does not exclude that the later property could be induced subsequently. Compared to a scenario of emergence of a system sharing directly both the properties associated with variation possibilities and kinetic features allowing natural selection, the stepwise process is much less improbable because the occurrence of a kinetically stable replicative DKS system in a non-equilibrium concentration can allow multiple solutions to be checked over extended periods of time (as long as environmental conditions remain favourable) under which the source of energy or activated reagents are available (Fig. 2). It can therefore take advantage of the growth of populations on geological time scales to circumvent low probabilities as soon as the metabolic replicator is present. However, it is obvious that the development of enzymatic activities during evolution is likely to have had a feedback effect on the initial metabolic cycle that may have been replaced by more efficient enzymatic reaction pathways and the resort to alternative energy sources so that the initial one can possibly no longer be identified in biochemistry.

Though it emphasizes the importance of metabolism, this scenario has no relationship with earlier hypotheses involving a so-called chemoautotrophic origin of life [37,38] since the latter are usually in relation with hypotheses in which the essential process is considered as the synthesis of organic matter (anabolism) in a way coupled to subsequent processes. On the contrary, the metabolic role that is considered in the present investigations is the one that

circumvents the contradiction between a spontaneous self-organization process and the directives of the Second Law [8,39]. It addresses the role of the metabolism in enabling self-organization through coupling the process with dissipation, which has no mandatory linkage to anabolism and is more likely to be related to catabolism.

### **A driving force for self-organization**

The present work demonstrates that processes, which would at first sight be considered as unlikely, can reach stability if they can undergo a specific kinetic amplification that is efficient in a manner that allows it to be disconnected from thermodynamic stability. The probability that such a system could spontaneously emerge is much higher than could be assessed by considering stable reactants alone since all the intermediates of the system need to be unstable to facilitate further evolution, which in turn widens the available chemical space to include species having a low thermodynamic stability. The kinetic amplification expressed by the corresponding process unfolds in a way very similar to that of living organisms except that it lacks the variability features needed for natural selection that are not likely to be present among low molecular weight reagents. However, it enables an evolutionary process to be initiated provided that it can be coupled with other systems that could bring about some heritable properties. These properties could allow the self-organization of life to proceed without need for an additional driving force that could have played a role in the gap between a chemical world driven by the Second Law and the biological world ruled by natural selection. They are consistent with the views expressed more than a century ago whereby natural selection may be considered as a physical principle [40]. The specific properties of an EAS are not directly associated with structures bearing variations. On the contrary, they are the result of a systems property of unstable chemical components in an arrangement that carries within its network architecture autocatalytic behaviour. It is transferred and grows in the same

way as an epigenetic factor could do. Even if it lacks the non-limited variability needed for open-ended evolution, its presence expresses the viability of a potential evolutionary process since the association of this factor with an evolvable system could be made more favourable. It could therefore be considered that a possibility of triggering a genuine evolutionary process could lie in the coupling of a transmissible non-genetically encoded factor that brings about *viability* with a genetic system providing non-limited variability.

An unresolved question lies in the strategy that could be implemented for experimentally identifying such kinds of systems. Both the energized character shown here to be essential for these systems as well as the requirement for irreversibility of the autocatalytic cycle [11] should orient researchers towards sources of energy capable of providing a high potential [7]. The most difficult part is likely to lie in the search for the unstable but chemically reactive intermediates of the replicative DKS cycles.

### **General consequences for life**

The onset of EASs, by establishing a drive towards increased DKS, gives rise to two different properties that are essential for life. The first one is the ability to grow along the spatial dimension as long as the source of energy feeding the system is available (Fig. 4). The second one results from the fact that any change in a transmissible factor capable of altering the kinetic stability of the system would undergo selection depending on the resulting DKS value so that any improvement would be conserved. Considering the emergence of EASs and separating these two properties is suggested to be crucial for describing life and evolution in physical terms. Initially evolution may take place by the replacement of a primordial EAS by a more effective one emerging independently, which corresponds to the exploration of possibilities of epigenetic diversity. More sophisticated paths of evolution involving complex networks may be available from this perspective [24]. The association or symbiosis [28] of



