

## Preservation of information in a prebiotic package model

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The coexistence between different informational molecules has been the preferred mode to circumvent the limitation posed by imperfect replication on the amount of information stored by each of these molecules. Here we reexamine a classic package model in which distinct information carriers or templates are forced to coexist within vesicles, which in turn can proliferate freely through binary division. The combined dynamics of vesicles and templates is described by a multitype branching process which allows us to write equations for the average number of the different types of vesicles as well as for their extinction probabilities. The threshold phenomenon associated with the extinction of the vesicle population is studied quantitatively using finite-size scaling techniques. We conclude that the resultant coexistence is too frail in the presence of parasites and so confinement of templates in vesicles without an explicit mechanism of cooperation does not resolve the information crisis of prebiotic evolution.

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### I. INTRODUCTION

The information crisis in prebiotic or chemical evolution stems essentially from two observations: (i) the length of a replicating polymer (i.e., RNA-like template) is limited by the replication accuracy per nucleotide [1], and (ii) templates that differ significantly from each other cannot coexist in a purely competitive setup [2]. Realistic estimates of the error rate of primitive replication mechanisms predict a too scanty information content per template—less than 100 nucleotides—to permit the complete codification of the mechanism in just one template. Currently an operative replication mechanism requires at least three basic sets of different reactions (initiation, elongation, and termination) [3], thus the primitive information integrator systems must have shared the necessary information in a number of distinct templates. Yet, attainment of template coexistence in a plausible prebiotic scenario is still a highly controversial issue.

An attractive solution to this crisis is the hypercycle, a cyclic reaction scheme in which each replicating polymer aids in the replication of the next one, in a regulatory cycle closing on itself [4]. This scheme requires that the primordial replicators functioned both as templates and replicases (i.e., catalysts for replication), a prospect confirmed by the discovery of the catalytic activity of RNA in the early 1980s [5,6]. However, the key assumption that each replicator has two separate functions, namely a replicase for the next member of the hypercycle and a target for the previous member, encountered strong criticism [7,8]. In fact, natural selection can make each element of the hypercycle a better target for replication, but it cannot favor the cooperative part of the scheme, i.e., to make the replicator a better replicase for other replicators. Hence this function is bound to degenerate rapidly as natural selection does not protect it against deletions and mutations that create the so-called parasites—molecules that do not reciprocate the catalytic support they receive.

Another proposal to resolve the problem of the coexistence between templates, which is in line with the classical works on the origin of life [9,10], is to enwrap the replicators

in isolated compartments or vesicles. It is presumed that the information to code for a common replicase is shared among  $d$  distinct template types so that template replication is feasible only if all template types coexist within a vesicle [11]. In this scheme the replicators play the template role only whereas the replicase role is taken on by a protein—the replicase. In addition, it is assumed that a vesicle splits into two daughters after a certain number of template copies are produced. Alternatively, we may suppose that an effective coupling among different template types comes about through a common metabolism which is ultimately responsible for the survival and reproduction of the vesicle, and that the functioning of this metabolism requires the contribution of all template types [12].

It should be noted, however, that the proponents of the hypercycle have always acknowledged the essential function of compartments, particularly in the evaluation of the translation products of the information coded in the templates [13] (see [14] for the *in vitro* realization of this idea). In reply, the advocates of the so-called package models observe that once the replicators are put into compartments, the hypercyclic organization is dispensable [7].

So far practically all package models proposed to investigate template coexistence (see, e.g., [12,15–18]) assume that the vesicles proliferate or divide with a rate that depends on their template compositions. This assumption can be interpreted as a group selection pressure acting at the vesicle level to favor vesicles of a particular makeup. Despite years of intensive research on vesicle dynamics, however, there is no experimental evidence that the vesicle fission rate could depend on the nature of the chemicals confined inside it [19,20]. Hence a more conservative stand is to admit that vesicle fission is triggered by the total concentration of the confined templates rather than by their individual proportions. (Of course, the total template concentration does depend on the existence of the replicase and hence on the presence of all  $d$  template types.) Interestingly, in their seminal work Niesert *et al.* take this cautious position, but to avoid the unbounded growth of the vesicle population, they discard supernumerary vesicles according to an arbitrary prospective value which essentially gauges the odds of a vesicle to leave

viable descendents [11]. Then the resulting model becomes very similar to the group selection models mentioned above.

In this paper we propose and study analytically a variant of the original package model of Niesert *et al.* where the number of vesicles is unbounded and no fitness or prospective values are assigned to the vesicles. In particular, we derive a recursion equation for the average number of vesicles with a given template composition, and a set of equations for the extinction probability of the distinct vesicle types. Our results indicate that an important conclusion of the original work—high values of the replicase processivity compromises the viability of the population in the presence of parasites—is probably an artifact of sampling the vesicles according to a prospective value. In this line, we use finite size scaling to show how a strategy of discarding supernumerary vesicles at random can efficiently recover the analytical results.

## II. MODEL

We follow the original package model proposed by Niesert *et al.* [11] and consider a metapopulation composed of a variable number of vesicles, each of which encloses a certain number of templates. There are  $d$  distinct functional types of templates  $l=1, \dots, d$  and a nonfunctional type  $l=0$ , termed parasite, which has an impaired function but an unchanged replication rate. Due to imperfect replication, functional templates mutate to parasites with probability  $u$ . Back mutations as well as mutations between functional templates are neglected. To be consistent with the conjecture that all templates display identical targets to the replicase since they derive from a common ancestor (most likely were members of the same quasispecies [1]), the replication rate is assumed to be the same for all templates (including the parasite). Here we do not contemplate two additional processes allowed for in the original model, namely, the possibility of mutation to lethal genes or the possibility of accidents. Both actions prompt the immediate demise of the vesicle.

