

1 **Inevitability of the emergence and persistence of genetic parasites caused by**
2 **thermodynamic instability of parasite-free states**

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16

17 **Abstract**

18 Genetic parasites, including viruses and mobile genetic elements, are ubiquitous among cellular
19 life forms, and moreover, are the most abundant biological entities on earth that harbor the bulk
20 of the genetic diversity. Here we examine simple thought experiments to demonstrate that both
21 the emergence of parasites in simple replicator systems and their persistence in evolving life
22 forms are inevitable because the putative parasite-free states are thermodynamically unstable.

23

24 **Background**

25 Nearly all cellular life forms are hosts to various types of genetic parasites that exploit functional
26 systems of the host cells to replicate their own genomes [1]. Only some bacteria with highly
27 reduced genomes that themselves lead a symbiotic or parasitic lifestyle seem to lack genetic
28 parasites that undoubtedly have been lost during the reductive evolution of these bacteria from
29 free-living ancestors. Genetic parasites include viruses, transposons, plasmids and other semi-
30 autonomous genetic elements (SAGE) [2] that display a broad range of relationships with the
31 hosts, from acute antagonism, whereby a virus rapidly kills the host, to symbiosis when SAGE
32 are not costly to the host and could even have beneficial effects [3, 4].

33 Strikingly, virus particles appear to be the most common biological entities on earth. In most
34 environments, the ratio between virus particles and cells varies between 10 and 100 [4-7]. This
35 enormous physical abundance of viruses is matched by vast genetic diversity so that most of the
36 gene repertoire of the biosphere appears to be concentrated in viruses, even as exact number
37 remain a matter of debate [8-10]. The prevalence of viruses in the biosphere is also paralleled by
38 the abundance of SAGE integrated in genomes of cellular life forms. Integrated SAGE are
39 present in virtually all genomes of cellular organisms (again, missing only in some intracellular
40 symbionts and parasites), and in genomes of multicellular eukaryotes, SAGE-derived sequences
41 quantitatively dominate the genome, comprising at least 50% of the DNA in vertebrates and up
42 to 90% in plants [11]. Recruitment of sequences from SAGE for cellular functions is a common
43 phenomenon that made substantial contributions to the evolution of cellular life forms [12-14].

44 The entire course of the evolution of life is a history of host-parasite co-evolution [15-17]. Being
45 subject to the constant onslaught of genetic parasites, cellular life forms have evolved a plethora
46 of defense mechanisms. A typical organism harbors and interacts with multiple types of genetic
47 parasites (e.g. viruses, different families of transposons, and plasmids) which it holds at bay
48 thanks to multiple defense strategies that include parasite exclusion, innate immunity and
49 adaptive immunity [18-23]. The SAGE respond with counter-defense mechanisms that range
50 from simple mutational escape from defense to dedicated multigene systems that specifically
51 inactivate host defense systems. Notably, defense systems and SAGE including their counter-
52 defense machineries are tightly linked in evolution. Enzymes involved in the mobility of SAGE,
53 in particular, transposons are often recruited by host defense systems for roles in parasite genome

54 inactivation and other functions, and conversely, SAGE recruit components of defense systems
55 that then evolve to become agents of counter-defense [24-26].

56 Thus, the arms race, along with cooperation, between genetic parasites and their hosts are
57 perennial features of the evolution of life. Why is this the case? Why do the parasites emerge in
58 the first place? And, could some cellular organisms actually get rid of the parasites through
59 highly efficient defense systems? Empirically, the answer to the latter question seems to be
60 negative. Conceivably, the general cause of the inability of the hosts to eliminate the genetic
61 parasites is the unescapable cost of maintaining sufficiently powerful defense systems [27-30].
62 Analysis of theoretical models of parasite propagation suggests that an important source of this
63 cost, perhaps the primary one in microbes, could be that efficient anti-parasite defense has the
64 side effect of curtailing horizontal gene transfer (HGT), which is an essential process in
65 microbial evolution that allows microbes to avoid deterioration via Muller's ratchet [31, 32].
66 Another major factor could be the effectively unavoidable autoimmunity [29, 33, 34]. However,
67 what about the first, arguably, the most fundamental question: why do genetic parasites evolve to
68 begin with? Again, empirically, there is a strong impression that the emergence of such parasites
69 is inevitable. Not only are they ubiquitous in cellular life forms but they also evolve in various
70 computer simulations of replicator system evolution [35-39]. Furthermore, it appears intuitive:
71 genetic parasites can be considered cheaters, in game-theoretical terms, and as soon as, in a
72 replicator system, there is a distributable resource, such as a replicase, cheaters would emerge to
73 steal that resource without producing their share of it [40]. These, however, are informal
74 considerations. Here we ask the question: is it possible to develop a theoretical framework that
75 would allow a formal demonstration of the inevitability of the emergence of genetic parasites in
76 evolving replicator systems, or else, that parasite-free replicator systems are after all possible?

