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Accessibility
Sustainability of Transient Kinetic Regimes and Origins of Death

Dmitry Yu. Zubarev & Leonardo A. Pachón

It is generally recognized that a distinguishing feature of life is its peculiar capability to avoid equilibration. The origin of this capability and its evolution along the timeline of abiogenesis is not yet understood. We propose to study an analog of this phenomenon that could emerge in non-biological systems. To this end, we introduce the concept of sustainability of transient kinetic regimes. This concept is illustrated via investigation of cooperative effects in an extended system of compartmentalized chemical oscillators under batch and semi-batch conditions. The computational study of a model system shows robust enhancement of lifetimes of the decaying oscillations which translates into the evolution of the survival function of the transient non-equilibrium regime. This model does not rely on any form of replication. Rather, it explores the role of a structured effective environment as a contributor to the system-bath interactions that define non-equilibrium regimes. We implicate the noise produced by the effective environment of a compartmentalized oscillator as the cause of the lifetime extension.

Between ill-conditioned and ill-posed problems, the origin of life must be in a class of its own. Life on Earth is the only type of life known to us, its chemical basis is very constrained, and information about the initial condition of prebiological evolution has been lost. Attempts to solve this problem have evolved along two complementary routes. One includes experimental and observational efforts to find connections between prebiological chemistry and biochemistry. It yielded multiple insights ranging from Urey-Miller experiment to the recent cyano-sulfidic scenario and prompted active search for habitable exoplanets. The other is dedicated to establishing driving forces of abiogenesis and abstraction of the general evolutionary principles from their known biochemical realizations. Examples of such efforts include, but are not limited to, development of the theory of hypercycles and quasispecies and evolution of chemical kinetics into population dynamics, thermodynamic foundations of cellular metabolism and replication, information transfer in mutually catalytic systems and, of course, the general area of non-equilibrium thermodynamics.

A hallmark of life that strongly pushes for the formulation of a general evolutionary principle is its unique position with respect to the equilibrium. One way to express it is to borrow a quote from Schrödinger: "It is by avoiding the rapid decay into the inert state of 'equilibrium' that an organism appears so enigmatic". The enigma of "avoiding the rapid decay" is intimately related to the enigma of death as the event that has to be avoided. Unlike the origin of life, cellular death is ubiquitous, can be replicated and systematically studied. Aside from the catastrophic events, it involves elaborate regulatory processes that recruit the genetic, metabolic and enzymatic systems in what is called "programmed cell death". Moving back in time to the origin of the respective biochemical mechanisms, how much would the notion of death change? What are the prebiological precursors of the evolved mechanisms of cell death?

Given generality of the question, the ambiguity of the answer is unavoidable. Our general motivation is to identify phenomena that look similar to cell death in prebiological context in the absence of the evolved biochemical systems. If identified, they can serve as a foundation for analogical models of chemical evolution and enable studies of life-like physical-chemical systems that are not necessarily prebiologically plausible. We think of life in terms of non-equilibrium chemical processes with a peculiar spatio-temporal organization that can be maintained over a finite time. From this point of view a living organism exists in a transient regime - a regime encountered on the system's way to the state that can be maintained for as long as the respective external conditions are maintained, such as thermodynamic equilibrium, chemical equilibrium, or a steady state. What makes life unique in the sense of the above-mentioned quote, is that there exist mechanisms that extend the lifetime.
of this transient regime well beyond what one would expect from a typical non-equilibrium system decaying exponentially fast. Such mechanisms are either intrinsic, i.e., contained within the system, and their engagement is inevitable, or they come from some special structure of the environment. The latter is possible but difficult to address. Our conjecture is that death comes into play in prebiological world as a point of failure of the intrinsic mechanisms that ensure sustainability of the transient kinetic regimes.

