

Synthetic Transitions: Towards a New Synthesis

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Synthetic transitions: towards a new synthesis

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The evolution of life in our biosphere has been marked by several major innovations. Such major complexity shifts include the origin of cells, genetic codes or multicellularity to the emergence of non-genetic information, language or even consciousness. Understanding the nature and conditions for their rise and success is a major challenge for evolutionary biology. Along with data analysis, phylogenetic studies and dedicated experimental work, theoretical and computational studies are an essential part of this exploration. With the rise of synthetic biology, evolutionary robotics, artificial life and advanced simulations, novel perspectives to these problems have led to a rather interesting scenario, where not only the major transitions can be studied or even reproduced, but even new ones might be potentially identified. In both cases, transitions can be understood in terms of phase transitions, as defined in physics. Such mapping (if correct) would help defining a general framework to establish a theory of major transitions, both natural and artificial. Here we review some advances made at the crossroads between statistical physics, artificial life, synthetic biology and evolutionary robotics.

Keywords: Major transitions, artificial life, synthetic biology, evolutionary robotics, phase transitions

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I. INTRODUCTION: SYNTHETIC TRANSITIONS

Looking backward to the unfolding of life on our planet, it is possible to identify several major qualitative changes that deeply marked evolutionary history. They have been labelled as the Major Evolutionary Transitions (METs) due to the fundamentally unique nature of the changes involved [1]. The emergence of life, the genetic code, complex cells, multicellular organisms and language are some of the best known examples. They

all involve a novel class of organisation with high-order properties not reducible to the properties of the lower-scale units. The list of METs differs among authors [1-7] and in this paper we will address a revised list of major transitions incorporating different proposals. A first classification of METs would include: (1) a loss of replicative potential by the units once belonging to a higher-order entity, (2) a specialisation of different units in different tasks, which requires a nonlinear mapping between genotype and phenotype and (3) changes in the ways information is processed and stored. But more importantly, we want to consider METs under the light of the theoretical, experimental and engineering perspectives involving the modelling, synthesis and imitation of living systems. For example, we can create a new multicellular system by engineering new cell-cell signals on single cells. Similarly, a proto-grammar can emerge in a group of interacting, evolvable robots. These are *synthetic transitions* that are not necessarily related to standard evolutionary paths, but they do involve ways to generate major innovations starting from simpler systems. We will use a general term to label this broad class of non-natural transitions: *Major synthetic transitions* (MST). The study of MST provides a whole parallel approach to natural evolution and to the origin of innovations in complex systems, biological or artificial.

How similar are these two scenarios? Random events are known to play some role in evolutionary history [7,8,9] and they offer some clues to the origins (and likelihood) of some innovations. However, convergence seems also a widespread feature of evolved systems [10] as illustrated by the observation that some major innovations have emerged independently in different groups and often sharing surprisingly similar design principles. Such universal patterns could be a consequence of fundamental

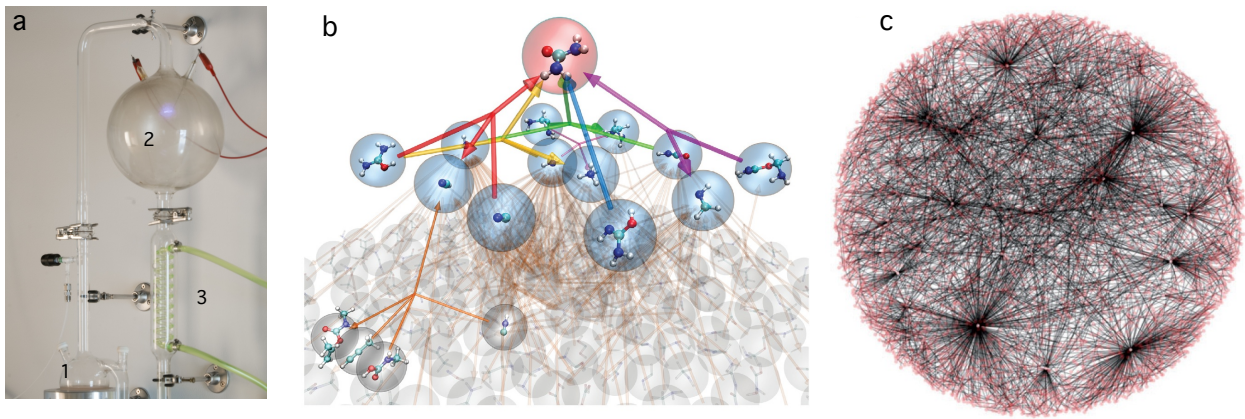


FIG. 1 Synthetic prebiotic chemistry. Miller's experiment (a) provided the first evidence for an abiotic scenario of generation of biologically relevant molecules (image courtesy of Adam Brown). The mixture is heated (1) receives electrical discharges (2) and is condensed in (3). (b) Many different molecules are generated, linked through a reaction network (modified from [28]). The overall reaction network is similar to *in silico* networks of reactions in organic chemistry that can be obtained from databases, as shown in (c) where nodes are molecules and connections indicate possible reactions (modified after [31]).

constraints beyond the specific nature of biological systems [11-13] and thus would be also inevitable in their synthetic counterparts. By understanding the role of constraints in both evolved and artificially generated innovations, we might achieve some understanding of the uniqueness of the known biology that we know [14].

Other important questions that can benefit from the analysis of MST are understanding why some transitions seem common while others seem rather unique [7]. Are hard-to-obtain synthetic transitions connected to hard-to-evolve biological novelties? On the other hand, we might also ask if there are *other* major transitions associated with the potentially different MST universe. What is their nature and why are they absent in the biological realm? No less important is the fact that major transitions occur when a given set of preconditions is in place. Preconditions are relevant to our discussion since they imply the presence of a landscape of possibilities pervading the emergence of a major qualitative change. Moreover, there are remarkable commonalities shared by disparate systems. These universal traits are to be found in those principles stemming from the physics of complex systems [15,16], phase transitions [17,18] and the algorithmic logic of artificial life models [19,20]. In this context, it has been suggested that phase transitions [21,22] can help understanding the patterns exhibited by METs. Since phase transitions are known to exhibit robust, universal laws [23,24] they will help understanding the general nature of natural and artificial transitions, perhaps opening the construction of a general theory of what we can label as *Major Transitions* (MT).

II. SYNTHETIC PREBIOTIC CHEMISTRY

We start our list with a special problem: the presence of qualitative transitions in a pre-biological biosphere be-

fore true replicators emerged. We are thus closer to the domain of prebiotic systems chemistry [25] which define the landscape of pre-conditions required for the rise of molecular replicators and genetic codes. The first attempts aiming for the creation and analysis of synthetic prebiotic systems were Stanley Miller's electric discharge experiments [26,27] which can be accurately simulated using molecular dynamics [28]. Miller's approach was simple and elegant: take a set of candidate molecules that were likely to be present in the primitive atmosphere and make it react under a constant energy source (figure 1a-b). The experiment generated aminoacids (AA) and other molecules thus providing support to Oparin's conjecture that biochemical complexity can arise from purely chemical processes [29]. Further studies developed by the Catalan chemist Joan Oró showed that relevant building blocks of nucleic acids, such as adenine, could also emerge using ammonium cyanide [30].

Since biochemical diversity of basic monomers pervades the development of true living entities, the synthetic soup created in these experiments provided the source of chemical variation to be exploited by further innovations. In general terms, a set of reactions can be described by a general reaction scheme:

$$\sum_i^{N_a} \alpha_i A_i \rightleftharpoons \sum_i^{N_b} \beta_i B_i \quad (1)$$

where α_k, β_j indicate stoichiometric coefficients associated to the N_a substrates and N_b products of the reactions, indicated by A_k and B_j , respectively. But too much chemical diversity can also make more difficult reacting molecules to find each other. The potential network of reactions rapidly explodes as is shown in figure 1c, where only the 0.1% of organic molecules from a database is included [31]. In this context, the set of reactions shown in figure 1b is just a minimal subset of

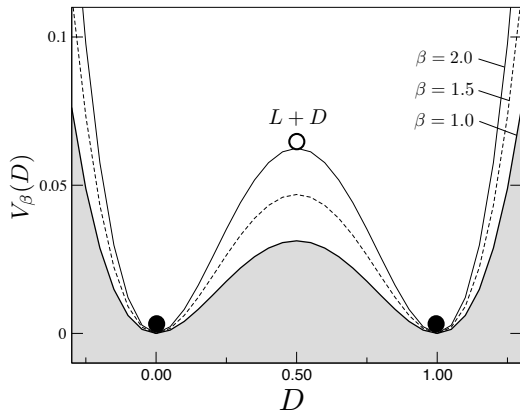


FIG. 2 Symmetry breaking and the origin of homochirality. Using Frank's model (see text) the potential function $V_\beta(\rho_1) = -\int f_\beta(\rho_1)d\rho_1 = \beta(\rho_1^4/2 - \rho_1^3 + \rho_1^2/2)$ associated to the dynamics of a racemic mixture under the reaction set (1-3) is displayed (for different β). The unstable point (open circle) is associated to the $\rho_1 = 1/2 = \rho_2$ racemic mixture, which is unstable. Deviations from this symmetric state lead to either $[D] = 0, [L] = 1$ or a $[D] = 1, [L] = 0$ final state.