77

78 **Thermodynamic instability of parasite-protected replicators**

79 Let us try, as a gedunken experiment, to construct a self-replicating entity that is strictly resistant
80 to parasites. Consider a simple system consisting of a replicator, serving as a template for itself,
81 and the replicase it encodes (Figure 1). The replicator is assumed to contain the replicase-
82 encoding signal (RES) (the replicase could be a protein, a ribozyme, under the RNA World

83 model, or, in theory, any other entity capable of catalyzing replication of a template) and the
84 replicase recognition signal (RRS).

85 Evolvability is a fundamental and inescapable property of such a replicator-replicase system
86 [41]. To be evolvable, a system must possess three basic properties: 1) heredity (whereby the
87 location of progeny in the phenotype space is correlated with that of the parents), 2) variability
88 (whereby the progeny is not identical to the parents), and 3) differential reproduction (whereby
89 the capability of a replicator to leave progeny is part of the phenotype). Heredity is ensured by
90 replication with fidelity above the error catastrophe threshold. The replicator theory that was
91 developed primarily by Eigen and colleagues demonstrates that, under simple fitness landscapes,
92 there exists a replication fidelity threshold, below which the master sequence in a population of
93 replicators cannot be efficiently passed across generations, so that the entire population collapses
94 [42, 43]. Elucidation of the molecular mechanisms of primordial replication that could provide
95 for crossing the error catastrophe threshold remains a daunting task that is central to the entire
96 origin of life field. However, for the purpose of the present discussion, we assume that a
97 sustainable replicator system with a minimally acceptable fidelity has evolved.

98 Variability is ensured because, at any temperature above 0 K, any process is subject to entropy-
99 increasing fluctuations and, therefore, replication is inherently error-prone, under the second and
100 third Laws of Thermodynamics.

101 Differential reproduction ensues from the fact that the replicator encodes the replicase that, in
102 turn, copies the replicator itself. Mutations in both RES and RRS can affect the efficiency of
103 replication.

104 If the resources that are available to the system are limited (i.e. the system does not support
105 unlimited growth of all possible constituent parts), competition between individual replicators
106 ensues and selection arises. In a system with finite memory storage, all information exchange,
107 transfer and utilization processes carry memory clearing cost of at least $kT\ln 2$ J/bit, where k is
108 Boltzmann constant and T is temperature (the existence and value of this minimum information
109 cost is known as Landauer's principle that is a corollary of the Second Law of
110 Thermodynamics); in all known systems, this cost is many orders of magnitude higher [44-46].
111 Therefore, selection for cost reduction acts not only on the constituent parts of the system, but

112 also on the information transfer processes themselves, effectively ensuring an upper limit on the
113 fidelity of information recognition.

114 Selection acts on both RES (eliminating replicators encoding inefficient replicases) and RRS
115 (eliminating replicators that are inefficient as templates, e.g. are poor replicase-binders), but
116 these two selection processes act on the replicator through physically different agents (the
117 replicator-encoded replicase and the replicator itself, respectively).

118 The dual nature of the replicator (acting as both the template and, directly or indirectly, as the
119 replicase) necessitates that the information embedded in the RES and RRS is realized via
120 physically different processes. The RES guides the formation of the replicase which, in turn,
121 recognizes the RRS. Such recognition implies comparing the RRS in the replicator with some
122 form of memory encoded in or attached to the replicase (Figure 2).

123 A general, simple way of parasite emergence involves skipping part of the RES during
124 replication, resulting in a shorter replicator that consists of the RRS and, in the extreme, nothing
125 else (Figure 3). This straightforward mechanism for parasite evolution is inspired by and is
126 similar to the process of RNA shrinking that was observed during *in vitro* evolution in the classic
127 early experiments of Spiegelman and colleagues [47-49].