EASs with genetic replicators would introduce the possibility of open-ended evolution along the dimension of variability associated with genetic information. But any other dimension corresponding to factors capable of increasing DKS values, as for instance cognitive capabilities, may indeed be integrated in this evolutionary description, in which these dimensions become virtually available even though they are not functional yet. In this way, the status of cognitive abilities and genetic storage might not be considered as fundamentally different with respect to the use of information by living organisms since both of them require the pre-existence of an autonomous system to be functional. They might just be considered as belonging to different dimensions (Fig. 4). An overall framework can be devised from the properties of EASs developed in this work. It encompasses the origin of life and evolutionary biology within a single scenario in which the genetic contribution responsible for life's complexity can be completed by other transmissible factors (Fig. 4). The drive of EASs towards increased kinetic stability results in a series of transitions corresponding to the recourse to factors associated with new dimensions. However, the fact that the whole process may be initiated by the contingent advent of a single activated molecule in a disequilibrium environment must be emphasized. This approach would therefore make the transition much less improbable than a highly unlikely spontaneous emergence of a genetic polymer, while integrating the material and non-material features of life within a single evolutionary scheme. No *driving force* other than kinetic selection is needed in this overall framework and no chasm separating processes ruled by chemical kinetics from the theory of evolution exists. Nothing in this scenario is incompatible with Darwin's description of evolution and the improvement of fitness through natural selection may indeed be considered as the biological manifestation of kinetic selection driven by DKS maximization [3].

In addition to these theoretical advances, the separation between an ability to grow of an epigenetic nature and evolutionary features linked to genetic variability may be helpful to

account in a simple way for experiments showing the possibility of exchanging the genome of a cell without damaging its viability [41]. These experiments indeed suggest that two factors having a different essence are needed to get a living organism: the first one having a genetic kind and another that is non-genetically encoded and related to the energized physical status of the cellular compartment. It also suggests the possibility of understanding life as the association of viability and evolvability. Viability is associated with a factor of an epigenetic nature characterizing the potential of a system to be autonomous (at least to a very rudimentary degree by remaining in an energized replicative DKS state) and its ability to grow in an open-ended way within the limits of an environment ensuring the presence of a gradient of energy between a convenient energy source and a sink. On the other hand, evolvability is associated with genetic information characterizing the ability of the system to explore the dimension of complexity (with the meaning of degree of organization) in an open-ended way. Without concluding about the possibility of defining life as a coupling of viability and evolvability, it is worth noting that the association of autonomy and open-ended evolution has previously been proposed as a definition of life [42]. The concept of autonomy is defined by the authors in a way compatible with the property of a “far-from-equilibrium system that constitutes and maintains itself establishing an organizational identity of its own, a functionally integrated (homeostatic and active) unit based on a set of endergonic exergonic couplings between internal self-constructing processes, as well as with other processes of interaction with its environment.” It is worth noting that viability and evolvability are associated with *open-endedness* relative to two different dimensions: that of occupying the physical space (growth) for the former one and that of complexity for the later. The advantage of the present approach is that its reference to models based on physicochemical processes is self-consistent and may provide a more accurate definition than general terms like ‘pre-genetic metabolic organization’ used by Ruiz-Mirazo et al. [42] to characterize functional

organization responsible for the autonomy of living organisms beyond that of genetic information. Actually, the opportunistic kinetic behaviour of these systems may not be limited allowing them to explore the dimension of complexity as well as other dimensions such as that of cognition, simply because these dimensions are available [18–20].

This splitting of self-organization along different dimensions may also be considered in relation with the suggestion that organisms constitute “vehicles” or “survival machines” for genes [43]. This suggestion gives no answer to the questions of how these devices could work and of what could be the physicochemical principles on which they are based. The suggestion made here that the role of survival machines or vehicles could be associated with a heritable factor that is not genetically encoded sheds a new perspective on this issue. More generally, defining the metabolism-based organization as non-genetic or epigenetic in a quite pejorative way may lead to overlook the importance of the corresponding processes that may be more accurately described by the terms of ‘viability’ or ‘vitality’ since their occurrence is largely responsible for the tendency of the corresponding chemical processes to grow and develop as long as energy is available to the system. Moreover, this choice might lead to a new perspective on *vitalism*, which postulated that a vital force is responsible for the transmission of life from living beings to other living beings. The analysis proposed here suggests that replicative systems made of thermodynamically unstable chemical components capable of reaching a kinetically stable state could indeed correspond to a concept reminiscent of a vital force except that they are not associated with organic matter of biogenic origin nor incompatible with physical laws and include a possibility of emergence with a low but non-zero probability. Interestingly, the emergence of these rudimentary systems may also be confronted with the term of *spontaneous generation* that was rejected by biologists on experimental grounds. It might however be addressed in a scientific way according to the scenario developed here for the onset of autocatalytic processes constituted of highly unstable