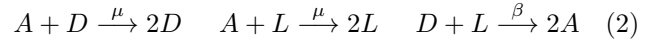
possible reactions, many of them leading to biologically irrelevant components. Two key questions in this context are: (a) are there multiple molecular alternatives for a living biosphere emerging from the primitive soup? and (b) What processes can drive the highly diverse molecular soup towards a non-random biochemistry?

The first question has been repeatedly addressed using a broad range of approximations, and, strictly speaking, the answer is affirmative [32]. It is possible to obtain (or theoretically conceive) diverse and different types of organic molecules using solvents different from water and at extreme temperatures, with two universal limitations are the presence of non equilibrium conditions and temperature intervals allowing chemical bonds to form and break in reliable ways. In most of these alternative chemical scenarios it is suggested that the candidate alternatives are *feasible*. But feasible does not imply that the synthesis is likely to occur and -more importantly- what is needed to generate non-random mixtures of molecules.

To depart from chemical randomness, two classes of dynamical phenomena might have been relevant. One is connected to the chirality problem [33,34]. A characteristic pattern displayed by all biochemical species is a choice of one given configuration of molecular structures among the two possible (chiral) mirror forms (L and D): nucleic acids incorporate only D-ribose and D-deoxyribose while proteins use L enantiomers of amino acids. However, Miller's-like experiments typically lead to a *racemic* mixture, where both types of handedness are equally represented. The rise of replicators capable of evolving Darwinian selection thus requires first to solve the problem of how to break this chemical symmetry. Evidence from chemical analysis of meteorites indicates that aminoacids (AA) display a slight asymmetry towards L forms. Since comets and asteroids might have been a major source

of biomolecular precursors [35] a given asymmetry could bias handedness.

But even if that is the case, the ideal scenario with a dominance of a single type of form requires an explanation. In this context, several models suggest that homochirality can spontaneously result from simple chemical reactions. The simplest model that accounted for this phenomenon included two types of chemicals, indicated by D and L and corresponding to the two forms [36,37]. They can react with an additional molecule A following the set of reactions:



If we indicate by D and L the concentrations of the two forms, we can derive the equations describing the dynamics of this mixture and analyse them using linear stability¹. Let us indicate as $\rho_1 = [D]$ and $\rho_2 = [L]$. Assuming a constant population constraint (CPC) i. e. $[D] + [L] = 1$ we have:

$$\frac{d\rho_1}{dt} = \mu\rho_1 - \beta\rho_1\rho_2 - \rho_1\Phi(\rho_1, \rho_2) \quad (3)$$

$$\frac{d\rho_2}{dt} = \mu\rho_2 - \beta\rho_1\rho_2 - \rho_2\Phi(\rho_1, \rho_2) \quad (4)$$

where the first two terms in the rhs correspond to the formation of molecules of each type and their conversion in A . The last terms introduce a dilution associated to an outflow. From the CPC, we have: $\Phi(\rho_1, \rho_2) = \mu - 2\beta\rho_1\rho_2$ and it can be shown that

$$\frac{d\rho_1}{dt} = f_\beta(\rho_1) = \beta\rho_1(1 - \rho_1)(2\rho_1 - 1) \quad (5)$$

(a symmetric solution exists for $[L]$). The three equilibrium states are: $\rho_1^* \in \{0, 1, 1/2\}$. The first two are stable, homochiral states, whereas the third corresponds to an unstable racemic. A *symmetry breaking* phenomenon takes place [17,18,22,23] where two alternative stable states $\rho_1 = 0, 1$ are possible, both accessible from $\rho_1 = 1/2$ through an amplification phenomenon. This can be seen using the so called potential function $V_\beta(\rho_1)$ defined from:

$$\frac{d\rho_1}{dt} = -\frac{\partial V_\beta(\rho_1)}{\partial \rho_1} \quad (6)$$

Here the potential² is defined in such a way that its max-

¹ For a one-dimensional system described by a single differential equation $dx/dt = f_\mu(x)$, where x indicates the state of the given variable (a population, for example) and μ is a parameter or set of parameters. The potential equilibria are defined by those x^* such that (dx/dt) at x^* is zero (i. e. no changes occur) or, in other words, $f_\mu(x^*) = 0$. For each fixed point we determine the sign of the parameter $\lambda(x^*) = (\partial f_\mu(x)/\partial x)$. It can be shown that a stable (unstable) point x is such that $\lambda < 0$ ($\lambda > 0$).

² As defined, since we have $dx/dt = f(x)$, the potential function is simply $V(x) = -\int f(x)dx$ and it is easy to show that its maxima and minima correspond to the unstable and stable fixed points, i. e. those x^* such that $f(x^*) = 0$, following linear stability analysis.

ima and minima correspond to unstable and stable equilibria, respectively. This allows to think in the potential under a mechanical picture of balls rolling on a landscape towards the bottom of the valleys. The specific form of $V_\beta(\rho_1)$ is shown in figure 2. Here the (unstable) racemic mixture ($D + L$) and the two alternative (stable) homochiral configurations are displayed as empty and filled circles, respectively. Once we slightly deviate from the perfect racemic mixture, the ball rolls down towards one of the alternatives: the symmetry is broken towards a given chiral configuration [37,39,40].

A different approach to the evolution of non-random sets of molecules is provided by autocatalytic sets (ACS, fig 3c-d) first proposed by Stuart Kauffman [41,42]. Here, in a rich chemical soup closed loops of catalytic reactions can occur, leading to an ACS, defined as a set of molecules in which every member can be created catalytically by other entities within the set. An example (the only natural known example) is the *formose reaction* [43] (figure 3a-b). As discussed by J. Peretó ([44] and references cited) one of the fundamental questions that remains open is how the first autocatalytic cycles became incorporated into the chemistry of life. As pointed out by this author, one major goal of both models and synthetic approaches to prebiotic chemistry should address understanding how small networks involving inefficient reactions became large and dominated by efficient enzymes.

While waiting for further evidence from synthetic chemical networks, some relevant features of ACS are predicted by theoretical models, such as their potential for explosive growth. Consider a s -dimensional model where a set of s chemical species $\{x_1, \dots, x_s\}$ such that $\sum_i x_i = 1$ [45]. The model involves a set of coupled equations:

$$\frac{dx_i}{dt} = \sum_{k=1}^s C_{ik} x_k - x_i \sum_{k,j=1}^s C_{kj} x_j \quad (7)$$

provided that $x_i, dx_i/dt > 0$. Here $C_{ij} \in [-1, +1]$ indicates the interaction strength between species i and j which can be cooperative (positive) or inhibitory (negative) and such that $C_{kk} = 0$. The model evolves exponentially (and inevitably) to a connected, diverse ACS. This type of phenomenon might have influenced the early evolution of RNA, as discussed below.

III. SYNTHETIC MOLECULAR REPLICATORS

To address the problem of how self-replicating, information-carrying molecules emerged in the primitive biosphere implies considering the true nature of what separates chemistry from life. We know that the molecular logic of self-replication based on nucleic acids is the universal code of life. But is this the only possible logical scheme? Could it be based on different molecular supports? The earliest attempt that gave tentative answers

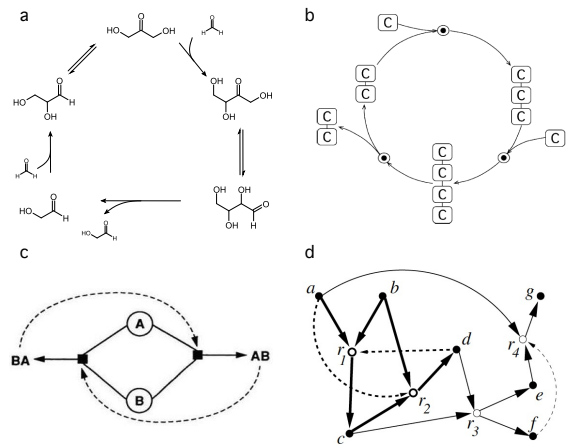


FIG. 3 Autocatalytic cycles. (a) The formose reaction involves the formation of sugars from formaldehyde. The overall reaction of the pathway above is of the form $2A + B \rightarrow 2B$, where A and B indicate formaldehyde, and glycolaldehyde, respectively. As B can not be created of A only, but the existence of B leads to more than one B , we say that B is an autocatalytic compound. A simplified picture of this cycle is shown in (b) where only the carbons are indicated. In (c) a two-member ACS is shown and in (d) a reaction network is shown including an ACS.

to the previous questions was von Neumann's theory of minimal self-replicating machines [46]. Years ahead of molecular biology, von Neumann concluded that self-replicating machines should be composed by: (1) a *constructor*, able to build a new system by using the available raw materials, (2) The *instructions* for the constructor. (3) a *duplicator* which takes the instructions and duplicates them and (4) a *controller* required to guarantee a reliable process. This picture is surprisingly close to an algorithmic description of a biological replication event. More importantly in our context, the agreement between this theoretical picture and reality suggests that a universal logic of self-replication.

