Noise-Induced Mechanism for Biological Homochirality of Early Life Self-Replicators

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The observed single-handedness of biological amino acids and sugars has long been attributed to autocatalysis. However, the stability of homochiral states in deterministic autocatalytic systems relies on cross inhibition of the two chiral states, an unlikely scenario for early life self-replicators. Here, we present a theory for a stochastic individual-level model of autocatalysis due to early life self-replicators. Without chiral inhibition, the racemic state is the global attractor of the deterministic dynamics, but intrinsic multiplicative noise stabilizes the homochiral states, in both well-mixed and spatially extended systems. We conclude that autocatalysis is a viable mechanism for homochirality, without imposing additional nonlinearities such as chiral inhibition.

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One of the very few universal features of biology is homochirality: every naturally occurring amino acid is left-handed (L chiral) while every sugar is right-handed (D chiral) [1,2]. Although such unexpected broken symmetries are well known in physics—for example, in the weak interaction—complete biological homochirality still defies explanation. In 1953, Charles Frank suggested that homochirality could be a consequence of chemical autocatalysis [3], frequently presumed to be the mechanism associated with the emergence of early life self-replicators. Frank introduced a model in which the D and L enantiomers of a chiral molecule are autocatalytically produced from an achiral molecule A in reactions $A + \mathrm{D} \to 2\mathrm{D}$ and $A + \mathrm{L} \to 2\mathrm{L}$, and the enantiomers are consumed in a chiral inhibition reaction, $\mathrm{D} + \mathrm{L} \to 2A$ [4]. The state of this system can be described by the chiral order parameter ω defined as $\omega \equiv (d - l)/(d + l)$, where d and l are the concentrations of D and L. The order parameter ω is zero at the racemic state, and ± 1 at the homochiral states. Frank's model has three deterministic fixed points of the dynamics; the racemic state is an unstable fixed point, and the two homochiral states are stable fixed points. Starting from almost everywhere in the D-L plane, the system converges to one of the homochiral fixed points [Fig. 1(a)].

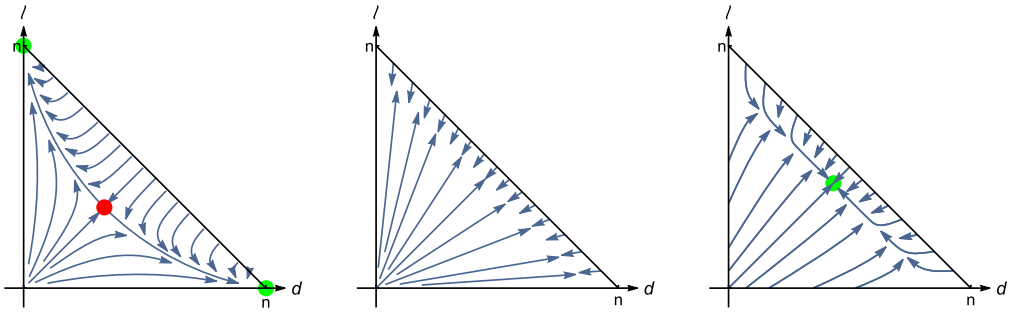
In the context of biological homochirality, extensions of Frank's idea have essentially taken two directions. On the one hand, the discovery of a synthetic chemical system of amino alcohols that amplifies an initial excess of one of the chiral states [5] has motivated several autocatalysis-based models (see Ref. [6] and the references therein). On the other hand, ribozyme-driven catalyst experiments [7] have inspired theories based on polymerization and chiral inhibition that minimize [8–10] or do not include at all [11,12] autocatalysis. In contrast, a recent experimental realization of ribonucleic acid replication using a novel ribozyme shows such efficient autocatalytic behavior that chiral inhibition does not arise [13]. Further extensions accounting for both intrinsic noise [6,14] and diffusion [15–18] build further upon Frank's work.

