Dissipation-driven selection of states in non-equilibrium chemical networks

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Life has most likely originated as a consequence of processes taking place in non-equilibrium conditions (e.g. in the proximity of deep-sea thermal vents) selecting states of matter that would have been otherwise unfavorable at equilibrium. Here we present a simple chemical network in which the selection of states is driven by the thermodynamic necessity of dissipating heat as rapidly as possible in the presence of a thermal gradient: states participating to faster reactions contribute the most to the dissipation rate, and are the most populated ones in non-equilibrium steady-state conditions. Building upon these results, we show that, as the complexity of the chemical network increases, the velocity of the reaction path leading to a given state determines its selection, giving rise to non-trivial localization phenomena in state space. A byproduct of our studies is that, in the presence of a temperature gradient, thermophoresis-like behavior inevitably appears depending on the transport properties of each individual state, thus hinting at a possible microscopic explanation of this intriguing yet still not fully understood phenomenon.
The emergence of cellular life has likely been preceded by the appearance of molecular replicators, namely molecules able to use basic building blocks present in the environment to create copies of themselves. RNA and other long macromolecules, such as proteins, are considered as the best candidates for the first replicators.

Although in the present oxidative conditions long biomolecules such as RNA are not thermodynamically stable, it is possible that they could be thermodynamically stable in the primordial Earth conditions (see refs. 5–7 for the still-open debate). Nonetheless, no conditions have been found to date such that their building blocks and their precursors could be thermodynamically stable and abundant enough to further proceed to their spontaneous polymerization and subsequent self-replication. Relying on equilibrium thermodynamics is thus unlikely to provide a route to explain the emergence of life. The potential relevance of non-equilibrium conditions in this context has also been highlighted in several recent works.

A different scenario is the possibility that, from the onset, external sources of energy might have driven prebiotic molecules away from equilibrium, allowing higher-energy states (i.e., more complex and/or longer molecules) to be abundant, even against their natural tendency to decay according to their equilibrium fate. Consistently with these arguments, Braun and coworkers have for example shown that, in the presence of thermal gradients, the accumulation of molecules in regions of lower temperature (thermophoresis) increases polymerization beyond the prescriptions of mass-action kinetics at equilibrium.

In the present work, we hint at the possibility of broadening the perspective: external energy sources, here a thermal gradient, can tilt the populations of the different states that participate to a reaction network, by favoring states not only according to their energy, but also according to the dissipation along the pathways they are part of. In particular, we study linear reaction networks to highlight the basic rules deciding which states are the most favorable, relating them to kinetic and dissipation rates. Despite the simplicity of the model, it highlights the onset of unexpected features in non-isothermal chemistry, leading to potential applications in real-world examples.

Results
A temperature gradient favors states involved in faster reaction pathways. The simple toy model that we propose here comprises three states, A, B, and C, which diffuse in space in the presence of a temperature gradient $\Delta T$. A pedagogical way to describe this system retaining all its essential non-equilibrium features is by means of a two-box model as depicted in Fig. 1a.

Here diffusion is captured by allowing each state to move back and forth between the two boxes, with transport rates $d_A$, $d_B$, and $d_C$. The system evolves according to a Master Equation:

$$
\frac{dP(X_i)}{dt} = \sum_{Y_i} \left( k_{X_i \rightarrow Y_i} P(Y_i) - k_{Y_i \rightarrow X_i} P(X_i) \right) + \frac{dX_i}{ \Delta T} (P(X_i) - P(Y_i))
$$

where $X, Y = A, B, C$. To take into account the energy differences between the different states, the following relations between the transition rates must be respected:

$$
k_{A_i \rightarrow B_i} = e^{(E_a - E_b)/kT} k_{B_i \rightarrow A_i}
$$

$$
k_{A_i \rightarrow C_i} = e^{(E_a - E_c)/kT} k_{C_i \rightarrow A_i}
$$

$$
k_{A_i \rightarrow B_i} = e^{(E_a - E_b)/kT} k_{B_i \rightarrow A_i}
$$

$$
k_{A_i \rightarrow C_i} = e^{(E_a - E_c)/kT} k_{C_i \rightarrow A_i}
$$

with $T_1 = T_m + \Delta T/2$ and $T_2 = T_m - \Delta T/2$. We define the average temperature $T_m$ and the temperature gradient $\Delta T$, which is responsible for the maintenance of a non-equilibrium steady state. To further emphasize the effects that we want to highlight, we set the energies of the states B and C to be equal, $E_b = E_c$ (and $\Delta E = E_a - E_b = E_a - E_c$), with the additional condition on the height of the barrier that, à la Arrhenius, determines the velocity of the reactions:

$$
k_{B_i \rightarrow A_i} = e^{-\Delta \epsilon/kT} k_{C_i \rightarrow A_i}
$$

with $\Delta \epsilon = \Delta E_b - \Delta E_C > 0$. Equations (3) imply that, irrespective of the temperature (hence, in both boxes) the chemical transitions between C and A are faster than the ones between B and A. Here, we are implicitly assuming that we can identify each state as a localized well in the chemical potential landscape, i.e., the activation energy for each reaction is much larger than the thermal energy available.

We are interested in the probability of finding the system in the lowest energy states, B and C, at stationarity. In the following, $P(B)$ is identified as $P(B_1) + P(B_2)$, and analogously for $P(C)$. When equilibrium conditions are met, (namely $d_A = d_B = d_C = 0$ and/or $\Delta T = 0$), the system asymptotically converges to $P^e_1(B) = P^e_1(A)$ in each box and consequently $P^e(B) = P^e(A)$ overall. In non-equilibrium conditions the picture dramatically changes, because the energy symmetry between states B and C is kinetically broken. In order to emphasize the role of the barrier difference, $\Delta \epsilon$, we set all the transport rates to be equal, $d_A = d_B = d_C = d$. In this simple setting, away from equilibrium the state with the lowest energy barrier, C in this case, is the most populated at steady-state in the presence of a temperature gradient. This is quantified by the ratio between the probabilities of the C and B states, $R_{CB} = P(C)/P(B)$, whose logarithm can be interpreted as the effective stabilization energy of C relative to B (Fig. 1b). $R_{CB}$ is always greater than 1, and in most physical cases reaches a maximum in the $d \to \infty$ limit, i.e., when diffusion between the two boxes is much faster than all other processes in the system. In this limit, it is possible to find the analytic expression of $R_{CB}$ for an arbitrary number $n$ of boxes:

$$
\lim_{d \to \infty} R_{CB} = \frac{k_{B \rightarrow A} k_{A \rightarrow C}}{k_{C \rightarrow A} k_{A \rightarrow B}}
$$

with $k_{X \rightarrow Y} = \sum_{i=1}^{n} k_{X_i \rightarrow Y_i}$.

The simple model that we have proposed here provides a clear example of kinetic symmetry-breaking due to the energy barriers, which is effective only in a non-equilibrium scenario. In particular, the state which is more favorable away from equilibrium, C, participates in the reactions that, according to (3), are the fastest. The role of $\Delta \epsilon$ in the selection process is revealed in a small $\Delta T$ expansion of Eq. (4):

$$
R_{CB} = 1 + \frac{\Delta E \Delta T^2}{4T_m^2} \Delta \epsilon + O(\Delta T^4).
$$

As expected, the zeroth order is equal to 1, since at equilibrium the states B and C are equally populated. Furthermore, all the odd-order terms vanish because the selection of the fastest state cannot depend on the direction of the temperature gradient.
Optimal gradient for selection. When $\Delta T \rightarrow 2T_{m}$, the cold box tends to be kinetically inert. Hence, the system is dominated by the warm side, and all populations will eventually relax to their equilibrium value, corresponding to $R_{CB} = 1$. Since $R_{CB} = 1$ also when $\Delta T = 0$, and is always positive, it must have a maximum at a given $\Delta T^*$, suggesting that maximal selection would stem from a fine tuning of the parameters of the chemical network for any given $\Delta T$.