intermediates, which is far from being incompatible with the views expressed by Darwin himself though he considered the issue of the origin as inaccessible to science at that time [44].

Splitting evolution along different dimensions may also help in analyzing the status of viruses with respect to life. Viral particles do not usually possess the autonomy corresponding to a self-sustaining metabolism. Though they carry possibilities of variability ensured by genes, they can only reach vitality by infecting cells.

## **Conclusions**

Investigations aimed at identifying the factors that could influence kinetic processes involved in life and its origins uncovered the fact that it is possible to separate a kinetic factor that is formally independent of the usual description of genetic heredity responsible for variability and evolvability. This separation is suggested to be possible because these factors relate to independent dimensions. The former one corresponds to the ability of occupying the dimension of space and requires a non-limited ability to grow as illustrated by the behaviour of the EAS model presented earlier [8] and analyzed more deeply here. The later one, genetic heredity, gives rise to the ability to explore the dimension of structural and functional complexity and would likely require the former factor to be present in order that selection can proceed according to Darwinian behaviour. But other dimensions, notably including that of cognition [18–20], might be added in this multi-dimensional scheme, which represents a first step in integrating non-material aspects of life within a physical description. The kinetic state of an EAS, an autocatalytic cycle constituted only of thermodynamically unstable intermediates, can indeed be described as an epigenetic factor. Such a system is able to couple dissipation with its own reproduction in an irreversible way. It can in principle grow and be transferred in any environment in which it can develop by harnessing the free energy difference between a source and a sink that can be coupled to the corresponding chemical

transformations. Its behaviour reproduces essential features of life, including its vitalist appearance and its compliance with a processual description [13], which enables a further evolutionary process as shown by its ability to undergo selection accordingly to dynamic kinetic stability as well as its ability to collapse and to be replaced by a more efficient analogue in terms of DKS. The initiation of systems corresponding to these properties is suggested to constitute an essential stage in the emergence of life allowed by the huge diversity of abiotic organic matter. Some evolutionary possibilities involving alternative EASs might even be conceived. However, the symbiotic association [28] of these autonomous systems with molecules or systems exhibiting amphiphilic properties or genetic polymers could very probably facilitate subsequent evolution since it could enable the possibility of unlimited developments brought about by variability. These core processes could indeed have been associated with amphiphiles or polymers reproducible through template replication therefore triggering the first steps of an open-ended evolutionary process toward organizational complexity starting from molecular assemblies. Along this pathway, the different mechanisms became so intimately linked that they no longer appear to possibly come from different origins.

## References

1. Monod, J. *Le hasard et la nécessité* (Editions du Seuil, Paris, 1970).
2. Walker, S.I. Origins of life: a problem for physics, a key issues review. *Rep. Prog. Phys.* **80**, 092601 (2017).
3. Pross, A. *What is Life? How Chemistry Becomes Biology* (Oxford University Press, Oxford, 2016).
4. Pascal, R. & Pross, A. Stability and its manifestation in the chemical and biological worlds. *Chem. Commun.* **51**, 16160–16165. (2015).