What kind of synthetic replicating systems can be constructed from biological and non-biological substrates? The first example of an experimental autocatalytic (fig 4a) set was obtained by von Kiedrowski. Using short nucleotide sequences that mutually catalyse each other's formation [47]. Other synthetic schemes have been proposed, including peptide ligation (fig 4b) systems [48] and several non-biological non-standard mechanisms [49], but also other mechanisms that even lead to exponential growth [50] despite lack of template-based replication (fig 4c). The synthetic alternatives to polymers indicate that other mechanisms can exist capable of generating large molecular structures. However, in general they have also a very limited capacity of storing information, since the units included in their molecular assemblies tend to be homogeneous, thus preventing information growth. If a diverse polymer is a condition for any evolvable replicating system, potential candidates include RNA and RNA-

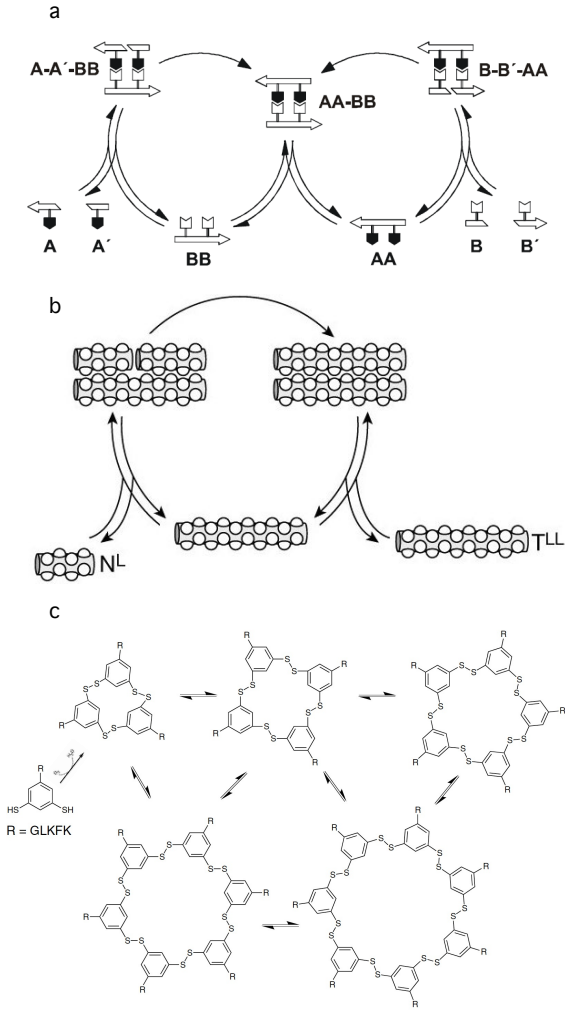


FIG. 4 Synthetic molecular replicators: (a) von Kiedrowski's template-based replication (adapted from [47]); (b) Gadhiri's peptide ligation system (adapted from [48]). In (c) we show part of the replication mechanism presented in [50]. Here a building block (R) containing two thiol functionalities leads to a mixture of growing cyclic structures. The hexamers self-assembly forming piled fibres that eventually break up. The number of fibres grows exponentially in time. Adapted from [50].

based systems [51] since they can act both as catalysts and as templates, thus including both genetic information stored in a sequence and a phenotype derived from the catalytic properties of the molecule.

Many different experiments involving designed, simulated and evolved synthetic RNA molecules and ribozymes have revealed promising avenues as well as limitations. Interestingly, it was also shown that RNA molecules can cooperate [51] even forming ACS [52] thus supporting the picture of autocatalytic RNA networks. The presence of cooperative interactions might be a crucial component in defining the conditions for success of early replicators in terms of phase transitions. In this context, artificial models of RNA networks provide ev-

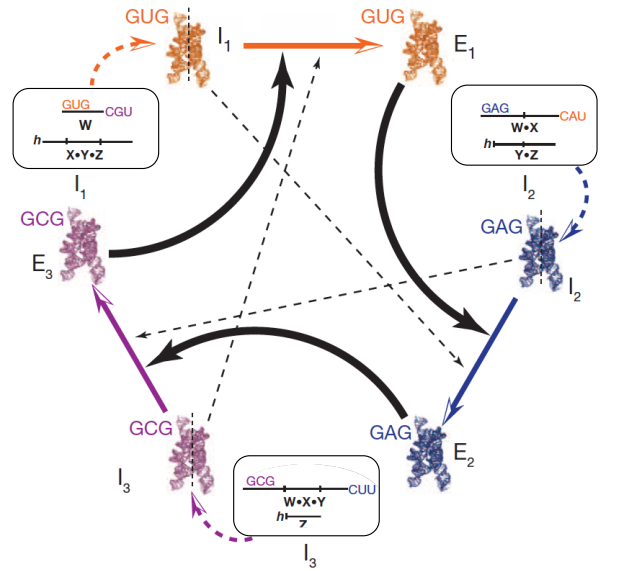


FIG. 5 Experimental realisation of a cooperative (ACS) cycle among ribozymes (adapted from Vaidya et al. [52]). Here an intron ribozyme from *Azoarcus* can be broken into fragments that can covalently self-assemble by catalysing recombination reactions in an autocatalytic fashion.

idence for a high probability of developing ACS under experimental conditions [53].

There is a very important reason to suggest that these class of RNA networks might have been a crucial condition for the growth of genetic information. Early theoretical arguments [54,55] indicated that there is a maximum length L_c associated to RNA chains that scales as the inverse of mutation rate μ (i. e. $L_c \sim 1/\mu$). Beyond this L_c , the system experiences a so called *error catastrophe*, a phase transition where genetic information is lost. An elegant solution to this complexity limit was provided by the *hypercycle*, defined as a cyclic set of mutually enhancing catalytic components [56]. The hypercycle is a system in which autocatalytic replicators also heterocatalytically aid each other's replication so that replication of each member is catalyzed by at least one other member under a second-order kinetics³. A system of coupled reactions involving an RNA-based ACS (figure 5) was obtained by Vaidya et al. [52] showing that mixtures of RNA fragments self-assemble into self-replicating ribozymes through the emergence of evolvable catalytic cycles. The synthetic RNA system thus suggests that ACS could have been crucial to overcome some thresholds of survival and information storage.

³ Although this definition poses some strong constraints on the potential candidates to a hypercyclic dynamics, the exact implementation might not be so relevant while looking for the generic (universal) properties of systems that include in their effective kinetics second-order terms.

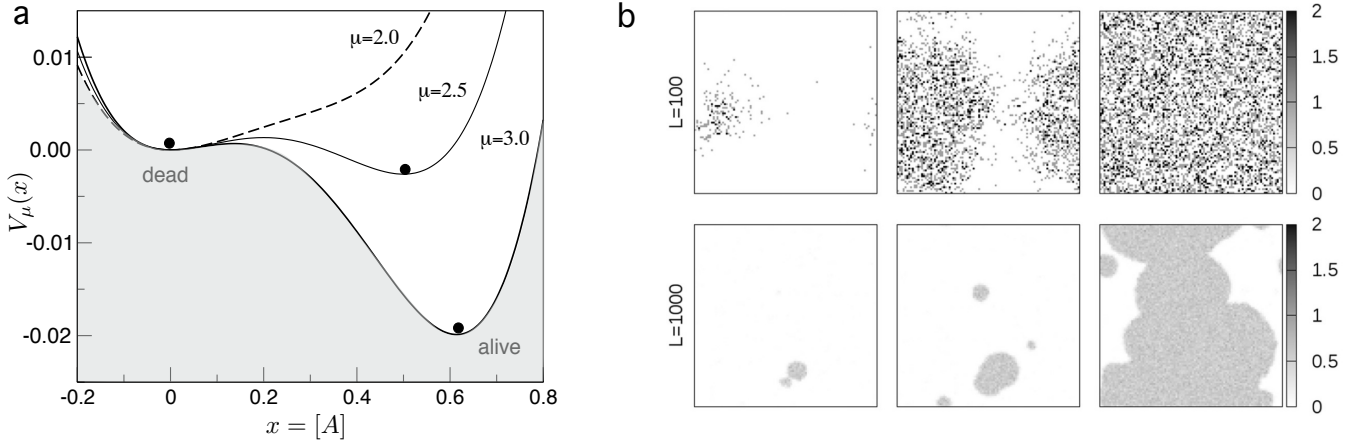
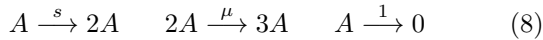