Figure 1 shows a schematic representation of the stages of time-evolution of a living system. Here, we refer to the entire time-evolution from some non-equilibrium state (Point 1, Fig. 1) to the equilibrium (Point 3, Fig. 1) as a transient process (segment 1–3 in Fig. 1). In this study, we will think about life as a transient regime (segment 1–2 in Fig. 1) which is a part of the transient process. As a stage of the equilibration process, the transient regime has some unique features that make it identifiable. The loss of the transient regime in Point 2 corresponds to death. At this point the system is still away from the equilibrium – for example, hydrolysis of components of living cells, such as nucleic acids, will proceed on the time scale of years\(^{19}\) outside living cells. The equilibration process continues until the equilibrium is reached (segment 2–3 in Fig. 1). As far as avoiding rapid equilibration, the enigma of life comes from the mechanisms that extend the lifetime of the transient regime 1–2 and delay transition from the segment 1–2 to the segment 2–3. Sustainability of the transient regime, therefore, is the capability of the system to sustain respective features of time-evolution continuously over extended periods of time as a result of particular mechanisms associated with the system. It is beyond the scope of this paper to constraint the classes of features that are suitable for the identification of the transient regimes that precisely correspond to life. It suffices to assume that the transient regimes of interest are identifiable operationally, for example, from the special structure of the time-series of concentrations, responses to perturbations, distribution of fluctuations, etc.

The setting depicted in Fig. 1 can be interpreted in a different manner. Segment 1–2 can be understood as a long-lived state of high free energy. If the activation energy, i.e., the reaction barrier, for such state is sufficiently high, its lifetime is enhanced due to the kinetic hindrance of the relaxation processes. This line of thinking has motivated multiple studies\(^{8,20,21}\). Our study proceeds from a different vantage point. The barriers and rate constants are never modified. Instead of the lifetimes of molecules we are concerned with the organization of the processes that involve molecules. Molecules participate in reactions, reactions form networks, and reaction networks interact with each other. It is the level of the intra- and inter-network interactions that we investigate. Our goal is to identify non-equilibrium modes of time-evolution that are accessible at this level and characterize lifetimes of the encountered transient kinetic regimes.

We deliberately avoid including replication-related events into the diagram because self-replication is contingent on the lifetime of the replicating entity. If the lifetime is shorter than the replication period, the replicator cannot produce an offspring. Such a contingency is accounted for in the models of population dynamics. However, lifetimes of replicators in such models are externally defined model parameters. In other words, population dynamics and related concepts of the population stability\(^{20,21}\) can explain selection and fixation of the replicators with appropriately long lifetimes, but they do not describe the mechanism of the emergence of long lifetimes. Within the concept of sustainability of transient kinetic regimes, death is fundamentally independent of the development of self-replicating capability but rather implies some level of complexity in the organization of the system, cf. interacting complex reaction networks.

The primary goal of this paper is to illustrate the concept of sustainability of transient kinetic regimes that was introduced above. To this end, we consider a model extended system - a lattice of compartmentalized chemical oscillators under batch and semi-batch conditions. In the extended system each compartment is exposed to the effective environment created by its immediate and distant neighbors. We show that this leads to a noticeable increase of the sustainability of transient oscillating regime. Specifically, the average lifetimes of oscillations in the compartments increase under batch conditions. As a consequence, the survival function of the oscillations in the extended system is enhanced under semi-batch conditions.
Chemical oscillations are a convenient choice of an operationally identifiable transient kinetic regime. Under batch conditions the reactants are loaded into the system only once and can be completely consumed. In this case, oscillations have a finite lifetime. After the oscillations have stopped, the chemical system is still away from the equilibrium, which matches the structure of the diagram in Fig. 1. Multiple compartmentalized oscillators that are allowed to interact with each other, for example, via diffusion of one or several molecular species, form an extended system. The most interesting feature of the extended systems is their potential to exhibit collective phenomena, such as spontaneous synchronization of oscillations. This behavior is extensively studied in the classical context following work of Kuramoto22, and it was demonstrated to exist in the quantum world, too23. The processes developing in each compartment of the extended system are exposed to the noise produced by the rest of the system. Oscillating kinetic regimes are remarkably sensitive to the intrinsic and extrinsic noise, that can serve as i) a trigger of oscillations and ii) a “control knob” that modifies parameters of oscillations24–26. Spatial confinement has been shown to play role in the development of oscillating regimes27. Experimental studies of the networks of chemical oscillators, such as test of Turing’s theory in morphogenesis and observation of chemical differentiation in chemical cells28, are facilitated by development of microfluidics. Cooperative phenomena in extended systems have a capability to evolve as the consequence of the system's growth. An example of such evolutionary development is “dynamical quorum sensing”. This term covers a range of phenomena where the population density of compartments controls their transition to coordinated activities. Synchronization of oscillations is a particular case that is studied in colonies of unicellular organisms29 and model chemical systems30,31. Interestingly, quorum sensing has been implicated as a part of the differentiation mechanisms that enable bacterial colonies to adapt to shortage of nutrients in the environment via changing developmental program of some cells and inducing death of others15.