5. Pross, A. Stability in chemistry and biology: Life as a kinetic state of matter. *Pure Appl. Chem.* **77**, 1905–1921 (2005).
6. Pascal, R. & Pross, A. Chemistry's kinetic dimension and the physical basis for life. *J. Syst. Chem.* **7**, 1–8 (2019).
7. Pascal, R., Pross, A. & Sutherland, J. D. Towards an evolutionary theory of the origin of life based on kinetics and thermodynamics. *Open Biol.* **3**, 130156 (2013).
8. Pross, A. & Pascal, R. On the emergence of autonomous chemical systems through dissipation kinetics. *Life* **13**, 2171 (2023).
9. Pross, A., Pascal, R. How and why kinetics, thermodynamics, and chemistry induce the logic of biological evolution. *Beilstein J. Org. Chem.* **13**, 665–674 (2017).
10. Moberg, C. Schrödinger's What is Life?—The 75th anniversary of a book that inspired biology. *Angew. Chem. Int. Ed.* **59**, 2550–2553 (2020).
11. Danger, G., d'Hendecourt, L. & Pascal, R. On the conditions for mimicking natural selection in chemical systems. *Nat. Rev. Chem.* **4**, 102–109 (2020).
12. Adamski, P., Eleveld, M., Sood, A., Kun, Á., Szilágyi, A., Czárán, T., Szathmáry, E., Otto, S. From self-replication to replicator systems en route to de novo life. *Nat. Rev. Chem.* **4**, 386–403 (2020)
13. Dupré, J. & Nicholson, D. J. A manifesto for a processual philosophy of biology. In *Everything Flows: Towards a Processual Philosophy of Biology*, (eds. Nicholson, D. J. & Dupré, J.) 3–46 (Oxford University Press, Oxford, 2018).
14. Lifson, S. On the Crucial Stages in the Origin of Animate Matter. *J. Mol. Evol.* **44**, 1–8 (1997).

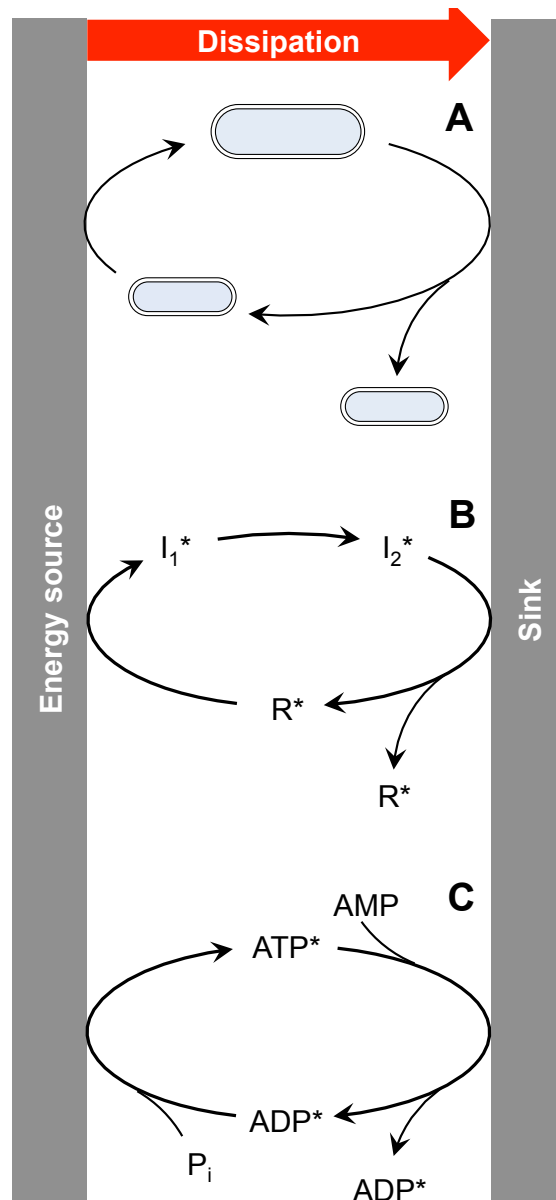
15. Vasas, V., Szathmáry, E., & Santos, M. Lack of evolvability in self-sustaining autocatalytic networks constraints metabolism-first scenarios for the origin of life. *Proc. Natl. Acad. Sci. U.S.A.* **107**, 1470–1475 (2010).
16. Vasas, V., Fernando, C., Santos, M., Kauffman, S. & E. Szathmáry, Evolution before genes. *Biol. Direct* **7**, 1 (2012).
17. Pross, A. How can a chemical system act purposefully? Bridging between life and non-life. *J. Phys. Org. Chem.* **21**, 724–730 (2008).
18. Pascal, R. & Pross, A. On the chemical origin of biological cognition, *Life* **12**, 2016 (2022).
19. Pascal, R. & Pross, A. in *Evolution “On Purpose”: Teleonomy in Living Systems*, Vienna Series Theoretical Biology (eds. Corning, P. A. et al.) 257–274 (MIT Press, Cambridge, MA, 2023).
20. Pascal, R. & Pross, A. Mind from matter: the chemical connection. *Isr. J. Chem.* **63**, e202300038 (2023).
21. Pross, A. The evolutionary origin of biological function and complexity. *J. Mol. Evol.* **76**, 185–191 (2013).
22. Schwartz, A. W. Intractable mixtures and the origin of life. *Chem. Biodiversity* **4**, 656–664 (2007).
23. Schmitt-Kopplin, P., Gabelica, Z., Gougeon, R. D., Fekete, A., Kanawati, B., Harir, M., Gebefuegi, I., Eckel, G., Hertkorn, N. High molecular diversity of extraterrestrial organic matter in Murchison meteorite revealed 40 years after its fall. *Proc. Natl. Acad. Sci. U.S.A.* **107**, 2763–2768 (2010).
24. Peng, Z., Linderoth, J. & Baum, D. A. The hierarchical organization of autocatalytic reaction networks and its relevance to the origin of life. *PLoS Comput. Biol.* **18**, e1010498 (2022).

