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Comment

How universal is Darwin's principle?

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Charles Darwin derived his principle of natural selection form observations he made in Britain and on his voyage as naturalist on board of HMS Beagle. All his conclusions were derived from studies on higher organisms, animals and plants [1], and yet the principle applies equally well to unicellular organisms, protists, eubacteria and archaebacteria. Even the evolution of viruses, viroids, and molecules in the test-tube is perfectly described by Darwin's ideas. Moreover, competing computer programs [2] and other objects outside biology follow the rules of natural selection. The Darwinian mechanism sets in whenever biomolecules, cells, organisms, societies, computer devices or other entities capable of reproduction are on the stage and compete for resources. Why is Darwin's approach almost universal? The answer is simple: Neither details of reproduction nor the nature of the multiplying entities matter in the contest. The only property that counts is the number of progeny in future generations and the genius Charles Darwin recognized this fact through making an enormous abstraction from the wealth of details in the adaptations of species he saw in nature.

Extrapolations of Darwin's principle to pre-cellular life were made ever since the nineteen sixties when the idea of a world of biomolecules optimizing the rate of reproduction in the sense of Darwin was born. Sol Spiegelman's experiments with RNA molecules [3] and Manfred Eigen's kinetic theory of evolution [4] provided evidence that adaptation and evolution do not require cellular life. Tom Cech and Sidney Altman discovered that RNA molecules are not only information carriers but can also act as highly specific catalysts [5,6]. Walter Gilbert's and others postulated the existence of an RNA-world [7], which has preceded the DNA-RNA-protein world we are familiar with. The central idea, in essence, is that RNA molecules are acting as both, information carriers and catalysts, and constitute thereby a sufficiently rich repertoire of functions for evolution. The experimental support for the idea of an RNA-world becomes stronger and stronger, however, a few problems on the way from chemistry towards the origin of life remain still unsolved, among them: (i) how came the first RNA or RNA-like molecules into existence, and (ii) how did the first general replicating enzyme on RNA-basis arise that was able to amplify arbitrary RNA sequences. In the spirit of Leslie Orgel this means if in a chain of events a single one is implausible the entire chain is implausible [8,9]. Although there is an ample body of knowledge on processes that might have been relevant for the origin of life on Earth, we do not know yet whether there has been an RNA-world as a precursor of conventional biological evolution but, nevertheless, it remains an exciting hypothesis and RNA based scenarios are definitely worth being studied by experiment, theory, and computer simulation.

Nobuto Takeuchi and Paulien Hogeweg [10] present a comprehensive review on mathematical and computational approaches to early replication and focus on the aspects of creation and processing information under origin of life

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conditions. Computational studies have enormous advantages as well as serious drawbacks. The main advantage is the enormous flexibility in adapting to problems: Reduction to the essential features and abstraction form the unnecessary and obscuring details are straightforward. There is no time scale problem, since simulations covering processes taking place in thousands or millions of years can be performed easily. The review studies also systems that are based on reproduction but don't lead to Darwinian behavior [11]. Hypercycles [12], symbiosis, and "arms races" in host-parasite systems may serve as examples. The role of space is well appreciated in biology but Takeuchi and Hogeweg demonstrate and discuss the importance of spatial separation already in prebiotic chemistry.