There is a long standing interest in the phenomenon of oscillation death, that designates loss of the oscillations as a result of the interaction between oscillators in an extended system32,33. The possibility of the extension of the lifetimes of decaying oscillations has not been addressed to our knowledge. The main reason is that the majority of the studies dedicated to the emergent phenomena in arrays of coupled chemical oscillators require oscillations to persist longer than it takes to perform target measurements.

Before we proceed to the discussion of the results, we would like to explicitly formulate the considerations that motivate our effort and provide the context for the assessment of its outcome:

- emphasis on the protection of spatio-temporal organization of processes, i.e., sustainability of kinetic regimes, rather than protection of molecular species via kinetic hindrance of chemical reactions.
- exploration of the mechanisms “built into” the system, rather than special requirements to the environment.
- bias toward the question “What life is?”, rather “How did life emerge on Earth?”

**Methodology**

We consider the Brusselator system of mass-action kinetic equations34,35 (Eq. 1) as the source of chemical oscillations under batch conditions.

\[
\begin{align*}
A & \xrightarrow{k_1} X \\
B + X & \xrightarrow{k_3} Y + D \\
2X + Y & \xrightarrow{k_5} 3X \\
X & \xrightarrow{k_4} E
\end{align*}
\]

The Brusselator is an abstract model that captures the phenomenon of chemical oscillations. It includes two reactants, A and B, two intermediates, X and Y, and two products D and E. Oscillations are encountered in the concentration profiles of the intermediates X and Y. Under open-flow conditions the reactants are available without shortage and the oscillations are sustained indefinitely long. Under batch conditions the amounts of the reactants are finite, so that the oscillations extinct over finite time as reactants are consumed. Under semi-batch conditions finite amounts of the reactants are added to the system with finite delays. If the reactants are replenished before the oscillations have stopped, there is a possibility that the oscillation lifetime will be extended. Of course, the latter effect is contingent on whether the system remains within the scope of the oscillating regime upon the addition of the reactants. This consideration constrains such parameters as the reactants supply rates, lower and upper bounds on reactants concentrations, etc. In the limit of the vanishing delays the semi-batch regime approaches an open-flow regime, and in the limit of the infinitely long delays it approaches a batch regime. In the rest of the paper we use arbitrary units of time and concentration as a consequence of the abstract nature of the kinetic model. To illustrate the concept of sustainability of transient kinetic regimes, we construct the simplest extended system – a finite-size square lattice of compartmentalized Brusselators (Fig. 2). We start with inhomogeneous initial concentrations across the lattice by forming the vector of initial concentrations in the i-th compartment, \(c_i(0)\), in the following way:
Where \( N(\mu, \sigma) \) is a normal distribution with mean \( \mu = 0 \) and standard deviation \( \sigma = 10 \). We use one set of the inhomogeneous initial concentrations to run kinetic simulations of two versions of the system. In the non-interacting version, the compartments are isolated from each other (bottom left). In the interacting version, each compartment is diffusively coupled to its four nearest neighbors (bottom right). An ensemble of random realizations of the initial conditions is explored in this manner. Further details of the kinetic simulations of the compartmentalized Brusselators are provided in Supporting Information.

The model in the described form has a sizable parameter space. We will discuss a single combination of the parameters in order to accomplish the main goal of our study – to illustrate the concept of sustainability of transient kinetic regimes. Specifically, we limit simulations to a \( 30 \times 30 \) square lattice with 5000 random realizations of the inhomogeneous initial conditions. Initial concentrations of A and B are drawn from a normal distribution with mean of 100 and 200 units, respectively, both with standard deviation of 10. Compartments are coupled via intermediate \( Y \) with a homogeneous coupling constant \( k_{y}. \) A detailed investigation of the parameter space and characterization of all possible kinetic regimes is left for future studies.

