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The evolution of replicators

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Replicators of interest in chemistry, biology and culture are briefly surveyed from a conceptual point of view. Systems with limited heredity have only a limited evolutionary potential because the number of available types is too low. Chemical cycles, such as the formose reaction, are holistic replicators since replication is not based on the successive addition of modules. Replicator networks consisting of catalytic molecules (such as reflexively autocatalytic sets of proteins, or reproducing lipid vesicles) are hypothetical ensemble replicators, and their functioning rests on attractors of their dynamics. Ensemble replicators suffer from the paradox of specificity: while their abstract feasibility seems to require a high number of molecular types, the harmful effect of side reactions calls for a small system size. No satisfactory solution to this problem is known. Phenotypic replicators do not pass on their genotypes, only some aspects of the phenotype are transmitted. Phenotypic replicators with limited heredity include genetic membranes, prions and simple memetic systems. Memes in human culture are unlimited hereditary, phenotypic replicators, based on language. The typical path of evolution goes from limited to unlimited heredity, and from attractor-based to modular (digital) replicators.

Keywords: replicator; heredity; evolution; limited heredity; genetic membranes; paradox of specificity

1. INTRODUCTION

The replicator, as introduced by Dawkins (1976), has become one of the central concepts in evolutionary theory. He identified two types of replicator with unbounded evolutionary potential: genes and memes. These ideas have turned out to be extremely fruitful: they have elicited renewed interest in the philosophy of evolution (e.g. Hull 1980), and have led to the recognition of other types of replicators with very important roles in evolution (Maynard Smith & Szathmáry 1993, 1995). In this paper I will give a coarse-grained, and surely incomplete, survey of the different kinds of replicators known to chemists, biologists and scholars interested in cultural evolution.

The notion of autocatalysis plays a central role in replicator theory. Biologists are interested in replicators with heredity, or informational replicators. The importance of this idea was spelled out by Maynard Smith (1986) in his fire example: fire spreads autocatalytically but its characteristic features (such as colour, shape and temperature) are determined by the external conditions and not by the fact of whether it was ignited by a match or a burner. This is important because processes akin to fire can lead to replication in chemical systems as well. In the case of some reaction–diffusion systems, for example, spots with colour and composition different from the surrounding medium can form and replicate. A theoretical analysis of this phenomenon was presented by Reynolds *et al.* (1994) and shown to be analogous to 'fire replication'. Suppose that chemical A consumes material X for its own autocatalytic growth. If the system is not stirred, diffusion plays a crucial role in the dynamics. If X is consumed fast in the initial region (spot), then A will spontaneously grow in directions where X is plentiful. This tendency, combined with some numerical parameter values, can lead to spontaneous spot replication. Although fascinating, we are interested in something more—the cases where heredity sets in.

A classification of replicators was presented by Maynard Smith & Szathmáry (1993, 1995) and it has been refined a number of times (Szathmáry 1995, 1999*a*). Most widely known replicators, including genes, are strongly tied to the world of chemistry—this is obviously not true for memes. Some replicators have only limited heredity (Maynard Smith & Szathmáry 1993, 1995), meaning that the number of possible types is smaller than, or roughly equal to, the number of individuals (copies, sequences, etc.) in a plausible (realistic) system. Conversely, in the case of unlimited hereditary replicators, the number of types by far exceeds that of individuals in the population (Szathmáry & Maynard Smith 1997). This shows that a classification of replicators is not naturally hierarchical: there exist molecular and non-molecular replicators with limited or unlimited hereditary potential. It is not my aim to present here a classification of replicators—rather I would like to help the reader familiarize themself with the important concepts, through the appreciation of some relevant examples. I include almost no explicit discussion of conventional DNA replicators—rather, I spare space for the lesser known cases. Examples of replicators discussed in this paper are listed in table 1, along with their crucial properties.