The life cycle (i.e., one generation) of the metapopulation comprises three events—template replication, vesicle fission, and vesicle extinction—that take place in this order. In this contribution we modify the first two events in order to produce an analytical formulation of the metapopulation dynamics. In particular, we assume that the quantity of templates confined in each vesicle before replication is fixed to a certain value  $\Lambda$ . Template replication doubles this number but then fission of the mother vesicle into two daughters of identical size restores it to the original value. Hence  $\Lambda$  can be interpreted as the number of replicated molecules between two vesicle fissions, which is essentially the processivity of the replicase, i.e., the number of template copies the replicase can produce in a unit of time, taken here as the time between two consecutive fissions.

In contrast, in the formulation of Niesert *et al.* [11] the two daughter vesicles can have different sizes  $s=0, \dots, S$  and  $S-s$ , with  $s$  distributed by the binomial distribution  $\binom{S}{s}2^{-S}$  where  $S$  is the size of the mother vesicle after template replication, so that the number of templates can vary among the vesicles. The processivity  $\Lambda$  of the replicase, however, is the

same for all vesicles and so, in the average, the number of templates within each vesicle equals  $\Lambda$ . Thus, essentially, our formulation neglects fluctuations in the number of templates inside the vesicles. As we will show in Sec. V, these variations in the modeling of the vesicle dynamics do not change qualitatively the main results of the model.

In our model, the composition of each vesicle is fully characterized by the vector  $\vec{k}=(k_0, \dots, k_d)$ , where the entries  $k_l$  yield the number of templates of type  $l=0, \dots, d$  in the vesicle and satisfy the constraint  $\sum_{l=0}^d k_l = \Lambda$ . So there are exactly  $\mathcal{N}_T = \binom{\Lambda+d}{\Lambda}$  distinct types of vesicles—the number of compositions of  $\Lambda$  into  $d+1$  parts. To keep track of all vesicle types we use a combinatorial algorithm to generate and label those compositions [21].

The more restrictive assumption of the model is probably the choice of equal replication rates for the distinct types of functional templates as well as for the parasites. The supposition that the parasite and the functional classes have equal replication rates is plausible since a parasite is essentially a functional template whose activity was impaired by a mutation in the region coding for a piece of the replicase. In any event, allowing the parasites to replicate faster or slower than the functional templates has an effect similar to that of increasing or decreasing the mutation probability  $u$ . The choice of different replication rates for the functional templates, however, has drastic consequences in the limit of large  $\Lambda$ , where the intravesicle dynamics becomes deterministic: the more efficient template type drives the other functional templates to extinction, thus preventing coexistence even in the absence of parasites. In fact, in a class of models where the number of vesicles is fixed and very large, there is a limiting value of  $\Lambda$  above which template coexistence is impossible [17,18]. We note, however, that a more realistic scenario would allow the replication rates of the functional templates to vary under the pressure of natural selection. Since only the exact balancing of those rates guarantees coexistence (and so survival) for large  $\Lambda$ , one expects the selection of this ideal symmetric setting. This reasoning supports the assumption of equal replication rates for the functional templates.

### A. Template replication

We assume that the replication of the  $\Lambda$  templates engaged in a vesicle follows a Wright-Fisher process in which the  $\Lambda$  offspring are chosen in parallel [22]. Admitting equal replication rates and unidirectional mutation to the parasite class, the probability that a set of templates  $k_0, \dots, k_d$  produces the set of offspring  $i_0, \dots, i_d$  is given by the multinomial distribution

$$R(i|\vec{k}) = \frac{\Lambda!}{i_0! \dots i_d!} [w_0 + u(1-w_0)]^{i_0} \prod_{l=1}^d [w_l(1-u)]^{i_l}. \quad (1)$$

where  $w_l = k_l/\Lambda$  for  $l=0, \dots, d$  so that  $\sum_{l=0}^d w_l = 1$ . The interpretation of Eq. (1) is straightforward. On the one hand, the probability of producing a functional offspring of type  $l$  is given by the probability of choosing a template of the same type,  $w_l$ , times the probability that the copy produced is faithful,  $1-u$ . Parasites, on the other hand, are produced by

unfaithful copies of functional templates with probability  $u(w_1 + \dots + w_d)$  or by copies of parasites themselves, with probability  $w_0$ . Once the template replication process is completed, we are left with a vesicle of size  $2\Lambda$  and composition  $k_0 + i_0, \dots, k_d + i_d$ . This procedure is repeated for all vesicles in the metapopulation.

In the original model [11] the replication procedure is sequential rather than parallel. For a given vesicle we choose a template at random (from those inside the vesicle) and make a copy of it. If the template is of a functional type then the copy will become a parasite with probability  $u$ . If the chosen template is a parasite then the copy will also be a parasite. Both template and copy (corrupted or not) are returned to the vesicle and the process is repeated  $\Lambda$  times, so exactly  $\Lambda$  new templates are added to the vesicle. This difference in the modeling of the template replication process does not affect the results in any significant way.

### B. Vesicle fission

The doubling of the size of the vesicles caused by the template replication process leads to the splitting of the vesicle in two daughters. Our simplifying assumption here is that the vesicle of size  $2\Lambda$  splits into two vesicles of size  $\Lambda$ . The assignment of the  $\Lambda$  templates to one of the daughter vesicles is modeled by a process of sampling without replacement which is described by a multivariate hypergeometric distribution. Explicitly, given the composition of the mother vesicle after template replication  $\vec{k} + \vec{i}$ , the probability that one of the daughter vesicles has composition  $m_0, \dots, m_d$  is simply

$$F(\vec{m}|\vec{k} + \vec{i}) = \frac{\prod_{l=0}^d \binom{k_l + i_l}{m_l}}{\binom{2\Lambda}{\Lambda}} \quad (2)$$

with  $m_l \leq k_l + i_l$  and  $\sum_{l=0}^d m_l = \Lambda$ . Of course, if one of the daughter vesicles is described by  $\vec{m}$ , then the other will be described by  $\vec{k} + \vec{i} - \vec{m}$ . The random assortment of templates to the daughter vesicles is the only mechanism responsible for the loss of the essential genes for survivorship, a phenomenon termed assortment load. The loss of a functional template occurs when it is assigned to an inviable vesicle, i.e., a vesicle that does not contain the complete set of functional templates.