Regardless of the specific model details, all of these models share the three-fixed-points paradigm of Frank's model, namely, that the time evolution of the chiral order parameter ω is given by a deterministic equation of the form [6]

$$\frac{d\omega}{dt} = f(t)\omega(1 - \omega^2), \tag{1}$$

where the function $f(t)$ is model dependent. However, the homochiral states arise from a nonlinearity which is not a property of simple autocatalysis but, for instance in the original Frank's model, is due to chiral inhibition [see Fig. 1(b)]. The sole exception to the three-fixed-points model in a variation of Frank's model is the work of Lente [19], where purely stochastic chiral symmetry breaking occurs, although chiral symmetry breaking is only partial, with $\omega \neq 0$ but $|\omega| < 1$.

The purpose of this Letter is to show that efficient early life self-replicators can exhibit universal homochirality, through a stochastic treatment of Frank's model *without* requiring nonlinearities such as chiral inhibition. In our stochastic treatment, the homochiral states arise not as fixed points of deterministic dynamics, but instead are states where the effects of chemical number fluctuations (i.e., the multiplicative noise [20]) are minimized. The mathematical mechanism proposed here [21–24] is intrinsically different from that of the class of models summarized by Eq. (1). In the following, we propose a model which we analytically solve for the spatially uniform case and the case of two



(a) $A + \text{D} \to 2\text{D}$, $A + \text{L} \to 2\text{L}$, $\text{D} + \text{L} \to 2A$ (b) $A + \text{D} \to 2\text{D}$, $A + \text{L} \to 2\text{L}$, $\text{D} \to A$, $\text{L} \to A$ (c) $A + \text{D} \to 2\text{D}$, $A + \text{L} \to 2\text{L}$, $\text{D} \rightleftharpoons A$, $\text{L} \rightleftharpoons A$

FIG. 1 (color online). (a) Phase portrait of Frank's model: the racemic state is an unstable fixed point (the red dot), while the homochiral states are stable fixed points (the green dots). (b) If chiral inhibition is replaced by a linear decay reaction, the ratio of D and L molecules stays constant. (c) Adding even the slightest amount of nonautocatalytic production of D and L molecules makes the racemic state (the green dot) the global attractor of the dynamics.

well-mixed patches coupled by diffusion. We then show, using numerical simulations, that the results persist in a one-dimensional spatially extended system. We conclude that autocatalysis alone can, in principle, account for universal homochirality in biological systems.

Stochastic model for well-mixed system.—Motivated in part by the experimental demonstration of autocatalysis without chiral inhibition [13], we propose the reaction scheme below, which is equivalent to a modification of Lente's reaction scheme [19] through the additional process representing the recycling of enantiomers:

$$A + \text{D} \xrightarrow{k_a} 2\text{D}, \qquad A + \text{L} \xrightarrow{k_a} 2\text{L},$$
$$A \underset{k_d}{\overset{k_n}{\rightleftharpoons}} \text{D}, \qquad A \underset{k_d}{\overset{k_n}{\rightleftharpoons}} \text{L}. \tag{2}$$

Compared to Frank's model, the chiral inhibition is replaced by linear decay reactions which model both recycling and nonautocatalytic production. The rate constants are denoted by k, with the subscript serving to identify the particular reaction. The only deterministic fixed point of this model is the racemic state [Fig. 1(c)]. This model can be interpreted as a model of the evolution of early life where primitive chiral self-replicators can be produced randomly through nonautocatalytic processes at very low rates; the self-replication is modeled by autocatalysis, while the decay reaction is a model for the death process [25].

We now approximate reaction scheme (2) by means of a stochastic differential equation for the time evolution of the chiral order parameter, ω, which shows that in the regime where autocatalysis is the dominant reaction, the functional form of the multiplicative intrinsic noise from autocatalytic reactions stabilizes the homochiral states. We consider a well-mixed system of volume V and total number of molecules N. As shown in the Supplemental Material (SM) [26], for $N \gg 1$, we obtain the following equation for ω, defined in the Itō sense [20]:

$$\frac{d\omega}{dt} = -\frac{2k_n k_d V}{N k_a}\omega + \sqrt{\frac{2k_d}{N}(1-\omega^2)}\eta(t), \tag{3}$$

where $\eta(t)$ is normalized Gaussian white noise [20].