An approximate estimation of the optimal gradient for selection can be obtained in the infinite diffusion limit. We note that, up to the second order in $\Delta T$ in the exponents, $\dot{\theta}_{X \rightarrow A} \approx \frac{1}{2} e^{-\Delta \epsilon_{X}/T_{m}} \left( e^{\Delta \epsilon_{X} \Delta T/2T_{m}^{2}} + e^{-\Delta \epsilon_{X} \Delta T/2T_{m}^{2}} \right)$ (6)

It is possible to identify two different regimes depending on whether $\theta_{X} \equiv e^{\epsilon X \Delta T/2T^{2}}$ is much larger or much smaller than 1. Since $X = B, C$, we set as a control parameter the average between $\theta_{X}$ and $\theta_{C}$, thus estimating the optimal gradient as the crossing value for the two regimes:

$$\Delta T^* = \frac{4T_{m}^{2}}{\Delta \epsilon_{B} + \Delta \epsilon_{C}}.$$ (7)

In Fig. 1c we show that indeed this formula provides a good estimate for the actual $\Delta T^*$.

State selection is governed by dissipation. An intuitive grasp of the mechanism leading to selection of the fastest state can be provided by Fig. 2a, where the direction of the currents have been highlighted. Thermal energy is converted into chemical energy, namely excess of $C$ over $B$, through diffusive cycles taking place in the system. Particles are heated up in the hot box ($B$ and $C$ toward $A$), thus absorbing heat, whereas they relax ($A$ to $B$ and $C$ in the cold box, thus releasing heat. This unbalance generates a current of $A$ from the warm to the cold box, where it splits preferentially along the faster decay path, that is, toward $C$, before being transported back into the hot box. Hence, $C$ is depopulated during the heat absorption phase and populated when the heat is dissipated. This cycle is thus driven by the constant absorption and dissipation of energy, which is related to entropy production$^{16,22}$:

$$\dot{S} = \sum_{i=1}^{2} \sum_{X \in \{B,C\}} J_{X \rightarrow A} \ln \frac{k_{A \rightarrow X}^{i}}{k_{X \rightarrow A}^{i}},$$ (8)

where $J_{X \rightarrow A} = k_{X \rightarrow A} P(A_{i}) - k_{A \rightarrow X} P(X_{i})$ is the flux from $A_{i}$ to $X_{i}$ with $i$ indicating the box. We used $J_{X \rightarrow A} = -J_{A \rightarrow X}$ (Fig. 2), and the contributions from the interbox currents vanish because the rates in the two directions are equal. $\dot{S}$ is positive because the currents flow away from $A$ at the colder temperature ($T_{2}$) and toward $A$ at the warmer one ($T_{1}$).

Expanding Eq. (8) up to the second order in $\Delta T$, and using Eq. (5), we have:

$$R_{CB} \simeq 1 + \frac{\dot{S}}{\Delta \epsilon} \frac{1}{P_{m}(A)} e^{-\Delta \epsilon/T_{m}} + e^{-\Delta \epsilon/T_{m}}.$$ (9)

Despite the validity of this formula only for small gradients and fast diffusion, it suggests a correlation between $R_{CB}$, which quantifies selection, and $\dot{S}/\Delta \epsilon$, which is related to dissipation in the system. Intuitively, a similar relation could have been deduced noting that the probability fluxes towards $C$ are associated with the dissipation phase of the system.

In Fig. 2b, we show that indeed $R_{CB}$ and $\dot{S}/\Delta \epsilon$ are highly correlated for a set of (random) thermal gradients $k_{B} \Delta T = k_{B}(T_{1} - T_{2})$ and values of the typical energy scale $\Delta \epsilon$. Here it is clear that the gradient $\Delta T$ quantifies the available (thermal) energy driving the selection of the fastest state $C$ through dissipation. Indeed, as $\Delta T$ increases, the probability of escaping from $B$, diffusing, and populating $C$ by dissipating energy increases as well. However, as said before, when the
gradient is too high, chemical selection is abolished. Remarkably, fixing the thermal gradient, $R_{CB}$ is always strongly correlated with the steady-state entropy production, rescaled by the probability of the high-energy state in analogy with Eq. (9), as a function of the energy $\Delta E$ (Insets of Fig. 2b). In the Supplementary Discussion, we show that the correlation is preserved also in the case of finite diffusion and for for different values of energy barriers and temperature gradient (see Figs. S2 and S3).