25. Szathmáry, E. The origin of replicators and reproducer. *Philos. Trans. R. Soc. London, Ser. B* **361**, 1761–1776 (2006).
26. R. Pascal, in *Astrochemistry and Astrobiology: Physical Chemistry in Action*, (eds. Smith, I. W. M., Cockell, C. & Leach, S.) 243–269 (Springer, Berlin Heidelberg, 2013).
27. Benner, S. A., Kim, H.-J. & Carrigan, M. A. Asphalt, water, and the prebiotic synthesis of ribose, ribonucleosides, and RNA. *Acc. Chem. Res.* **45**, 2025–2034 (2012).
28. Babajanyan, S. G. et al. Coevolution of reproducers and replicators at the origin of life and the conditions for the origin of genomes. *Proc. Natl. Acad. Sci. U.S.A.* **120**, e2301522120 (2023).
29. Hanczyc, M. M. & Szostak, J. W. Replicating vesicles as models of primitive cell growth and division. *Curr. Opin. Chem. Biol.* **8**, 660–664 (2004).
30. Luisi, P. L., Ferri, F. & Stanó, P. Approaches to semi-synthetic minimal cells: a review. *Naturwissenschaften* **93**, 1–13 (2006).
31. Chen, I. A. & Walde, P. From self-assembled vesicles to protocells. *Cold Spring Harb. Perspect. Biol.* **2**, a002170 (2010).
32. Gánti, T. *The Principles of Life*. (Oxford University Press, Oxford, 2003).
33. Ruiz-Mirazo, K., Briones, C. & de la Escosura, A. Prebiotic systems chemistry: new perspectives for the origins of life. *Chem. Rev.* **114**, 285–366 (2014).
34. G. von Kiedrowski, A self-replicating hexadeoxynucleotide. *Angew. Chem. Int. Ed.* **25**, 932–935 (1986).
35. Szathmáry, E., Gladkih, I. Sub-exponential growth and coexistence of non-enzymatically replicating templates. *J. Theor. Biol.* **138**, 55–58 (1989).

