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Reply to comments

Reply to the commentaries on "Evolutionary dynamics of RNA-like replicator systems: A bioinformatic approach to the origin of life"

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1. Introduction

Our paper [1] reviews computational studies on prebiotic evolution. In particular, it seeks to address how a system of simple RNA-like replicators increases its complexity through evolution. Some of the commentaries mention the topics that are not covered in our review. For the reader's convenience, we list these topics as follows:

- Di Mauro [2] mentioned the energetic and geochemical studies on the origin of life [3,4]. These studies deal with a crucial aspect of life's origin, namely, the source of energy required to drive primordial biochemical reactions.
- Peliti [5] mentioned the dichotomy between the metabolism-first and replicator-first scenarios for the origin of life [6] or, as he reformulated it, the dichotomy between analog information and digital information (or attractor-based inheritance and storage-based inheritance [7]). This dichotomy continues to be a focus of intense debate [8–11].
- Manrubia [12] mentioned theoretical studies on the origin of RNA replicators in the RNA world [13–15].
- Lehman [16] mentioned the importance of recombination for the evolution of RNA replicators [17–19]. Although not described in our review, the effect of recombination has been investigated in the quasi-species theory (see Ref. [20], for a pioneering study; see Refs. [21,22], for recent studies) and in a model of protocells [23]. It was also investigated, albeit cursorily, in the model incorporating the genotype–phenotype-interaction map of replicators (see Ref. [24], Authors' response to Reviewer's report 2).

In what follows, we give a point-by-point response to the comments that are directly concerned with the studies reviewed in our paper. Our response is divided into sections corresponding to those of our review.

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2. Replicators without interactions

2.1. Quasi-species theory for finite populations

Hu questioned whether the quasi-species theory remains valid if it assumes a finite population to incorporate stochasticity [25]. The answer is "yes" as described below.

First, the quasi-species theory says that evolution operates not on individual genotypes, but on genotype neighborhoods (see our review, Section 3.2 "Quasi-species theory"). A corollary of this statement is the possibility of neutral evolution of mutational robustness. Although we did not emphasize it, this possibility has been actually demonstrated by the model assuming a finite population (see, e.g., our review, Section 4.1 "RNA folding genotype–phenotype map"). Therefore, the neutral evolution of mutational robustness does not require an infinite population. It, however, does require that an evolving population contain sufficiently great genetic heterogeneity (see Ref. [26], for details).

Second, the amount of information that can be maintained by evolution in non-interacting replicators is limited by erroneous replication. This statement, too, remains valid even if the quasi-species theory incorporates stochasticity; in fact, stochasticity decreases the maintainable amount of information [27–29]. This result makes intuitive sense because the population size of the fittest genotype becomes vanishingly small as the mutation rate increases to the error threshold (see, e.g., Ref. [1, Fig. 2]).

Hu also asked whether population genetics and the quasi-species theory are compatible with each other [25]. This issue has been dealt with in the paper by Wilke [30] (Wilke's paper, however, contains an erroneous conclusion based on a study of Wagner and Krall [31], which investigates the model described by Eq. (9) of our review; see Ref. [32], for more details).

2.2. Product inhibition

Schuster pointed out the problem of over-simplifying chemical reactions, which potentially leads to unrealistic conclusions ("paper chemistry" as he called it) [33]. As an example, he discussed the enzyme-free replication reaction of nucleic acid molecules. This reaction is commonly assumed to be a one-step process as in the quasi-species equation; namely, $\mathrm{X}+\mathrm{R}\rightarrow 2\mathrm{X}$ where X denotes a replicator, and R denotes the resource for replication. Under this assumption, a replicator population undergoes exponential growth. However, in reality, he argued, such reaction entails the production of stable duplexes; consequently, a replicator population displays parabolic growth, and Darwinian selection does not occur, as opposed to what the quasi-species equation indicates.

Below, we briefly review how duplex formation can lead to the (partial) failure of Darwinian selection [34–41]. The following equation has been suggested as a model describing the population dynamics of replicators whose growth is parabolic (see Ref. [36] and the references therein)

$$\dot{x}_i = A_i x_i^p - \phi x_i \tag{1}$$

where $p = 1/2$ and $\phi = \sum_i A_i x_i^p$. In general, if $p < 1$, the growth of replicators is sub-exponential (if $p = 1$, the equation is identical to the quasi-species equation with mutations ignored). Eq. (1) assumes that the replication rate per individual of replicators approaches infinity as their concentration approaches zero; that is, $A_i x_i^p / x_i \rightarrow \infty$ as $x_i \rightarrow 0$. Under this assumption, no replicators can go extinct [36], hence the "survival of everybody" [37]. Thus, Eq. (1) indicates the absence of Darwinian selection, which, however, is due to the unrealistic assumption mentioned above.