**Characteristic lengthscale for selection.** Extending this two-box model to a thermal gradient in continuous space is of course more realistic, and reveals further features that are inaccessible to the discrete box description. In continuous space (say, $x \in [0,1]$), the system evolves according to the differential Chapman–Kolmogorov equation\textsuperscript{12}:

$$
\partial_t p(x) = \sum_{y} \left( k_{y \rightarrow x} p(y) - k_{x \rightarrow y} p(x) \right) + D \Delta^2 p(x),
$$

(10)

where $X, Y = A, B, C$. We impose no-flux boundary conditions, i.e., $\partial_x p(x) = 0$ at $x = 0,1$. In Eq. (10), the Laplacian captures diffusion while the part involving discrete transitions captures the chemical reactions between species, which are governed by rates analogous to the ones introduced before:

$$
k_{x \rightarrow y}(x) = e^{(E_y - E_x)/k_B T(x)} k_{y \rightarrow x}(x),
$$

(11)

with the additional condition on the energy barriers:

$$
k_{A \rightarrow B}(x) = e^{-\Delta E/k_B T(x)} k_{B \rightarrow A}(x).
$$

(12)

Also in this case, the transport coefficient is the same for all states: $D_x \equiv D, \forall X$. In what follows $P(X) = \int dx p(x)$ (note that we use $p$ for the space dependent distribution, and $P$ to indicate their integral over space).

Although it is difficult to solve Eq. (10) analytically for any value of the parameters, approximate solutions can be worked out in selected cases. The limit of large diffusion ($D \rightarrow \infty$), which is analogous to the case of infinitely fast transport between the two boxes analyzed above, can be tackled using the standard approach of time-scale separation\textsuperscript{15,23}. To the leading orders in $1/D$, the solution is uniform in space, and $R_{CB}$ is the same as in Eq. (4), with $k_{x \rightarrow y} = \int dx k_{x \rightarrow y}(x)$.

The case of a linear temperature gradient $T(x) = T_0 + \Delta T x$ can also be analytically explored for small $\Delta T$. Expanding all rates and probabilities in powers of $\Delta T$ as

$$
k_{x \rightarrow y} = \sum_{n} \frac{1}{n!} x^n \Delta T^n \partial_x^n k_{x \rightarrow y} |_{\Delta T=0},
$$

(13)

inserting them in (10) and solving it order by order it is easy to obtain at 0th order

$$
P_B^{(0)} = P_C^{(0)} = \frac{e^{\Delta E/k_B T_x}}{2e^{E_B/k_B T_x} + 1},
$$

(14)

which is the equilibrium solution for $\Delta T = 0$.

Up to second order, $R_{CB}$ is

$$
R_{CB} = 1 + \frac{\Delta T^2}{2P_B^{(0)}} \left( P_C^{(2)} - P_B^{(2)} \right),
$$

(15)

where $P_C^{(n)}$ is defined as the integral of $p_n(x)$ over the whole domain. After a further expansion in $\Delta E$, i.e., the symmetry between $B$ and $C$ is only infinitesimally broken by the kinetics, we obtain

$$
P_C^{(2)} - P_B^{(2)} = \frac{\Delta E}{T_0} P_{eq} T_x \left( 1 - 2L_x \tanh \left( \frac{1}{2L_x} \right) \right) \Delta E,
$$

(16)

with $L_x = \sqrt{D/(k_{B \rightarrow A} + 2k_{A \rightarrow B})}$ and $P_{eq} = P_B^{(0)} = P_C^{(0)}$. This difference is always positive, implying that states participating in fast reactions are always favored in this system, and it vanishes when $D \rightarrow 0$, as expected because the system locally relaxes at equilibrium. In particular, $L_x$ represents a typical length-scale that can be interpreted as the space traveled by the system between two state transitions, namely the distance below which the system can absorb and dissipate energy, thus setting a lengthscale for dissipation-driven selection.