The main disadvantage of the computational approach concerns a general problem of "paper chemistry": It is commonly easy to write down a simplified mechanism but to find out whether or not it is relevant in reality is the hard part. Two examples should serve as illustrations. The first example, independent replication of nucleic acid molecules is the basis of cell-free selection by means of Darwin's mechanism. It is commonly described by an autocatalytic one-step process $A + X = 2X$, or by two-step plus-minus replication $A_- + X_+ = X_- + X_+$ and $A_+ + X_- = X_+ + X_-$ where X_+ and X_- are two complementary strands, and A, A_+, and A_- represent the materials consumed in template induced synthesis. In reality, however, the enzyme-free process is complicated by the formation of a stable $X_+\ X_-$ duplex, the growth function is parabolic rather than exponential, and no selection occurs [13,14]. In the enzyme catalyzed replication exponential growth and Darwinian selection are restricted to the concentration regime where the enzyme is in excess of RNA template molecules [15]. The second example is dealing with enzyme-free autocatalytic metabolic cycles which are often addressed as candidates for prebiotic metabolism. Several such cycles, for example the reverse citric acid cycle, have been proposed but none of them was found to work in reality. Leslie Orgel pointed at the problems that are not apparent when drawing formulas on paper: An uncatalyzed reaction produces many byproducts at each step, and after ten or more steps the output of the cycle becomes negligible, whereas specific enzymes in present day biochemistry raise the yield to almost 100% [16].

The Darwinian mechanism is almost universal and has shaped pre-cellular as well as cellular evolution but a close look on mechanistic details shows the limitations of natural selection consisting of the requirement of suitable internal and external circumstances. Evolution as it seems is driving systems towards the proper conditions in order to enable the operation of the unbeatable power of optimization and adaptation in nature.

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Comment

How robust are the models of the origin of life? Commentary on "Evolutionary dynamics of RNA-like replicator systems: A bioinformatic approach to the origin of life"

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How information is integrated and how functional complexity evolves in systems of RNA-like replicators is one of the key origin-of-life questions [1]. Takeuchi and Hogeweg [2] provide a well-structured, easy-to-follow review of this problem. After a short but correct introduction, they survey their recent work in this field along an articulate logical line. Focus and clarity are strong merits of this paper, but I think this is also a small weakness; readers of reviews wish to see alternative ideas and debatable points.

So in this comment I should like to mention a delicate problem in the field, the problem of robustness. This problem is underrepresented in most papers (including this one), although I think poses a crucial challenge. There is a general question in biology regarding how evolution acts on systems and what the evolutionary stable states are (if any) in different circumstances. More specifically, the evolutionary trajectory of any given biological phenomenon depends sensitively on the evolutionary units [1] involved and on the kind(s) of variants that can emerge by mutation. That is, how do units replicate and interact with each other, and what is the degree of heritability in the studied system? (In physical systems, by contrast, such questions can typically be ignored.) Moreover, evolving systems are inherently nonlinear because self-replication and interactions among environment and replicators. As a result, structural robustness, which I define as qualitative behaviors that remain unchanged despite modification (perturbation) of a system's structure, seems to be an exception in evolutionary dynamics, not a typical behavior. Despite this, the structural robustness of models is rarely characterized.

To be more specific: Takeuchi and Hogeweg [2] studied the dynamics of different replicator-parasite systems, naturally in well-defined models. According to their assumptions, parasites are templates, while replicators are replicases and templates at the same time. Thus, parasites replicate faster, but they need replicase for replication. In other respects, these molecules are identical, including, for example, the diffusion rates of the molecules. However, if smaller or bigger macromolecules can emerge by mutation (and naturally they do), then diffusion rates can easily diverge. Further, it is reasonable to assume that smaller parasites reproduce and diffuse faster than longer replicate. The coexistence of parasites and replicators in the wave front is therefore rendered vulnerable to their relative diffusion rates, and the emergence of smaller and more mobile parasites probably demolishes stable coexistence. As another example, to keep models tractable, side reactions and spontaneous sequence elongations are generally ignored. However, such

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processes probably make nonenzymatic replication impossible [3]. This is a deep and again a generally neglected challenge.

In Section 7, where the evolution of compartmentalized replicators is studied, Takeuchi and Hogeweg introduce a very specific parasite that replicates by using the replicase function of "altruist" molecules (a clear parasitism), but parasites in folded state increase the volume of the compartment. Since compartments divide if their volume is above a critical size, and thus increased production of parasites and/or an increased fraction of parasites being in folded state increases the replication rate of, and thus the fitness of, compartments. In this way, parasites can be argued to play a key positive role in the function of compartments; parasites take part in membranogenesis, for example. Alternative and perhaps more realistic chemical scenarios are possible [4] in which parasites can be pure selfish molecules. The important point here is that multilevel selection can maintain units in which molecular coordination and cooperation are selected for via the long-term replication success of these units, and thus, multilevel selection can suppress the evolution of parasites [1]. So in contrast to the previous examples, we (theorists) have good news now, since the qualitative behavior of compartments can robustly resist the effects of changes in assumptions regarding complicated and generally unknowable chemical details.

