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The social coevolution hypothesis for the origin of enzymatic cooperation

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At the start of life, the origin of a primitive genome required individual replicators, or genes, to act like enzymes and cooperatively copy each other. The evolutionary stability of such enzymatic cooperation poses a problem, because it would have been susceptible to parasitic replicators that did not act like enzymes but could still benefit from the enzymatic behaviour of other replicators. Existing hypotheses to solve this problem require restrictive assumptions that may not be justified, such as the evolution of a cell membrane before the evolution of enzymatic cooperation. We show theoretically that, instead, selection itself can lead to replicators grouping themselves together in a way that favours cooperation. We show that the tendency to physically associate with others and cooperative enzymatic activity can coevolve, leading to the evolution of physically linked cooperative replicators. Our results shift the empirical problem from a search for special environmental conditions to questions about what types of phenotypes can be produced by simple replicators.

Even the simplest genomes are made up of hundreds of genes and thousands of base pairs; yet, by necessity, life started with single, short sequences, or replicators. Lacking the ability to produce large enzymes, these first replicators would have had high error rates in replication, preventing them from elongating into a genome[1,2]. There is a significant gap between the maximum size replicators could reach without large error-correcting enzymes and the minimum size needed to produce those enzymes[2]. Consequently, to bridge this gap and make the first step towards building a primitive genome, different replicators would have had to act as enzymes to help copy each other[2–4]. In this way, the individual replicators could remain small and below the error threshold, but the collection of replicators could grow sufficiently large to produce big enzymes.

The problem is that a collection of cooperative replicators would have been susceptible to parasitic replicators that did not act as enzymes but were able to benefit from the enzymatic activity of others[5]. All else being equal, such molecular parasites (cheats) would have had a higher replication rate, making cooperation between replicators unstable, and hence preventing the evolution of a genome. What, then, can explain the maintenance of the cooperative enzymatic activity required for the genome to evolve? One hypothesis is that different types of replicators were grouped together in a primitive cell, or proto-cell, so that selection acted on groups of replicators[3,6–10]. An alternative hypothesis is that replicators were on some surface that limited their diffusion, but also led to interactions between different types of cooperative replicators[11–17]. Both of these hypotheses favour cooperation by grouping cooperative replicators together, and hence limiting the extent to which they could have been exploited by parasites[18].

However, these hypotheses require restrictive assumptions that may not be justified. To have replicators grouped by a cell membrane, we would require the evolution of a cell membrane before we had a genome that was sufficiently complex to produce that membrane. This solves the problem of explaining one complex feature (cooperative replicators) by invoking another complex feature (cell membrane). The proto-cell could be an abiotic feature, such as a droplet of oil, but that would require that the division of that droplet was linked to the rate at which replicators copy, in a way that just happened to make group selection work[3,6–10]. The limited diffusion hypothesis requires evolution on a particular type of surface to group replicators together in a very specific way, which: (1) limits diffusion, so that parasites cannot exploit replicators; (2) has high enough diffusion to keep different types of replicators well mixed; and (3) has some property that ensures binding sites contain different types of replicators, rather than copies of identical replicators[15,17]. It is not clear how a surface could produce all of these properties. In addition, many previous models require simple replicators to have conditional phenotypes, and to only act as cooperators in certain interactions, which is a relatively complex behaviour for a very short sequence[17,19].

We propose an alternative hypothesis, where selection itself leads to replicators grouping themselves together in a way that favours cooperative enzymatic activity. We hypothesize a scenario, where: (1) one type of replicator can evolve to act as an enzyme to help copy other replicators (cooperation); and (2) another type of replicator can evolve to physically associate with or 'stick' to other replicators. We show theoretically that coevolution between these two traits can lead to cooperation between replicators being evolutionarily stable, in conditions where it would not otherwise be favoured. This occurs because the evolution of physical association allows the benefits of enzymatic cooperation to return to cooperators and their identical copies. Our relatively simple hypothesis does not require restrictive features of the environment to group replicators together in certain ways, or the evolution of another complex feature of life, such as a cell membrane. Instead, selection drives the replicators to solve the problem of cooperation themselves. Consequently, our hypothesis shifts empirical focus from special external environmental conditions to questions about what kinds of phenotypes can be produced by simple molecular replicators.

