The social coevolution hypothesis for the origin of enzymatic cooperation

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Abstract

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 don't 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 to 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.

Introduction

1 Even the simplest genomes are made up of hundreds of genes and thousands
2 of base-pairs, and yet, by necessity, life started with single, short sequences, or
3 replicators. Lacking the ability to produce large enzymes, these first replicators
4 would have had high error rates in replication, preventing them from elongating
5 into a genome (Eigen, 1971; Eigen and Schuster, 1977). There is a significant gap
6 between the maximum size replicators could reach without large error-correcting
7 enzymes, and the minimum size needed to produce those enzymes (Eigen and
8 Schuster, 1977). Consequently, to bridge this gap and make the first step towards
9 building a primitive genome, different replicators would have had to act as
10 enzymes to help copy each other (Eigen and Schuster, 1977; Maynard Smith and
11 Szathmari, 1995; Bourke, 2011). In this way, the individual replicators could

12 remain small and below the error threshold, but the collection of replicators
13 could grow sufficiently large to produce big enzymes.

14 The problem is that a collection of cooperative replicators would have been
15 susceptible to parasitic replicators that don't act as enzymes, but are able to
16 benefit from the enzymatic activity of others (Maynard Smith, 1979). All else be-
17 ing equal, such molecular parasites (cheats) would have had a higher replication
18 rate, making cooperation between replicators unstable, and hence preventing
19 the evolution of a genome. What, then, can explain the maintenance of the co-
20 operative enzymatic activity required for the genome to evolve? One hypothesis
21 is that different types of replicators were grouped together in a primitive cell, or
22 proto-cell, so that selection acted on groups of replicators (Maynard Smith and
23 Szathmáry, 1995; Szathmáry and Demeter, 1987; Frank, 1994; Zintzaras et al.,
24 2002; Bianconi et al., 2013; Zintzaras et al., 2010). An alternative hypothesis is
25 that replicators were on some surface which limited their diffusion, but also led
26 to interactions between different types of cooperative replicators (Boerlijst and
27 Hogeweg, 1991, 1995; Cronhjort and Blomberg, 1997; McCaskill et al., 2001;
28 Szabó et al., 2002; Sardanyés and Solé, 2007; Shay et al., 2015). Both of these
29 hypotheses favour cooperation by grouping cooperative replicators together, and
30 hence limiting the extent to which they can be exploited by parasites (Higgs and
31 Lehman, 2015).

32 However, these hypotheses require restrictive assumptions that may not be
33 justified. In order to have replicators grouped by a cell membrane, we would
34 require the evolution of a cell membrane before we had a genome that was
35 sufficiently complex to produce that membrane. This solves the problem of
36 explaining one complex feature (cooperative replicators) by invoking another
37 complex feature (cell membrane). The proto-cell could be an abiotic feature,
38 such as a droplet of oil, but that would require that the division of that droplet
39 was linked to the rate at which replicators copy, in a way that just happened to
40 make group selection work (Maynard Smith and Szathmáry, 1995; Szathmáry
41 and Demeter, 1987; Frank, 1994; Zintzaras et al., 2002, 2010; Bianconi et al.,
42 2013). The limited diffusion hypothesis requires evolution on a particular type
43 of surface to group replicators together in a very specific way, which: (i) lim-
44 its diffusion, so that parasites cannot exploit replicators; (ii) has high enough
45 diffusion to keep different types of replicators well-mixed; (iii) has some prop-
46 erty which ensures binding sites contain different types of replicators, rather
47 than copies of identical replicators (Szabó et al., 2002; Shay et al., 2015). It is
48 not clear how a surface could produce all these properties. In addition, many
49 previous models require simple replicators to have conditional phenotypes, and
50 only act as cooperators in certain interactions, which is a relatively complex
51 behaviour for a very short sequence (Shay et al., 2015; Levin and West, 2017).