128 Under the scheme in Figure 3, parasites emerge as long as the information content of the RRS is
129 less than that in the full replicator, i.e. when the RRS is at least partially separable from the RES.
130 If this is the case, a replicator containing the full RRS, but omitting at least some of the RES
131 ($RRS_p \equiv RRS$, $RES_p \rightarrow 0$; the subscript 'p' denotes the respective signals in the parasite), would
132 not only serve as a template as efficient as the original replicator, but would also enjoy an
133 evolutionary advantage because replication of the smaller replicator is faster and requires less
134 resources (building blocks, such as nucleotides, and energy). This makes the parasite-free
135 equilibrium point of the replicator-parasite system unstable because deletion of any part of the
136 RES yields more efficient replicators (Figure 4). Therefore, the system is vulnerable to parasite
137 invasion, and moreover, such an invasion is inevitable under a non-zero parasite emergence rate
138 (see Appendix for a more formal demonstration).

139 It appears that, under this scheme, the only way to render the replicase-producing replicator
140 parasite-protected is to make the RRS to include the entire RES (Figures 2 and 4). Such

141 RRS \equiv RES configuration evidently rules out the emergence of a parasite because any mutation
142 of the RES would also inactivate the RRS and prevent replication.

143 However, such a parasite-protected state is subject to the aforementioned instability (Figure 4).
144 In the absence of parasites, perfect protection does not carry any benefits, but incurs a greater
145 cost than less protected states. Given that the system is evolvable, an RRS < RES state will
146 inevitably arise and outcompete the RRS \equiv RES progenitors that are, as shown above, prone to
147 emergence of genetic parasites (RRS_p \equiv RRS, RES_p \rightarrow 0).

148 From a more abstract perspective, the fully protected RRS \equiv RES system corresponds to the
149 maximally constrained, i.e. minimum entropy, state. The second law of thermodynamics
150 effectively guarantees that it evolves into a higher entropy state, such that RRS < RES, and at
151 least some parts of the RES can be mutated or deleted without compromising replication. The
152 ensemble of higher entropy states is obviously more robust than the unique RRS \equiv RES state. In
153 biological parlance, the higher entropy states are favored by selection via the ‘survival of the
154 flattest’ route [50]. They will necessarily prevail because there are plenty of such states with
155 similar fitness values, whereas the RRS \equiv RES state is singular. However, the problem with the
156 ‘relaxed’ states of the replicator is that they are no longer protected from parasites because a
157 parasite now can evolve that would exploit the RRS without producing the replicase (Figure 3).
158 The Third Law of Thermodynamics dictates that the minimum (zero) entropy state can be stable
159 only at 0 K. Under the detailed correspondence between thermodynamics and population
160 genetics [51], the equivalent of temperature is the inverse effective population size, and
161 accordingly, 0 K corresponds to an infinite population, which can exist only as an abstraction.
162 Thus, in any realistic population, a parasite-free replicator system is inherently unstable and
163 either goes extinct or rapidly spawns parasites (Figure 4). The latter case inevitably triggers the
164 host-parasite arms race, whereby in the simplest case, the hosts evolve by selection for changed
165 RRS allowing them to escape the parasites, whereas the parasites catch up. Furthermore, the
166 competition also occurs between the parasites themselves and could eventually result in the
167 emergence of ultimate parasites, those that consist entirely of the RRS. Such (near) ultimate
168 parasites were the end result of Spiegelman’s experiments [49] and also exist in nature, namely
169 the viroids, small, non-coding parasitic RNAs that cause disease in plants and rely entirely on a
170 host-derived replication machinery [52, 53].

171 It should be noted that, because, at least in the simplest replicator system, the replication rate is
172 inversely proportional to the genome length, the parasite have an intrinsic advantage in the arms
173 race. In the well-mixed case, the preferential replication of parasites drives the host to extinction
174 which, obviously, results in the collapse of the entire system (no replicase is produced anymore) .
175 However, compartmentalization can stabilize host-parasite systems. Thus, parasites, drive
176 evolution of biological complexity [37-39, 54].