Results

The life cycle. There a number of different questions with regards to the origin of a primitive genome, ranging from chemical questions about what types of molecules can achieve autocatalysis to

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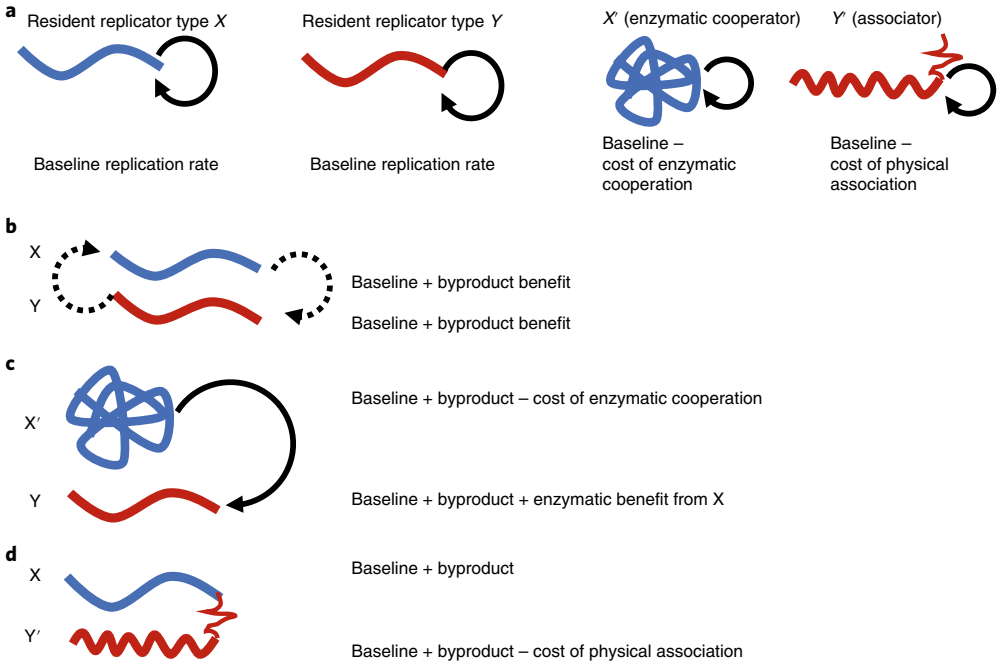

Fig. 1 | Interactions and fitness effects. a, Two replicators, *X* and *Y*, each have some baseline replication rate on their own, but can acquire mutations (*X′* and *Y′*), which reduce their replication rate. **b**, Each replicator (*X* and *Y*) has a higher replication rate whenever in complexes, due to passive benefits (byproduct benefits). **c**, Mutant *X′* increases the replication rate of *Y* in complexes (enzymatic benefit from *X*). **d**, Mutant *Y′* increases the rate at which the mutant forms associations with *X*, and decreases the rate at which these associations break down.

function questions about how a genome divides up tasks to function as a whole. There are also a number of different possible modelling approaches, ranging from simulations that incorporate substantial biochemical details[17] to very simple adaptation-driven models of replicator cooperation[7,19].

Here, we focus exclusively on the problem of cooperation between replicators as a step towards a primitive genome. We follow in the vein of a number of other researchers who have studied this problem[1–3,5–9,11,13,15–18]. Our goal is to capture the problem in a very simple model, which strips away many of the biochemical details in order to attain easily interpretable results. Rather than model a very specific biological scenario, our aim is to produce a model that could be applied to many types of catalytic replicators, be they RNA or not.

We imagine two different replicators, *X* and *Y*, which are independent populations but can form *XY* complexes, where a complex is an interacting pair of replicators. For simplicity, we do not track *XX* and *YY* pairings, as we assume that these pairings do not affect the replication rate (in the Supplementary Information, we show that a model that explicitly tracks these pairings leads to similar conclusions). These replicators could be RNA-like molecules, but the model is not limited to the RNA-world hypothesis. The only requirement is that the molecules are able to self-replicate (they are 'autocatalytic') and can potentially act as catalysts for the replication of others (they possess 'enzyme-like' behaviour) (Fig. 1).

We make no explicit assumptions about population structure except that after replication there is some chance, which can vary, that replicators interact locally before dispersing into the global population mixture. Consequently, our model could apply to replicators interacting on a surface (where this chance might be very high) or free-floating (where this chance could be very low).

We can consider the population of replicators as divided into three populations: *X* replicators on their own; *Y* replicators on their own; and *XY* complexes. The densities of these populations are free to grow and shrink, and these densities affect the rates at which different interactions occur. The *X* and *Y* replicators each have some baseline, potentially distinct rates of replication ($\rho_{i\in X,Y}$) and destruction, or death ($\mu_{i\in X,Y}$). These two types of replicator form complexes with each other at some low baseline rate (β), and these complexes dissociate at some (relatively high) baseline rate (δ), or else are ended by the destruction of one of the replicators (notation summarized in Supplementary Table 1). All replication rates are density dependent.