Next, let us explicitly take account of duplex formation during replication (instead of directly assuming parabolic growth). To this end, we assume the following replication reaction [39]:

$$X + R \xrightarrow{\kappa} D \underset{k}{\overset{k'}{\rightleftharpoons}} 2X$$

where X denotes a replicator; R, the resource for replication; and D, a duplex, which consists of two molecules of X. D is assumed to be unable to replicate. Thus, the above reaction involves a negative feedback loop, which can be referred to as product inhibition. The population dynamics of X and D can be described as follows (assuming a continuous population and well-mixed system) [39,40]:

$$\dot{X} = -\kappa R X - 2kX^2 + 2k'D - d_X X \tag{2}$$

$$\dot{D} = \kappa R X + kX^2 - k'D - d_D D \tag{3}$$

where d_X and d_D denote the decay rate of X and D, respectively. (In what follows, we assume that R approaches zero as X or D increases; the exact form of R, however, need not be specified.) Assuming that $\dot{D} = 0$ in Eq. (3) (the quasi-steady state assumption), we obtain $D = (\kappa RX + kX^2)/(k' + d_D)$. Substituting this into Eq. (2), we obtain

$$\dot{X} = \kappa R(2K - 1)X - 2k(1 - K)X^2 - d_X X$$

where $K = 1/(1 + d_D/k')$. This equation can be extended to incorporate the competition between different genotypes. Assuming that interactions between different genotypes occur only through the competition for the resource R, we get

$$\dot{X}_i = \kappa_i R(2K - 1)X_i - 2k(1 - K)X_i^2 - d_X X_i \tag{4}$$

where the subscript i denotes a genotype (for simplicity, we assumed that k, d_X, and K are independent of i). The first term on the right-hand side of Eq. (4) represents the growth of X_i due to replication ($K > 1/2$ is required for X_i to grow at all). The second term, which is always negative (since $K < 1$ by definition), represents the effect of product inhibition. This term is mathematically identical to a within-species competition term in the competitive Lotka–Volterra equations. In the Lotka–Volterra equations, if within-species competition is sufficiently strong, multiple species can stably coexist with each other [42]. Likewise, in Eq. (4), if the product inhibition is sufficiently strong (i.e., $k(1 - K)$ is sufficiently large), multiple species of replicators can stably coexist with each other even if they replicate at different rates (κ_i) [40]. This coexistence, however, does not mean the survival of everybody, as it depends on the parameter conditions [40]. For example, differences in replication rates cannot be arbitrary large for the coexistence to occur (with all other things held constant). Thus, Darwinian selection can still operate.

Finally, we add that the coexistence described above differs from that described in Sections 4–8 of our review, in that it does not involve any differentiation between replicators in terms of their ecological or catalytic functions.

3. Replicators with genotypes and phenotypes

Scheuring wrote, "Kun et al. showed that most genotype-level mutations are buffered by phenotypes" [43]. This seems to be a common way to interpret Kun et al.'s study [44] (e.g., Refs. [45,46]). This interpretation, however, misses the primary reason why Kun et al. obtained a profound relaxation in the limitation to the amount of information that can be maintained by evolution. Kun et al. used the following condition to obtain the maximum length $L_{\max}$ of sequence patterns that can be maintained by evolution: $L < \ln s / \ln(q + \lambda - q\lambda)$ where L denotes the sequence length; s, the selective advantage of the fittest phenotype class as compared with mutants; $1 - q$, the mutation rate per nucleotide (only base substitutions are considered); and λ, the probability of a base substitution being neutral [47] (this condition is approximately identical to Condition (11) in our review, where L and s are denoted by ν and σ, respectively). Kun et al. estimated that $\lambda \approx 0.26$ and $s \approx 318$ (see below). Eigen's original study [48], as well as many subsequent studies, assumed that $\lambda = 0$ and $s \approx 10$. An increase of λ from 0 to 0.26 amounts to 35% increase in $L_{\max}$; by contrast, an increase of s from 10 to 318 amounts to 150% increase in $L_{\max}$. Therefore, the relaxation suggested by Kun et al. is much more due to the increased selection pressure (i.e., an increase in s) than due to the buffering effect of phenotypes (i.e., an increase in λ).

To estimate s and λ, Kun et al. assumed that the fitness landscape of RNA replicators is approximated by the catalytic landscape of a ribozyme [44]. That is, the replication rates of RNA molecules are approximated by the catalytic activity (e.g., k_{cat}) of a specific type of ribozyme such as the Neurospora VS ribozyme. In Kun et al.'s study, however, RNA replicators are conceived of as RNA molecules capable of self-replication without any help of trans-acting enzymes or ribozymes. Given the functional difference between such self-replicating RNA molecules and a ribozyme, it is unclear to what extent the approximation is precise.

4. Replicators with interactions

Scheuring questioned the robustness of the surface model [43]. In particular, he suggested the possibility that catalysts cannot coexist with parasites if parasites have a greater diffusion rate than that of catalysts. By contrast, the compartment model, he argued, is robust because the coexistence in this model is independent of assumptions regarding the chemical details. In particular, the coexistence does not require the assumption that parasites function as catalysts to promote the growth of compartments [49]. This statement holds even if the evolution of parasites is incorporated into the model [50].