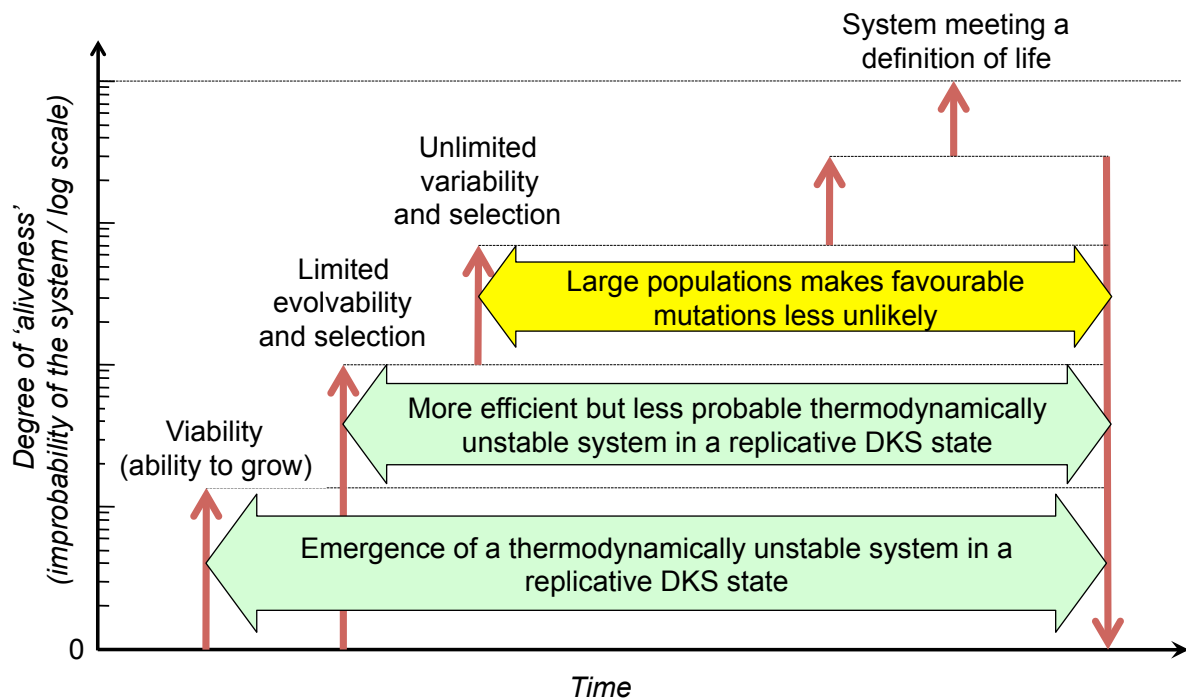


36. Eigen, M. & Schuster, P. The hypercycle. A principle of natural self-organization. Part A. The emergence of the hypercycle. *Naturwissenschaften* **64**, 541–565 (1977).
37. Wächtershäuser, G. Before enzymes and templates: theory of surface metabolism. *Microbiol. Rev.* **52**, 452-484 (1988).
38. Martin, W. & Russell, M. J. On the origins of cells: a hypothesis for the evolutionary transitions from abiotic geochemistry to chemoautotrophic prokaryotes, and from prokaryotes to nucleated cells. *Philos. Trans. R. Soc. London, Ser. B* **358**, 59–85 (2003).
39. Schrödinger, E. *What is life?* (Cambridge University Press, Cambridge, 1944).
40. Lotka, A. J. Natural selection as a physical principle. *Proc. Natl. Acad. Sci. U.S.A.* **8**, 151–154 (1922).
41. Gibson, D. G., Glass, J. I., Lartigue, C., Noskov, V. N., Chuang, R.-Y., Algire, M. A., Benders, G. A., Montague, M. G., Ma, L., Moodie, M. M., Merryman, C., Vashee, S., Krishnakumar, R., Assad-Garcia, N., Andrews-Pfannkoch, C., Denisova, E. A., Young, L., Qi, Z.-Q., Segall-Shapiro, T. H., Calvey, C. H., Parmar, P. P., Hutchison, C. A., III, Smith, H. O., Venter, J. C. Creation of a bacterial cell controlled by a chemically synthesized genome. *Science* **329**, 52–56 (2010).
42. Ruiz-Mirazo, K., Pereto, J. & Moreno, A. A universal definition of life: autonomy and open-ended evolution. *Orig. Life Evol. Biosph.* **34**, 323–346 (2004).
43. Dawkins, R. *The Selfish Gene*. (Oxford University Press, Oxford, 1976).
44. Peretó, J., Bada, J. L. & Lazcano, A. Charles Darwin and the origin of life. *Orig. Life Evol. Biosph.* **39**, 395–406 (2009).