The time-dependent distribution of Eq. (3) can be computed exactly [24,27]. The stationary distribution [20],

$$P_s(\omega) = \mathcal{N}(1-\omega^2)^{\alpha-1}, \quad \text{with} \quad \alpha = \frac{Vk_n}{k_a}, \tag{4}$$

depends on a single parameter, α, where the normalization constant $\mathcal{N}$ is given by

$$\mathcal{N} = \left(\int_{-1}^{+1}(1-\omega^2)^{\alpha-1}d\omega\right)^{-1} = \frac{\Gamma(\alpha+\frac{1}{2})}{\sqrt{\pi}\Gamma(\alpha)}. \tag{5}$$

Equation (4) is compared in Fig. 2 against Gillespie simulations [28] of scheme (2). For $\alpha = \alpha_c = 1$, ω is

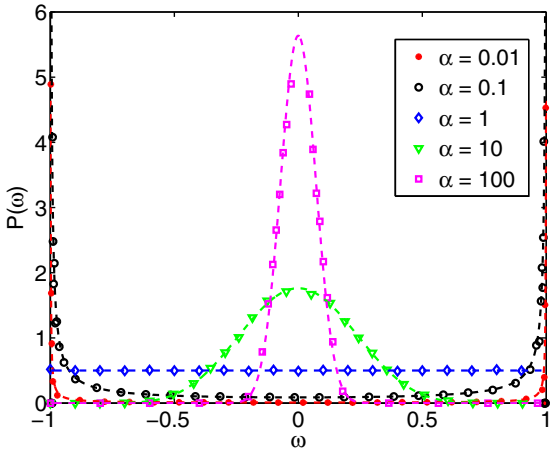


FIG. 2 (color online). Comparison between the stationary distribution, Eq. (4) (dashed lines), and Gillespie simulations of the reactions (2) (markers), for different values of α. Simulation parameters: $N = 10^3$, $k_a = k_n = k_d = 1$.

uniformly distributed. For $\alpha \gg \alpha_c$, where the nonautocatalytic production is the dominant production reaction, $P_s(\omega)$ is peaked around the racemic state, $\omega = 0$. For $\alpha \ll \alpha_c$, where autocatalysis is dominant, $P_s(\omega)$ is sharply peaked around the homochiral states, $\omega = \pm 1$. The simulations were performed for $N = 1000$, where the analytic theory is expected to be accurate; for smaller values of N, the theory is qualitatively correct, but very small quantitative deviations are observable compared to the simulations. For example, for $N \sim 100$, $\alpha_c \sim 1.005$.

The deterministic part of Eq. (3) has one fixed point at the racemic state, consistent with the phase portrait in Fig. 1(c). The multiplicative noise in Eq. (3) vanishes at homochiral states and admits its maximum at the racemic state. For $\alpha \ll \alpha_c$, where autocatalysis is dominant, the amplitude of the noise term in Eq. (3) is much larger than the amplitude of the corresponding deterministic term. In this regime, the system ends up at homochiral states where the noise vanishes.

To understand this result physically, note that the source of the multiplicative noise is the intrinsic stochasticity of the autocatalytic reactions. While, on average, the two autocatalytic reactions do not change the variable ω, each time one of the reactions takes place, the value of ω changes by a very small discrete amount. As a result, over time the value of ω drifts away from its initial value. Since the amplitude of the noise term is maximum at racemic state and zero at homochiral states, this drift stops at one of the homochiral states. The absence of the noise from autocatalysis at homochiral states can be understood by recognizing that at homochiral states, the molecules with only one of two chiral states D and L are present; hence, only the autocatalytic reaction associated with that chiral state has a nonzero rate. This reaction produces molecules of the same chirality, keeping the system at the same homochiral state without affecting the value of ω, and, therefore, the variable ω does not experience a drift away from the homochiral states due to the autocatalytic reactions.