FIG. 6 (a) Phase transition from death to living states. Using the simple model described in the text, a potential function shows the phase change that occurs once the cooperation parameter μ crosses a given threshold. (b) Phase transition in a synthetic RNA world with molecular cooperation on a two-dimensional space. Snapshots of the catalytic polymer concentration in the RNA polymerization model at the beginning (left), during (center), and after (right) the transition from the dead state to the living state for different system sizes ($L = 10^2, 10^3$) and with local hopping rules. Adapted from Wu and Higgs [63]

A potential drawback of cooperative systems is that they can destabilise due to the presence of parasites [57]. However, theoretical arguments indicate that compartments can strongly constrain their impact [58]. On the other hand, the appropriate nonlinear replication kinetics can help also a rapid expansion of replicators. To illustrate this idea, let us first consider a toy model [59] in which a set of replicators A cooperate and decay following:



If we use $x = [A]$ to indicate the concentration of replicators, it is possible to show that

$$\frac{dx}{dt} = -x + sx(1-x) + \mu x^2(1-x) \quad (9)$$

where a limiting value $x_{max} = 1$ has been introduced. This system exhibits three equilibrium points, namely $x^* = 0$ or *dead* state, as well as to additional points

$$x_{\pm}^* = \frac{1}{2\mu} \left[\mu - s \pm \sqrt{(\mu + s)^2 - 4\mu} \right] \quad (10)$$

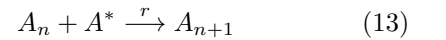
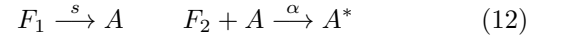
The main result of this model is the existence of a discontinuous (first-order) phase transition separating the two possible phases. This is shown by using the potential function associated to our system, namely:

$$V_{\mu}(x) = (1-s)\frac{x^2}{2} + (s-\mu)\frac{x^3}{3} + \mu\frac{x^4}{4} \quad (11)$$

which is plotted in figure 6a. The minima defining the alive phase coexist with an alternative minimum where extinction is also an alternative possibility. When $\mu < \mu_c = 2.25$ a unique minimum is observable, associated to the extinction scenario (or *dead* phase) whereas for

$\mu > \mu_c$ we will observe two minima, being the *alive* fixed point placed in a deeper valley.

A robust result leading to a phase transition from non-living to living was suggested by Wu and Higgs [60] by considering a spatially extended model of catalytic RNAs. The use of space is known to play a key role in stabilising or even allowing some key replicator dynamics to occur. In the RNA system, two precursor molecules are available in the environment at concentrations F_1 and F_2 . The RNA monomers, denoted by A , can be synthesized from F_1 . These monomers can react with F_2 to produce activated monomers, A^* . RNA polymers of length n are denoted A_n . An activated monomer can react with a polymer to extend its length. The transitions are now:



additionally, we also consider constant degradation rates for all molecules, which decay (or are removed) at a rate δ . The associated system of equations thus reads:

$$\frac{dA}{dt} = sF_1 - \alpha F_2 A - rAA^* - \delta A \quad (14)$$

$$\frac{dA^*}{dt} = \alpha F_2 A - rA^*(A + P) - \delta A^* \quad (15)$$

$$\frac{dA_n}{dt} = rA^*(A_{n-1} - A_n) - \delta A_n \quad (16)$$

where we indicate as $P = \sum_{\mu \geq 2} A_{\mu}$ and the polymerisation rate is given by $r = r_0 + kP_n$, with $P_n = \sum_{\mu \geq n} A_{\mu}$. As it occurs with the previous model, there is also a phase transition between a state with little or no polymerisation and a "living" state where the catalytic reactions lead to high levels of polymer concentrations. If this is simulated using a discrete implementation, including stochastic fluctuations, a threshold of local concentrations must

be crossed in order to switch to the living state. Once this occurs, the living state propagates through the entire space (figure 6b). The initial local transition can require a long time to occur, but the propagation is rather fast [60]. If we extrapolate this to the origin of life, this rapid spread might imply that early life just evolved once in our planet⁴. In general, artificial models of spatially co-operative replicators with and without parasites reveal significant differences with respect to the mixed system [61-64].

IV. SYNTHETIC GENETICS AND XENO-CODES

A crucial step towards a life-dominated planet required the establishment of a system able to expand and adapt under changing conditions. To such goal, information and codes might have played a central role as a pre-condition for open-ended evolution. This requires both the presence of an alphabet and polymer strings as well as appropriate physical properties allowing the molecules to fold into compact structures. Molecular genetics grew along with information technology in the early 1950s. Many relevant terms, including coding and decoding, translation or transcription became adopted. A first glimpse of the possible nature of the molecular code of life was suggested by Erwin Schrödinger in 1944 the idea that an information-carrying molecule should be some class of *aperiodic crystal* [65].

An obvious question that has been raised by many different researchers is the uniqueness of the genetic code. All known organisms in our current biosphere share a common molecular synthetic genetic code [66] with very little variation in the mapping between codons and AAs summarised in figure 7a. What can happen if we scramble the letters of this diagram? Could different arrangements work as well as this one? The early days of decoding the genetic code soon revealed that the potential size n of codons should not exceed nor move below $n = 3$. Having 20 AAs as the building blocks of proteins, four nucleotides, small codons with $n = 2$ could only give $4^2 = 16$ aminoacids while for $n = 3$ we have $4^3 = 64$ and the genetic code would be able to account for the AA repertoire provided that some amount of degeneracy was present. Such degeneracy was known -from coding theory- to be a potential source of robustness, since errors in transmission can be compensated [67]. The uniqueness of the genetic code, along with some features that suggested some sub-optimal traits that it might be a "frozen accident" and thus opened the possibility for multiple alternative codes. Is DNA the only possible molecular option for our biosphere or just one among many?

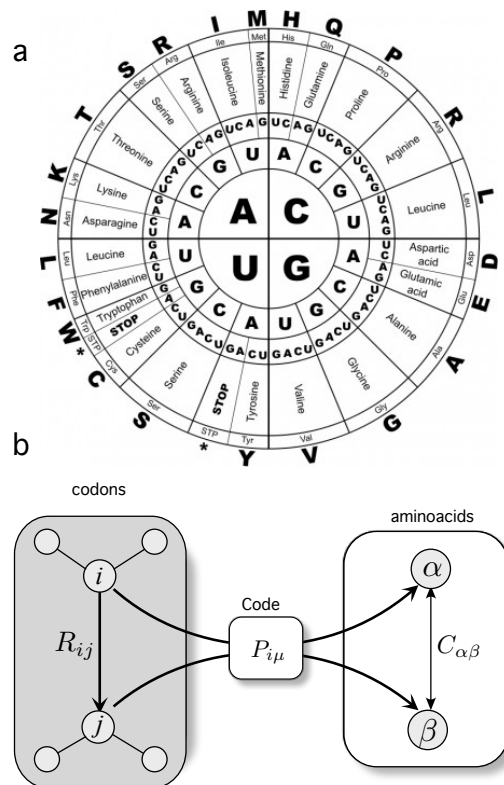


FIG. 7 The universal character of the genetic code (a) and evidence for its optimality was obtained through an *in silico* analysis of millions of synthetic alternative codes, where the coding for amino acids from the triplets defining codons has been randomly scrambled. (b) By treating the genetic code as a problem of information channels (b) we can find additional support for the optimality of the genetic code. Here we indicate by R_{ij} the probability of codon i to be misread as codon j , whereas $P_{i\mu}$ is the probability of codon i to encode aminoacid μ . The distance between aminoacids α and β is indicated as $C_{\alpha\beta}$.

Given the single-case scenario provided by all living forms in our biosphere, we need to consider "synthetic" alternatives that can be reached either from computational models or through the experimental synthesis and analysis of new molecular codes. A systematic exploration of the space of possible codes based on $n = 3$ codons and their mapping into different potential aminoacids was performed [68,69]. Different genetic codes were randomly generated by partitioning the codon space into 21 non-overlapping sets and considering the impact of mutations on the efficiency of the code. Here mutations to all codons were performed for each synthetic code and the change in aminoacid hydrophobicity was determined. This property is connected to a very important feature of AAs (and proteins): how they interact with water. Hydrophobic AAs do not interact with water whereas polar ones easily make contact with water. Different aminoacids have different hydrophobicities, and the analysis measured to what extent was this parameter changed by mutations. The sampled space included 10^6

⁴ The minimal model consistent with this set of reactions, as pointed in [60] is $dx/dt = (s + rx + kx^2)(1 - x) - ux$ which again exhibits a potential function similar to the Fontanari-Ferreira model [59]

alternative codes, much smaller than the potential 10^{18} but it nevertheless provides a strong argument in favor of the optimality of the natural code. In fact, when other biological and chemical constraints are considered, the possible repertoire shrinks to around 270 millions of alternative codes. When the frequency of codes against their efficiency (measured in terms of the error level) was obtained, it was found that the genetic code was the second best or, as the authors said "one in a million". Here we have a powerful case for optimality.