52 We propose an alternative hypothesis, where selection itself leads to replica-
53 tors grouping themselves together in a way that favours cooperative enzymatic
54 activity. We hypothesise a scenario, where: (i) one type of replicator can evolve
55 to act as an enzyme to help copy other replicators (cooperation); and (ii) an-
56 other type of replicator can evolve to physically associate with or 'stick' to other
57 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 are 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 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 which incorporate substantial biochemical details (Shay et al., 2015) to very simple adaptation-driven models of replicator cooperation (Frank, 1994; Levin and West, 2017).

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 (Eigen, 1971; Eigen and Schuster, 1977; Szathmáry and Demeter, 1987; Maynard Smith, 1979; Boerlijst and Hogeweg, 1991; Frank, 1994; Maynard Smith and Szathmáry, 1995; Cronhjort and Blomberg, 1997; ?; Sardanyés and Solé, 2007; Bianconi et al., 2013; Shay et al., 2015; Higgs and Lehman, 2015). 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 replication rate (in the Supplementary Material 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) (Figure 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 would 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 summarised in Table S1). 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, like 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 (though this is not required). In the Supplementary Material, we show that the population dynamics of these three different populations are described by:

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

Evolutionary dynamics

We used an adaptive dynamics approach to study the evolution of cooperative enzymatic activity and physical associations in these replicators (Metz et al., 1992; Rand et al., 1994; Geritz et al., 1997; Dieckmann and Law, 1996). We used methods developed to examine interactions between interacting populations (Van Baalen and Jansen, 2001; Hurford et al., 2009), 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 (Maynard Smith and Price, 1973).

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

$$\frac{F'_i}{\beta'[j]} + \frac{P'_i}{M'_{ij}} > 1. \quad (2)$$

139 $F_i = (\rho_i - \mu_i)$ is the replication rate of replicator $i \in X, Y$ on its own,
 140 $P_i = (\mu_j + \theta_i + \delta)$ is the replication rate of $i \in X, Y$ in complexes, and $M_{ij} =$
 141 $(\mu_i + \mu_j + \delta - \rho_{ij})$ is loss (destruction or dissociation) of complexes. The primes
 142 indicate mutant values in replicator $i \in X, Y$, and mutants are denoted $i' \in$
 143 X', Y' . Equation 2 shows how a trait can spread via its effect on the replication
 144 rate of a replicator on its own (F'_i), the effect on its replication rate in pairs (P'_i),
 145 the effect on the loss of complexes (M'_{ij}), and the effect on pairings with the
 146 other replicator type ($\beta'[j]$). Van Baalen and Jansen (2001) developed a similar
 147 expression for the invasion of a rare mutant in the context of studying common
 148 defence of a predator by two prey populations (Supplementary Material S4).
 149 We now proceed to study the evolution of cooperative enzymatic activity and
 150 physical association.

151 Enzymatic cooperation

152 We first asked whether selection would favour replicators to act as enzymes that
 153 help copy other replicators. This can be thought of as evolution towards more
 154 cooperative replicators, which would facilitate the evolution of the genome. We
 155 examined this possibility by allowing replicator X to mutate in a way that made
 156 it better at helping copy replicator Y , by increasing the density independent
 157 replication of Y by a factor $1 + \omega d'$ when Y is in a complex with a mutant
 158 (X'). We assumed that this mutation would cause the X replicator to be less
 159 efficient at copying itself, by reducing the replication rate of X by a factor
 160 $1 - d'$. For example, this could be a conformational change which reduces X 's
 161 autocatalytic rate, but causes X to act as a catalyst to increase the replication
 162 rate of Y . Consequently, we are assuming a trade-off between the rate at which a
 163 replicator can help copy other replicators, and the rate at which that replicator
 164 can copy itself.