Some minor comments at the end. I liked Section 6 most, since this study of mapping genotype and phenotype in the RNA world and showing the evolution of complex RNA-ecology on a surface is really a pathbreaking work. The authors might like to know about a meta-analysis, where by studying different ribozymes, Kun et al. [5] showed that most genotype-level mutations are buffered by phenotypes, which nicely reinforces Takeuchi and Hogeweg's study. The last point is connected again with the work on spatial RNA-ecology. The described ecosystem evolution is an "escape–radiation" process originally proposed by Ehrlich and Raven [6] for explaining the coevolution of plants and herbivores. Although it turns out that in the original case of plants and herbivores, this type of coevolution does not appear to be an adequate explanation of cladogenesis, escape and radiation could explain host-parasite coordinated gene evolution if parasites put strong-enough selection pressure on hosts. In the studied replicating RNA system, parasites are the only selection pressure, and as a consequence we observe a nice "escape–radiation" process.

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Comment

Survival of the fittest or the flattest? Commentary on "Evolutionary dynamics of RNA-like replicator systems: A bioinformatic approach to the origin of life" by Nobuto Takeuchi and Paulien Hogeweg

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In this thought-provoking review [1], Takeuchi and Hogeweg have thoroughly reviewed important models on evolutionary dynamics of RNA-like replicator systems. Their paper has been largely devoted to the quasispecies theory and has focused on such questions as how information could be acquired and maintained by those replicators. A quasispecies is an ensemble of related genotypes arising from a highly mutagenic environment. Different from classical population genetics, quasispecies theory describes the evolution of an infinite population of asexual replicators. The theory was initially formulated by Eigen in 1971 to understand the "RNA world hypothesis" [2] and has recently been applied to explain RNA virus (e.g., HIV) evolution [3]. In this commentary, I attempt to supplement the target review [1] by promoting discussions on the differences and connections between quasispecies theory and population genetics.

Darwinian theory states that organisms with higher fitness will outcompete those with lower fitness in the race of evolution. Higher fitness usually means faster replication, which, given a high mutation rate, may be more prone to deleterious mutations. If mutants closely related to the fittest genotype have very low fitness, the fittest one may even disappear in the selection-mutation process. Selection, in this case, will favor those more slowly replicating mutants which belong to a group with yet a higher average fitness. In other words, mutational robustness matters more than individual fitness. This is the key insight of quasispecies theory and is dubbed "survival of the flattest" [4] to distinguish from the Darwinian dogma.

One characteristic of quasispecies theory is that the frequency of any mutant depends on not only its own replication rate but also the probability that it will arise from erroneous replication of other mutants in the population [2]. Such mutational coupling links individual mutants together so that the entire population evolves as a single "species". This

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contrasts with population genetics which directs selection toward individual variants. Thus it seems that quasispecies theory is at odds with population genetics. Is it possible to reconcile these two competing theories? For example, can we view one theory as a special case of the other? Or, are they just two sides of the same coin? Another feature of quasispecies theory is its assumption of infinite populations and deterministic description [2]. For comparison, most population genetics models deal with finite populations and incorporate stochastic effects. A hallmark of population genetics is genetic drift – the change in allele frequencies driven by random sampling. This drift is purely random and can be beneficial, neutral, or detrimental. The law of large numbers indicates little importance of genetic drift in large populations, but when the population is small or the allele frequency is low, genetic drift is expected to be significant. Remarkably, in quasispecies theory, it is the absence of genetic drift that allows for mutational coupling and hence group selection. This caveat raises the next question: Is quasispecies theory applicable to finite populations? Although there has been both theoretical and experimental progress in the past few decades, its applicability is still under vigorous debate [5]. Some scholars hold that we still lack unequivocal evidence to claim that real organisms such as RNA virus indeed form quasispecies [5].