We use the following procedure to determine the oscillation lifetimes in the compartments. First, the moving-average is constructed for the concentration profile of the oscillating component. Second, the points of intersection between the original and averaged time-series are found. Finally, the first and the last intersection points are taken as the times of the oscillation onset and extinction, so that the oscillation lifetime can be obtained. We truncate the time-series if separation between two consecutive intersection points becomes too large. This step helps to avoid artifacts associated with slowly developing non-monotonic concentration changes (see Fig. S1 in Supporting Information for details). The oscillation lifetimes in the \( i \)-th compartment of the diffusively coupled (interacting) system is designated as \( \gamma_i \); the oscillation lifetime in the same compartment of the uncoupled (non-interacting) system is \( \lambda_i \). We define the relative lifetime enhancement for the \( i \)-th compartment as a ratio of these lifetimes:
multiple feedings that occur with a constant feeding lag. This choice of the model enables us to describe semi-batch regime using the information obtained from batch simulations. If the lifetime of oscillations in the interacting system, blue curve – to the interacting.

\[ \gamma_i = \frac{\lambda_c}{\lambda_i} \]  

Oscillators with infinite relative lifetime, i.e., those that do not exhibit oscillations in the uncoupled system, are assigned \( \gamma = 0 \). If the average period of the oscillations in the coupled system increases more than 2-fold relative to the uncoupled case, the relative lifetimes are treated as unreliable and such oscillators are also assigned \( \gamma = 0 \).

**Results and Discussion**

First, we note that the lifetimes of the compartmentalized oscillations depend on the coupling strength between the compartments. Relative lifetime \( \gamma \) is trivially 1 in the limit of vanishing diffusion constant \( k_{\lambda} \). It goes to 0 as the diffusion constant becomes much larger than the rate constants of the Brusselator model. The latter behavior fits into the concept of the oscillation death. It should be encountered in the models with dimensionless rate constants and coupling constants, such as the one considered in the present study. Such behavior in the limit of strong diffusive coupling is not transferable to the models that involve dimensional constants with different dimensionalities.

Next, we compare the raw data that describe oscillation lifetimes in the non-interacting and interacting (coupling constant \( k_{\lambda} = 0.08 \)) systems. The histograms of the lifetimes of each individual compartment over the ensemble of the simulated lattices are shown in the left panel of Fig. 3. The histogram of the non-interacting system has a single sharp feature at 100 time units. The width of the feature is due to the variance in the initial concentrations of the reactants between compartments (see Methodology). In the case of the interacting system the histogram has two broad features at 160 and 320 time units. We used the same ensemble of the initial concentrations to run kinetic simulations of the interacting and non-interacting systems. Therefore, the higher count of longer lifetimes is the consequence of the diffusive coupling between compartments. The central panel of Fig. 3 shows the histogram of the relative lifetimes \( \gamma \) computed according to Eq. 2 for each individual compartment over the simulation ensemble. The peak of the histogram corresponds to \( \gamma = 1.5 \) and a shoulder is formed at \( \gamma = 3 \).

So far we were concerned with the outcomes of the simulations under batch conditions. Now we will investigate how differences between interacting and non-interacting systems play out under semi-batch conditions. In this case, reactants A and B can be added to the compartments multiple times with some delay. We will refer to this delay as a “feeding lag” \( t_{fl} \). For simplicity, we will assume that the delivered amounts of the reactants effectively reset their concentrations to the values consistent with the procedure that was used to generate initial conditions for the kinetic simulations under batch regime (see Eq. 2 and Methodology), reactants are delivered to all compartments simultaneously, i.e., a single feeding lag value applies to the entire lattice, and the feeding lag is constant. This choice of the model enables us to describe semi-batch regime using the information obtained from batch simulations. If the lifetime of oscillations in the \( i \)-th compartment, \( \lambda_i \), is longer than the lag \( t_{fl} \), the reactants are replenished before the oscillations die out, so that the transient regime is sustained without failure; otherwise, the transient regime is lost. Therefore, we can describe the behavior of the interacting and non-interacting systems under semi-batch conditions in terms of the survival function of the oscillations in the lattice compartments. We use the following definition of the survival function \( S(t_{fl}) \):

\[ S_i(t_{fl}) = P(\lambda_i > t_{fl}), \]

\[ P(\lambda_i > t_{fl}) = \int_{t_{fl}}^{\infty} d\lambda f(\lambda). \]  