Since the stationary distribution of ω in Eq. (4) is only dependent on α, the decay reaction rate, k_d has no effect on the steady state distribution of the system. The only role of this reaction is to prevent the A molecules from being completely consumed, thus providing a well-defined nonequilibrium steady state independent of the initial conditions. The parameter α is proportional to the ratio of the nonautocatalytic production rate, k_n, to the self-replication rate, k_a. In the evolution of early life, when self-replication was a primitive function, k_a would be small and the value of α would therefore be large; however, as self-replication became more efficient, the value of k_a would have increased and thus α would have decreased. Therefore, in our model, we expect that life started in a racemic state, and it transitioned to complete homochirality through the mechanism explained above, after self-replication became efficient (i.e., when $\alpha \ll \alpha_c$).

It is important to note that all of the previous mechanisms suggested for homochirality rely on assumptions that cannot be easily confirmed to hold during the emergence of life. However, even if all of such mechanisms fail during the origin of life, our mechanism guarantees the emergence of homochirality since it only relies on self-replication and death, two processes that are inseparable from any living system.

Stochastic model with spatial extension.—We now turn to the study of reaction scheme (2) generalized to the spatially extended case [29]. We discretize space into a collection of M patches of volume V, indexed by i. The geometry of the space is defined by $\langle i \rangle$—the set of patches that are nearest neighbor to patch i (e.g., for a linear chain, $\langle i \rangle = \{i-1, i+1\}$). We indicate the molecules of species A in patch i by A_i and similarly for the other species. Each patch is well mixed and reactions (2) occur within, while molecules can diffuse between neighboring patches with diffusion rate δ. In summary, the following set of reactions defines the spatial model:

$$\begin{aligned} &A_i \underset{k_d}{\overset{k_n}{\rightleftharpoons}} \mathrm{D}_i, \qquad A_i \underset{k_d}{\overset{k_n}{\rightleftharpoons}} \mathrm{L}_i, \qquad i = 1, \ldots, M, \\ &A_i + \mathrm{D}_i \xrightarrow{k_a} 2\mathrm{D}_i, \qquad A_i + \mathrm{L}_i \xrightarrow{k_a} 2\mathrm{L}_i, \\ &\mathrm{D}_i \overset{\delta}{\rightleftharpoons} \mathrm{D}_j, \qquad \mathrm{L}_i \overset{\delta}{\rightleftharpoons} \mathrm{L}_j, \qquad j \in \langle i \rangle. \end{aligned} \tag{6}$$

We now derive the following set of coupled stochastic differential equation for the time evolution of the chiral order parameter ω_i, of each patch i (see the SM [26])

$$\begin{aligned} \frac{d\omega_i}{dt} = &-\frac{2k_n k_d V}{N k_a}\omega_i + \delta \sum_{j \in \langle i \rangle} (\omega_j - \omega_i) \\ &+ \sqrt{\frac{2k_d}{N}(1-\omega_i^2)}\eta_i(t) + \sqrt{\frac{\delta}{N}}\xi_i(\vec{\omega}, t), \end{aligned} \tag{7}$$

where now N represents the average number of molecules per patch, η_i's are independent normalized Gaussian white noises, ξ_i's are zero mean Gaussian noise with correlator

$$\begin{aligned} \langle \xi_i(t)\xi_j(t') \rangle = \Big(&2\sum_{k \in \langle i \rangle} (1 - \omega_i\omega_k)\delta_{i,j} \\ &+ (\omega_i^2 + \omega_j^2 - 2)\chi_{\langle i \rangle}(j) \Big) \delta(t - t'), \end{aligned} \tag{8}$$

and $\chi_{\langle i \rangle}(j)$ is equal to one if $j \in \langle i \rangle$ and zero otherwise.