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Comment

Comment on "Evolutionary dynamics of RNA-like replicator systems: A bioinformatic approach to the origin of life" by Nobuto Takeuchi and Paulien Hogeweg

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As emphasized, e.g., by Dyson [1] one can envisage life processes from two points of view: the *metabolic* processes, in which a cascade of free-energy dissipating physico-chemical reactions maintain the living system out of thermodynamical equilibrium, and the *information* process, whose eventual effect is to allow the living form to produce offspring similar to itself – and to incorporate information about the environment by the mechanism of natural selection. Thus explaining the origin of life poses a two-pronged question: the origin of metabolism, and the origin of biological information. "Either life began only once, with the functions of replication and metabolism already present in rudimentary form and linked together from the beginning, or life began twice, with two separate kinds of creatures, one kind capable of metabolism without exact replication and the other kind capable of replication without metabolism" [1]. However, while "metabolism without exact replication" is already a form of information processing, "replication without metabolism" is highly unlikely to take place, since replication itself cannot take place except far from equilibrium, and to keep a system out of equilibrium some form of metabolic process should take place. I think that this dilemma is ill-placed: the essential difference lies between a mainly analogical and a mainly digital form of information processing. In the present life forms, information is essentially processed in a digital form represented by the nucleotide sequences in the form's DNA. But one can imagine a kind of prebiotic system similar to Oparin's coacervates [2] or to Luisi's liposomes [3], which are able to (inaccurately) reproduce, carrying information to their offspring via their composition, i.e., in analogic language.

Takeuchi and Hogeweg [4] start by assuming the existence of a digital reproduction mechanism, in the form of a collection of self-replicating RNA molecules. However, the system is not able to stabilize its information-processing properties without exploiting some form of localization or compartmentation, allowing for the stable coexistence of template and actuator molecules. The need for spatial structure and some form of compartmentation mechanism to avoid the dire consequences of the error threshold was emphasized long ago by Michod [5]. Then the "analogic" information is inscribed in the relative local fraction of template and actuator molecules. Takeuchi and Hogeweg elegantly show that spiral reaction waves can provide some of the necessary localization mechanisms, even in the absence of strict compartmentation. The appearance of active compartmentation adds of course stability to the mechanism. (See, e.g., the mechanisms for the maintenance of producer–nonproducer coexistence in a synthetic biological system reported in [6].) They show moreover that the transition from an RNA-based system to a dual DNA- and RNA-based

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system, where DNA acts essentially as a template and RNA mainly as an actuator, can take place essentially by the same mechanism suggested by Maynard Smith and Sazthmáryi [7] for the origin of chromosomes via the evolutionary advantage of linking, closing the circle to a digital form of information again.

It is no secret that the basic weakness of the RNA-world scenario lies in the plausibility of fully abiotic synthesis of self-replicating RNA molecules. I wonder if the hierarchical scenario so interestingly put forward by Takeuchi and Hogeweg could not work at a deeper level, also to solve this problem. This review gives food for thought.

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Comment

Comments on "Evolutionary dynamics of RNA-like replicator systems"

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This review [6] is a large scale study of replicating molecular systems based on the excellent PhD thesis of Nobuto Takeuchi. It provides a very good review of important issues as well as presenting a lot of original research. It is difficult to do it justice in a few paragraphs. I will concentrate on what I think are the two most important questions, neither of which is fully resolved, in my opinion.

In what way is the spatial distribution of replicators important?