What are the conditions allowing a genetic code to arise? Are there here too phase transitions associated to the emergence of such codes? A model approach [70,71] developed by Tsvi Tlusty considers genetic codes as noisy information channels (figure 7b) with two sets associated with codons and AAs, respectively. An error-prone molecular reader (left) can sometimes lead to misread of symbol i into symbol j , thus leading to a misread in the meaning space (right). The distance between the expected and actual outputs is also considered. Specifically, let us define three key quantities, namely: (a) if $P_{i\alpha}$, the probability that codon $i = 1, \dots, N_c$ encodes the $\alpha = 1, \dots, N_s$ AA (thus we have $\sum_{\alpha} P_{i\alpha} = 1$) (b) $C_{\alpha\beta}$, ($\alpha, \beta = 1, \dots, N_s$) i. e. the distance matrix separating two AA (in terms of their hydrophobic properties) and (c) R_{ij} the probability of misreading two symbols. We can define the following three quantities. The first two provide a measure of the error load L and the code diversity D :

$$L = \sum_{i,j} \sum_{\alpha,\beta} R_{ij} P_{i\alpha} P_{j\beta} C_{\alpha\beta} \quad (17)$$

$$D = \sum_{i,j} \sum_{\alpha,\beta} (1 - \delta_{ij}) P_{i\alpha} P_{j\beta} C_{\alpha\beta} \quad (18)$$

while a third one weights the cost of the coding system, defined by

$$D = \sum_{i,\alpha} P_{i\alpha} \ln \left(\frac{P_{i\alpha}}{P_{\alpha}} \right) \quad (19)$$

All these quantities can be obtained from the information channel description and allow defining a fitness function, where code diversity is a positive entry whereas error load and cost introduce negative components. All the three constraints are combined by means of an energy function H to be maximised, namely $H = -L + w_D D - w_C C$ with w_D and w_C two parameters, to be applied to many synthetic codes. The optimal code occurs at a phase transition point, where the mapping between codons and AAs moves from random (uniform) to non-random. Right at this point, the statistical regularities exhibited by the genetic code are recovered.

Beyond the *in silico* counterparts, synthetic biology offers the possibility of expanding the experimental repertoire defined by RNA and DNA. This can be done while including the potential for Darwinian evolution [72,73]. Moreover, orthogonal ribosomes have been synthetically

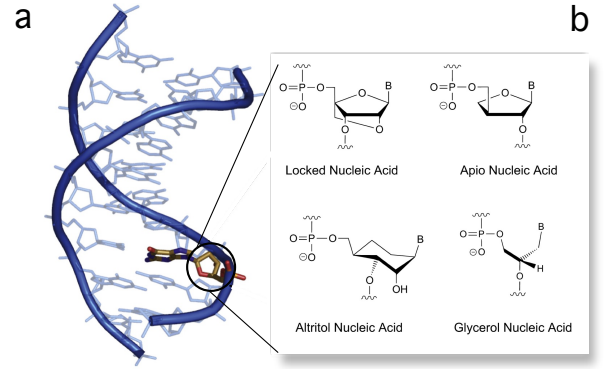


FIG. 8 The XNA alternatives for Synthetic Genetics. Several promising candidates have been designed and tested using a growing list of structurally diverse XNAs. The right panel shows several examples, each capable of undergoing Darwinian evolution.

evolved to decode quadruplet codons, thus allowing the encoding of unnatural AAs [74]. One particularly interesting path has been followed by designing, evolving and characterising so called XNAs [74] as well as synthetic catalysts (XNAzymes, see [75]) that allows to speak of a *synthetic genetics* [76]. These studies have revealed XNA polymerase evolution and design allows to use alternative polymers that can undergo Darwinian evolution. Examples of alternative backbones for a given XNA are shown in figure 8a-b. It is worth noting that the possibility of using glycerol and other simple molecules as alternative backbone provides a valuable approach to the origin of the genetic code, since (as opposed to glycerol) ribose is a complicated sugar, less likely to be formed under prebiotic conditions [77]. A space of the possible XNAs can be defined [73] where an idealised space of possible XNAs is constructed using three axes corresponding to sugar, base and backbone modifications, respectively. Most XNAs that have been studied so far (except peptide nucleic acid or PNA) lie on these axes. More divergent phenotypes should become accessible through a fuller exploration of the XNA space, that is, the replication and evolution of XNAs comprising a combination of modifications to base, sugar and backbone.

V. SYNTHETIC CELLS

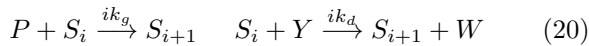
An old saying of biology is that "every cell comes from another cell". This statement connects us with our ancestral cellular origins through a billions of years old tree of life forms. The cell is the most obvious minimal unit of life and its origins one of the crucial steps towards our understanding of METs. Both synthetic and virtual protocells have been designed and explored in search for the requirements needed to move through a whole cycle of growth, instability and division [78-81]. Cells might have been a precondition for an expansion of complex

life. In particular, compartments might have been essential to escape from parasitic replicators and a powerful way of enclosing together the right reaction components at reasonable concentrations.

The challenge of creating an artificial cell has been addressed in both top-down and bottom-up approaches (figure 9). In the former, we start from existing genomes. Since numerous genes are involved in cell-cell communication while others have been shown to be non-essential to cell functioning, it was earlier suggested that it would be possible to reduce genome complexity to a minimal set of N genes able to sustain metabolism and reproduction. Computational and theoretical arguments suggest that about $N \approx 200 - 250$ genes could be a minimal set size [82,83] although the smallest synthetic cell, has reached a $N = 473$ essential genes [84] although the function of 149 of them is unknown.

The second, bottom-up approach is closer to chemistry and deals with the creation of protocells from the assembly of interacting chemical components [78] and thus involves a major transition between non-living and living matter. In figure 9 we depict this as a combination of three potential ingredients, namely metabolism (M), compartment (C) and genetic information (G). They can be combined in different ways, including a complete protocell capable of self-maintaining itself and self-replicating (M+C+G) but also information-free systems (M+C) or even non-replicating systems, where polymer self-replication might occur but not self-reproduction. The latter would correspond to a limit case involving liposome-like systems capable of self-maintenance but not self-reproduction. The crucial problem is how these three components (none of them defining life) need to cooperate among them in order to lead to a self-replicating macromolecular entity.

Most models and implementations of protocells make use of either micelles or vesicles (fig 10a) as compartments. A canonical protocell model is provided by a so called *autopoietic* system (figure 10b) where P and S stand for the membrane precursor and the surfactant molecules, respectively [80]. Here P is transformed into S which is incorporated in the vesicle. If a vesicle S_k is made of k monomers, and assuming that monomers can degrade, we have:



The balance between growth and division determines the outcome of the protocell dynamics. If we indicate by v_g and v_d the rates of single events (fig 10b) the vesicle would follow $d[S]/dt = (v_g - v_d)[S]$ and its solution is thus

$$[S] = [S]_0 e^{(v_g - v_d)t} \quad (21)$$

Three potential regimes are allowed by this kind of kinetics: (a) growth, when $v_g > v_d$, (b) homeostasis, for $v_g = v_d$ and collapse, when $v_g < v_d$ [80]. Under this

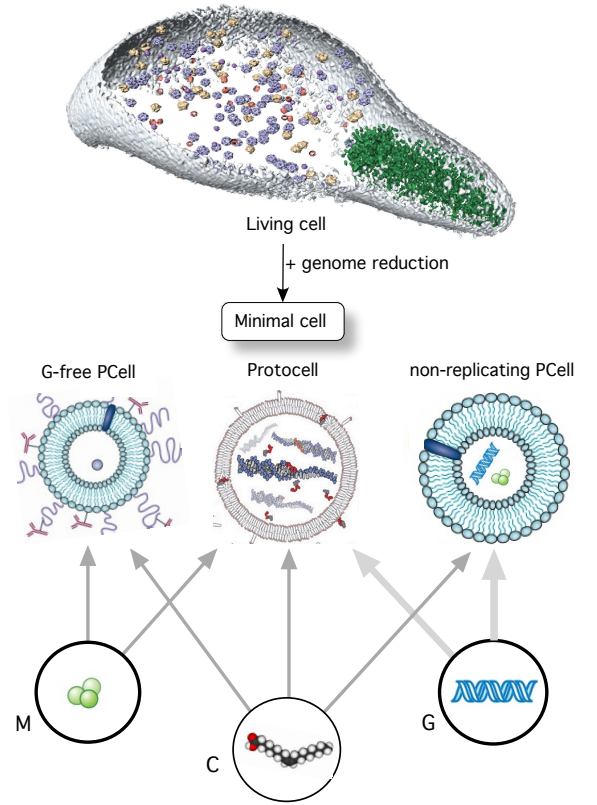


FIG. 9 Pathways towards synthetic cells. Two major approaches to create an artificial cell involve either a top-down or a bottom-up approach. The first starts from a living, complex cell such as *Mycoplasma sp.* (top) and proceeds through genome reduction. The second makes use of a molecular toolkit from which different forms of assembly produce different types of artificial protocells.

rather crude approximation, the system would be stable at criticality and capable of undergoing growth and division cycles provided that $v_g > v_d$.