177 There seems to be a symmetry between the hypothetical, minimum entropy, parasite-resistant
178 replicator and the ultimate parasite with $RRS_p \equiv RRS$, $RES_p \equiv 0$, another minimum entropy state,
179 this one being the theoretical end result of the competition between parasites (Figure 3). As a
180 minimum entropy state, the ultimate parasite cannot be evolutionarily stable either. The
181 gedunken experiment described above certainly is an idealization. Realistically, when the
182 minimum entropy state relaxes, the host-parasite arms race takes more complex forms. Most
183 parasites are far from this ultimate state but rather possess a number of genes and encode a
184 variety of functions. This complexity of parasites has to do with two strategies that parasites
185 evolve to maximize their evolutionary success, namely: 1) overcoming the defense systems
186 which the hosts evolve under the pressure for resistance to the parasites, and 2) surviving outside
187 the host and disseminating among hosts [4]. The question, then, emerges: even though the above
188 analysis shows that evolution of parasites in simple replicator systems is inevitable, is there a
189 chance that evolution of defense systems would exterminate parasites?

190

191 **Costs and compromises of anti-parasite defense**

192 The thought experiment described above also answers the question whether a perfect defense
193 system can exist. A perfect self vs non-self discrimination, whereby a replicator possesses the
194 means to reject or destroy any potential cheater, that is, any sequence other than a perfect copy of
195 itself, is nothing but the same parasite-protected system with recognition based on the complete
196 information on the self, i.e. $RRS \equiv RES$. We have already shown above that such a system is
197 evolutionary unstable from pure thermodynamic considerations because it provides no benefit in
198 the absence of parasites, and will inevitably devolve to an $RRS < RES$ configuration (“leaky”
199 defense).

200 The existence of an unavoidable cost implies that maintenance of any form of defense is subject
201 to a cost-benefit tradeoff. Notably, a recent quantitative assessment of the selection coefficients
202 (a measure of fitness cost) associated with different classes of genes in microbial genomes has
203 shown that defense systems are as costly as the more benign SAGEs, such as transposons [30].
204 This result seems to be a genome-scale reflection of the intrinsic costliness of defense dictated by
205 thermodynamics. In the actual biological context, this cost can be manifested in different forms,
206 such as autoimmunity or interference of defense systems with HGT. The curtailment of HGT, in
207 particular, could be a key factor that makes defense systems costly and causes their repeated loss
208 [32]. However, at the bottom of it all seems to be the thermodynamic cost of information.
209 Certainly, defense is not the only process associated with an information cost. Such cost is
210 intrinsic to all processes of information transmission including replication, transcription,
211 translation, as well as signal transduction. However, loss of genes encoding those other functions
212 is often strongly deleterious to the organism, resulting in positive mean selection coefficients for
213 the respective classes of genes [30]. This is not the case for defense systems because, of which
214 the mean selection coefficient values for the defense genes are negative [30], and in accord with
215 this observation, defense genes are lost in the course of evolution significantly more often than
216 genes of other functional categories [55]. Due to these fitness costs, evolving organisms cannot
217 build up defense systems to the extent that is required to eliminate parasites (Figure 4).

218

219 **A quasi-formal demonstration of the inevitability of the emergence and persistence of** 220 **parasites**

221 In the above, we demonstrate that a parasite-protected state, one in which $RRS \equiv RES$, is
222 thermodynamically unstable. The inevitability of the emergence of parasites and their subsequent
223 persistence follows from this demonstration. To present the argument succinctly and quasi-
224 formally:

225 (1) The two signals that are essential in a replicator system, RRS and RES, are encoded in
226 different genomic sequences.

227

228 (2) Thus, at least some parts of the RES can be deleted without inactivating the RRS. Hence
229 genetic parasites emerge.

230

231 (3) The shorter the genome sequence of a genetic element the more efficient its replication is.
232 Hence parasites accumulate in a replicator system and may bring it to collapse in a well-mixed
233 case.

234
235 (4) A perfect defense system should, in the least, be able to recognize parasitic elements, i.e.
236 detect missing parts of the host genome. At the end of the replication cycle, this information
237 should be deleted. Under the Landauer principle, the cost of memory cleaning is at least $kTn\ln 2$ J
238 (n bits distinguish the host and the parasite). This cost makes defense systems evolutionary
239 unstable and precludes elimination of parasites.