It is clear that accounting for spatial position of replicators in evolutionary models makes a big qualitative difference. The main effect is that in spatial models with local rules for reproduction and limited spatial diffusion, clusters of related individuals arise, and this benefits cooperators. This is easy to understand in the archetypal prisoner's dilemma model [5]. In the non-spatial case, corresponding to random encounters between individuals, defectors outcompete cooperators. In the spatial version, clusters of cooperators do better than they would if they were mixed with defectors, whereas clusters of defectors do worse than they would if they were mixed with cooperators. This allows coexistence of cooperators and defectors and prevents defectors taking over the whole system. The equivalent effect in molecular replicator models is due to the fact that when a molecule functions as a replicator it is being altruistic because it copies another sequence as a template rather than copying itself. Also during the time it spends acting as a replicator, it cannot itself be a template for another replicator. This effect is present in the RP system (Section 5.3 of this paper) and also in other models such as Konnyu et al. [3] and Brogioli [2]. In contrast, being a template is selfish. Hence, in non-spatial models, better templates can evolve but not better replicators. Spatial clustering of replicators allows better replicators to evolve and avoids invasion by parasitic templates. Thus far, I am fully convinced.

Now let us consider the question of how selection might act on higher level spatial structures such as spiral waves or travelling waves. Spiral waves arise in the hypercycle model (Section 5.1) and in other models with a cyclic structure [1,7]. The spatial model solves some of the problems present in the original hypercycle model, but creates others (as described in the paper). Furthermore, it is not clear to me why replicators should interact in the very specific cyclic arrangement that is the basis of the hypercycle. I think 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. Questions of spiral wave evolution and competition are only relevant if the underlying dynamics has this structure. The hypercycle work in this paper is insightful, but it suggests that hypercycles

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are not very relevant to RNA replicator evolution. I find the travelling waves in the RP model (Section 5.3) more interesting, since they seem to be somewhat more generic and less finicky. Nevertheless, higher-level structures like waves are more likely to emerge in models that have a limited set of possible states. I do not think we yet have a good understanding of any spatial structures that might exist in complex models with many different types of molecules and continued evolution of molecular properties and interactions. Although I am convinced that spatial correlations will be present and will be important in more complex and realistic models, I am still unconvinced that there will be obvious higher-level spatial structures that could be considered as units of a higher-level selection process.

In what way did selection on cells take over from selection on molecules?

The higher-level structure that obviously *is* important is the cell. If replicators are enclosed in compartments, like lipid vesicles or protocells, then selection can act on the compartment as well as individual molecules. Selection on the compartment favours cooperation between the molecules inside, and can prevent the spread of parasitic molecules that would occur in a well-mixed system with no compartments, as has been known for some time [4], and as is discussed in Section 7 of this paper. This can occur even if there is complete mixing of molecules inside one compartment, and complete mixing of the compartments. Thus, the presence of compartments means that spatial structure either above or below the level of compartments is no longer an essential feature.

It seems likely that lipids might have been present on the very early Earth, and that membranes and vesicles might form rather easily. Thus they could well have been around at the time that replicating biopolymers were beginning to emerge. The unresolved issue is whether we should be thinking from the outset of reactions of small groups of molecules enclosed in compartments, or whether we should be thinking of an extended spatial system with local spatial correlations that only later became incorporated within compartments. In the former case, we are led to questions of how protocells could divide and faithfully pass on sets of unlinked genetic molecules. In the latter case, we are led to consider just how far a spatial system without compartments could get in terms of sequence diversity, adaptation and cooperative metabolic networks involving multiple sequences.

In the standard evolutionary framework used in population genetics, there is a population of individuals, each of which has a fitness. Each individual reproduces in proportion to its fitness. There is competition for resources between individuals, and this serves to limit the total population, but apart from this, the fitness of an individual depends on its own properties and not on the properties of other individuals. A protocell or lipid vesicle is an individual in this sense, and competition can occur within populations of protocells in the usual way. In contrast, a single RNA replicator is not an individual because it relies on other sequences to replicate it. An RNA sequence does not have a fitness of its own because it depends on which other sequences are in its neighbourhood. It is also not clear that groups of spatially correlated replicators or spatial structures like waves can really be considered as individuals. So the origin of compartments really marks the origin of individuals and hence the origin of "biology" in the usual sense. Before that, we have "chemistry" involving distributed networks of molecules without individuals. In my view, evolution and natural selection still work in the chemical era, but this is much less well studied than evolution in the biological era. We know that individual cells *did* emerge and were successful at some point, probably fairly early in the history of life. I think the key unresolved questions are why, how and when this occurred.