As mentioned before, in the original model [11] the sizes of the daughter vesicles are binomially distributed random variables and so some vesicles can become very large since what prompts vesicle fission is not its absolute size, but the production of  $\Lambda$  template offspring. This asymmetry in the fission process renders the population more susceptible to the presence of parasites (see Sec. V), but as already mentioned, does not change qualitatively the results of the model.

### C. Vesicle extinction

The viability of a daughter vesicle is guaranteed provided it has at least one copy of each functional template. Any

vesicle lacking one of those templates is dismissed. Strictly, we do not need to assume that the inviable vesicles disappear from the metapopulation, but since the templates caged in those vesicles are unable to replicate—their replicase is not codified for—there is no point to follow their evolution any further. We note that the total number of viable vesicles  $\mathcal{N}_V = \sum_{k_0 \geq 0, k_i \geq 1} \delta(\sum_l^d k_l, \Lambda)$ , where  $\delta(m, n)$  is the Kronecker delta, is simply  $\binom{\Lambda}{d}$ . To the leading order in  $\Lambda$  both quantities  $\mathcal{N}_V$  and  $\mathcal{N}_T$  increase as  $\Lambda^d$  and for large  $\Lambda$  we find  $\mathcal{N}_V/\mathcal{N}_T = 1 - d^2/\Lambda + O(\Lambda^{-2})$ .

### D. Metapopulation dynamics

From the processes described above, it is clear that the size of the metapopulation (i.e., the number of viable vesicles) can, in some cases, increase without bounds. Such unbounded growth renders a direct simulation approach of the vesicle population dynamics unfeasible, except for the few initial generations. To circumvent this difficulty, here we derive a set of recursion equations for the average number of vesicles of type  $\vec{m}$  at generation  $t$ , denoted by  $\Phi_t(\vec{m})$ .

The basic idea is to derive a transition matrix that connects the mother vesicle  $\vec{k}$  with the two daughter vesicles  $\vec{m}_a$  and  $\vec{m}_b$ . From Eq. (2) we can immediately write down the transition probability from the mother vesicle to the first daughter,

$$G_a(\vec{m}_a|\vec{k}) = \sum_{\vec{i}} F(\vec{m}_a|\vec{k} + \vec{i}) R(\vec{i}|\vec{k}). \quad (3)$$

The derivation of the transition probability from  $\vec{k}$  to the second daughter  $\vec{m}_b = \vec{k} + \vec{i} - \vec{m}_a$  is more involved because of the dependence on the intermediate states  $\vec{i}$  which we ultimately want to sum over, as done in Eq. (3). Given that the first daughter has composition  $\vec{m}_a$ , the probability that the second daughter has composition  $\vec{m}_b$  is

$$H(\vec{m}_b|\vec{m}_a) = \frac{F(\vec{m}_a|\vec{m}_b + \vec{m}_a)}{G_a(\vec{m}_a|\vec{k})} R(\vec{m}_b + \vec{m}_a - \vec{k}|\vec{k}) \quad (4)$$

which is obtained by considering only the term  $\vec{i} = \vec{m}_b + \vec{m}_a - \vec{k}$  in Eq. (3) and properly normalizing. Clearly, the joint probability that the daughter vesicles are of types  $\vec{m}_a$  and  $\vec{m}_b$  given that the mother vesicle is of type  $\vec{k}$  is simply

$$P_{ab}(\vec{m}_a, \vec{m}_b|\vec{k}) = H(\vec{m}_b|\vec{m}_a) G_a(\vec{m}_a|\vec{k}), \quad (5)$$

and so the desired transition probability is

$$G_b(\vec{m}_b|\vec{k}) = \sum_{\vec{m}_a} P_{ab}(\vec{m}_a, \vec{m}_b|\vec{k}) = \sum_{\vec{i}} F(\vec{i}|\vec{m}_b + \vec{i}) R(\vec{m}_b + \vec{i} - \vec{k}|\vec{k}), \quad (6)$$

where we have replaced the dummy index  $\vec{m}_a$  by  $\vec{i}$  to facilitate the comparison with Eq. (3). The transition matrices given by Eqs. (3) and (6) allow us to write a recursion equation for the average number of the different types of vesicles in the metapopulation,

$$\Phi_{t+1}(\vec{m}) = \sum_{\vec{k}}' \Phi_t(\vec{k}) [G_a(\vec{m}|\vec{k}) + G_b(\vec{m}|\vec{k})], \quad (7)$$

where the primed sum is over viable vesicles, i.e., vesicles that contain at least one copy of each functional gene,  $k_l > 0$  for  $l > 0$ . This restriction is the expression of the vesicle extinction process.

In principle, the solution of the recursion equations (7) yields detailed information on the time evolution of the metapopulation. But the computational resources needed to generate the entries of the matrices  $G_a$  and  $G_b$  seriously constrain the range of  $\Lambda$  and  $d$  that can be studied in practice. In this contribution we show how this difficulty can be circumvented by considering a finite population of vesicles with the same growth rate per generation as the ideal, unrestricted metapopulation described above. Nevertheless, some interesting information can be obtained from the analytical approach as described in Sec. III.