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

173 We found that cooperative enzymatic activity was not favoured. Specifically,
 174 more cooperative X' mutants ($d' > 0$) were never able to invade a population
 175 of resident X and Y , and that the X population rests stably at a value of zero

176 cooperation (Figure 2a). We found cooperation could not spread because it
 177 reduced the replication rate of the mutant, and there was no mechanism by
 178 which the benefit to Y could be fed back to X' . While cooperative enzymatic
 179 activity increases the density of Y , the baseline association rates are sufficiently
 180 low that this effect is not strong enough to favour such activity. Specifically,
 181 cooperation reduces both terms in equation 2, by reducing both replication in
 182 complexes and alone (the numerators), and leaving the association with the
 183 other type ($\beta'[j]$) unaffected. Cooperation reduces the loss of complexes in
 184 the second term (M'_{ij}), but this is not enough to outweigh the direct cost to
 185 replication. This is analogous to the standard evolutionary result that, all else
 186 being equal, a cooperative behaviour that benefits an unrelated individual will
 187 not be favoured (Hamilton, 1964).

188 Physical association

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

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

208 We found that association could be favoured (Figure 2b). Specifically, if
 209 the byproduct benefits gained by being paired with an X (κ), and the relative
 210 increase in association rate caused by the mutation ($\frac{\alpha c'}{c'}$) are sufficiently high
 211 ($>> 1$), successive mutations with higher values of association ($c' > 0$) will
 212 invade a population of resident X and Y , until the association rate comes to
 213 rest at some equilibrium value (c^*). Some level of association is favoured because
 214 while it causes an immediate reduction in replication rate, this is outweighed by
 215 the increase in replication rate due to being in complexes with X more often.
 216 Specifically, association reduces the first term in equation 2 (via the numerator),
 217 but this is outweighed by an increase in the second term (via the denominator).

218 Coevolution

219 We then examined what happens when both enzymatic cooperation and asso-
 220 ciation are allowed to co-evolve. We did this by allowing for mutations in both
 221 replicators: X to evolve to be more cooperative ($d' > 0$), and Y to associate
 222 at a greater rate ($c' > 0$). To allow for coevolution, we analysed the selection
 223 gradient on both traits in both mutant populations simultaneously, which tells
 224 us which direction in state space the population is moving at any given point.
 225 By repeating this across all of state space for both traits, we can determine
 226 which direction both replicator types will evolve in.

227 In the Supplementary Material we show that, when both traits are allowed
 228 to coevolve, selection can drive enzymatic cooperation (d^*) to its maximal value
 229 and association (c^*) to a higher value than when evolving on its own (Fig. 2c).
 230 Coevolution favours enzymatic cooperation when the association and enzymatic
 231 cooperation increase the chance that replicators produced by complexes pair
 232 again ($\lambda, \alpha \gg 1$), and when byproduct benefits are large ($\kappa \gg 1$). Further,
 233 even under conditions in which association would not evolve on its own (e.g.
 234 when $\zeta = 0$), if association still increases the duration of pairings ($\xi > 0$), then
 235 coevolution can favour enzymatic cooperation and association.

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

242 Our results show that the key factor favouring positive co-evolution between
 243 cooperation and physical association is that the two traits increase the chance
 244 that copies produced from complexes pair again. We captured this in the term
 245 $(1 + \lambda d')(1 + \alpha c')\rho_{ij}$, which leaves unspecified exactly how the two traits in-
 246 crease immediate pairing. In the Supplementary Material, we derive an explicit
 247 model, tracking the individual copies produced from pairs, and modelling how
 248 they repair. The explicit model recovers the results of the more general model,
 249 showing that co-evolution is only favoured when both traits increase the chance
 250 of pairing again.

251 For simplicity, we have limited our model to two types of replicators, X and
 252 Y , but once cooperation and association evolve, there is no reason why more
 253 replicators cannot be added, further elaborating the genome. Further, Frank
 254 (1995) pointed out that the conditions favouring cooperation need only be tem-
 255 porary, as once replicator functions come to depend on the association, reversals
 256 become more difficult. Finally, our model is not intended to be quantitative, but
 257 qualitative; highlighting the relationship between parameters and the potential
 258 for specific selective forces to favour cooperation. For those developing specific,
 259 quantitative models, for a given chemical system, we discuss the quantitative
 260 significance of our results in the Supplementary Material.