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Comment

Survival of the pre-fittest
Commentary to N. Takeuchi and P. Hogeweg review article "Evolutionary dynamics of RNA-like replicator systems: A bioinformatic approach to the origin of life"

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In the article "*Evolutionary dynamics of RNA-like replicator systems: A bioinformatic approach to the origin of life*" (Physics of Life Reviews, this Issue) Nobuto Takeuchi and Paulien Hogeweg courageously consider the generation, acquisition, maintenance and storage of information by replicators. Each process is examined in its specific frame of pertinence: the maintenance of already present information is considered as a function of the interactions to-be, the generation and the acquisition of new information are examined in the context of the complex network of genotype-phenotype interactions and reciprocal effects, the storage of information is faced in the set of overlapping functions characterising systems that dedicatedly keep and replicate it.

Mathematical and computational modelling of the earliest evolution entails adhesion to RNA world scenarios, where quasi-species struggled to conquer a distinction between genotype and phenotype. When molecules reached the point where they did something more than merely replicate themselves and generated, acquired, maintained, stored and transmitted information, at that point the threshold between non-living and living had been identified and crossed.

Life is difficult to define and the result of the quest for a definition has been dubbed as essentially futile [1]. The best possible solution in this search has been obtained [2], reducing the properties of the living into the words: "Life is self-reproduction with variations". This aphorism encompasses all the processes examined in this study, whose fringe benefit is that Takeuchi and Hogeweg attempt to quantitatively *describe* life, beyond bristly definitory efforts.

To tackle description of complex systems with the aim of boiling it down to mathematical treatment is a particularly meritory endeavour. Especially so when the complexity is expected to grow exponentially as a function of successive waves of systemic interactions (as the authors recognise, "evolution is a multilevel process"). The merit of this effort is particularly evident when attention is focused on the evolutionary dynamics of DNA-like replicators (i.e., replicators that serve as templates, but not as catalysts, of replication) or when it is shown that high-stochasticity phenomena (i.e., the higher evolutionary dynamics of parasites within compartments) arise from the interaction of two systems (namely, replicators and compartments). It is in this frame that the terms *genotype* and *phenotype* acquire real meaning allowing chemical complexity to actually become life and providing the category of *hypercycles* with a deep-rooted

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biological purport. The fact that reasonable and credible scenarios, not necessarily in contradiction among themselves, are being sketched [3,4] adds to the interest of this all-embracing effort.

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Comment

The theoretical underpinnings of primordial RNA replication Comment on "Evolutionary dynamics of RNA-like replicator systems: A bioinformatic approach to the origin of life" by Takeuchi and Hogeweg

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Takeuchi and Hogeweg [1] take us on a systematic tour of the evolutionary potential — and the severe pitfalls along the way — of RNA-based replication as envisioned in an RNA World. The recurring theme is that a bioinformatics approach to modeling the dynamics of RNA evolution can lead to some interesting conclusions, most of which have direct bearing on either the definition of life or on the history of the advent of life on the Earth (or elsewhere). By bioinformatics they mean a coding relationship between genotypes and phenotypes. RNA must accommodate both in providing a chemical means to acquire information, maintain information, and evolve novel functions. The authors present this definition: life is an information-processing system or a symbol-processing system, but not vise versa [2].