When in complexes, replicators produce new individual replicators at a rate ($\theta_{i\in X,Y}$), which we assume to be higher than their rate of replication when on their own. This could be due to a beneficial waste product, such as a nucleotide, produced during replication, or a conformational change passively induced by the other replicator, which increases the efficiency of replication. This byproduct benefit is measured by κ, such that $\theta_{i\in X,Y} = (1+\kappa)\rho_{i\in X,Y}$. We also assume that the new replicators produced by complexes can immediately pair again, due, for example, to proximity (r_{XY}). We imagine that, initially, this happens very rarely (although this is not required). In the Supplementary Information, we show that the population dynamics of these three different populations are described by:

$$\begin{aligned}\frac{\mathrm{d}[X]}{\mathrm{d}t} &= (\rho_X-\mu_X)[X]-\beta[X][Y]+(\mu_Y+\theta_X+\delta)[XY]\\ \frac{\mathrm{d}[Y]}{\mathrm{d}t} &= (\rho_Y-\mu_Y)[Y]-\beta[Y][X]+(\mu_X+\theta_Y+\delta)[XY]\\ \frac{\mathrm{d}[XY]}{\mathrm{d}t} &= \beta[X][Y]-(\mu_X+\mu_Y+\delta-r_{XY})[XY]\end{aligned} \quad (1)$$

Evolutionary dynamics. We used an adaptive dynamics approach to study the evolution of cooperative enzymatic activity and physical associations in these replicators[20–23]. We used methods developed to examine interactions between interacting populations[24,25], and followed three steps. First, we considered a mutant whose cooperative enzymatic activity or tendency to associate and dissociate differs from the resident population. Second, we determined what direction these traits would evolve in, by studying the spread of mutants (given by the initial asymptotic growth rate of a mutant with deviant

trait values, or invasion fitness). Third, by allowing for successive mutants, we determined numerically the evolutionarily stable resting state of the population[26].

We show in the Supplementary Information that the condition for the spread of a rare mutant in replicator X or Y ($i \in X, Y$) can be expressed as:

$$\frac{F_i'}{\beta'[\bar{j}]} + \frac{P_i'}{M_{ij}'} > 1 \quad (2)$$

$F_i = (\rho_i - \mu_i)$ is the replication rate of replicator $i \in X, Y$ on its own, $P_i = (\mu_j + \theta_i + \delta)$ is the replication rate of $i \in X, Y$ in complexes, and $M_{ij} = (\mu_i + \mu_j + \delta - \rho_{ij})$ is the loss (destruction or dissociation) of complexes. The primes indicate mutant values in the replicator $i \in X, Y$, and mutants are denoted $i' \in X', Y'$. Equation (2) shows how a trait can spread via its effect on the replication rate of a replicator on its own (F_i'), the effect on its replication rate in pairs (P_i'), the effect on the loss of complexes (M_{ij}') and the effect on pairings with the other replicator type ($\beta'[\bar{j}]$). Van Baalen and Jansen[24] developed a similar expression for the invasion of a rare mutant in the context of studying the common defences from a predator of two prey populations (Supplementary Section 4). We now proceed to study the evolution of cooperative enzymatic activity and physical association.

Enzymatic cooperation. We first asked whether selection would favour replicators acting as enzymes that help copy other replicators. This can be thought of as evolution towards more cooperative replicators, which would facilitate the evolution of the genome. We examined this possibility by allowing replicator X to mutate in a way that made it better at helping copy replicator Y, by increasing the density-independent replication of Y by a factor of $1 + \omega d'$ when Y is in a complex with a mutant (X'). We assumed that this mutation would cause the X replicator to be less efficient at copying itself, by reducing the replication rate of X by a factor of $1 - d'$. For example, this could be a conformational change that reduces the autocatalytic rate of X′, but causes X to act as a catalyst to increase the replication rate of Y. Consequently, we are assuming a trade-off between the rate at which a replicator can help copy other replicators and the rate at which that replicator can copy itself.

Replicator copies produced from complexes may immediately form pairs again, and it is possible that, through increasing the local density of Y replicators, an X' mutant increases the chance that its copies immediately pair again with a Y. To account for this, we assume an X' mutant increases the rate at which replicators produced from complexes immediately find a partner by a factor of $1 + \lambda d'$ (where λ might equal ω but is free to vary). In the Supplementary Information, we extend the model to explicitly track this effect, and recover similar results.