Ganty's *Chemoton* model (figure 10c) provides an example of an explicit proposal for a protocell where several coupled cycles involving M+C+G are considered [81]. The model is spatially implicit and thus does not take into account the requirement for membrane instabilities: once a critical amount of material components has been accumulated, the model artificially splits the cell in two equal parts. The chemoton allows studying different relevant problems related to the role played template competition and error thresholds [85].

A major problem arises when dealing with an explicit implementation of the physics of compartments particularly in relation with the instabilities required for replication to occur. While the process of vesicle or micelle formation has to do with a minimisation of energy leading to a more or less symmetric structure, the growth-instability

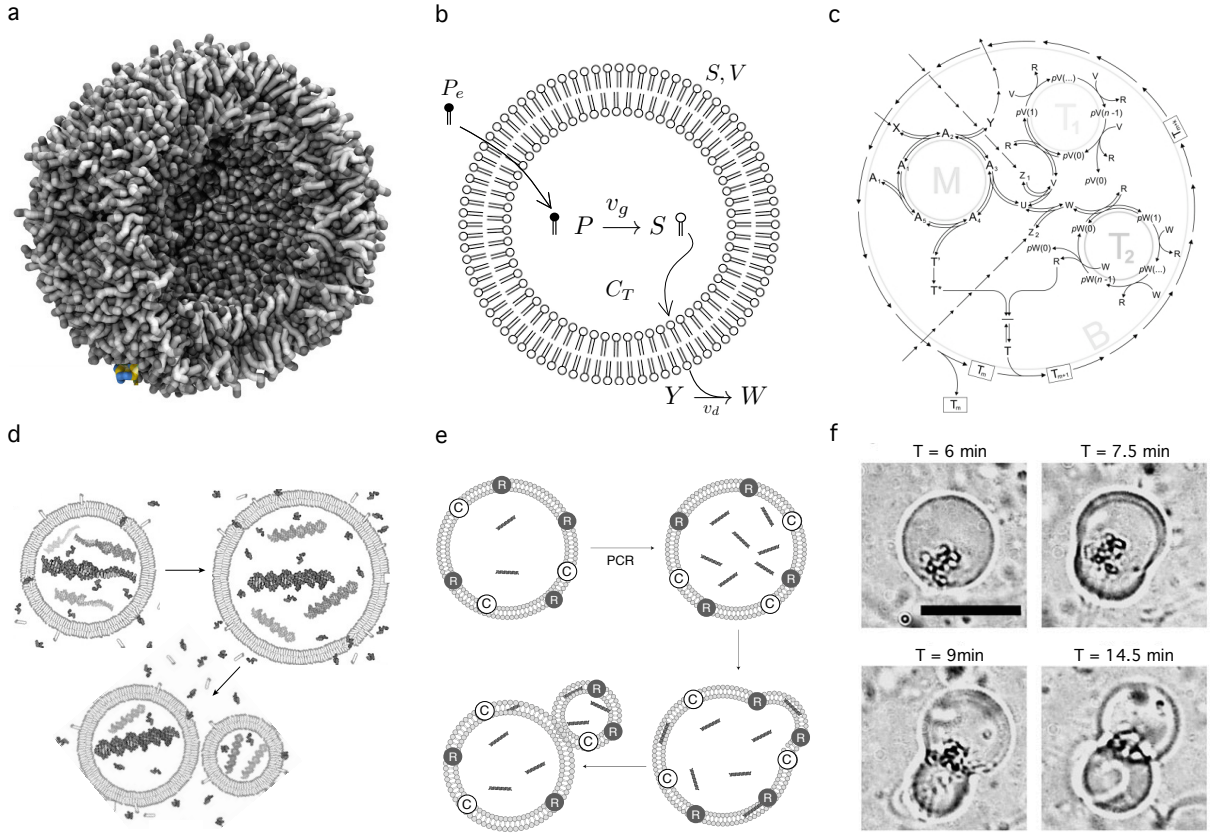
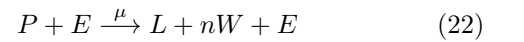


FIG. 10 Synthetic protocells. (a) A common component of most protocells is a spherical vesicle involving a lipid bilayer. In (b) we show a minimal model of an autopoietic cell, where an external precursor P gets transformed into surfactant molecules S and can also degrade under the presence of a given Y , into a waste product W . Here S, V and V_c stands for external surface, total and internal volumes, respectively. One version of Ganti's chemoton is shown in (c). Here the metabolic cycle is indicated by $M = \{A_j\}$ and z_k are external resources. In this example, two types of templates, indicated by T_1, T_2 , coexist in the same cell. Three different synthetic protocell cycles are shown in (d-f): (d) an RNA-based heterotrophic protocell [96] (e) Kurihara et al's model [97] and (f), after [98].

process involves an out-of-equilibrium process⁵. In order to destabilise the system, the symmetry of the spherical configuration needs to be broken. In this context, the contained and its coupling with metabolism and information define the genotype-phenotype mapping [86,87].

The efforts aimed to create an artificial cell must deal with different ways of triggering membrane instabilities leading to cell division. All these systems share a given environment where available membrane precursors required to achieve a critical size. Current living systems share a genetic control of the cell division, but early

stages in the evolution of protocells must have been dependent on physical properties of membrane curvature. Theoretical models address this in two main ways. The first class uses a parameter ϕ_c (the so called reduced surface⁶) defining the critical value associated to vesicle division. Here too a phase transition scenario is present. A general condition for achieving a cell division cycle has been derived in [88,89]. A simple example close to the autopoietic cell would be a self-reproducing enzymatic vesicle where the key reaction is given by:



⁵ Micelle formation, for example, can be described as a cooperative reaction $nA_1 \xrightarrow{K} A_n$ where a closed system A_n composed by n monomers A_1 gets formed provided that a critical concentration $x = [A_1]$ is present. This cooperative behaviour is an important part of the self-organisation of micellar structures and indicates that, once a given concentration of monomers is crossed, the system experiences a spontaneous transition towards macromolecular assemblies. These self-assembly properties are shared by a vast range of molecular candidates, both natural and artificial.

⁶ This parameter is defined as $\phi = S / \sqrt[3]{36\pi V^2}$ where S and V are the surface and volume of the vesicle, respectively. When $\phi = 1$ we have a spherical, stable vesicle, whereas lower values lead to inflated vesicles (which can burst) and higher values favour deformed vesicles. A critical value is given at $\phi_c = \sqrt[3]{2}$. A stable vesicle can be shown to exist within a domain $1 - \epsilon < \phi < \sqrt[3]{2}(1 + \eta)$ where ϵ, η are measurable coefficients.

with E being, for example, an enzyme located inside the vesicle and n waste molecules are released. This model is a good approximation to some experimental setups using giant vesicles that produce inside them, with the help of a catalyst, the main membrane component [90]. For this system, it can be shown that the critical balance obtained when

$$\frac{S}{V}\xi_p ([P]_e - [P]) + nr_L = \left(\frac{C_T\alpha_L}{2}\right) \left(\frac{N_A V r_L}{S}\right) \quad (23)$$

where $r_L = k[P]/N_A V$ and ξ the membrane permeability. The previous equation provides a critical condition required to achieve cell division. Moreover, it introduces constraints between different components of the system and their couplings.

The second class of models gets closer to the physics of membrane instability by explicitly considering this factor as part of the process. Here the use of the membrane energy is required⁷.

Mathematical and experimental investigations of vesicles shows that phase transitions separate spherical from asymmetric vesicles associated to symmetry breaking [91]. The explicit energy associated to synthetic protocell growth has been introduced in different ways. These include pattern formation through Turing instabilities [92] or micelle-metabolism coupling in nanocells [93-95]. These artificial cell models suggests that instabilities can be easily generated provided that a given molecule gets asymmetrically distributed within the vesicle, thus creating spatial inhomogenities. Alternatively, the packing of lipid molecules into a given spherical aggregate is strongly constrained by the shape of the surfactants. Once a critical number of these molecules is reached, the aggregate is no longer stable.