2. ENSEMBLE REPLICATION IN A HYPOTHETICAL LIPID WORLD

In order to become familiar with the lesser known forms of replication, I now consider a molecular system

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Table 1. *Properties and examples of replicators*

	maintenance		set		mode		level		potential	
	attractor	storage	ensemble	solitary	holistic	modular	genotypic	phenotypic	limited	unlimited
genes	—	×	—	×	—	×	×	—	—	×
lipid vesicles	×	—	×	—	—	×	×	—	×	—
protein nets	×	—	×	—	—	×	×	—	×	—
formose cycle	×	—	—	×	×	—	×	—	×	—
peptide templates	—	×	—	×	—	×	×	—	×	—
prions	×	(×)	—	×	×	—	—	×	×	—
genetic membranes	—	×	×	—	—	×	—	×	×	—
human memes	—	?	?	—	?	×	—	×	—	×

with limited hereditary potential. Imagine first a set of replicating DNA molecules such as occurs in the macronucleus of hypotrych ciliates. In this case the set is replicating only because all its elements are. Ensemble replication is quite a different process—only the set as a whole is able to replicate. In the lipid world scenario (Segré *et al.* 2000) it is postulated that there can exist a set of different lipid molecules that catalyse the formation–incorporation of some members in the set, so that ultimately the formation–incorporation of all members is catalysed by at least one member in the set (Segré *et al.* 1998). Such systems are called 'reflexively autocatalytic' (e.g. Kauffman 1986, 1993) since there is no direct template replication or copying.

(a) *Cyclic stoichiometry: a useful tool*

As Orgel (1992) noted, in the molecular world autocatalyis and replication are two sides of the same phenomenon. As early as 1974, Gánti realized that the formation of membranes is autocatalytic (Gánti 1974). In order to appreciate this, I shall apply simple equations from cyclic stoichiometry (Gánti 1971, 1979, 1987). The basic idea is rather simple. Consider first a simple catalytic process

$$\mathrm{E} + \mathrm{X} \xrightarrow{\mathrm{E}} \mathrm{E} + \mathrm{Y}, \tag{1}$$

where it is assumed that molecule E (e.g. an enzyme) catalyses the transformation of X to Y. Simple 'classroom' rules of chemical stoichiometry would command the cancellation of E from both sides of the equation, but this would distort reality. This is why it is customary to put the 'E' on top of the arrow. However, in this case we do not gain information about the quantities involved in the reaction, which should be the essence of chemical stoichiometry. Recognizing this problem, Gánti introduced cyclic stoichiometry, according to which the equation can correctly be formulated as

$$\mathrm{E} + \mathrm{X} - \textcircled{1} \rightarrow \mathrm{E} + \mathrm{Y}, \tag{2}$$

where the cyclic process sign indicates that one molecule of X is transformed into one molecule of Y at one turn of one molecule E (Gánti 1971). Therefore, one can change the turning number accordingly:

$$\mathrm{E} + u\mathrm{X} - \textcircled{u} \rightarrow \mathrm{E} + u\mathrm{Y}. \tag{3}$$

An autocatalytic process results in the formation of the same molecule that performs the catalysis. In Gánti's general notation,

$$\mathrm{A} + \mathrm{X} - \textcircled{1} \rightarrow 2\mathrm{A} + \mathrm{Y}, \tag{4}$$

where A is an autocatalyst, or replicator. Note that this is a definition: a molecular autocatalyst must be a replicator. Again we may change the turning number:

$$\mathrm{A} + (2^u - 1)\mathrm{X} - \textcircled{u} \rightarrow 2^u\mathrm{A} + (2^u - 1)\mathrm{Y}, \tag{5}$$

indicating the capacity for exponential growth given adequate resources. For the case of membrane replication Gánti introduced the following notation:

$$\boxed{\mathrm{T}_m} + \mathrm{T} \rightarrow \boxed{\mathrm{T}_{m+1}}, \tag{6}$$

which shows that the existing membrane (marked with the frame) is composed of m pieces of the membrane-forming molecule T. Through a series of consecutive additions expressed above, one may arrive at a membrane of doubled surface. Membrane vesicles can undergo spontaneous growth, and under appropriate conditions of the medium they spontaneously divide into two:

$$\boxed{\mathrm{T}_m} + m\,\mathrm{T} - \textcircled{1} \rightarrow 2\boxed{\mathrm{T}_m}, \tag{7}$$

which is clearly analogous to equation (4). The membrane vesicle is a molecular replicator. It is also a trivial replicator since it incorporates ready-made building blocks from the medium. Bachmann *et al.* (1992) presented an excellent experimental example of the above process.