In order to see how the coupling of well-mixed patches affects their approach to homochirality, it is instructive to consider the simplest case of two adjacent patches ($M = 2$). In the two-patch model, various scenarios can happen: the system may not exhibit homochirality ($\omega_1 \sim \omega_2 \sim 0$); each patch can separately reach homochirality ($\omega_1 = \pm 1$ and $\omega_2 = \pm 1$); the system exhibits global homochirality ($\omega_1 = \omega_2 = \pm 1$). We first analyze the condition for each patch reaching homochirality using perturbation theory, in

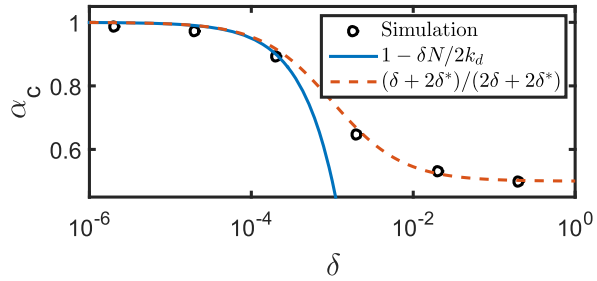


FIG. 3 (color online). Parameter α_c^{patch} in the two-patch system as a function of the diffusion rate δ. Gillespie simulations (markers) are compared against Eq. (11) (the solid blue line) and Eq. (13) (the dashed red line). Simulation parameters as in Fig. 2.

the case of slow diffusion. The stationary probability density function of the chiral order parameter of a single patch, $Q_s(\omega)$, is defined by

$$Q_s(\omega) = \int_{-1}^{+1} Q_s(\omega, \omega_2) d\omega_2 = \int_{-1}^{+1} Q_s(\omega_1, \omega) d\omega_1, \quad (9)$$

where $Q_s(\omega_1, \omega_2)$ is the joint probability distribution of ω_1 and ω_2 at steady state from Eq. (7). If $\delta \sim k_d/N$ or smaller, then (see the SM [26]) the stationary distribution reads

$$Q_s(\omega) = Z(1-\omega^2)^{\alpha+(\delta N/2k_d)-1}, \quad (10)$$

where $\mathcal{Z}$ is a normalization constant. This result shows that the critical α in a single patch, up to the first order correction in δ, is given by

$$\alpha_c^{\text{patch}} \approx 1 - \delta \frac{N}{2k_d}, \quad \text{for } \delta \approx 0. \quad (11)$$

We can now turn to the case of high diffusion. Recall that the patches are defined as the maximum volume around a point in space in which the system can be considered well mixed. This can be interpreted as the maximum volume in which diffusion dominates over the other terms acting on the variable of interest (in this case ω). From Eq. (7), this condition is fulfilled for $\delta \sim 2k_d\alpha/N$. In the vicinity of the transition, α is on the order of one; therefore, the condition becomes $\delta \sim k_d/N$. For $\delta \gg k_d/N$, the whole system can be considered well mixed, and we can find the critical value of α for each patch, starting from $\alpha_c = 1$, from the well-mixed results, and using as volume the volume of the whole system, i.e., MV. This indicates that, in a single patch,

$$\alpha_c^{\text{patch}} \approx \frac{1}{M}, \quad \text{for } \delta \gg 0. \quad (12)$$

A simple formula that interpolates between these extreme limits, asymptotic to $1/M$ (with $M = 2$) for large δ and to Eq. (11) for small δ, is

$$\alpha_c^{\text{patch}} = \frac{\delta + 2\delta^*}{2\delta + 2\delta^*}, \qquad \delta^* = \frac{k_d}{N}. \quad (13)$$

Figure 3 shows agreement between α_c^{patch}, measured from Gillespie simulations of the two-patch system, and Eq. (13). At the parameter regime below the α_c curve in Fig. 3, individual patches are homochiral. Also, we find that the correlation between the homochiral states of the two patches increases with diffusion rate δ, and the patches become completely correlated when $\delta \sim k_d/N$ or more. In this regime the system reaches global homochirality.