Here, \( S_i(t_{fl}) \) is the survival function for the \( i \)-th compartment. It is given by the probability \( P(\lambda > t_{fl}) \) that the oscillations in the compartment last longer than some value \( t_{fl} \). \( f(\lambda) \) is the probability distribution of the oscillation
higher frequencies of longer relative lifetimes including a shoulder at higher \( \gamma \) above the respective compartment. Using frequencies of raw oscillation lifetimes (Fig. 3, left panel) as proxies for \( R(\lambda) \), we obtain survival functions for the interacting and non-interacting versions of the system under semi-batch regime (Fig. 3, right panel). As one would expect, a very narrow distribution of the oscillation lifetimes in the non-interacting system (Fig. 3, left panel, red curve) causes a very fast fall-off of the survival function. If the feeding lag exceeds 25 time units, there is essentially zero probability of the survival of the transient oscillating regime on the lattice (Fig. 3, right panel, red curve). The lifetime distribution in the interacting system is broader and its peak is shifted toward higher values (Fig. 3, left panel, blue curve); the lifetimes are typically enhanced by a factor of 1.5 relative to the non-interacting case (Fig. 3, central panel). As a consequence, the survival function for the interacting system indicates much higher sustainability of the transient kinetic regime. For example, feeding lag of 25 time units corresponds to the survival of oscillations in 70% of the compartments. Up to 10% of the compartment will sustain the transient regime with the feeding lag up to 54 time units. The complete loss of the transient regime will occur if the lag exceeds 74 time units, which extends the limits of sustainability by factor of 3 in comparison to the uncoupled system. Of course, a more complicated model of the semi-batch regime can be considered, that includes randomization of the feeding lag values between compartments and between feeding events. As long as the interacting system has longer lifetimes per one feeding event, the qualitative result, i.e., higher sustainability of the transient regime in the interacting system, will hold.

All the results discussed in this paper are obtained using a finite-size model. It is instructive to discern the spatial structure of the distribution of the relative lifetimes \( \gamma \) (Fig. 3, central panel) in order to understand the role of the edges. We average relative lifetimes for each compartment over the ensemble of the model realizations; the obtained compartment-specific values are further averaged between the lattice sites related by symmetry on square lattice. The symmetrized distribution of the averaged site-specific relative lifetimes is shown in the right panel of Fig. 4. The relative lifetime of the transient regime in the compartments in the vicinity of the edges is higher than in the “bulk” region; it reaches the highest values close to the lattice corners. Right panel of Fig. 4 shows histograms of the frequencies of the relative lifetimes for the near-corner site and the central site of the lattice over the simulation ensemble.

The histograms have very similar shapes with peaks at \( \gamma \approx 1.5 \). The histogram of the near-corner site shows higher frequencies of longer relative lifetimes including a shoulder at \( \gamma \approx 3.0 \), that explains the shoulder on the histogram in the central panel of Fig. 3. In contrast, the histogram of the central site shows enhanced frequencies of lower relative lifetimes. This explains the difference in the averaged values for the respective regions of the lattice. From the structural point of view, the edges and the corners of the lattice are 1- and 0-dimensional defects, respectively. A typical simulation strategy might aim to remove or minimize such effects in order to understand the behavior of “bulk”. However, the goal of our study is to discuss the factors that facilitate emergence of the sustainable transient kinetic regimes. The role of the lattice defects in this regard is very interesting. It hints that a less trivial spatial structure of the extended system, such as a network of small lattices that effectively mimic 0- and 1-dimensional defects, might lead to a much stronger improvement of the sustainability.

Finally, we can discuss some aspects of the mechanism that ensures the enhancement of the oscillation lifetimes in the system of coupled compartments. In the non-interacting case, i.e., uncoupled lattice, the interactions of any compartment with the environment are limited to the introduction of the reactants \( A \) and \( B \) into the compartment. However, in the interacting system the notion of the environment changes. In addition to the environment that serves as the source of reactants, any given compartment can be considered as embedded in the effective environment that represents the rest of the lattice and interacts with the compartment via diffusion of one or several components. Therefore, we will treat the interacting system in the spirit of mean-field approximation and replace the effective environment of a single compartment by an effective field (noise) that drives the single compartment (system). The strongest contributors to the noise are the nearest neighbors of the