(b) *Attractor-based heredity*

The information carried by DNA is largely decoupled from the chemical differences (reactivity, conformation, etc.) of the different sequences. Replication and repair of DNA is a generalized, largely aspecific process: an indefinitely large number of sequences can be propagated stably by the same canonical informational mechanism. In contrast to this, a network of appropriate reactions can only ensure generalized lipid membrane inheritance.

Note that membrane replication in its generality hinges on two conditions: (i) any membranogenic molecule with an appropriate amphiphilic molecular structure will be inserted; and (ii) the membrane may catalyse not only the insertion, but also the formation of membranogenic molecules. It is easy to characterize this process in general:

$$\boxed{\sum_i m_i \mathrm{T}_i} + \mathbf{X} - \textcircled{1} \rightarrow 2\boxed{\sum_i m_i \mathrm{T}_i} + \mathbf{Y}, \quad (8)$$

where m_i is the number of species T_i in the membrane, $\mathbf{X}$ and $\mathbf{Y}$ are the summed consumed raw and produced waste molecules, respectively, in the corresponding stoichiometric amounts (hence the boldface). (The symbol above the cyclic process sign has been omitted for simplicity.) Equation (8) shows that membranes may be non-trivial replicators, contributing to the synthesis of their building blocks.

Note that if systems characterized by equation (8) can in fact exist, then they qualify as ensemble, attractor-based replicators with limited heredity. I will discuss the new terms in turn. There is nothing like the fixed sequence of the constituents in nucleic acids. The molecular ensemble as a whole is replicating, where the spatial position of the T_i molecules plays no role (in accordance with the fluid mosaic nature of biomembranes). The system is also attractor based (Hogeweg 1998) since it is the dynamical nature of the network of reactions that makes replication possible, and the identity of the network is preserved by its dynamical stability (the system's basin of attraction). Information carried by gene-like replicators is, in contrast, storage based (Hogeweg 1998): to a good approximation all possible gene sequences are equally stable and transmissible, using the same copying mechanism.

(c) *Limited heredity*

Contemporary DNA-based organisms have an unlimited hereditary potential, since the number of types that one can construct from the purely informational point of view vastly exceeds the number of individuals that the earth can maintain. What is then the hereditary potential of attractor-based systems? As emphasized before (Maynard Smith & Szathmáry 1993, 1995), they can have limited heredity only. First of all, it is only the composition rather than the steric configuration of the system that is maintained. In order to appreciate this point, consider n types of molecules that we use to build our replicator of size k. In the case of template replication, all possible sequences are potential replicators; hence their number is given by

$$\mathcal{N}_\mathrm{s} = n^k, \quad (9)$$

as follows from elementary combinatorics. In the case of ensemble replicators the positions do not matter—hence the upper bound for the number of possible types is

$$\mathcal{N}_\mathrm{c} = \binom{n+k-1}{k} = \frac{(n+k-1)!}{(n-1)!k!}. \quad (10)$$

This is clearly an upper bound since every possible subset cannot be realized by the alternative attractors associated with the system. For the same n and k, $\mathcal{N}_\mathrm{s}$ is always larger than $\mathcal{N}_\mathrm{c}$, usually by orders of magnitude. Indeed, by the application of the Stirling formula for factorials one can deduce an approximate equation for the proportion of the number of types:

$$\mathcal{N}_\mathrm{s}/\mathcal{N}_\mathrm{c} \approx k^{n+1/2}(n-1)^{n-1/2}\, n^k (n+k-1)^{1/2-k-n}\sqrt{2\pi}, \quad (11)$$

which, for sufficiently large n and k, further approximates to

$$\mathcal{N}_\mathrm{s}/\mathcal{N}_\mathrm{c} \approx k^k n^{k+n}(n+k)^{-k-n}\sqrt{2\pi}. \quad (12)$$