We found that cooperative enzymatic activity was not favoured (specifically, more cooperative X' mutants ($d' > 0$) were never able to invade a population of resident X and Y) and that the X population rested stably at a value of zero cooperation (Fig. 2a). We found that cooperation could not spread because it reduced the replication rate of the mutant, and there was no mechanism by which the benefit to Y could be fed back to X'. While cooperative enzymatic activity increases the density of Y, the baseline association rates are sufficiently low that this effect is not strong enough to favour such activity. Specifically, cooperation reduces both terms in equation (2), by reducing replication both in complexes and alone (the numerators) and leaving the association with the other type ($\beta'[\bar{j}]$) unaffected. Cooperation reduces the loss of complexes in the second term (M_{ij}'), but this is not enough to outweigh the direct cost to replication. This is analogous to the standard evolutionary result that, all else being equal, a cooperative behaviour that benefits an unrelated individual will not be favoured[27,28].

Physical association. We then examined the consequences of allowing the Y replicator to mutate in a way that causes it to associate or form complexes with the X replicator, increasing the baseline association rate (β) by a factor of $1 + \zeta c'$, and decreasing the rate at which complexes dissociate (δ) by a factor of $1 - \xi c'$ (where $0 \geq \xi \leq 1$). We refer to this as an 'association' trait, as it can capture the possibility that Y' physically binds to X (for example, 'stickiness'), but also includes any kind of trait that increases the rate of association between X and Y' and/or increases the duration of these associations, such as a trait that induces a conformational change in X, increasing the chance they form a pair. We allow only mutations in Y, holding X constant.

We assume that this association mutation is costly and decreases the rate at which Y' can replicate itself by a factor of $1 - c'$. This could be, for example, if the folding pattern that increased association were less easily replicated as a template. We account for the possibility that this association trait increases the chance that copies produced from complexes immediately pair again by allowing the mutation to increase the rate of pairing by a factor of $1 + \alpha c'$. A baseline assumption might be that $\alpha = \zeta$, because this effect is simply due to the increase in association rate caused by the association mutation, but our model allows for the effect to be weaker or stronger.

We found that association could be favoured (Fig. 2b). Specifically, if the byproduct benefits gained by being paired with an X (κ) and the relative increase in association rate caused by the mutation ($\frac{\alpha c'}{c'}$) are sufficiently high ($>>1$), successive mutations with higher values of association ($c' > 0$) will invade a population of resident X and Y until the association rate comes to rest at some equilibrium value ($c*$). Some level of association is favoured because, while it causes an immediate reduction in the replication rate, this is outweighed by the increase in replication rate due to being in complexes with X more often. Specifically, association reduces the first term in equation (2) (via the numerator), but this is outweighed by an increase in the second term (via the denominator).

Coevolution. We then examined what happens when both enzymatic cooperation and association are allowed to coevolve. We did this by allowing for mutations in both replicators, where X evolves to be more cooperative ($d' > 0$) and Y associates at a greater rate ($c' > 0$). To allow for coevolution, we analysed the selection gradient on both traits in both mutant populations simultaneously, which told us which direction in state space the population was moving at any given point. By repeating this across all of state space for both traits, we could determine which direction both replicator types would evolve in.

In the Supplementary Information, we show that, when both traits are allowed to coevolve, selection can drive enzymatic cooperation ($d*$) to its maximum value and association ($c*$) to a higher value than when evolving on its own (Fig. 2c). Coevolution favours enzymatic cooperation when the association and enzymatic cooperation increase the chance that replicators produced by complexes pair again ($\lambda, \alpha \gg 1$), and when byproduct benefits are large ($\kappa \gg 1$). Furthermore, even for conditions under which association would not evolve on its own (for example, when $\zeta = 0$), if association still increases the duration of pairings ($\xi > 0$), coevolution can favour enzymatic cooperation and association.

This result is driven by coevolution between the two traits. In the absence of the association trait, cooperation is not favoured because the benefits only accrue to members of the other replicator type. However, as association evolves, there is an increased chance that a cooperator's copies both form and remain in pairs with an associator mutant's copies. A cooperator increases the chance that its copies will find a Y partner by creating more Y copies.