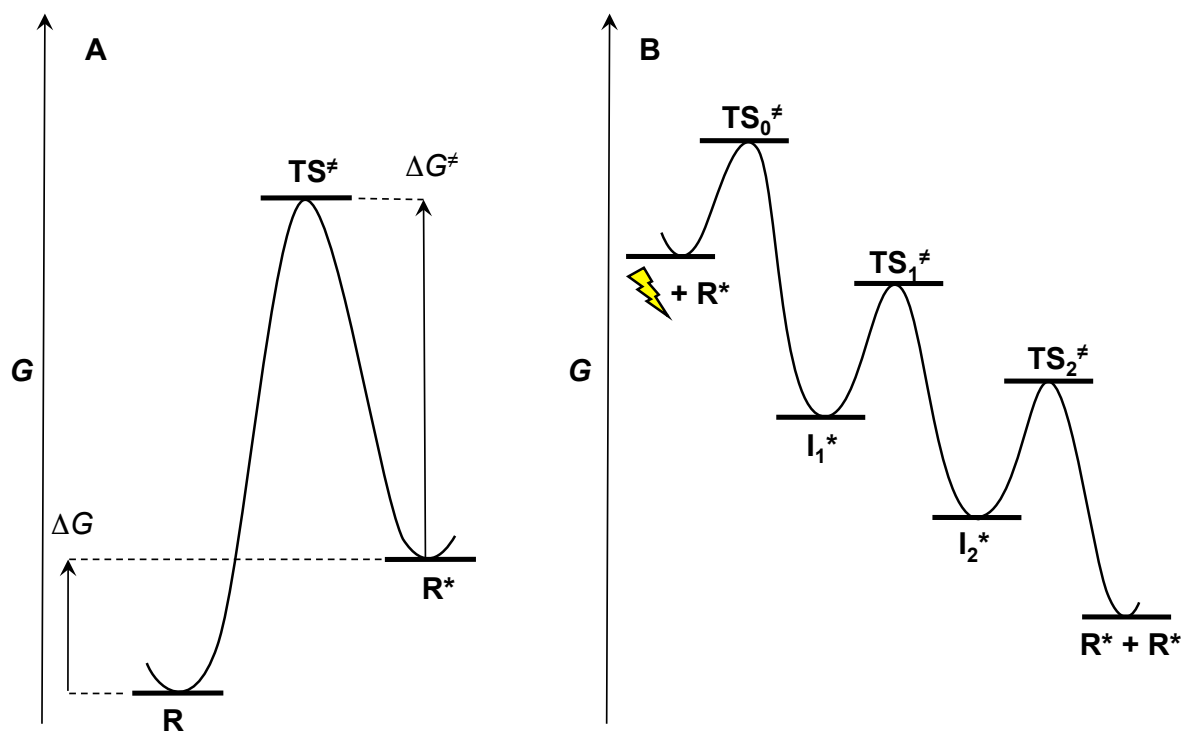
**Acknowledgements.** This manuscript originates from a long-term collaboration with Prof. Addy Pross through exchanges that were essential in the elaboration the ideas reported in this work. I am deeply indebted to him for this contribution, for his help in editing the manuscript as well as for making me aware of the work of John Dupré.