Analogously to the two-box scenario, an optimal gradient can be appreciated also in this case. Since the system lives in a continuous domain, its physical origin is slightly different. When $\Delta T \rightarrow \infty$, all states tend to be equally populated, i.e., $R_{CB} \rightarrow 1$, abolishing chemical selection. The positivity of $R_{CB}$, and the fact that it goes to zero when for a vanishing gradient, leads to the existence of a maximum at $\Delta T^*$. In the Supplementary Methods, we present a more in-depth discussion on this (see Fig. S1).
Non-trivial selection for more complex reaction-network topologies. How do the features of a simple three-state system extend to more complex network topologies? Here we study a chain of connected chemical reactions in an energy landscape, looking at the propagation of the local selection process along the chain, eventually leading to runaway and/or localization phenomena in the population of states.

We focus to the two-box scenario, which, as shown above, recapitulates most of the dissipation-driven selection phenomenon while being easier to analyze, in the limit of infinitely fast transport between the boxes. We consider a reaction network as the one sketched in Fig. 3a, which can also diffuse between two boxes at different temperatures as in Fig. 1. We can distinguish two different classes of three-state subsystems, with the faster reaction either on the right branch (henceforth indicated as R, encircled by an orange dash line in Fig. 3a), analogously to the three-state system depicted in Fig. 1a, or on the left (L, encircled by a blue dashed line in Fig. 3a). All lower energy states have the same energy, while the high energy state in each subsystem is characterized by a different energy $\Delta E$ and two different barriers $\Delta E_{\text{slow}}$ and $\Delta E_{\text{fast}}$, mimicking the presence of a non-trivial underlying energy landscape.

We have already computed $R_{\text{CB}}$ in Eq. (4), in the limit of infinitely fast diffusion. It quantifies the ratio between the population of two adjacent states, the fast over the slow one. It is possible to see from the Master Equation for the whole system in Fig. 3a, that the same relation holds between any two adjacent states in each subsystem. Since, we want to compute the population of each single species along the chain, we use $B$ as our reference state. The ratio between $P_{\text{C}_0}$ and $P_B$ is:

$$R_{\text{C}_0B} = \frac{P_{\text{C}_0}}{P_B}$$

with $P_B$ given by Eq. (4).

To simulate a generic chain of chemical reactions, we assign each subsystem to class $L$ with probability $p$, and to class $R$ with probability $q = 1 - p$. We then draw $\Delta E$, $\Delta E_{\text{slow}}$ and $\Delta E_{\text{fast}}$ from three different distributions, $P(\Delta E)$ and $P(\Delta E_{\text{slow}})$ and $P(\Delta E_{\text{fast}})$, respectively (details in the caption of Fig. 3). As we can see from Fig. 3b, even in the simple case in which $p = q = 1/2$, and both distributions are uniform, a localization phenomenon in the population of the states can spontaneously arise, where the favorability of an individual state does not depend only on its fast/slow status with respect to the adjacent reactions, but depends instead on the full path of reactions connecting it to the reference state, and hence on the full energy landscape. If all the fast reactions are on the same side of each three-state subsystem (all reactions of type $R$ or of type $L$), the population of states $C_i$ can become exponentially different from the one of $B$, as highlighted in the inset of Fig. 3b.

Also in this case, the selection for the most probable states is determined by dissipation. The argument outlined for the simple three-state system can be easily generalized in the case of infinitely fast transport between the boxes: $R_{\text{C}_0B}$ simply corresponds to the product of all the transition rates directed from $B$ to $C_i$, belonging to the path connecting the two, divided by the same product in the opposite direction. As a consequence, the states that will eventually be the most populated ones (with respect to a reference state $B$) are those whose connecting path to $B$ have the fastest dissipation. In the Note 1, we study a tree-like topology, showing that the kinetic properties of the path connecting lower and higher energy states become relevant to determine steady selection under non iso-thermal conditions (see Fig. S4). However, when the topology is further complicated, several distinct paths can connect the same pair of states, and all the transition rates will eventually contribute to determine a ranking for steady-state populations. In this case the determination of the fastest dissipating states becomes difficult, and we leave for future works the development of an efficient technique to tackle this problem.