Our results show that the key factor favouring positive coevolution between cooperation and physical association is that the two

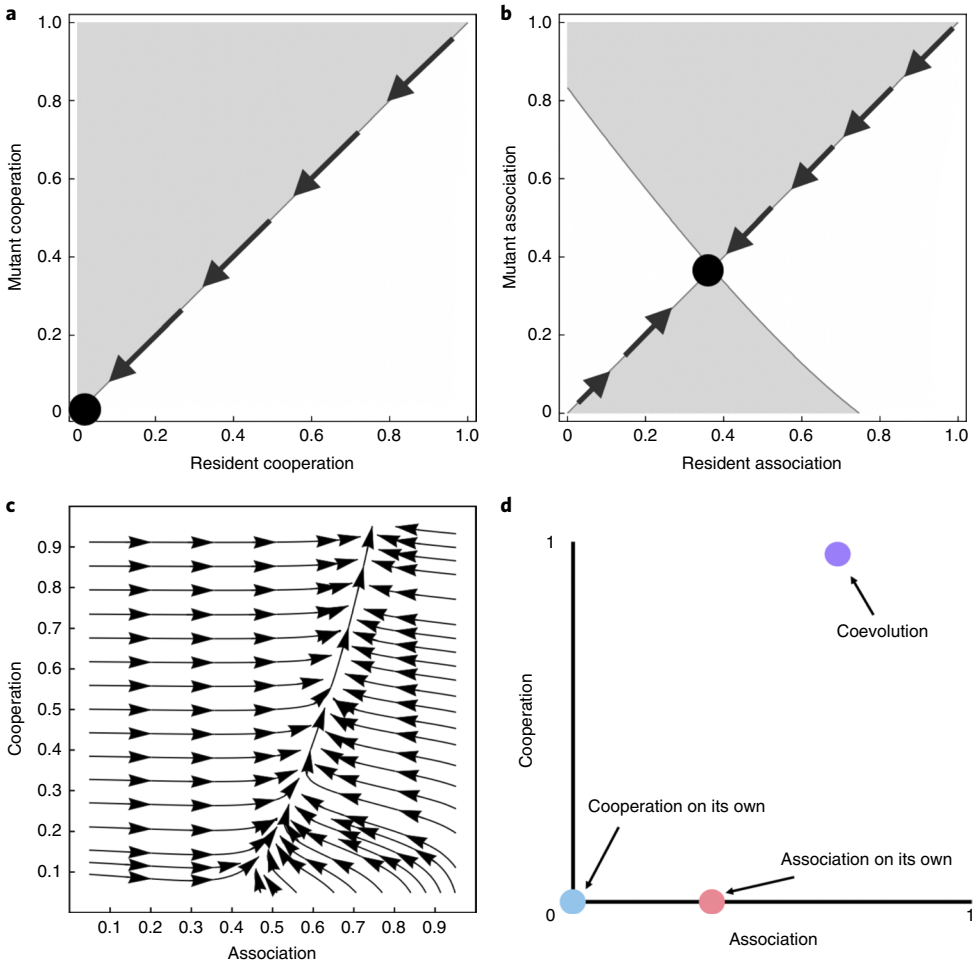

Fig. 2 | Coevolution of enzymatic activity and association. a, The evolution of enzymatic activity in *X* is not favoured. In the absence of association, cooperative enzymatic activity cannot evolve. **b**, Evolution of association in *Y*. In the absence of cooperative enzymatic activity in *X*, some intermediate level of association in *Y* is favoured. The grey and white areas in **a** and **b** show regions of state space where selection is negative and positive, respectively. Arrows depict the direction of evolution in state space along neutral lines. Evolutionarily stable strategies are depicted by solid circles. **c**, Coevolution of cooperative enzymatic activity and association. Arrows depict the direction of selection in both traits at a given point in state space. When traits are allowed to coevolve, cooperative enzymatic activity and association both evolve from anywhere in state space, with association reaching higher values than in **b**, and enzymatic activity evolving towards its maximum value of 1. **d**, Schematic of **a**–**c**. Solid circles depict the evolutionarily stable resting point of both populations depending on whether each population evolves independently or jointly. Coevolution favours higher values in both traits. Values for the parameters in **a**–**d** are: $\alpha = 20$, $\lambda = 20$, $\zeta = 5$, $\xi = 1$, $\omega = 20$, $r_Y = 2.3$, $r_X = 2.1$, $r_{XY} = 0.9$, $k = 0.01$, $\mu_Y = 1.1$, $\mu_X = 1.1$, $\kappa = 100$, $\beta = 0.01$ and $\delta = 0.9$. All figures were generated graphically from the equations described in the Supplementary Information using Mathematica software version 11.3.0.0.

traits increase the chance that copies produced from complexes pair again. We captured this in the term $(1 + \lambda d')(1 + \alpha c'))\rho_{ij}$, which does not specify exactly how the two traits increase immediate pairing. In the Supplementary Information, we derive an explicit model, tracking the individual copies produced from pairs, and modelling how they repair. The explicit model recovers the results of the more general model, showing that coevolution is only favoured when both traits increase the chance of pairing again.