Note that the number of attractors for such collective replicators has not been analytically calculated yet. In any case the ratio (12), showing the advantage of modular template replicators, is definitely underestimated. A satisfactory answer must take two considerations into account: (i) the number of attractors in sets of unlimited size (Kauffman 1993), and (ii) finite size k for realistic systems (Segré *et al.* 1998).

3. AUTOCATALYTIC CYCLES

(a) *Holistic replicators and their possible evolution*

Chromosomes made of DNA come in different lengths. They can harbour a small or a large number of genes. During replication of the bacterial chromosome it makes perfect sense to say that replication is half complete when one half is already present in two copies. This sharply contrasts with the following example.

Imagine a molecule A, which reacts with a number of compounds to yield two molecules of A after one turn of the cycle, as expressed by equation (4). Molecular systems of this kind do exist; examples include the formose reaction (figure 1), the reductive citric acid cycle (which is almost the exact reverse of the citric acid cycle and is used for carbon fixation by some bacteria) and the Calvin cycle (fixing carbon dioxide in plants; cf. Gánti 1979). They are not ensemble replicators in the sense that one, or a few, autocatalysts are sufficient to seed the system, and parts (the chemical moieties) of the autocatalytic molecules are held together by covalent bonds (and are thus sterically constrained). They are also stoichiometric in the sense that the elementary steps are simple chemical reactions (transformations). Two questions must be asked about such systems.

(i) Are they feasible as autonomous replicators (self-replicators)?
(ii) Is there hereditary information stored in them?

I will discuss these questions in turn.

The reductive citric acid cycle and the Calvin cycle (which is in fact a complex network) are not autonomous, in the sense that they require the operation of enzymes that are not produced by them. This is in contrast to the formose reaction, which does not require enzymes. Heredity requires alternative types of cycle. Currently, there are only hypothetical suggestions, put forward by Wächtershäuser (1988, 1992): they are various extensions of the (equally hypothetical) 'archaic' reductive citric acid cycle. Even if alternative forms of such systems can exist, most changes will be mere fluctuations and will not lead to hereditary alterations ('mutations' in the general sense). It is expected that the system will flip from the basin of one

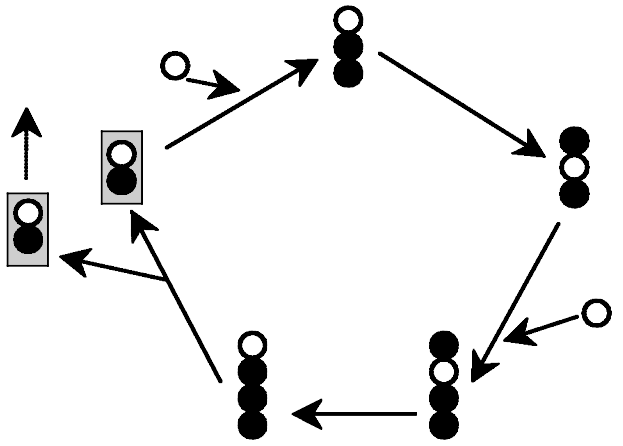

Figure 1. The formose 'reaction'. Open circle, one molecule of formaldehyde. The autocatalytic formation of the glycolaldehyde molecule (enframed) is apparent. Circles in clusters represent carbon-containing groups within larger molecules. This is just the central 'core' of a very complex network.

attractor into that of another one very rarely—hence there will be infrequent 'macromutations' only (Wächtershäuser 1988). Nevertheless, such macromutations may have been of paramount importance in chemical evolution. This idea is open to experimental test.

Such systems are holistic replicators (Maynard Smith & Szathmáry 1999). If one looks at the core of the formose reaction (figure 1) one sees that there is no real sense in which one could say that replication is 'half-way through', in sharp contrast to a piece of RNA or DNA. This is because replication is not template replication (copying) that rests on a modular polymerization of monomers.