240

241

242 **Conclusions**

243 The problem of the ubiquity and persistence of genomic parasites throughout the evolution of life
244 can be broken into two parts: i) emergence of parasites in primitive replicator systems, ii)
245 persistence of parasites in evolving organisms. Our analysis of the basic aspects of host-parasite
246 coevolution presented here suggests that there are fundamental thermodynamic causes of the
247 inevitability of parasites on both stages. To put it most succinctly, both the hypothetical parasite-
248 protected state in a simple replicator system and the putative secondary parasite-free state
249 resulting from efficient action of evolved defense systems are thermodynamically unstable and
250 can only exist transiently. These conclusions certainly are compatible with a wealth of
251 observational data indicating that genetic parasites, along with defense systems, are enormously
252 abundant in the biosphere and accompany virtually every cellular life form. The results of
253 numerous mathematical and computational modeling studies on replicator evolution, in which
254 parasites invariably appear, lead to the same conclusion. The simple thought experiments
255 described here that start, effectively, from first principles emphasize the growing understanding
256 that emergence as well as persistence of genetic parasites is an inalienable feature of evolving
257 replicators and, as such, one of the central principles of biology.

258

259 **Appendix A.**

260 Consider a simple system in which both the replicator and a parasite comprise single entities and
261 the replicator entity can also function as the replicase (e.g., both the replicator and the parasite
262 are single RNA molecules, and the replicator molecule in the native folded state can function as
263 the replicase ribozyme). Replication of the replicator entity is governed by the second-order
264 kinetics, where a template replicator meets an (identical) replicase to make a copy of the
265 template. There is also a natural decay of both types of entities, occurring with the first-order
266 kinetics. In an environment with a fixed carrying capacity (determined, e.g., by the influx of
267 consumable resources), such a system behaves as a classical logistic model, with one exception:
268 there exists a critical number of entities, below which the population is unsustainable due to the
269 (second-order) replication lagging behind the (first-order) decay.

270 Likewise, a parasite entity replicates upon meeting a replicator (acting as a replicase) and decays
271 spontaneously. The parasite population is subject to similar environmental restrictions as that of
272 the replicator due to the limitation by the same resources.

273 The more general model that we consider here also includes the existence of a (potentially
274 costly) defense system:

$$275 \quad \frac{dR}{dt} = \frac{1}{1 + \alpha e^*} R^2 \left(1 - \frac{R + P/q}{K} \right) - e_R R$$

$$276 \quad \frac{dP}{dt} = \frac{q}{1 + e^*} PR \left(1 - \frac{R + P/q}{K} \right) - e_P P$$

277 where R and P are the concentrations of the replicator and the parasite particles, respectively, e_R
278 and e_P are the corresponding decay rates and K is the environment carrying capacity (the
279 replicator growth rate is taken to be 1 without loss of generality). The parasite enjoys an
280 evolutionary advantage that is manifested in two ways: it both replicates faster and consumes
281 fewer resources by the same factor q (the simple conceptual model of this effect is based on an
282 RNA molecule that is shorter than the replicator by a factor of q). The parasite replication is
283 countered by the defense systems that are embedded in the replicase and discriminate against the
284 parasites with an efficiency e^* . The action of the defense system is costly to the replicator, with
285 the cost coefficient α (according to the Landauer principle, $\alpha > 0$)

286 Upon introduction of the parasite to the population of the replicator near the equilibrium ($P \rightarrow 0$,
287 $dR/dt \rightarrow 0$), the host defense prevents the parasite invasion ($dP/dt < 0$) only if

288
$$\frac{1 + e^*}{1 + \alpha e^*} > q \frac{e_R}{e_P} \cong q$$

289 or, in other words, only if the effect of defense on the invading parasite relative to the cost of
290 defense to the host is greater than the parasite advantage q (assuming comparable decay rates).

291 Obviously, the replicator population lacking the defense system ($e^* = 0$) cannot resist the
292 parasite invasion. A defense system combining high efficiency with low cost is capable of
293 protecting the host population, but the maintenance of such defense depends on regular invasion
294 of parasites (otherwise, the evolutionary disadvantage due to the cost of defense would drive the
295 defense system to extinction). In other words, a parasite-protected state of replicator system is
296 unstable.