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 co-operator or its genetic relatives (Frank, 1998; Foster and Wenseleers, 2006; Gardner et al., 2006; Wyatt et al., 2013). 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 (D’Souza et al., 2018). Our prediction is also analogous to Law and Dieckmann (1998)’s result that the evolution of vertical transmission could lead to stable symbiosis in exploiter/victim interactions.

Another force which could theoretically drive positive between-species co-evolution is synergy of fitness effects (Frank, 1995; Foster and Wenseleers, 2006; Gardner et al., 2006; Queller, 2011). Synergy occurs when two co-operators 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 there is some baseline byproduct benefit to being complexes. This leads to a population of replicators which 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 include: division of labour and mutual dependence between replicators; the efficiency of molecular interactions before compartmentalisation; the ability of a single molecule to fulfil the role of DNA and protein; and prebiotic synthesis of nucleotides (Higgs and Lehman, 2015; Cooper and West, 2018; Takeuchi et al., 2017). 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 Eigen

303 (1971); Szathmary and Demeter (1987); Maynard Smith (1979); Maynard Smith
304 and Szathmary (1995); Higgs and Lehman (2015). Our model does not rule out
305 the role of a cell in solving these other problems – instead we have shown that
306 a cell is not *required* to solve the problem of enzymatic cooperation.

307 Our results make the evolution of a primitive genome easier to explain, by
308 simplifying the conditions required. This does not mean that previous explana-
309 tions are invalid, just that they may come in at different stages in the evolution
310 of life. For a *primitive* genome, our results suggest that we don’t need to: (a)
311 invoke the cell, a potentially complex feature of life; (b) assume highly specific
312 population structures on special surfaces; or (c) grant simple replicators with
313 conditional phenotypes. Consequently, our result increases the kinds of envi-
314 ronments where the first steps towards a genome can evolve. It also means
315 that a more complex genome could have evolved to then produce the first cell,
316 because our result shows how genome complexity could increase without a cell
317 membrane. Finally, our results shift the focus of origin of the genome questions
318 from external features of the environment to biological features of replicators.
319 Specifically, what phenotypes are possible in simple molecules? Can they act to
320 increase the replication rate of others? Can they stick to each other?

321 Data availability statement

322 There are no data to report.

323 Code availability statement

324 All code has been made available, along with an implementation of the calcula-
325 tions, in the Supplementary Software.

326 Competing interests statement

327 The authors declare no competing interests.

328 Author contributions

329 SRL and SAW conceived of the manuscript. Modelling was carried out by SRL
330 and SG, and all authors contributed equally to the final presentation of the
331 manuscript.