Figure 4. Site-specific distribution of the relative lifetimes. Left panel: spatial distribution of the relative lifetime \( \gamma \) on the lattice after averaging over the ensemble of realizations of the initial conditions; the distribution is symmetrized. Right panel: histogram of the frequency distributions of relative lifetimes for the near-corner site (red) and central site (blue) obtained from the ensemble of realizations of the initial conditions; both sites are marked with white squares on the left panel.
This consideration simplifies derivation of the analytical expression for the noise as a function of time (see Eq. S15 in SI). Let us pick a representative compartment that shows enhancement of the oscillation lifetime in the interacting system. The time-series of interest (Fig. 5, left panel) are the concentration time-series of the component Y, \( c_Y(t) \), in the non-interacting system, \( c_Y(t) \) in the interacting system, and the time-series of the noise due to the effective environment of this compartment in the interacting system (Eq. S15 in SI). The dominant modes of these three time-series can be extracted using continuous wavelet transform. The right panel of Fig. 5 shows corresponding wavelet scalograms. All three scalograms have their main features at the scale ~0.1 Hz. This feature persists for ~100 time units in the non-interacting case. In the interacting case, it extends to ~200 time units in both \( c_Y \) and the noise time-series. The cross-spectrum wavelet analysis of \( c_Y \) and the noise time-series in the interacting system (see Fig. S2 in SI) indicates that the respective dominant modes remain coherent over the time of the sustained oscillations.

These results are interpreted as a fingerprint of causality between the time-evolution of the effective environment and a single compartment, i.e., the system. The noise produced by the effective environment acts on the damped non-linear chemical oscillations in the system as an external driving force. The effective environment is not completely controlled by the processes in the system, yet it is constitutionally related to the system. This leads to the resonance-like relationships between the respective signals. Tentatively, we identify these relationships as a form of stochastic resonance\(^36,37\). This phenomenon has been explored in the broad context of chemical oscillations\(^25,38,39\). In general, it refers to the modification, typically enhancement, of the system performance in the presence of noise. We note that the definitions and effects under the umbrella of the term “stochastic resonance” are diverse and not without controversies\(^37\). Our particular case fits into the “bona fide” concept of the resonance because the system and the noise have matching dominant modes in their time-series and the amplitude of the decaying oscillations in the system is enhanced due to the noise. As in the case of linear oscillators, inter-oscillator coupling and intrinsic noise have the effect of changing the spectrum of the local oscillators. In particular, for some oscillators the central spectral peak shifts towards higher frequencies (see, e.g., ref. 26). This means that for the same noise strength, the central frequency is more robust to that noise and therefore has a longer lifetime. We reserve detailed technical analysis of the dynamics of the extended system in terms of the phase space structure, such as types of attractors and bifurcations, for the future studies.

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Figure 5. Wavelet analysis of time series. Left panels: time series of the concentration of component Y, \( c_Y(t) \), in a representative compartment of the non-interacting system (top), \( c_Y(t) \) in the same compartment of the interacting system (center), and time series of the noise produced by the effective environment of the respective compartment in the interacting system (bottom). Right panels: scalograms of the continuous wavelet transform of the time series in the left panels. The scalogram encodes the wavelet coefficients using a color function represented by the color bar. The color function is scaled, so that its arguments lie in the range 0 to 1. Large coefficients correspond to the scales that contribute the most to the time-series. All three scalograms have their main features at the scale ~0.1 Hz. This feature is long-lived on the scalograms that correspond to the interacting systems. Black color masks cone of influence (COI). COI shows the regions of the scalogram that are strongly affected by the endpoints of the time-series.
Overall, effective environment emerging in our model is different from the regular thermal bath. It serves as a sink of energy for the system and a source of the driving force that becomes stochastic in the limit of the infinite number of compartments yet remains constitutionally related to the processes that develop in the system.