As Scheuring suggested [43], it is possible that parasites having a high diffusion rate destabilize traveling waves and so disable the coexistence between catalysts and parasites. Can a replicator system survive if parasites evolve their diffusion rates (e.g., by changing their molecular sizes)? Although this is an open question, a similar question has already been asked, namely, whether the system can survive if parasites evolve their replication speeds [50] (see also our review, Section 5.3.3 "Evolution at the level of traveling waves"). The answer to the latter question is as follows: The system can survive even if parasites evolve because parasites having high replication speeds cannot survive owing to the selection at the level of traveling waves. A similar situation might arise if parasites can evolve their diffusion rates (viz., parasites having high diffusion rates might not be able to survive because they destabilize the traveling waves that contain them).

Scheuring argued that the compartment model is more robust than the surface model in terms of the coexistence between catalysts and parasites [43]. However, the possibility of this coexistence actually depends on the parameters in both models [50]. In the surface model, catalysts cannot coexist with evolving parasites if the diffusion rate is sufficiently high [50, Fig. 12 and Supporting Information Text S1]. In the compartment model, catalysts cannot coexist with evolving parasites if the population size of replicators within each compartment is sufficiently large [50, Fig. 12]. Therefore, in both models, the efficacy of multilevel selection is parameter dependent. This fact does not indicate that the compartment model is more robust than the surface model.

One can further ask whether one model has a more realistic parameter region in which the multilevel selection is effective than that of the other model (e.g., see Ref. [50, Discussion section]). This is an open question and remains so even if the possibility discussed by Scheuring turns out to be real. For we must also take into account the fact that the compartment model, too, makes several important simplifications; for example, it takes for granted the entire process of compartment growth and division, the process that is likely to influence the population size of replicators within each compartment. We, therefore, think it is premature, if not impossible, at this moment to conclude which model is more robust than the other.

5. Replicators with genotypes, phenotypes, and interactions

Higgs wrote, "we should be studying models of replicators with more general possibilities for interactions and asking which kinds of interacting networks are likely to emerge, rather than starting with the assumption of a hypercycle" [51]. We agree with his suggestion. In fact, this was our motivation to study the model incorporating the genotype–phenotype-interaction map of replicators [24] (see also our review, Section 6 "Replicators with genotype, phenotype, and interactions").

6. Replicators with compartmentalization

Higgs wrote, "the fitness of an individual depends on its own properties and not on the properties of other individuals" in population genetics; a protocell is an individual in this sense, but RNA replicators are not, so "the origin of compartments really marks the origin of individuals and hence the origin of 'biology' " [51]. However, the absence of interactions between individuals (except competition) is a theoretical simplification, rather than biological realism, assumed in classical population genetics. In fact, any organisms interact with other organisms, and these interactions are often crucial to the reproductive success of organisms. In this sense, interacting RNA-like replicators (including traveling waves) display an important characteristic of biological systems that, however, is absent in protocells that are assumed not to interact with each other.

7. Replicators with DNA-like function

Peliti [5] wrote that the mechanism for the evolution of DNA-like molecules suggested by Takeuchi et al. [52] is essentially the same as that for the evolution of chromosomal linkage suggested by Maynard Smith and Szathmáry [53]. This view is incorrect for the two reasons described below.

First, the mechanism for the evolution of DNA-like molecules suggested by Takeuchi et al. is based on the division of labor between template and catalyst. The model of Maynard Smith and Szathmáry, however, does not distinguish between template and catalyst and so does not allow such division of labor.

Second, the mechanism for the evolution of chromosomal linkage suggested by Maynard Smith and Szathmáry is based on selection pressure to reduce assortment load, that is, the loss of beneficial genes during the division of protocells. Can this selection pressure also explain the evolution of DNA-like molecules observed in Takeuchi et al.'s model? The answer is "no". The replication cycle based solely on RNA molecules requires only one type of molecules to complete the cycle, namely, RNA molecules functioning as RNA polymerase (Rp^{RNA}, for short). By contrast, a replication cycle including DNA-like molecules requires four types (viz., Rp^{RNA}, Rp^{DNA}, Dp^{RNA}, and Dp^{DNA}; for the notation, see Ref. [52] or our review, Section 8 "Replicators with DNA-like function"). Requiring a greater number of distinct types of molecules, the cycle including DNA-like molecules causes greater assortment load than the cycle based only on RNA molecules. Therefore, selection pressure to reduce assortment load actually hinders the evolution of DNA-like molecules (nevertheless, DNA-like molecules can evolve because the disadvantage due to assortment load can be more than compensated by the advantage due to the division of labor between template and catalyst; see Ref. [52], for details).

For these reasons, the mechanism for the evolution of DNA-like molecules suggested by Takeuchi et al. differs from that for the evolution of chromosomal linkage suggested by Maynard Smith and Szathmáry. That being said, there is a close connection between the two studies. Namely, the assortment load aggravated by the evolution of DNA-like molecules might lead to—and could be reduced by—the evolution of chromosomal linkage [53] (see also Ref. [54]).

8. Conclusion

We thank the commentators for their remarks, which put our review in a broader context of prebiotic evolution and enabled us to clarify a number of points.

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