The bioinformatics approach here is really a compilation of a reasonably long history of thought on primordial replication, starting with Eigen [3] and Schuster's [4] work on hypercycles and quasi-species, weaving through Fontana, Wilke, and Stadler's [5–7] descriptions of genotype–phenotype mapping and mutational robustness, and ending with Szathmáry's [8] stochastic corrector model of replicator encapsulation. Of course many others have contributed to this discussion, and the authors' own works (e.g., [9]) have provided a large body of critical insight to make breakthroughs in the field. A common thread to all this, and an implicit conclusion of the current review, is that complexity can arise and evolve through intrinsic — and chemically inevitable — asymmetries that exist in RNA, such as the fact that the G–C nucleotide pair has different thermodynamic properties than the A–U pair, or that RNA is directional in that its 5′ end is distinct from its 3′ end.

These basic asymmetries, combined with the emergent phenomena such as multi-level selection, allow the authors to present a very convincing set of evolutionary transitions that RNA must have undergone to give rise to the central-dogma-type replication system we find in cells today. A recurring obstacle to this path is the need to overcome molecular parasites: those molecules that can serve as replication templates but do not contribute to the replication

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process themselves. Even before Eigen's pioneering treatise on the evolution of information in 1971 [3], this problem was observed and acknowledged as a critical issue in RNA evolution when "mini-monsters" took over Sol Spiegelman's test-tube evolution experiments in the late 1960s [10]. Takeuchi and Hogeweg show us how, given the standard parameterization of RNA replication, various ecological features can help solve this problem. Hypercycles can help, but by themselves are insufficient. Spatial heterogeneity helps even more, and the authors' simulations with cellular automata have shown that travelling waves can keep evolution going and parasites at bay. Protocellular compartmentalization also helps, but gives a distinctly different flavor to life (increased longevity) than does spatial heterogeneity without discrete boundaries (increased fecundity). Finally, coopting a slave molecule without a 2′ hydroxyl but with a methyl group on one informational unit (i.e., DNA), helps even further. The lesson the authors' would have one take from this, both literally and figuratively, is that parasitism and competition have by-and-large determined the particulars of the evolutionary history of life.

This review is a very thorough and fascinating summarization of the forces that shape RNA replication, and with it, life itself. The authors' efforts to build increasing levels of complexity into their models are highly commendable, and, as they note in the beginning of the paper, this is done without any preconception of the outcome so as to be the most useful to the scientific community. This is refreshing. Moreover the systematic addition of each element of realism: secondary structure considerations, cellular automata, wave dynamics, etc., allows the reader to easily interpret the effects of each component on the overall picture. In particular, since its original publication [11] I have always found the dynamics of traveling waves of a system containing both replicators and parasites (see Figs. 10, 11, and especially 13) to be a beautiful demonstration of how interactions among components in a system, rather than just the system elements themselves, can lead to a rather surprising and powerful result. In this case it is that these waves can actually display the three facets of evolution as originally delineated by Darwin: multiplication, inheritance, and variation.

What is missing from these elegant analysis is an (even) better connection to the chemical underpinnings and chemical realities inherent in RNA replication. This is less of a criticism of the current review than a plead for the authors to keep expanding their endeavor. An explicit assumption made in the parameterization is to ignore recombination, which could be an important, if not essential, feature of early polymer replication and search for function [12,13]. An RNA autoreplicase may be a late-comer to the evolutionary scene, or perhaps never existed. Furthermore the lab-based experiments in polymer evolution, such as those with RNA, proteins, and peptide nucleic acids [14–16], have much to offer to either constrain the models presented here or to provide new chemical features that are currently not incorporated. Of course one must start with simplicity and build outward, and that is what this review has done, but the time is ripe for exciting articulation of empirical work and theory.