(b) *The plague of side reactions*

Even though the formose reaction can run without enzymes, ultimately its constituents are irreversibly transformed into inert by-products. This is due to the fact that in a simple medium there can always be side reactions, stoichiometric and catalytic, which compromise the functioning of the network as a whole—which might otherwise look good on paper. Suppose, following King (1982, 1986), that there is a simple autocatalytic cycle of p steps (similar to the system in figure 1, where $p = 1$). At every possible point of the cycle two types of reaction can occur: the legitimate and the illegitimate. The latter give rise to all sorts of side reactions. Let the specificity of a reaction at step i be s_i: it is the rate of legitimate reaction divided by the total rate of all (legitimate + side) reactions. Successful growth of the cycle is guaranteed if

$$2\prod_{i=1}^{p} s_i > 1, \tag{13}$$

or, if we calculate with the geometric mean σ of the specificities:

$$\sigma^p > \tfrac{1}{2}, \text{ i.e. } p < -\log(2)/\log(\sigma). \tag{14}$$

This shows that the viable system size p increases hyperbolically with specificity.

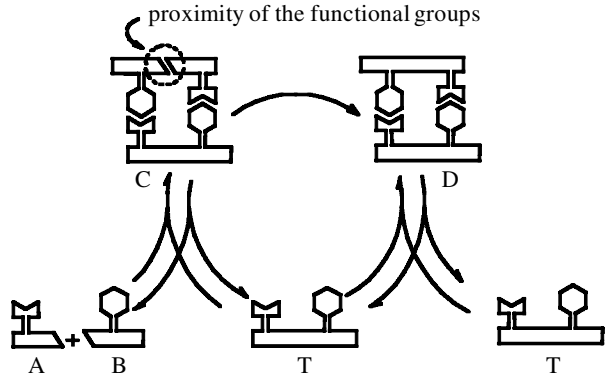

Figure 2. Scheme of simple modular self-replication (from Bag & Von Kiedrowski 1996). A and B, building blocks; T, template; C, catalytic complex; D, duplex. Note the reversible and irreversible reactions.

4. MODULAR REPLICATORS

(a) *Oligonucleotide analogues*

The first modular type of self-replicator (figure 2) was synthesized by Von Kiedrowski (1986). The palindromic arrangement of the template ensures that the copy will be identical to the template, despite complementary base pairing. There is now a large number of such experimentally produced replicators (for a review, see Von Kiedrowski 1999). A common criterion for the replication process is that the two strands (template and copy) must spontaneously separate. Since they are held together by hydrogen bonds (also necessary for replication) the strands cannot be too long or otherwise they would stick together for too long a time. Long pieces of nucleic acids can be replicated in the cell because enzymes of the replicase complex also ensure the unwinding of the strands—this cannot be assumed in non-enzymatic systems. These artificial replicators must hence be generally rather short. Although replication is modular, heredity is still limited because of size limitation (small k in equation (9)). These replicators have only a didactic relevance to evolution since they are not feasible in prebiotic environments. Chemical evolutionists nevertheless do believe in prebiotically feasible counterparts.

(b) *Template replication of peptides*

Some interesting cases of self-replicating peptides also belong to this modular, limited-hereditary replicator category (Szathmáry 1999*a*). Their replication mechanism closely follows the scheme shown in figure 2. There has been considerable confusion in the literature, starting with the title 'Emergence of symbiosis in peptide self-replication through a hypercyclic network' (Lee *et al.* 1997). In this extended system there are two replicator species, R_1 and R_2 that are auto- and cross-catalytic: each template catalyses replication of the other as well as of itself. Inspection of the reaction scheme reveals that they are like two oligonucleotide strands, where the two replicators are mutant versions of one another. This is simple self-replication with mutation, and no hypercycle and symbiosis are involved (Szathmáry 1999*b*).