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298

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308 EVK conceived of the project; EVK, YIW and MIK developed the theory and wrote the
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315 **Competing interests**

316 The authors declare that they have no competing interests.

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433 **Figure legends**

434 Figure 1. A replicator-replicase systems with heredity, variability and differential reproduction.

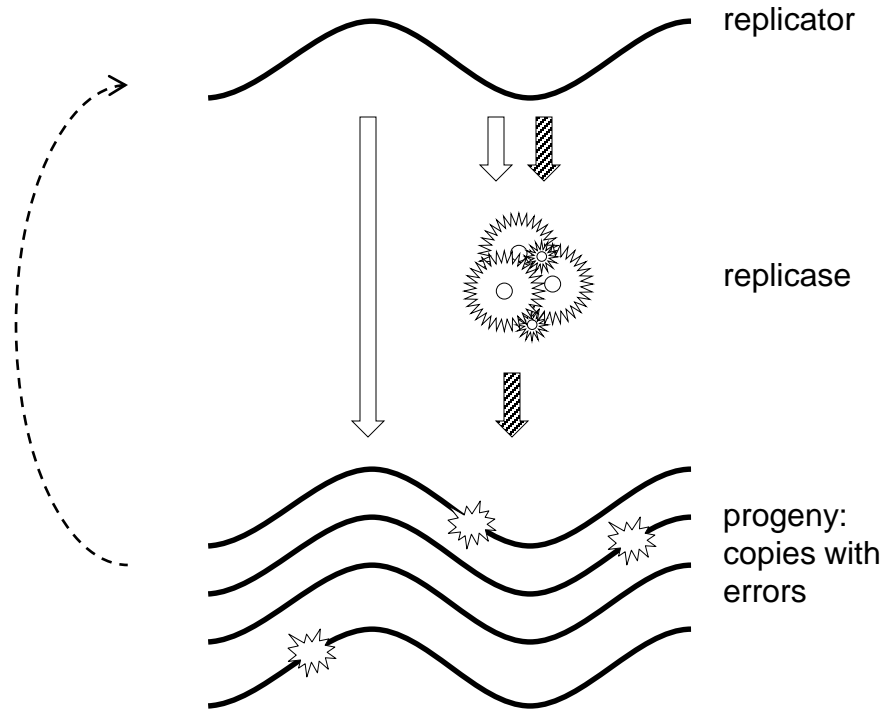
435 The dotted arrow denotes differential reproduction of the copies of the original replicator that
436 carry mutations.

437 Figure 2. The replicase-encoding signal (RES) and replicase-recognition signal (RRS) in
438 replicator-replicase systems. For generality, the RRS is shown as being distributed along the
439 length of the replicator although in real genomes, this signal is often localized such that, for
440 example, short terminal sequences are sufficient for the replication of a virus genome. The
441 replicase structure carries memory of the RRS allowing recognition of competent templates
442 (“pass/block mechanism”).

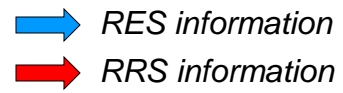
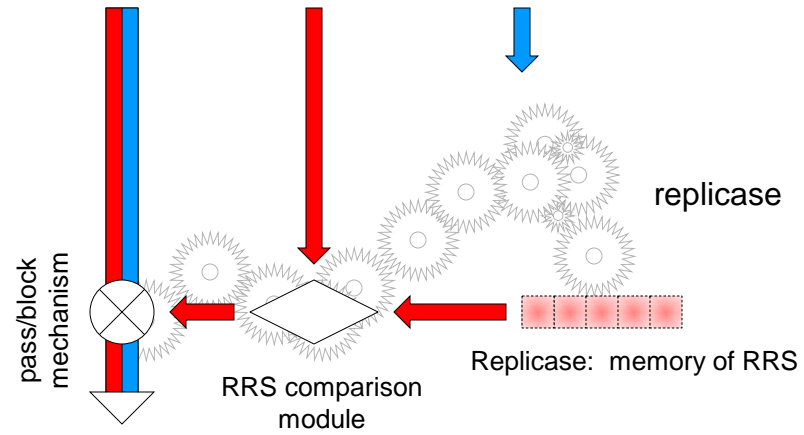
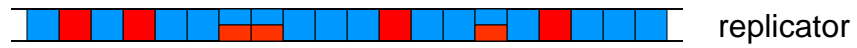
443 Figure 3. Emergence of parasites in replicator systems via deletion of portion of the RES.

444 Figure 4. A conceptual phase diagram of the evolution of replicator systems.

445



→ *information*
▨ → *action*

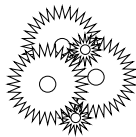




replicator



parasites



replicase

 *RES*
 *RRS*