For simplicity, we have limited our model to two types of replicators, *X* and *Y*, but once cooperation and association evolve, there is no reason why more replicators cannot be added, further elaborating the genome. Further, Frank[29] pointed out that the conditions favouring cooperation need only be temporary, as once replicator functions come to depend on the association, reversals become more difficult. Finally, our model is not intended to be quantitative, but qualitative, highlighting the relationship between parameters and the potential for specific selective forces to favour cooperation. For those developing specific, quantitative models, for a given chemical system, we discuss the quantitative significance of our results in the Supplementary Information.

Replicators as mutualisms. Cooperation between different replicators is conceptually analogous to cooperation between different species in mutualisms. The *X* and *Y* populations of replicators can be thought of as two different 'species'. Cooperation can be favoured between species when the benefits of cooperation return to the cooperator or its genetic relatives[30–33]. In our model, the physical association, or stickiness trait, provides a mechanism for the benefits of cooperation to return to the cooperator's copies, and prevents these relationships from breaking down. This mechanism could potentially be applicable to other systems, such as cross-feeding bacteria[34]. Our prediction is also analogous to Law and Dieckmann's[35] result that the evolution of vertical transmission could lead to stable symbiosis in exploiter/victim interactions.

Another force that could theoretically drive positive between-species coevolution is synergy of fitness effects[29,31,32,36]. Synergy

occurs when two cooperators together do better than expected because the whole is greater than the sum of the parts. While synergy is a possible alternative route to a primitive genome, and could be tested for empirically, we have shown that synergy is not needed. In addition, synergy can act together with the forces that we have analysed in this paper, to help drive the coevolution of cooperation and physical association (unpublished analyses).

Discussion

We proposed and tested a hypothesis that the coevolution between enzymatic activity and physical associations can explain cooperation between different types of replicators. We showed that if one population of replicators can act as an enzyme to increase the replication rate of another, and the other can act to increase the physical associations between the two, these traits can coevolve, given that there is some baseline byproduct benefit to being complexes. This leads to a population of replicators that are both cooperative and physically linked—two of the key features of a primitive genome. Specifically, in our scenario, the questions of why simple replicators would come together physically (byproduct benefits) and how they would overcome the error threshold (cooperation) resolve each other.

Cooperation is not the only puzzle about the origin of the genome. Other questions relate to the division of labour and mutual dependence between replicators, the efficiency of molecular interactions before compartmentalization, the ability of a single molecule to fulfil the role of DNA and protein, and prebiotic synthesis of nucleotides[18,37,38]. We have not addressed these other questions, which are certainly of interest, and instead focused on the initial first step in the evolution of the genome—different replicators coming together and cooperating[1,3,5,6,18]. Our model does not rule out the role of a cell in solving these other problems; instead, we have shown that a cell is not required to solve the problem of enzymatic cooperation.

Our results make the evolution of a primitive genome easier to explain, by simplifying the conditions required. This does not mean that previous explanations are invalid, just that they may come in at different stages in the evolution of life. For a primitive genome, our results suggest that we do not need to: (1) invoke the cell, a potentially complex feature of life; (2) assume highly specific population structures on special surfaces; or (3) grant simple replicators with conditional phenotypes. Consequently, our result increases the kinds of environments in which the first steps towards a genome can evolve. It also means that a more complex genome could have evolved to then produce the first cell, because our result shows how genome complexity could increase without a cell membrane. Finally, our results shift the focus of questions about the origin of the genome from external features of the environment to biological features of replicators. Specifically, what phenotypes are possible in simple molecules, can they act to increase the replication rate of others, and can they stick to each other?

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

There are no data to report.

Code availability

All code has been made available, along with an implementation of the calculations, in Supplementary Software 1, and is available on GitHub at https://github.com/srlevin/sticky.git.

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Author contributions

S.R.L. and S.A.W. conceived of the manuscript. The modelling was carried out by S.R.L. and S.G. All authors contributed equally to the final presentation of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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