5. REFLEXIVELY AUTOCATALYTIC (HYPOTHETICAL) PROTEIN SETS

(a) *Autocatalytic sets of catalytic proteins*

There is another class of peptide–protein replicators that has been suggested repeatedly (Eigen 1971; Dyson 1985; Kauffman 1986)—the hypothetical, reflexively autocatalytic peptide networks. Here one has a mixture of peptides up to a certain length and they then catalyse the formation of each other from the smaller fragments. In contrast to the previous system, no direct self-replication is assumed. Whether such systems are experimentally feasible is not known. It has been argued, for example, that the requirements for catalytic capabilities of random polypeptide sequences have been overestimated (Orgel 1992).

If such systems can exist, they will be attractor-based (Hogeweg 1998), limited-hereditary ensemble replicators. The fact that the peptides consist of amino acids should not confuse us since autocatalysis here is not at the level of the peptide strand, but is of the ensemble as a whole, somewhat similar to the process shown in equation (8). Nevertheless, replication is a modular process, resting on the sequential additions of amino acids and peptides.

(b) *The paradox of specificity*

A rather large number (n) of different polypeptide sequences seems to be required for the imagined functioning of these autocatalytic protein nets (Kauffman 1986). A higher-level analogy of the side-reaction plague readily arises. Calculations of probabilities about such systems always assume that a protein may or may not catalyse a given legitimate reaction in the system but that it would not catalyse harmful side reactions. This is obviously an error. Hence the paradox of specificity strikes again—the feasibility of autocatalytic attractor sets seems to require a large number of component types (high n), whereas the plague of side reactions calls for small systems (low n). No satisfactory solution of this problem has yet been given.

6. PHENOTYPIC REPLICATORS

(a) *The importance of a limited set of building blocks in the environment*

There is an important precondition for successful replication of all molecular replicators—the environment must contain the right raw materials. This sounds trivial, but in fact it is not. Consider the case of RNA replication. This needs activated ribonucleotides of the right conformation. One can imagine (and in fact synthesize) mirror images of the currently used nucleotides. An RNA molecule would not be able to replicate in a medium consisting of a mixture of the left and right mirror-image nucleotides. This obstacle to prebiotic replication is called 'enantiomeric cross-inhibition' (Joyce *et al.* 1987). Replication needs the right raw materials in the environment of the replicator. For contemporary nucleic acids this environment is highly evolved—it is the cytoplasm of the cell, maintained to a large extent by the phenotypic effects of the genes themselves on the 'vehicles' (Dawkins 1976) or 'interactors' (Hull 1980) in which they are embedded and replicated. Note that this is a special case of the liberation from the adverse effects of side reactions in general, in that the environment is constrained in such a way that the chance of side reactions is diminished.

(b) *Extended phenotypes of molecular replicators*

At this point it is useful to distinguish between different kinds of phenotypes and phenotypic effects. Clearly, a replicating RNA itself has a phenotype, related to its conformation. One genotype can have different phenotypes in different environments (and thus lends itself to a 'reaction norm' analysis), but it can have, less frequently, alternative phenotypes even in the same environment. Also, if an RNA replicator is encapsulated in a compartment, it can exert a catalytic effect on the metabolism of the protocell as a whole (cf. Maynard Smith & Szathmáry 1995), having a pronounced phenotypic effect at that level. One must appreciate, then, that Dawkins' 'extended phenotype', when the genes have an effect on a vehicle different from that where they sit (Dawkins 1982), is a case of secondary extension from the point of view of the molecular replicator: RNA has a phenotype related to its conformation, a phenotypic effect on the cell in which it sits, and it may have an effect on some component of the external world. DNA can also have a (molecular) phenotype that is relevant to epigenetic inheritance processes (the 'chromatin marking system' in Jablonka & Lamb (1995)). If a molecular replicator is part of a larger system, and it carries heritable information for the functioning of the system as whole (i.e. for functions not directly affected by its replication *per se*), we can speak of a coded phenotypic property of the system (organism, vehicle). Such coded information in general requires modular replication, which renders a considerable degree of decoupling of vehicle phenotype from possible replicator phenotypes (cf. Michod 1983). (Logically, the molecular phenotype of a replicator in an organism is obviously a subset of organismic phenotype.)