Synthetic protocell reproduction has been experimentally investigated using a diverse range of settings. None of them has been successful so far in showing a full, simple cell cycle following the growth-deformation-instability-division process. One candidate is a container (made of simple amphiphiles) enclosing oligonucleotides shows a template copying process in the cell interior [96]. The interest of this system (figure 10d) is that shows how prebiotically reasonable membrane compositions can be enough to provide a system capable of division driven by both internal and external forces. Other successful strategies have used different alternative ways of departing from the spherical symmetric compartment. An example of these synthetic systems (fig 10e) involved a giant vesicle (GV)-based model enclosing DNA molecules

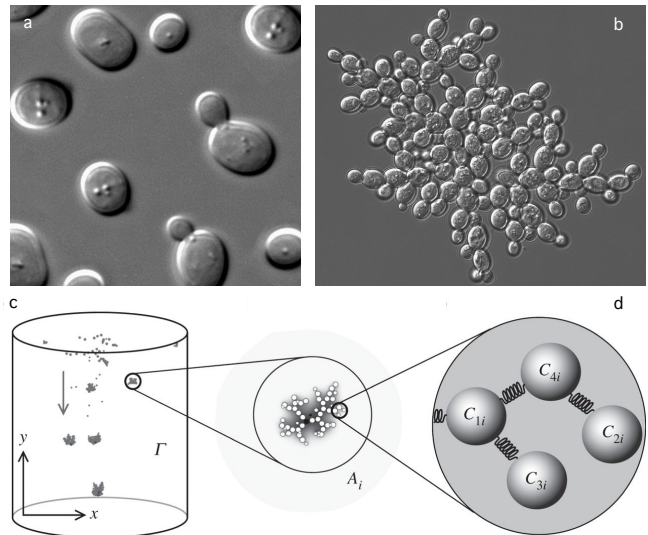


FIG. 11 Synthetic evolved multicellularity. Using yeast strains (a) involving single-living cells (image from <https://en.wikipedia.org/wiki/Yeast>) it has been shown that selection favouring the formation of aggregates (b) leads to the emergence of multicellular systems (image courtesy of W. Ratchiff). This type of experiment can be easily modelled using embodied simulations (c) where wells are represented as physical objects that can adhere to each other.

that are amplified through PCR [97]. In this system, membrane precursors are provided and the amplified DNA moves within the two lipid layers, triggering a local growth and budding process that ends in vesicle division. In another setting [98] the artificial cells contain RNA encoding a self-encoded RNA replicase that can be evolved over time. The artificial evolution experiments show that self-replication occurs (figure 10f) with the use of PCR and the input of fresh translation system under vigorous mixing.

All these examples require the help of some extrinsic factors to trigger or facilitate instability. In that respect, synthetic versions of protocells suggest that the path towards spontaneous instability and division might be more difficult than expected. But there is also another possibility: that the origin of protocells might have required such extrinsic factors to occur. In this context, a very active research has also been done exploring the emergent properties associated to membranes [99]. One particularly important finding is the potential role played by vesicles as functional promoters and regulators of chemical reactions [100]. Moreover, synthetic vesicles can compete and interact in nonlinear ways providing further layers of complexity beyond simple compartments [101-103].

VI. SYNTHETIC MULTICELLULARITY AND ORGANISMALITY

Multicellularity has evolved multiple times through the history of our planet [104-106]. This transition has taken

⁷ The energy associated to the bending of the vesicle is defined through the integral of the free energy on the surface. In its simplest form and considering low temperatures (i. e. thermal fluctuations are ignored) we have $\mathcal{H}_b = \oint_S \frac{\kappa[\mathbf{S}]}{2} (C(\mathbf{S}) - C_0(\mathbf{S}))^2 d\mathbf{S}$ where $\kappa[\mathbf{S}]$ is the bending modulus and $C(\mathbf{S}) - C_0(\mathbf{S})$ is the mean curvature of the vesicle surface at \mathbf{S} . The result of the minimisation of such energy function, i.e. the solutions of $\delta\mathcal{H}_b = 0$

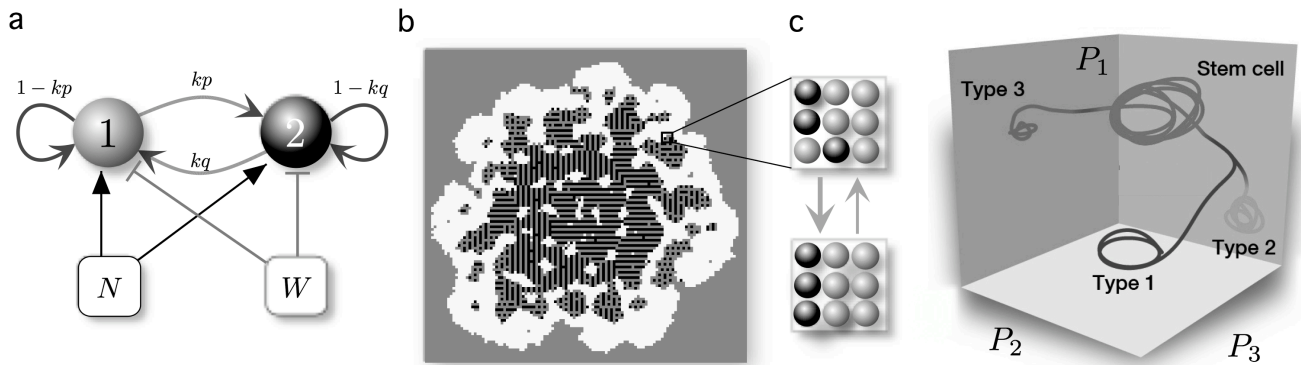


FIG. 12 Emergence of in silico proto-organisms. A simple spatial model can lead to complex multicellular assemblies involving organismality. Using (a) a two-state model of cells with division of labor, a complex spatially organised system emerges (b) as a result of artificial evolution under a selective medium where both nutrients and waste are present (see [133]). The spatial dynamics is driven by a model of differential adhesion (c). A different class of model involves considering cells as complex networks whose phenotypes (P_1, P_2, \dots) are defined by attractors derived from stem cells [135].

place either cell increased aggregation and adhesion (as it occurs with myxobacteria and some slime molds) or loss of cell separation after cell division (this includes bacteria and ciliates). Most classical models of the transition to multicellularity ignored physical interactions between cells within cell aggregates. In this context, these models [107] have been formulated in terms of a two-loci dynamical system where the transition implies an increase of cooperation among cells along with the regulation of conflict within the emerging organism. However, spatial structures create novel conditions that necessarily affect the fitness of the multicellular assemblies. Considering the embodied nature of these aggregates is not only required as an additional feature but it can actually be crucial to understand the transition itself. It is worth noting that the use of physical models of multicellularity reveals that even under very simplistic assumptions, complex forms easily emerge [108-113].

The transition to multicellularity required the presence of alternative cellular states along with stable, physical interactions among previously isolated cells [114-116]. Extant multicellular systems develop under tight controls of genetic networks [117,118]. Synthetic multicellular systems can be obtained in several ways, from non-clonal adhesion-differentiation processes to engineered consortia. In this context, achieving developmental properties necessarily require to overcome thresholds of organisation intimately connected to transition phenomena. It has been suggested that a small set of dynamical patterning modules (DPM) might have played a major role in the evolution of complex organisms. These DPM affect adhesion, diffusion, cross-inhibition or synchronization of cellular and tissue-level interactions through a set of key molecular actors [119]. In this context, artificially evolved multicellular aggregates [120] synthetic multicellular analogs [121] and their model counterparts [122-124] have shown the potential for novel explorations of an old issue.

A successful strategy to create synthetic multicellular systems was put forward in a recent set of experiments [120] in which the authors sequentially subcultured *S. cerevisiae* cells with the fastest sedimentation in order to force the selection of cooperating aggregates (figure 11). Remarkably, after just 60 selection rounds, the so called snowflake phenotype appeared consistently in all cultures (fig 11b). These are roughly spherical clusters of cells formed not by aggregation but by defective separation of cells after division. It was found that clusters did not reproduce through events associated to single cells but instead involved a group-level set of events. This was achieved through a division of labor in the form of the active control of apoptosis, which caused the asymmetrical splitting of the cluster once it reached a threshold size [120].

In order to understand the origins of these multicellular structures, a simple model was developed [123] that was also used to test other potential scenarios for the rise of multicellular ensembles (fig 11c). Here yeast cells and their interactions are simulated using a physical embodiment, with evolving adhesion rates. The model was able to reproduce the reported patterns in cluster size distributions and localised mortality. Moreover, the model suggests an alternative pathway to cell clusters and their fission based on a passive apoptotic effect of nutrient deprivation in cells at the center of the aggregate.