This latter result suggests that in the spatially extended model, when autocatalysis is the dominant reaction (i.e., α is small enough) and when the diffusion rate is in the order of k_d/N or larger, all patches converge to the same homochiral state. Figure 4 shows the dynamics of a Gillespie simulation of a one-dimensional chain of 100 patches, initializes at the racemic state, in the pure autocatalytic limit ($k_n \to 0$). Very quickly, small islands of different homochirality (blue and red) are formed. Islands of opposite chirality compete against each other, until the system reaches global homochirality. Note that for

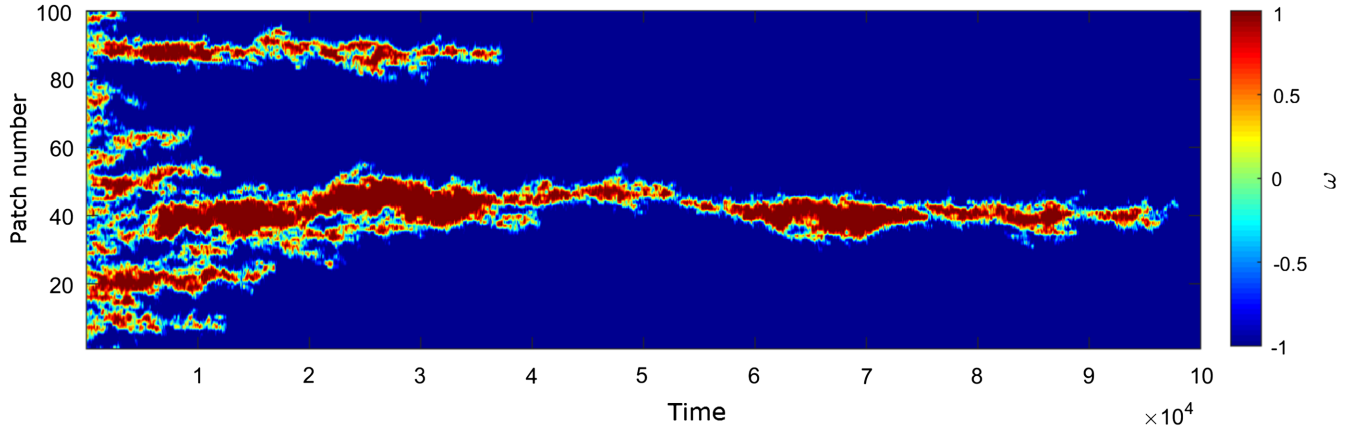


FIG. 4 (color online). Gillespie simulation of scheme (6) for a one-dimensional system of $M = 100$ patches, starting from the racemic state and ending with all of the patches in the same homochiral state, $\omega = -1$. Simulation parameters: $N = 1000$, $k_a = k_d = 1$, $\delta = 10^{-3}$, and $k_n = 0$.

$\delta \sim k_d/N$ we can treat the diffusion process deterministically by ignoring the last term in Eq. (7). In this regime, Eq. (7) is the same as the equation describing the one-dimensional voter model, implying that the transition to homochirality is in the universality class of compact directed percolation [30].

In conclusion, a racemic population of self-replicating chiral molecules far from equilibrium, even in the absence of other nonlinearities that have previously been invoked, such as chiral inhibition, transitions to complete homochirality when the efficiency of self-replication exceeds a certain threshold. This transition occurs due to the drift of the chiral order parameter under the influence of the intrinsic stochasticity of the autocatalytic reactions. The functional form of the multiplicative intrinsic noise from autocatalysis directs this drift toward one of the homochiral states. Unlike some other mechanisms in the literature, this process does not require an initial enantiomeric excess. In our model, the homochiral states are not deterministic dynamical fixed points but are instead stabilized by intrinsic noise. Moreover, in the spatial extension of our model, we have shown that diffusively coupled autocatalytic systems synchronize their final homochiral states, allowing a system solely driven by autocatalysis to reach global homochirality. We conclude that autocatalysis alone is a viable mechanism for homochirality, without the necessity of imposing chiral inhibition or other nonlinearities.