(c) *Genetic membranes of contemporary organisms*

We have already seen the hypothetical case of self-reproducing lipid vesicles. Sonneborn (1964) observed a long time ago that inverted kinetids (cilia plus associated structures) in the cortex of ciliates could be propagated stably without alteration of the genetic material. The explanation for cortical inheritance seems to be that the old kinetid provides a molecular scaffold on which the new one is built and thus an inverted orientation of the kinetid will be passed on.

Cavalier-Smith (1995) formally introduced the concept of genetic membranes. It refers to existing, as opposed to the previously presented hypothetical, cases of membrane inheritance in cells. As said before, membrane growth is autocatalytic because lipids already incorporated in the membrane enhance the incorporation of further lipid molecules. In addition, present-day genetic membranes are also autocatalytic for protein incorporation, in the following way. Consider, for example, the growth of the mitochondrial membrane. The majority of mitochondrial proteins are now coded for by genes in the nucleus and thus they have to be imported into the organelle. For this purpose a specific apparatus is used that recognizes proteins to be imported by their N-terminal signal peptides. However, the proteins in the import machinery

Table 2. *Genetic membranes (compiled from Cavalier-Smith 1995)*

primary genetic membranes
prokaryotes
one (Unibacteria: Posibacteria and Archaebacteria) or two (Negibacteria) cytoplasmic membranes + thylakoid membrane (cyanobacteria)
eukaryotes
endoplasmic reticulum + plasma membrane
Golgi membrane?
secondary genetic membranes (in eukaryotes)
two mitochondrial membranes
two plastid outer membranes + thylakoid membranes
peroxisome membrane?

must also be imported—this is the crucial autocatalytic component of membrane growth at the protein level. This is also the reason why the so-called *petite* mutant of yeast contains reproducing mitochondrial 'ghosts'—although these organelles have lost all DNA and thus cannot respire, their membrane grows and divides by the process described above. There are different kinds of genetic membranes in the cell that must propagate their kind (table 2), for example, plastid membranes must grow with the maintenance of plastid identity. Thus plastids use a signal sequence for protein import that is different from those of mitochondria, peroxisomes or the nucleus.

The role of membrane heredity can further be appreciated by the following thought experiment (Maynard Smith & Szathmáry 1999). Imagine that you leave the DNA in the nucleus and leave the plastids and mitochondria intact but you replace every import apparatus in the plastids by the mitochondrial version. Such cells would soon lose the ability to photosynthesize and the plastid membranes would become more and more mitochondrial in nature. Ultimately plastid DNA would also be lost because the necessary replication proteins would not be imported either. All this would happen without prior alteration of any of the genomes involved. Membrane inheritance is clearly of a limited type but it is extremely important for the maintenance of the cell.

There is something peculiar about membrane inheritance. Newly synthesized proteins are recruited on the basis of a very limited aspect of their molecular phenotype, namely the presence of the cognate signal peptide, whose primary sequence is usually not conserved. A template-like effect does play a role in this recognition process (the shape of the membrane receptor and that of the signal peptide of the imported molecule must be sufficiently complementary) but heredity is limited. Genetic membranes are ensemble, phenotypic replicators (Szathmáry 1999*a*). They are not attractor based because their identity also requires genes, external to them.

(d) *Prions: limited hereditary replicators*

Prions are another example of molecular phenotypic replicators. Prions can have alternative conformations; molecules with bad conformation (phenotypes) transform peptides with the right conformation into ones with bad conformation (Mestel 1996). There is a direct phenotype–phenotype transmission, without modular copying of constituents, which is in sharp contrast to the case of RNA for which the phenotypes are correlated because the sequence is replicated. Interestingly, further evolution of this initially purely selfish system has been co-opted by yeast where it transmits a certain phenotypic trait—the read-through of all three nonsense codons (Patino *et al.* 1996).