### E. Extinction probability

To point out the stochastic nature of the underlying vesicle dynamics—the approach based on the recursion equations (7) is deterministic as the focus is on the average number of a given vesicle type—here we describe a general formulation to calculate the extinction probability  $P_e(\vec{k})$  of the lineage sprouted by a vesicle of type  $\vec{k}$ . Generalizing the classic approach to evaluate the extinction probability in the Galton-Watson process [23,24] we can write the following set of equations:

$$P_e(\vec{k}) = \sum_{\vec{m}_a, \vec{m}_b} P_{ab}(\vec{m}_a, \vec{m}_b|\vec{k}) P_e(\vec{m}_a) P_e(\vec{m}_b), \quad (8)$$

with the convention that  $P_e(\vec{m})=1$  if the vesicle of type  $\vec{m}$  is inviable. Note that  $P_e(\vec{k})=1, \forall \vec{k}$  is always a solution. Surprisingly, this system of  $\mathcal{N}_V$  nonlinear coupled equations easily yields to the simple iterative solution method that begins with the guess  $P_e(\vec{k})=0$  for all viable vesicles.

### III. UNRESTRICTED GROWTH

It is clear from Eq. (7) that the asymptotic regime of the dynamics is characterized either by the simultaneous divergence or by the simultaneous vanishing of  $\Phi_\infty(\vec{m})$  for all viable vesicles. The main goal here is to find the values of the control parameters  $\Lambda$ ,  $d$ , and  $u$  that separates these two regimes. In general, this critical parameter setting can be found by direct numerical iteration of the recursion equations.

Let us discuss first the simpler, extreme case  $\Lambda=d$  for which there is only one type of viable vesicle, namely,  $\vec{m}_*=(0, 1, 1, \dots, 1)$ . In this case, Eq. (2) simplifies considerably and allows us to carry out analytically the summations in Eqs. (3) and (6). We find  $G_a(\vec{m}_*|\vec{m}_*)=G_b(\vec{m}_*|\vec{m}_*)=\Omega_d(u)$ , where

$$\Omega_d(u) = \sum_{i=0}^d \binom{d}{i}^2 \frac{i!}{d^i} (1-u)^i \Big/ \binom{2d}{d}, \quad (9)$$

and so  $\Phi_{t+1}(\vec{m}_*)=2\Omega_d(u)\Phi_t(\vec{m}_*)$ . A straightforward numerical evaluation of Eq. (9) for  $u=0$  yields  $\Omega_2(0)=7/12$  and  $\Omega_{d>2}(0)<1/2$ . Since  $\Omega_d$  is a monotonically decreasing function of  $u$ , the latter inequality implies that  $\Omega_{d>2}(u)<1/2$  for nonzero  $u$  as well. This indicates that template coexistence is unattainable for  $\Lambda=d>2$ . For  $\Lambda=d=2$ , however, the picture is different: the average size of the vesicle population will increase exponentially with increasing  $t$  provided  $u<u_c$  where  $u_c=3-2\sqrt{2}$  is the solution of  $\Omega_2(u)=1/2$ . We find this simple analytical result reassuring because it proves that, even for finite vesicle capacities, functional templates can persist in the presence of a steady drain towards the parasite class.

The evaluation of the extinction probability is also straightforward in the case  $\Lambda=d$ . Using Eq. (5) we write the probability that a viable vesicle produces two viable daughters (i.e., vesicles of type  $\vec{m}_*$ ) as

$$p_2 = d! \left( \frac{1}{d} (1-u) \right)^d 2^d \Big/ \binom{2d}{d}. \quad (10)$$

Now, Eq. (9) yields the probability that the first daughter of a viable vesicle is also viable, regardless of the condition of the second daughter, so the probability that a viable vesicle produces a single viable offspring, no matter whether it is the first or the second daughter, is  $p_1=2(\Omega_d-p_2)$ . Hence the probability of producing two inviable daughters is  $p_0=1-p_1-p_2$ . In this case Eq. (8) reduces to the simple quadratic equation  $P_e=p_0+p_1P_e+p_2P_e^2$  with  $P_e=P_e(\vec{m}_*)$ . The two solutions are  $P_e=1$  and  $P_e=(2\Omega_d-1)/p_2$ . The latter is physical provided  $\Omega_d>1/2$  which, as pointed out before, holds only for  $d=2$  and  $u<3-2\sqrt{2}$ .

For  $\Lambda>d$ , we must resort to the numerical iteration of Eq. (7) or to the numerical solution of Eq. (8) to obtain the critical parameter setting that determines the regime of viability of the metapopulation. In the former method, we begin the iteration ( $t=0$ ) with a single parasite-free vesicle, whose composition of functional templates is as balanced as possible, e.g.,  $(0, \Lambda/d, \dots, \Lambda/d)$  in the case of integer  $\Lambda/d$ .

The results for the case of perfect replication accuracy  $u=0$  are summarized in Fig. 1. The critical processivity value  $\Lambda_c$  above which the size of the metapopulation diverges is very well described by the fitting  $\Lambda_c=d^2/2$  as shown in the figure. This indicates that the assortment load can be compensated for if the redundancy  $\Lambda/d$  is larger than half the diversity value, i.e., provided that each vesicle contains at least  $d/2$  copies of each functional template. This simple result shows that there is no fundamental impediment to the coexistence of an arbitrary number of template types in the case of error-free replication if the cost of redundancy is neglected. To understand the scaling  $\Lambda_c \sim d^2$  at the critical boundary in the error-free replication limit we must look at the ratio  $r$  between the number of viable vesicles  $\binom{\Lambda-1}{d-1}$  and the total number of vesicles  $\binom{\Lambda+d-1}{\Lambda}$ , given by

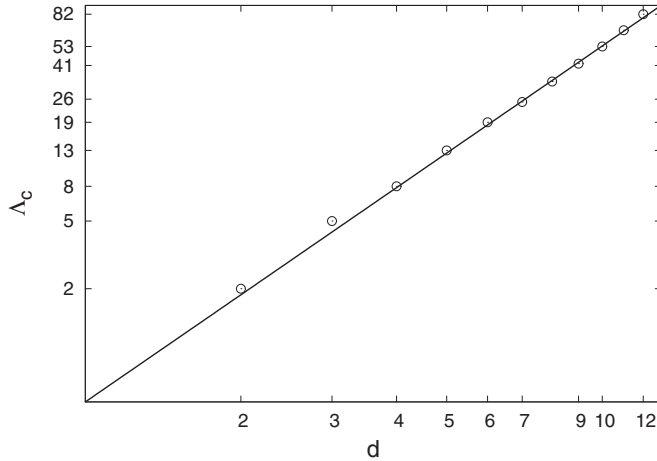


FIG. 1. Logarithmic plot of the value of the processivity  $\Lambda_c$  above which the population size diverges against the number of functional templates  $d$  in the case of error-free replication  $u=0$ . Below  $\Lambda_c$  the extinction of the lineage is certain. The solid line is the fitting  $\Lambda_c=d^2/2$ .