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[1] D. G. Blackmond, Cold Spring Harbor Persp. Biol. **2**, a002147 (2010).
[2] M. Gleiser and S. I. Walker, Int. J. Astrobiol. **11**, 287 (2012).
[3] F. C. Frank, Biochim. Biophys. Acta **11**, 459 (1953).
[4] In the original model by Frank, the concentration of the A molecules was kept constant to reduce the degrees of freedom by one, and the chiral inhibition was introduced by the reaction $\mathrm{D} + \mathrm{L} \to \emptyset$. This model leads to indefinite growth of D or L molecules and does not have a well-defined steady state. To resolve this problem, we let the concentration of A molecules be variable and replaced this reaction by $\mathrm{D} + \mathrm{L} \to 2A$, which conserves the total number of molecules. This conservation law reduces the number of degrees of freedom by one again. The mechanism to homochirality in the modified model is the same as the original model by Frank.
[5] K. Soai, T. Shibata, H. Morioka, and K. Choji, Nature (London) **378**, 767 (1995).
[6] Y. Saito and H. Hyuga, Rev. Mod. Phys. **85**, 603 (2013).
[7] G. Joyce, G. Visser, C. Van Boeckel, J. Van Boom, L. Orgel, and J. Van Westrenen, Nature (London) **310**, 602 (1984).
[8] P. Sandars, Origins Life Evol. Biosphere **33**, 575 (2003).
[9] M. Gleiser and S. I. Walker, Origins Life Evol. Biosphere **38**, 293 (2008).
[10] M. Gleiser, B. J. Nelson, and S. I. Walker, Origins Life Evol. Biosphere **42**, 333 (2012).
[11] R. Plasson, H. Bersini, and A. Commeyras, Proc. Natl. Acad. Sci. U.S.A. **101**, 16733 (2004).
[12] A. Brandenburg, H. J. Lehto, and K. M. Lehto, Astrobiology **7**, 725 (2007).
[13] J. T. Sczepanski and G. F. Joyce, Nature (London) **515**, 440 (2014).
[14] G. Lente, Symmetry **2**, 767 (2010).
[15] R. Shibata, Y. Saito, and H. Hyuga, Phys. Rev. E **74**, 026117 (2006).
[16] R. Plasson, D. K. Kondepudi, and K. Asakura, J. Phys. Chem. B **110**, 8481 (2006).
[17] D. Hochberg and M.-P. Zorzano, Chem. Phys. Lett. **431**, 185 (2006).
[18] D. Hochberg and M. P. Zorzano, Phys. Rev. E **76**, 021109 (2007).
[19] G. Lente, J. Phys. Chem. A **108**, 9475 (2004).
[20] C. W. Gardiner, *Handbook of Stochastic Methods for Physics, Chemistry and the Natural Sciences*, 4th ed. (Springer, New York, 2009).
[21] Y. Togashi and K. Kaneko, Phys. Rev. Lett. **86**, 2459 (2001).
[22] M. N. Artyomov, J. Das, M. Kardar, and A. K. Chakraborty, Proc. Natl. Acad. Sci. U.S.A. **104**, 18958 (2007).
[23] D. I. Russell and R. A. Blythe, Phys. Rev. Lett. **106**, 165702 (2011).
[24] T. Biancalani, L. Dyson, and A. J. McKane, Phys. Rev. Lett. **112**, 038101 (2014).
[25] For the nonautocatalytic reaction to occur at a very small rate compared to the decay rate, the self-replication process must be an energy-consuming reaction, as is the case in biological systems. Hence, in order to maintain irreversible self-replication, the system has to be driven by an external source of energy that maintains the steady state of the system far from equilibrium. As usual, the source of this driving energy is not included in our model.
[26] See Supplemental Material at http://link.aps.org/supplemental/10.1103/PhysRevLett.115.158101, which includes Refs. [20, 26, 27, 30, 31], for derivation of the Eq. (2) and (7) from the individual level models and the derivation of Eq. (10) using perturbation theory.
[27] T. Biancalani, L. Dyson, and A. J. McKane, J. Stat. Mech. (2015) P01013.
[28] D. T. Gillespie, J. Phys. Chem. **81**, 2340 (1977).
[29] A. J. McKane and T. J. Newman, Phys. Rev. E **70**, 041902 (2004).
[30] R. Dickman and A. Y. Tretyakov, Phys. Rev. E **52**, 3218 (1995).
[31] N. G. van Kampen, *Stochastic Processes in Physics and Chemistry*, 3rd ed. (Elsevier Science, Amsterdam, 2007).
[32] A. J. McKane, T. Biancalani, and T. Rogers, Bull. Math. Biol. **76**, 895 (2014).