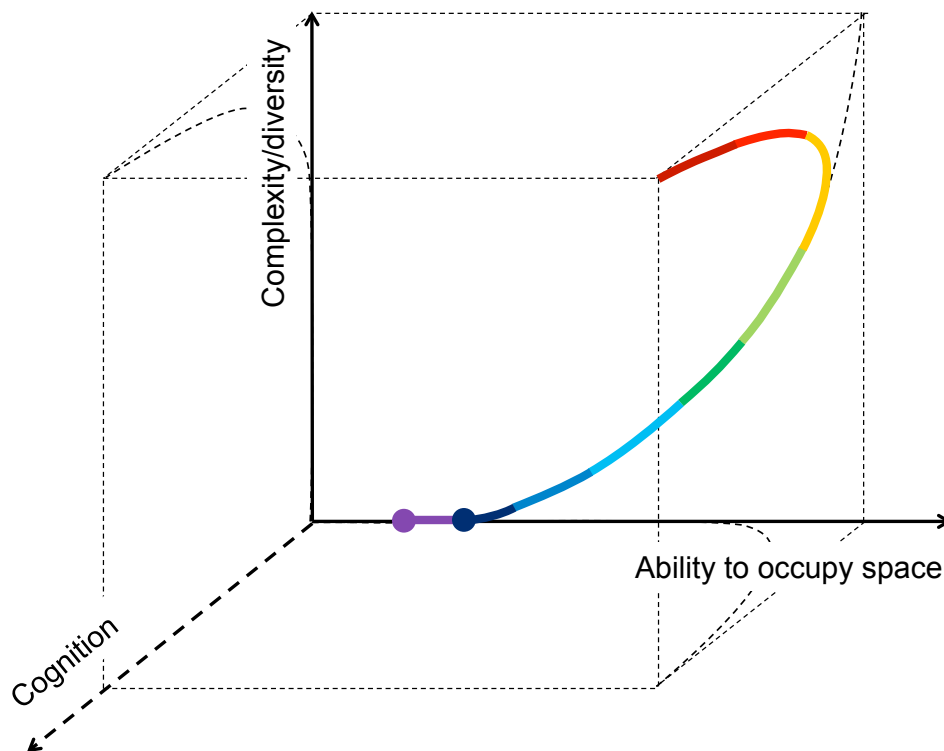
**Figure 1.** (A) The reproduction cycle of a living organisms is closely associated with dissipation, the conversion of the energy of a source into degraded forms. (B) An Emerging Autonomous System (EAS) based on totally unstable species (identified by an asterisk) mimicking the reproduction process. This system requires an initiation step (the introduction of one of the components of the cycle, which can be either  $R^*$ ,  $I_1^*$  or  $I_2^*$ ) and can collapse as a consequence of a shortage in the feeding with energy. The autocatalytic property results from the generation of more than 1 stoichiometric equivalent of  $R^*$  per round of the cycle. (C) A very simplified representation of the enzyme-dependent phosphate energy metabolism involving the high-energy anhydrides ADP and ATP, which emphasizes the relevance of the concept of EASs to biochemistry.



**Figure 2.** A scenario for the origins of life derived from the properties of autocatalytic systems made of highly unstable intermediates. The emergence of one of these systems settles DKS as an evolutionary criterion. Then similar systems may take over as a result of an improved efficiency. Lastly, merging these systems with a genetic polymer allows the exploration of a wider range of systems.



**Figure 3.** Energy diagram corresponding to the initiation (A, left) and the propagation (B, right) of the autocatalytic cycle of Fig. 1B. For autocatalysis to meet the conditions of stoichiometry, all the intermediates of the cycle must be protected by kinetic barriers (not shown) in such a way that the cycle develops without significant side-reactions at the timescale of the turnover time of the cycle (generation time). The two processes of initiation (A) and propagation (B) do not share any intermediate except  $\mathbf{R}^*$  and are therefore totally independent. For the activated intermediate  $\mathbf{R}^*$ , the important parameter is the lifetime of the deactivation reaction that must exceed the generation time thereby fixing a minimum value for the kinetic barrier  $\Delta G^\ddagger$ . The time needed for the formation of a single molecule of  $\mathbf{R}^*$  from  $\mathbf{R}$  can be determined from the value of the activation barrier ( $\Delta G^\ddagger + \Delta G$ ) but may also be reduced by a limited availability of  $\mathbf{R}$  in the environment or by the bi- or poly-molecular character of the reaction from reactants having low concentrations.



**Figure 4.** Idealistic diagram to illustrate a trajectory for evolution in a multidimensional overall scenario encompassing the origin of an EAS (through the generation of a single molecule of an energized intermediate of the system) and further developments of life through a pathway directed towards increased DKS (the fourth dimension represented by a colour scale from purple to dark red). The process is initiated by the generation (purple dot) of a primordial EAS having an ability to grow (able to occupy the space dimension with a value on the abscissa that is positive and different from zero) and most importantly to compete for the energy source that feeds the system with other systems emerged independently (dark blue dot). As soon as an EAS is present, further evolution may happen through changes along other dimensions that are made potentially available even though they do not contribute, yet. The only requirement for these dimensions is that they involve factors influencing DKS that are transmissible to subsequent generations like epigenetic and genetic information (responsible for the development of complexity and variability) or cognitive abilities. In this scheme, the coordinates must not be considered as fully independent since, for instance, any change in complexity/diversity is likely to affect the ability to occupy space. Moreover, the increase in DKS must not be considered as deterministic since it corresponds to an open system in which contingent events may occur changing the environment as for instance the emergence of a virus dooming the fate of a previously stable species. Indeed, DKS is seldom a measurable quantity since it also depends on the evolution of the environment including that of other autonomous systems.