$$r = \prod_{i=1}^{d-1} \frac{1-i/\Lambda}{1+i/\Lambda}. \quad (11)$$

We note that since the parasite class is not taken into account in this error-free replication analysis, the number of viable vesicles as well as the total number of vesicles differ from the quantities  $\mathcal{N}_V$  and  $\mathcal{N}_T$  introduced before. The only way to obtain nontrivial values of this ratio (i.e.,  $r \neq 0, 1$ ) for large  $\Lambda$  and  $d$  is to suppose that  $d^2/\Lambda$  remains of order of 1. In this case we find  $r \sim \exp(-d^2/\Lambda)$  and so  $r_c = e^{-2} \approx 0.135$  at the critical boundary.

We turn now to the analysis of the case where parasites are allowed, i.e.,  $u > 0$ . Figure 2 summarizes the main results, namely, the dependence on  $\Lambda$  and  $d$  of the critical mutation probability  $u_c$  above which the lineage is inviable.

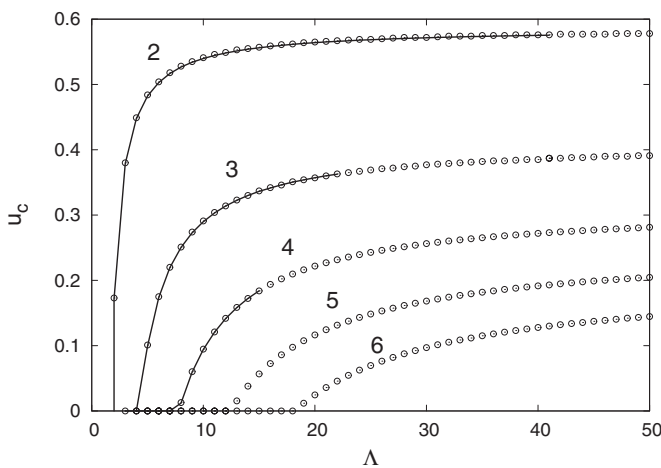


FIG. 2. Mutation probability  $u_c$  above which the metapopulation is inviable as a function of the replicase processivity  $\Lambda$  for template diversity  $d$  as indicated in the figure. The lines are the analytical results for unrestrained growth and the symbols are the results of the finite-size scaling analysis.

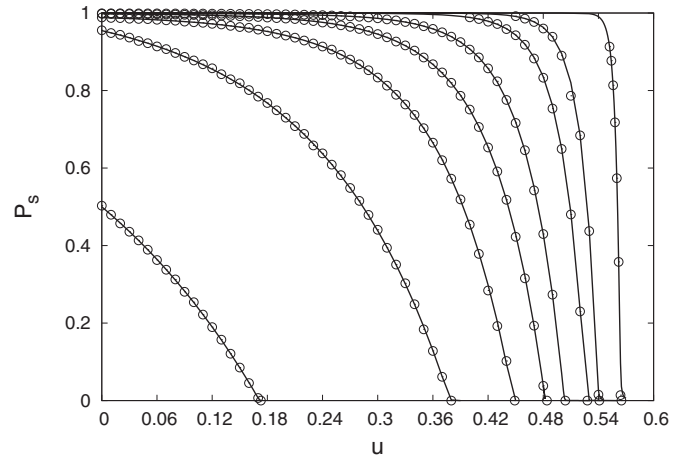


FIG. 3. Survival probability of the lineage produced by a single balanced, parasite-free vesicle as a function of the mutation probability  $u$  for  $d=2$  and (left to right)  $\Lambda=2, 3, 4, 5, 6, 8, 10$ , and  $20$ . The lines are the analytical results for unrestrained growth and the symbols are the results of the finite-population simulations with  $N=10^3$  and  $10^5$  independent samples.

The curves intersect the axis  $u_c=0$  at the values of  $\Lambda$  exhibited in Fig. 1. The remarkable result revealed in Fig. 2 is that, for fixed  $d$ , there exists a value of the mutation probability above which coexistence between the  $d$  functional templates is impossible regardless of the replicase processivity value or, equivalently, the redundancy value. This result follows from the fact that  $u_c$  tends to a well-defined value less than 1 in the limit  $\Lambda \rightarrow \infty$ . This is reminiscent of the error threshold transition of the quasispecies model for which the replication fidelity limits the length of the templates and hence the amount of information that can be stored in the molecular population [1]. Here the limitation is on the number of different types of functional templates that can coexist within a vesicle and so on the total amount of information that can be stored in the vesicle. Another result shown in Fig. 2 is the impracticability of the analytical approach for large  $\mathcal{N}_T$ : the time required to evaluate the matrix entries defined in Eqs. (3) and (6) is simply prohibitive so the curves are truncated at the values of  $\Lambda$  that surpass our computational resources. Fortunately, the analysis of a finite population can greatly extend these limits, as we will show in Sec. IV.

In addition to the threshold values exhibited in the preceding figures, the analytical approach allows us to obtain some detailed information about the composition of the metapopulation and the nature of the stochastic process. In particular, in Fig. 3 we show the survival probability  $P_s = 1 - P_e$  of the lineage sprouted by a balanced, parasite-free vesicle obtained by solving numerically Eq. (8) for  $d=2$ . For  $\Lambda=3$  and  $5$  the ancestor vesicle is  $(0, \frac{\Lambda+1}{d}, \frac{\Lambda-1}{d})$ . Since the template dynamics becomes deterministic in the limit  $\Lambda \rightarrow \infty$ , the survival probability must tend to a step function as indicated in the figure.