Selection under time-periodic variations of temperature. Another common method to maintain a system out-of-equilibrium is to periodically vary some external parameters, allowing it to reach a time-periodic non-equilibrium state. We imagine to have the three-state system detailed above, coupled to a reservoir whose temperature is varied periodically in time, with a period $T$.

$$T(t) = T_m + \eta_t(t)\Delta T,$$

with $\eta_t(t) = 0$ and $\lim_{t' \to t} \eta_t(t') = \delta(t - t')$, where the overline indicates the temporal average over one period. In analogy with

![Fig. 3 Selection of states in a chain of three-state subsystems in a thermal gradient.](image)
Eqs. (11) and (12), the time-dependent transition rates satisfy:
\begin{align}
    k_{A\rightarrow B}(t) &= \frac{e^{-E_A/E_K\tau(t)}}{k_A}, \\
    k_{A\rightarrow C}(t) &= \frac{e^{-E_A-E_C/E_K\tau(t)}}{k_{A\rightarrow C}}, \\
    k_{B\rightarrow A}(t) &= \frac{e^{-E_A/E_K\tau(t)}}{k_{B\rightarrow A}}.
\end{align}

The inverse period \( \tau^{-1} \) plays the same role as the diffusion rate \( d \) in the system in Fig. 1a. It favors cycles of constant absorption and dissipation of energy, hence igniting a chemical selection among species. The latter is de facto a continuous gradient. The zeroth-order in energy, \( k_0 \), is the concentration of particles, and \( k_{AB} \) is the transport coefficient of the different states, and it thus continuously dissipating energy supplied from an external source, thermophoresis-like behavior emerging as a spatial selection process in space for a three-state two-box model. As a byproduct of our study, we have presented a thermophoresis, as long as the two states have different transport coefficients (see Supplementary Note 2 and Fig. S5).

Equations (22) and (23) are analogous to Eqs. (5) and (9), and notably they are valid in the fast driving regime. We highlight the analogy between temporal cycles and diffusive cycles of the previous setting: they both force the system to explore different fundamental roles. Here, we have proposed simple reaction networks that could be investigated to reveal how selection and dissipation are intimately related. Furthermore, because of their simplicity, these models can be analytically and numerically solved and, importantly, are amenable of experimental validation. As a byproduct of our study, we have presented a thermophoresis-like behavior emerging as a spatial selection.

**Discussion**

Non-equilibrium conditions can trigger stabilization effects in molecular systems. In a similar fashion, here we have shown that high energy states can be stabilized out-of-equilibrium, by continuously dissipating energy supplied from an external source, a temperature gradient in our case. In particular, the deviation with respect to equilibrium directly correlates with dissipation, which is kinetically controlled by the rates of the system. Hence, the core ingredient is the breakdown of kinetic symmetry in the reaction rates: while at equilibrium the energies are the only relevant quantities, away from equilibrium the kinetics plays a fundamental role. Here, we have proposed simple reaction networks that could be investigated to reveal how selection and dissipation are intimately related. Furthermore, because of their simplicity, these models can be analytically and numerically solved and, importantly, are amenable of experimental validation. As a byproduct of our study, we have presented a thermophoresis-like behavior emerging as a spatial selection.
process. This is induced, again, by kinetic symmetry-breaking, in this case in the diffusion coefficients of different states. It is also worth noting that the relation between selection and dissipation stems from the thermodynamic necessity to transport heat from the warm to the cold side of the system. In this respect, selection becomes a necessary consequence of thermodynamics.

From a broader perspective, this work could provide a novel framework to develop schemes aimed at explaining the sustained abundance of otherwise only metastable molecules, which are necessary intermediates for the spontaneous synthesis of more complex macromolecules that, in turn, could lead to the first replicators. In this respect, the approach here presented recently stimulated a possible solution to the furanose conundrum.14, Hence, we are convinced that our results could represent an important previously unreported ingredient to connect the origin of life problem to the physical questions of what is possible in non-equilibrium conditions and what are the basic microscopic (molecular) rules governing the emergent phenomena.

Data availability
No datasets were generated or analysed during the current study.

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