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338 References

- 339 Bianconi, G., Zhao, K., Chen, I. A., and Nowak, M. A. (2013). Selection for
340 replicases in protocells. *PLoS Comput Biol*, 9(5):e1003051.
- 341 Boerlijst, M. C. and Hogeweg, P. (1991). Spiral wave structure in pre-biotic
342 evolution: hypercycles stable against parasites. *Physica D: Nonlinear Phenomena*, 48(1):17–28.
- 344 Boerlijst, M. C. and Hogeweg, P. (1995). Spatial gradients enhance persistence
345 of hypercycles. *Physica D: Nonlinear Phenomena*, 88(1):29–39.
- 346 Bourke, A. F. (2011). *Principles of social evolution*. Oxford University Press.
- 347 Cooper, G. A. and West, S. A. (2018). Division of labour and the evolution of
348 extreme specialization. *Nature ecology & evolution*, 2(7):1161.
- 349 Cronhjort, M. B. and Blomberg, C. (1997). Cluster compartmentalization may
350 provide resistance to parasites for catalytic networks. *Physica D: Nonlinear Phenomena*, 101(3-4):289–298.
- 352 Dieckmann, U. and Law, R. (1996). The dynamical theory of coevolution:
353 a derivation from stochastic ecological processes. *Journal of mathematical biology*, 34(5-6):579–612.
- 355 D’Souza, G., Shitut, S., Preussger, D., Yousif, G., Waschina, S., and Kost,
356 C. (2018). Ecology and evolution of metabolic cross-feeding interactions in
357 bacteria. *Natural Product Reports*, 35(5):455–488.
- 358 Eigen, M. (1971). Selforganization of matter and the evolution of biological
359 macromolecules. *Naturwissenschaften*, 58(10):465–523.
- 360 Eigen, M. and Schuster, P. (1977). A principle of natural self-organization.
361 *Naturwissenschaften*, 64(11):541–565.
- 362 Foster, K. R. and Wenseleers, T. (2006). A general model for the evolution of
363 mutualisms. *Journal of evolutionary biology*, 19(4):1283–1293.
- 364 Frank, S. A. (1994). Kin selection and virulence in the evolution of protocells and
365 parasites. *Proceedings of the Royal Society of London B: Biological Sciences*,
366 258(1352):153–161.
- 367 Frank, S. A. (1995). The origin of synergistic symbiosis. *Journal of theoretical biology*, 176(3):403–410.
- 369 Frank, S. A. (1998). *Foundations of social evolution*. Princeton University Press.

- 370 Gardner, A., West, S. A., and Barton, N. H. (2006). The relation between
371 multilocus population genetics and social evolution theory. *The American*
372 *Naturalist*, 169(2):207–226.
- 373 Geritz, S. A., Metz, J. A., Kisdi, É., and Meszéna, G. (1997). Dynamics of
374 adaptation and evolutionary branching. *Physical Review Letters*, 78(10):2024.
- 375 Hamilton, W. D. (1964). The genetical theory of social behavior. i and ii. *Journal*
376 *of Theoretical Biology*, 7(1):1–52.
- 377 Higgs, P. G. and Lehman, N. (2015). The rna world: molecular cooperation at
378 the origins of life. *Nature Reviews Genetics*, 16(1):7–17.
- 379 Hurford, A., Cownden, D., and Day, T. (2009). Next-generation tools for evolu-
380 tionary invasion analyses. *Journal of the Royal Society Interface*, 7(45):561–
381 571.
- 382 Law, R. and Dieckmann, U. (1998). Symbiosis through exploitation and the
383 merger of lineages in evolution. *Proceedings of the Royal Society of London.*
384 *Series B: Biological Sciences*, 265(1402):1245–1253.
- 385 Levin, S. R. and West, S. A. (2017). The evolution of cooperation in simple
386 molecular replicators. *Proceedings of the Royal Society of London B: Biological*
387 *Sciences*, 284(1864).
- 388 Maynard Smith, J. (1979). Hypercycles and the origin of life. *Nature*, 280:445–
389 446.
- 390 Maynard Smith, J. and Price, G. (1973). The logic of animal conflict. *Nature*,
391 246(5427):15–18.
- 392 Maynard Smith, J. and Szathmary, E. (1995). *The major transitions in evolu-*
393 *tion*. Oxford University Press.
- 394 McCaskill, J. S., Füchslin, R. M., and Altmeyer, S. (2001). The stochastic evolu-
395 tion of catalysts in spatially resolved molecular systems. *Biological chemistry*,
396 382(9):1343–1363.
- 397 Metz, J. A., Nisbet, R. M., and Geritz, S. A. (1992). How should we define
398 ‘fitness’ for general ecological scenarios? *Trends in Ecology & Evolution*,
399 7(6):198–202.
- 400 Queller, D. C. (2011). Expanded social fitness and hamilton’s rule for kin, kith,
401 and kind. *Proceedings of the National Academy of Sciences*, 108(Supplement
402 2):10792–10799.
- 403 Rand, D. A., Wilson, H., and McGlade, J. M. (1994). Dynamics and evolution:
404 evolutionarily stable attractors, invasion exponents and phenotype dynamics.
405 *Philosophical Transactions of the Royal Society of London. Series B: Biolog-*
406 *ical Sciences*, 343(1305):261–283.