Interestingly, we find that regardless of whether the process is subcritical ( $u \geq u_c$ ) or supercritical ( $u < u_c$ ) the fraction  $f$  of functional templates per viable vesicle, and consequently the fraction of parasites, rapidly tends to a steady-state value. This fraction, defined by

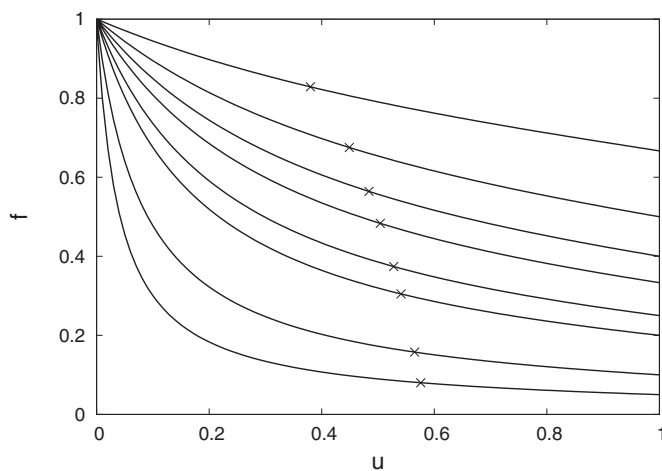


FIG. 4. Fraction of functional templates per viable vesicle in the steady-state regime for  $d=2$  and (top to bottom)  $\Lambda=3, 4, 5, 6, 8, 10, 20$ , and  $40$ . The symbol  $\times$  indicates the value of  $u$  beyond which the population is inviable.

$$f = \lim_{t \rightarrow \infty} \frac{\sum_{\vec{k}} (k_1 + \dots + k_d) \Phi_t(\vec{k})}{\Lambda \sum_{\vec{k}} \Phi_t(\vec{k})}, \quad (12)$$

is shown in Fig. 4 as a function of the mutation probability. For large  $\Lambda$  we find that  $f$  vanishes as  $\Lambda^{-1}$  provided  $u$  is nonzero and, in particular,  $\Lambda f = d = 2$  for  $u = 1$ . So in this limit there is only a finite number of functional templates in each vesicle, whereas the number of parasites grows linearly with  $\Lambda$ . The reason the population is viable (see Fig. 3) even in these circumstances is that the chances for choosing functional templates for replication in some vesicle is not negligible when the number of vesicles is greater than  $\Lambda$ , which is always the case in the supercritical regime after a few generations.

#### IV. FINITE POPULATION

As pointed out before, the impracticability of generating the entries of the matrices that govern the transitions between viable vesicles for large values of  $\Lambda$  and  $d$  limits the applicability of the analytical solution summed up in Eqs. (7) and (8). To get around this obstacle we consider here an alternative approach based on the Monte Carlo simulation of a finite population. In contrast to classical models of populations genetics (e.g., the Wright-Fisher and Moran models [22]) in which the population size is kept fixed, here we allow the number of vesicles to vary from 0 to a fixed maximum value  $N$ . The idea is to implement the dynamics exactly as done in the case of unrestrained growth, except that whenever the number of vesicles becomes greater than  $N$ , the surplus vesicles are discarded randomly. The discard takes place before the check of the viability of the vesicles (extinction process). This scheme is reminiscent of the so-called Russian Roulette used in the Monte Carlo simulation of neutron production in nuclear reactors [25].

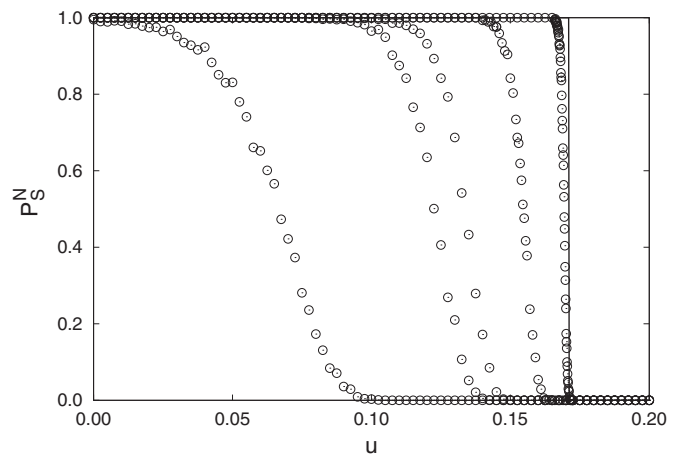


FIG. 5. The survival probability of a population composed initially by  $m=N$  balanced, parasite-free vesicles for  $\Lambda=d=2$  and (left to right)  $N=40, 80, 100, 200$ , and  $1000$ . The solid line is the analytical result for unrestrained growth. Each symbol represents an average over  $10^5$  samples.

In the subcritical regime, the introduction of the upper bound  $N$  is innocuous since the population size is likely to remain small before the extinction outcome anyway. In the supercritical regime, however, a too small bound may prevent the lineage to produce and retain a minimum number of viable vesicles that would avoid extinction and so one expects  $u_c(N) < u_c$ . [An operational definition of  $u_c(N)$  will be given later.] The finite population scheme is effective in the practical situation  $N \ll \mathcal{N}_V$  provided that only a small fraction of the  $\mathcal{N}_V$  viable vesicles would actually be present in the metapopulation if it were allowed to grow unrestrained.