The central motivation of the presented study is to introduce the concept of sustainability of transient kinetic regimes and to illustrate it via a numerical study of an abstract model. This model, however, can be taken as a basis for the experimental studies to validate the predicted behavior. It can be implemented literally, as a network of diffusively coupled compartmentalized chemical oscillators, such as Belousov-Zhabotinsky reactions or biochemical networks. Compartmentalization can be achieved using vesicles, loaded catalytic particles or even porous medium under percolation conditions. Growth of the density of compartments is the most obvious mechanism that renders such systems evolvable, cf. the studies of dynamic quorum sensing; another evolutionary factor is development of the spatial structure of the inter-compartment interactions. It can have multiple forms ranging from the regular lattices to random networks with static or dynamic coupling. A very different implementation comes to mind that is based on development of a network of coupled molecular vibrations, such as vibrations in polymers, where evolution of the system includes growth of the polymer chain and increase of the polymer concentration.

The choice of the oscillating transient regime was motivated by the operational simplicity of the analysis. At this point, there is no evidence of chemical oscillations in protometabolic chemistry; they could be envisioned, however, in the context of the emergence of informational and catalytic polymers and development of the precursors of gene regulatory networks. The nature of the transient kinetic regimes in prebiological chemical systems is, therefore, a question that needs further investigation. The answer will depend critically on what kind of systems and chemical transformations are considered. Protometabolic networks are the obvious candidates for the analysis, that can proceed along the lines explored in other branches of chemistry.

Having discussed behavior of the compartmentalized oscillators on a lattice, we can return to the conjecture proposed in the beginning of the paper: “Death comes into play in prebiological world as a point of failure of the intrinsic mechanisms that ensure sustainability of the transient kinetic regimes”. Let us enumerate implicit and explicit parameters of the studied model and evaluate their contribution to the sustainability of a transient kinetic regime. One group of implicit parameters is the lifetimes of molecules that participate in the reactions. These lifetimes depend on the barriers that ultimately determine the rate constants of the reactions (Eq. 1). The values of the rate constants of the Brusselator have to be related via some ratios in order for oscillations to be possible. Therefore, emergence of any kinetic regime is contingent on a specific hierarchy of molecular lifetimes which is an intrinsic feature. Any factor that changes this hierarchy, such as temperature, catalysis, or solvent, will change the viability and baseline characteristics of the kinetic regimes that can be observed. These factors are, however, extrinsic. Another group of implicit parameters covers structural properties of the compartments. We assumed that the structural integrity of the compartments is maintained over times that exceed the lifetime of the transient kinetic regime of interest. We also assumed that the composition and structure of the compartment wall do not change with time so that the diffusion constant is time-independent. These factors are extrinsic, but they can be modified due to the interactions of the compartment walls with reaction components. Such interactions can be easily introduced into the abstract model, but it is more important to find an actual realization of a system where they can exist. Finally, the spatial structure of the extended system was treated as frozen, which is a simplification. This factor is also extrinsic, but it can develop sensitivity to the progress of the compartmentalized reactions if the compartment structure is modified by the reaction intermediates or products. For example, collapse of the compartments, their “swelling”, or accumulation of charged species in the compartment walls can factor into the evolution of the spatial structure of the extended system. Overall, formation of an extended system and emergence of the effective environment serves as a bridge between extrinsic and intrinsic factors. Effective environment becomes a part of the mechanism that increases sustainability of the transient kinetic regime. Such mechanism will fail if the interactions within the extended system are compromised, e.g., due to compartment disintegration and/or degradation of the coupling between compartments.

The most important and the least model-dependent conclusion of our work concerns relationships between the system and its environment as a factor that determines the fate of the non-equilibrium systems. Presence of a dissipative environment is the single reason that leads to the onset of non-equilibrium regimes and emergence of structure. However, there are no known laws of nature, that grant that some such regimes will “learn” to maintain the appropriate external conditions and environments thus prolonging their own existence. Extended systems offer a way out of this conundrum. In our model formation of the extended system facilitates emergence of the effective environment interacting with a single compartment. In this system-environment partitioning the environment remains constitutionally related to the system. This leads to the increase of the lifetime of a non-trivial transient regime within the system, at least within the boundaries of the model applicability. The importance of tailoring the dissipative environments is realized in the area of quantum applications where particular dissipative environments are capable of supporting extremely long-lived oscillations. In this context, there have been developed strategies to characterize experimentally the spectral properties of the environments.

The emergence and evolution of the dissipative environments should become a focus of the prebiological chemistry along with the emergence and evolution of prebiochemical systems.

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**Author Contributions**
D.Y.Z. and L.A.P. conceived the project, developed methodology, carried out computations and wrote the manuscript.

**Additional Information**

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