- 407 Sardanyés, J. and Solé, R. V. (2007). Spatio-temporal dynamics in simple asym-
408 metric hypercycles under weak parasitic coupling. *Physica D: Nonlinear Phe-*
409 *nomena*, 231(2):116–129.
- 410 Shay, J. A., Huynh, C., and Higgs, P. G. (2015). The origin and spread of a
411 cooperative replicase in a prebiotic chemical system. *Journal of theoretical*
412 *biology*, 364:249–259.
- 413 Szabó, P., Scheuring, I., Czárán, T., and Szathmáry, E. (2002). In silico sim-
414 ulations reveal that replicators with limited dispersal evolve towards higher
415 efficiency and fidelity. *Nature*, 420(6913):340–343.
- 416 Szathmáry, E. and Demeter, L. (1987). Group selection of early replicators and
417 the origin of life. *Journal of theoretical biology*, 128(4):463–486.
- 418 Takeuchi, N., Hogeweg, P., and Kaneko, K. (2017). The origin of a primordial
419 genome through spontaneous symmetry breaking. *Nature communications*,
420 8(1):250.
- 421 Van Baalen, M. and Jansen, V. A. (2001). Dangerous liaisons: the ecology of
422 private interest and common good. *Oikos*, 95(2):211–224.
- 423 Wyatt, G., West, S., and Gardner, A. (2013). Can natural selection favour
424 altruism between species? *Journal of evolutionary biology*, 26(9):1854–1865.
- 425 Zintzaras, E., Santos, M., and Szathmáry, E. (2002). “living” under the challenge
426 of information decay: the stochastic corrector model vs. hypercycles. *Journal*
427 *of theoretical biology*, 217(2):167–181.
- 428 Zintzaras, E., Santos, M., and Szathmáry, E. (2010). Selfishness versus func-
429 tional cooperation in a stochastic protocell model. *Journal of theoretical bi-*
430 *ology*, 267(4):605–613.

431 **Figure 1 Caption**

432 Interactions and fitness effects. (a) Two replicators, X and Y , each have some
433 baseline replication rate on their own, but can acquire mutations (X' and Y')
434 which reduce their replication rate. (b) Each replicator (X and Y) has a higher
435 replication rate whenever in complexes due to passive benefits (byproduct bene-
436 fits). (c) Mutant X' increases the replication rate of Y in complexes (enzymatic
437 benefit from X). (d) Mutant Y' increases the rate at which the mutant forms
438 associations with X , and decreases the rate at which these associations break
439 down.

Figure 2 Caption

The coevolution of enzymatic activity and association. Grey shaded areas show regions of state space where selection is negative, and white areas where selection is positive. Arrows depict the direction of evolution in state space along neutral lines. Evolutionarily stable strategies are depicted by solid circles. (a) The evolution of enzymatic activity in X is not favoured. In the absence of association, cooperative enzymatic activity cannot evolve. (b) The evolution of association in Y . In the absence of cooperative enzymatic activity in X , some intermediate level of association in Y is favoured. (c) The 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 maximal value of 1. (d) A schematic of (a)-(c). Solid circles depict the evolutionarily stable resting point of both populations depending on whether each population evolves independently or evolve jointly. Coevolution favours higher values in both traits. Values for parameters in (a)-(d) are: $\alpha = 20, \lambda = 20, \zeta = 5, \xi = 1, \omega = 20, r_Y = 2.3, r_X = 2.1, r_{XY} = 0.9, k = 0.01, \mu_Y = 1.1, \mu_X = 1.1, \kappa = 100, \beta = 0.01, \delta = 0.9$. All figures generated graphically from the equations described in the Supplementary Material using Mathematica Software version 11.3.0.0.