The previous setup for the initial structure of the population—a single balanced, parasite-free vesicle—is not suited to study finite size effects on the estimate of the critical mutation probability, because there is no operational way to define  $u_c(N)$ . For that end an effective strategy is to begin with a population of  $m$  identical such vesicles. Since the vesicles evolve independently there is a simple relationship between the probability that a population with initial size  $m$  thrives, denoted by  $P_s^m$ , and the survival probability of a single vesicle  $P_s$  exhibited in Fig. 3, namely,

$$P_s^m = 1 - (1 - P_s)^m. \quad (13)$$

For  $m \rightarrow \infty$  this quantity tends to a step function that takes on the values 1 if  $u < u_c$  and 0 otherwise. In the finite population simulations we set  $m=N$ , since our focus is on the behavior of  $P_s^m$  when both quantities—the initial size  $m$  and the size upper limit  $N$ —become arbitrarily large. The results for  $P_s^N$  are shown in Fig. 5 for different population sizes  $N$ . As  $N$  increases, the finite-population results approximate those for the unrestrained growth represented by the step function. To quantify this approach, we arbitrarily define  $u_c(N)$  as the value of the mutation probability at which  $P_s^N = 1/2$  so that the critical value  $u_c$  for  $N \rightarrow \infty$  can be inferred as illustrated in Fig. 6.

Use of  $P_s^N$  instead of  $P_s$  is crucial for this analysis, since regardless of the definition of  $u_c(N)$  (e.g., we could define it

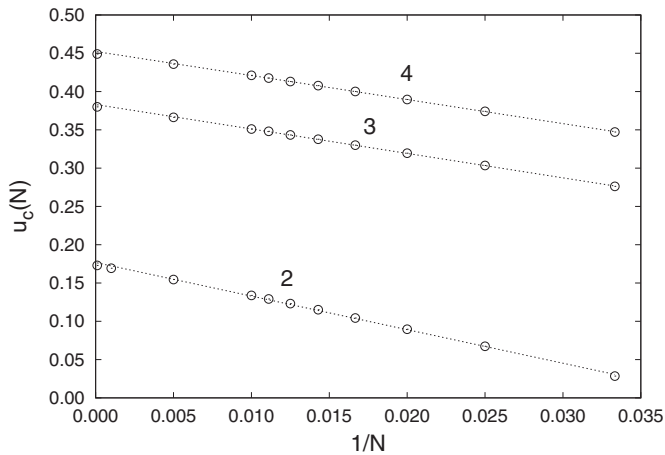


FIG. 6. Mutation probability  $u_c(N)$  at which 50% of the samples of a population of  $N$  balanced, parasite-free vesicles survive for  $d=2$  and  $\Lambda=2, 3$ , and 4. The linear fittings (dashed lines)  $u_c(N) = u_c - a_\Lambda/N$  allow us to estimate  $u_c$ .

as the mutation probability at which  $P_s^N = x$  for any  $0 < x < 1$ ) this quantity tends to  $u_c$  in the limit of  $N$  large. The extrapolated values to  $1/N \rightarrow 0$  are presented in Fig. 2 and agree perfectly with the available analytical predictions. This gives us confidence to use the finite population estimates in the cases where the analytical approach is not practical.

Figure 7 summarizes the results of the data collapsing method (see, e.g., [26,27]) applied to the data of Fig. 5. The survival probabilities  $P_s^N$  collapse into a single universal form (scaling function) if plotted against the scaled mutation probability  $(u - u_c)N$  where  $u_c$  is the critical mutation probability of the infinite population. This scaling function shows that, for  $u - u_c$  fixed,  $\lim_{N \rightarrow \infty} P_s^N$  tends to 1 if  $u < u_c$  and to 0 otherwise, and that the characteristics of the threshold transition persist across a range of  $u$  of order  $1/N$  about  $u_c$ . A similar finite-size scaling analysis was employed to fully characterize the error threshold transition of the quasispecies model in the cases where the population size as well as the molecules lengths are fixed and finite [28].

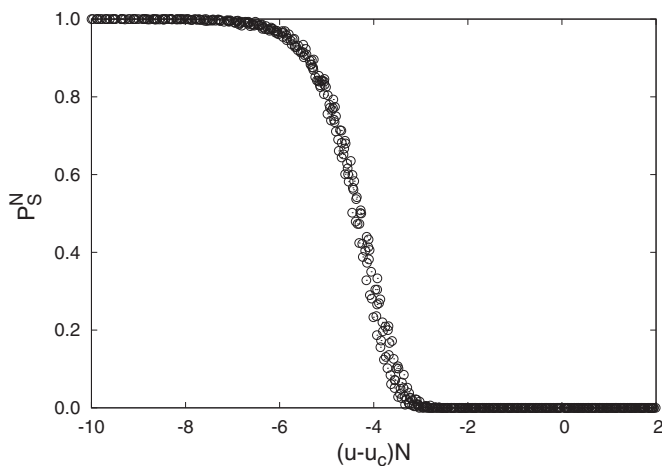


FIG. 7. The data of Fig. 5 ( $d=\Lambda=2$ ) plotted against the scaled mutation probability  $(u - u_c)N$  with  $u_c = 3 - 2\sqrt{2}$ . The collapse of the data into a single  $N$ -independent function signals the occurrence of a threshold phenomenon at  $u_c$ .

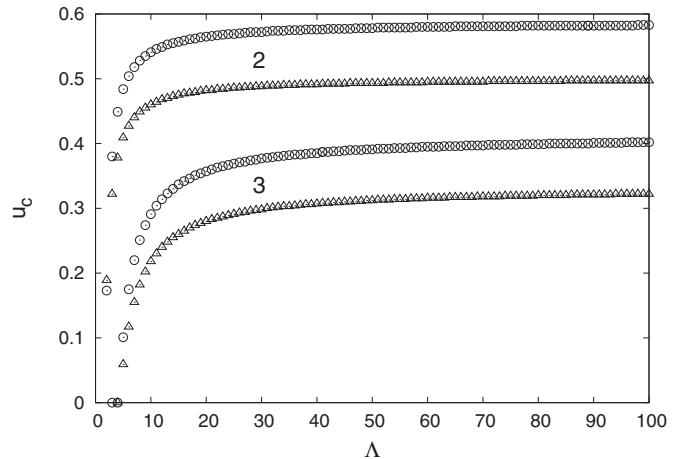


FIG. 8. Critical mutation probability obtained via finite-size scaling for the package model proposed by Niesert *et al.* ( $\Delta$ ) and the variant proposed in this paper ( $\circ$ ) for  $d=2$  and 3 as indicated.