Obviously, the constraint of the appropriate environment is apparent for genetic membranes as well as prions. The identity of plastid membranes is due to two facts: first, only proteins destined to function in the plastid carry the cognate signal peptide; and second, the functional identity of protein sequences is maintained by the replication of genes in the nucleus. Similarly, the sequences of prions are coded for by genes.

(e) *Memes: unlimited hereditary replicators*

Can there be phenotypic replicators with unlimited heredity? The only example I know of is the memes (Dawkins 1976), although the fact that they are typically phenotypic replicators was recognized only recently (Maynard Smith & Szathmáry 1999; Szathmáry 1999*a*). Consider, for example, Newton's second law. When a teacher teaches it to their students, there is no copying involved whatsoever. Copying would require the transmission of the synaptic configuration of the neural network storing the piece of information in question. There are reasons to believe that such a copying would produce no meaningful result. Instead, the emerging hypotheses in the student are tested according to performance (phenotype), until performance in student and teacher are sufficiently similar.

Why are we able to sustain an indefinitely large number of memes? I think the answer is human language. Language is a cultural inheritance system with indefinitely large semantic coverage (Maynard Smith & Szathmáry 1995). It is also digital, since an indefinitely large number of sentences can be generated with a limited alphabet. Although it is true that alphabets were superimposed on languages long after their invention, the number of basic phonemes we use in any language is a finite set. We construct words using this set. Even the number of words does not exceed 10^5. A good question is whether the underlying neural systems are digital or not (cf. table 1). I am almost certain that they are because I do not see how by any other means we could store and retrieve an indefinitely large number of concepts and their connections. Calvin (1996) presented a hypothetical model in which memes would be stored in replicative patterns of neuronal activity in the brain. Although I do not have space to dwell on this topic in detail, it seems to me that his structures are ultimately digital in nature.

This picture of memes replicating inside brains and hopping between them by different mechanisms is perhaps surprising. Accepting that memes within brains are also digital replicators, whose replication from brain to brain is phenotypic, could one think of a didactic molecular analogy? Here is one. There are two individuals A and B. Take protein X from individual A. Suppose you want to enable individual B to develop a molecule with the same phenotypic effect (enzymatic function, for example). If gene transfer from A to B is not allowed, one then must have (i) some generative mechanism for proteins in B, and (ii) some method for the assessment of

phenotype. This comes very close to an immune system in B. The crucial difference is that the task now is to produce 'antibody' Y, in individual B, that shares crucial phenotypic properties with 'antigen' X, from individual A. Although both molecules would have sequences, it is most unlikely that they would be close to one another in protein space (cf. Maynard Smith 1970). In all probability the pleiotropic effects of the two proteins would differ. This is why cultural heredity is bound to be inexact and why cultural evolution is faster than biological evolution.

7. EVOLUTION

Above I have described several molecular replicators in some detail. The typical path of evolution is from limited to unlimited, and from holistic to modular, replication (e.g. Szathmáry 1999*a*). Presumably, the categories of holistic and attractor-based replicators with unlimited heredity are empty. This evolutionary route is in fact recurrent at several levels of evolution (Maynard Smith & Szathmáry 1995; Szathmáry & Maynard Smith 1995). Primitive forms of epigenetic inheritance, namely the so-called steady-state systems and structural inheritance (Jablonka & Lamb 1995), have only limited heredity. The first kind (e.g. alternative, hereditary states of the operon) corresponds to attractor-based replicators, whereas the latter (e.g. cortical inheritance in ciliates) is an example of phenotypic replication. In contrast, chromatin-marking systems (such as methylation) have a much higher hereditary potential, which can be used to maintain and transmit a larger number of cellular phenotypes. Memes in animals are limited hereditary replicators, and this was true for our early ancestors on the hominid lineage. Memes have acquired unlimited heredity due to a special, digital information system—language. Since its origin, some other important breakthroughs took place, including the invention of writing, printing, computers and the Internet. These are parts of cultural, rather than biological, evolution.

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