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Comment

Neutral networks and chemical function in RNA Comment on "Evolutionary dynamics of RNA-like replicator systems: A bioinformatic approach to the origin of life"

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Understanding how complex chemical ecosystems could have emerged from simple interacting molecules is key to work out a plausible theory on the origin of life. Despite the many difficulties faced by empirical approaches to the problem [8], the conceptual framework of such a theory has been significantly developed [10] thanks to theoretical and computational studies often inspired by or relying on the properties of RNA molecules. The pioneering model of quasispecies introduced by Eigen [4] has more than guided the development of the field, conditioning our view of quasispecies dynamics through concepts such as the error threshold. In an insightful contribution [10], Takeuchi and Hogeweg begin by reviewing Eigen's model and several modifications that confer it an increasing degree of realism: The error threshold, for instance, does not depend only on the length of a sequence, but on its degree of neutrality as well. Quasispecies models have indeed tried to incorporate two important properties of RNA-like systems: the redundancy of the sequence-to-secondary structure map and, to a lesser extent, the complex topology of the sequence-to-function relationship, i.e., the fitness landscape.

The observation that an astronomically large number of RNA sequences fold into the same secondary structure [7] has major implications for short molecules, mainly, which are those of relevance in the context of the RNA world. For example, the $4^{12} \sim 1.7 \times 10^7$ possible RNA sequences of length 12 can be classified into 58 different secondary structures (or phenotypes) [1]. For the 6.9×10^{10} sequences of length 18, the number of different phenotypes raises only to 3211 [3]. The probability to access one phenotype from another is the quantity to substitute the microscopic transition probabilities between genotypes – as formulated in Eigen's original quasispecies theory. That probability depends on the skewed abundance of different phenotypes and on the topology of the corresponding neutral networks [1]. As a result, a more faithful picture of the bond between the phenotypes of a quasispecies is that of a network whose nodes represent phenotypes and whose links stand for the transition probabilities between mutually accessible nodes. Taking into account that the RNA secondary structures observed in nature typically present abundances above average [5], realistic models of quasispecies could be approximated by a core of strongly connected phenotypes. In this scenario, molecular quasispecies should be viewed as a robust, self-maintained entity with all typical phenotypes simultaneously present – unless some of them have zero fitness. The interpretation of the error threshold and the fate of the quasispecies under high enough mutation rates would have to be rethought, as well as the implications of this dynamics for

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systems, as viruses, where the quasispecies theory is applied [6]. Despite the efforts to extend quasispecies theory to more realistic settings, a theory that derives mesoscopic (phenotypic) equations for RNA sequences from the microscopic (local) properties of the space of genotypes is still lacking. A subsequent improvement in modeling implies the use of realistic fitness landscapes, which can be accurately estimated only in the light of empirical data. There are correlations between molecular structure and function in RNA, for instance, which should be considered. In this context, too simplified landscapes as the peak landscape are at best poor representations of actual phenotype–function relationships. Though RNA is the most thoroughly studied model with a non-trivial genotype–phenotype map, proteins or regulatory and metabolic networks share many of its qualitative features [11]. Our steadily increasing knowledge of these systems demands that the view of genotype and phenotype as entities fulfilling a one-to-one relationship be essentially abandoned.

Models based on the phenotype are still at their infancy and, when grown up, will likely confront us with new phenomenology, as in the following example. The existence of huge neutral networks affects not only the evolution and adaptation of replicator populations, but plays a main role in the absence of replication and selection, as well. Common RNA secondary structures (those with a frequency above average) are systematically found in reasonably large populations of random RNA sequences. The sequence-to-structure-to-function redundancy offers as a side effect an alternative, plausible solution to the problem of how long molecules could have been formed in the absence of an error-correcting, template copy mechanism [2]. It has been observed that hairpin-like secondary structures represent the most abundant structural family in short RNAs [9]. At present, hairpin structures are common in viral and cellular RNAs and some of them act as ribozymes that catalyze RNA ligase reactions. These structures should have been ubiquitous in populations of random polymers and may have enhanced the ligation of short molecules. Under appropriate environmental conditions, diverse populations of long enough molecules would appear and, eventually, this process of modular evolution could have begotten new chemical functions: It is plausible that a mechanism of this kind could have ushered in the emergence of the first replicase-like molecule. At that point, a scenario dominated by RNA-like replicators, as described in [10], could have been triggered.

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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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