Of course, the finite population scheme can be used to study the original setup in which the initial population comprises a single vesicle,  $m=1$ , as well. In this case the size limit  $N=1000$  suffices to obtain perfect agreement with the analytical results, as shown in Fig. 3.

## V. DISCUSSION

In Sec. II we have outlined the differences between the original package model proposed by Niesert *et al.* and our more tractable variant. Here we present a brief comparison between the main predictions of these models. The first important observation is that in the absence of parasites ( $u=0$ ) both models yield identical results for the viability boundary in the plane  $(d, \Lambda)$  (see Fig. 1). When parasites are present, however, there is a substantial quantitative difference between the critical mutation probability of the two models, as shown in Fig. 8. The scheme based on synchronous template replication and symmetric fission seems to be considerably more robust to the action of parasites than the less structured procedures of the original proposal. This result supports the view that the mechanisms of segregation of modern cells originated in response to mutation pressure [29].

It is hard to see why parasites are more harmful in the asynchronous replication and asymmetric fission setting. Considering that parasites are rare at the beginning, their spread should be hampered by the asynchronous replication scheme in the initial generations and then speeded up when the parasites become numerous. By simulating the two template replication schemes with the same fission mechanism, we have verified that the choice of the form of update—parallel or sequential—practically does not affect the critical mutation probability  $u_c$ . Thus the key element to explain the quantitative differences between the models illustrated in Fig. 8 must be the fission mechanism. To get some insight on that, let us consider the situation where a mother vesicle of size  $2\Lambda$  contains two functional templates of a certain type. Clearly, from the mother vesicle's perspective the optimal

strategy is to send one template to each of her daughters. The probability of this happening for the asymmetric fission strategy is  $1/2$  independently of the vesicle size. The symmetric fission scheme in turn yields a slightly larger probability for this event, namely,  $1/2 \times (1 - 1/2\Lambda)^{-1}$ . This tendency of the symmetric fission strategy to a more balanced distribution of templates of the same type to the daughters is probably the reason for its enhanced robustness against parasites.

Our finding that  $u_c$  is a nondecreasing function of  $\Lambda$  (see Fig. 8) is at variance with the results of Niesert *et al.* which predict that  $u_c$  would reach a maximum and then decrease towards zero as  $\Lambda$  increases further [11]. The reason may be the criterion for discard of supernumerary vesicles used in that work, which was based on three properties: the degree of equipartition of the copies among the different functional templates, the number of parasites and the overall redundancy of the functional templates. In fact, we have verified (see Fig. 4) that for large  $\Lambda$  and not too low  $u$ , the surviving vesicles in the supercritical regime are heavily loaded with parasites and so use of such selection criterion would purge them from the population resulting in a premature extinction.

Although the finite population simulations were used here as a tool to validate and complement the analytical results, they are of interest on their own. In particular, the Muller ratchet [30,31] and the mutational meltdown [32] are important stochastic phenomena that result in the accumulation of mutations in finite populations (see [33] for the study of both phenomena in growing lineages). In our framework, the counterpart of accumulation of mutations is the accumulation of inviable vesicles, which is explicitly ruled out by the assumption that those vesicles are unable to divide into daughter vesicles. This peculiar aspect of the model was severely criticized by Eigen *et al.* [13] who pointed out that the vesicles in the model of Niesert *et al.* [11] cannot evolve because of that assumption. Since there is no competition among the vesicles in the case of unrestricted growth, allowing the inviable vesicles to divide as well would have no effect at all on the dynamics of the viable vesicles because it is not possible to produce a viable vesicle by fissioning an inviable one. In the finite population case, on the other hand, the inviable vesicles would accumulate steadily and ultimately would reach fixation in the metapopulation.

## VI. CONCLUSION

The goal of the research on prebiotic evolution is to put forth a coherent scenario for the origin and early development of life. So at this stage it is appropriate to appraise the main results of our analysis of this classic package model, summarized in Fig. 2. Given the spontaneous error rate per nucleotide  $\epsilon$  and the molecule length  $L \gg 1$  we can readily obtain the value of the probability of mutation from functional templates to parasites,  $u = 1 - \exp(-\epsilon L)$ . A plausible estimate for these primary parameters is  $\epsilon \sim 10^{-2}$  and  $L \sim 100$  [1] which yields  $u \sim 0.6$ . A glance at Fig. 2 leads to the disastrous conclusion that even the coexistence between two templates is prohibited in these circumstances. It is instructive also to compare our results with those of the hypercycle which guarantees the stable coexistence of at most  $d=4$  templates [4] (see [34] for the analysis of the hypercycle in the presence of an error tail class similar to the parasite class considered here). According to Fig. 2,  $d=4$  functional templates can coexist provided that  $u < 0.3$  which implies that  $L < 35$ , resulting in a total of 140 nucleotides, a meager improvement over the 100 nucleotides prediction for a free replicator.

It should be observed, in addition, that the critical mutation probabilities  $u_c$  exhibited in Figs. 2 and 8 are best case results since neither lethal mutations nor accidents were considered in our calculations. Hence, contrary to the claims of Niesert *et al.* [11], the kind of template coexistence achieved in a simple package model does not resolve the prebiotic information crisis. Special mechanisms to prevent independent information carriers from competing with one another within the compartment must be posited. Although unwarranted assumptions like the hypercyclic organization [4] or the coupling between the templates and the package metabolism [15–18] may weaken the credibility of the models, so far they seem to stand as the only options to tackle the information crisis of prebiotic evolution.

## ACKNOWLEDGMENTS

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