An interesting observation in this area is the presence of a blurred zone at the boundaries separating some single-celled species from full-fledged multicellular entities. Bacteria in particular exhibit multicellular traits [125] specially in the face of high-stress events [126,127]. Simple multicellular systems, such as *Anabaena* or mixobacteria are such examples of minimal multicellular organisation [128,129] that can involve primitive developmental programs. A minimal form of multicellularity are *persister cells* associated to cell subpopulations that can spontaneously switch back and

forth among multiple resistant phenotypes, as a bet-hedging strategy [130,131]. Can this mechanism pre-date the transition to the first complex multicellular life forms? This is connected to the origins of what Queller and Strassman named *organismality* [132]. Specifically, it would be important to know if primitive forms of cell adhesion and diffusion under selective conditions can lead to proto-organisms where division of labor is tied to spatial organisation.

A minimal model has been proposed for the origins of proto-organisms [133] and is summarised in figure 12a-c. It includes (a) multistability, using a stochastic bistable phenotype, (b) differential adhesion and (c) a selective environment involving both nutrients (N) and harmful (W) diffusible molecules. Cells are distributed over a two-dimensional lattice Ω . The two cell types need N to grow whereas W causes increased cell death (fig 12a). Only cells of type 2 can degrade waste in medium, at the expense of reducing their growth rates. Under appropriate metabolic trade-offs, it was shown in [134] that evolution of undifferentiated multicellularity might pervade the coexistence of cell clusters. By adding adhesion, it can trigger the formation of proto-organisms (see figure 12 b-c). The result is the emergence of nested substructures and the creation of an internal environment. These results suggest very simple sets of pattern-forming rules can produce a rich, largely unknown landscape of structures predating the evolution of multicellular organisms [133,134]. Other types of similar proto-organisms have also been obtained by models involving dynamic differentiation under isologous diversification [135]. In this type of model, cell types are dynamical attractors in a high-dimensional landscape of expression (figure 12 d).

Synthetic biology offers a unique opportunity of testing theories concerning the origin of multicellularity as well as the emergence of developmental programs. Engineered cellular communication has already been achieved in different contexts allowing the creation of novel cellular consortia [136-138]. By engineering unicellular systems it is also possible to obtain novel forms of multicellular assemblies, able to complex computations [139-141]. Finally, cell reprogramming and tissue niche engineering have shown the way to design synthetic tissues and organs [142,143] and explore synthetic development and its limits [144].

VII. SYNTHETIC SYMBIOSIS

Symbiosis refers to a scenario where once independent replicators come to live together in close association [145]. This association is typically tied to a physical interaction that oftentimes involves one partner embedded or in close contact within the other and the system experiences vertical transmission [146]. This close relationship can be parasitic or mutualistic. In the first case, one partner (the parasite) exploits the second, with no return from the former. Mutualism describes a mutual cooperative

loop where both partners help each other.

What are the basis for the emergence and persistence of symbiosis? As with most of our previous examples, definitive answers might be difficult to obtain by studying natural systems. Instead, synthetic counterparts provide a powerful approach to the problem and several examples illustrate how to create *de novo* mutualisms. Synthetic biology has been successful to show that different types of symbiotic relationships can be engineered in novel ways [147-151]. Different strategies have been followed, including: (a) design of auxotrophic interactions (fig 13 a) creating a synthetic cooperative loop (a hypercycle) where each partner needs a molecular factor produced by the second [152]; (b) transformation of plant pathogens into legume symbionts [153-154]. The experiment started from a designed chimeric strain of a plant pathogen carrying a symbiotic rhizobial plasmid from a plant endosymbiont (fig 13 b). The initial strain evolved to a full endosymbiont after two key mutations allowing nodulation and plant cell infection. Here niche engineering provides an additional approach to the problem, where two chosen non-cooperative species are forced to coevolve under a forced exchange of carbon and nitrogen. The outcome of this experiment was a synthetic transition from free living life forms into obligate mutualists [155].

A last example is given by synthetic designed chimeric organisms (fig 13c). Here photosynthetic microorganisms were injected into zebra fish embryos [156,157] as well as mammalian cells [156]. Such type of symbionts exist in nature and have been found in different phyla [158]. Here the photobiont uses solar energy to provide reduced carbon as a source of energy to the metazoan host, which can provide nutrients in return. Successful invasion of mammalian cells (macrophages) by algae was improved by engineering the photosynthetic cells with invasins [156]. Interestingly, the algae remains alive and even reproduce while embryonic development takes place. This opens the possibility of future plant-vertebrate chimeras where an additional engineering level would allow the production of useful metabolites other than oxygen [157,158].

The *in silico* approach to the emergence of symbiosis has also been successful and insightful, specially from computer models of evolving digital genomes [159]. The best known example was given by Tom Ray's experiments with the *Tierra* model, based on a set of replicating and mutating computer programs competing for computer memory (the resource) [160]. After a first selection for shorter, faster replicating programs, shorter programs emerged, but unable to replicate by themselves: parasites came to (digital) life. Similarly, on the long run groups of slow-replicating programs were able to replicate faster by cooperating among them. Digital evolution supports the idea that the emergence of parasites might be an inevitable outcome of evolutionary dynamics [161,162]. One particular instance of man-made synthetic parasites is provided by the evolution of computer viruses (CVs).

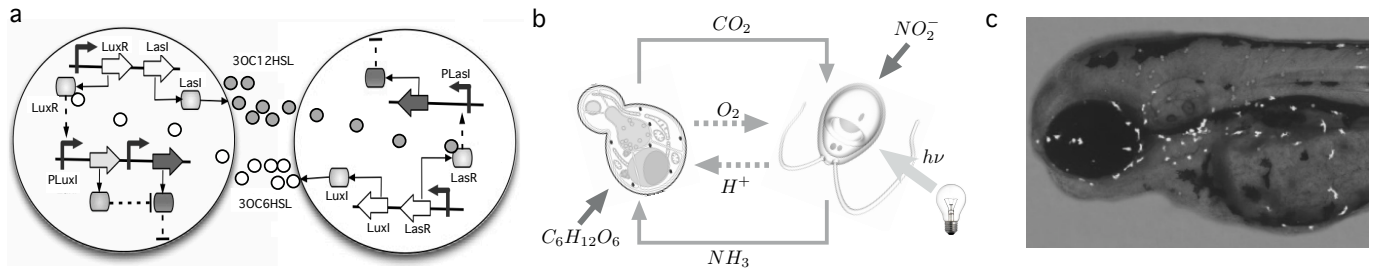


FIG. 13 Synthetic symbiosis. (a) A cooperative synthetic system involving designed auxotrophic interactions [152]. (b) Synthetic mutualism resulting from niche engineering. Here two species interact through a metabolic circuit based on carbon and nitrogen exchange. *S. cerevisiae* (left) metabolizes glucose ($C_6H_{12}O_6$) releasing carbon dioxide (CO_2), which is then assimilated photosynthetically by *C. reinhardtii* (right) to release oxygen (O_2). On the other hand, *C. reinhardtii* metabolizes nitrite (NO_2^-) and releases ammonia (NH_3) as a nitrogen source for *S. cerevisiae* [155]. In (c) we display a microscope image of a chimera zebra fish embryo containing living photosynthetic cells [156,157].

After their early appearance, CVs became more and more complex and diverse [163]. A crucial step in the historical development of CVs involved the creation of internal sources of variability that mimicked natural mutations. Variability was thus an invention, and a rather intentional one, as opposed to the intrinsic, inevitable errors that constantly take place in living systems. Moreover, in contrast with the typically harmful effect of mutations on viral genomes, random changes in CVs have no impact to their viability: Here no interactions are allowed to occur affecting functional traits. Computer viruses eventually evolved towards more silent, apparently harmless designs based on their potential to "integrate" themselves within the host machines, where they remain undetected [164,165].

VIII. SYNTHETIC COGNITIVE AGENTS AND SWARMS

The emergence of a special class of biological agents, the *neural individuals* [166] introduces a new layer of complexity: the rise of behavioral systems [167]. In this case, information transmission and processing is done *within* individuals. Here *behaviour* can be defined in terms of patterns of interactions between individuals and their environment where the actions of the organism and its perceptions interact, eventually affecting future actions and perceptions. Here we will consider two broad classes of synthetic cognitive systems and the key conditions for their emergence or synthesis: (a) individual cognitive agents and (b) societies, i. e. large sets of interacting agents displaying colony-level behaviour. The latter is tied to the problem of how cooperative societies came about and how such swarm intelligence can be engineered. Grey Walter's work in particular was the first systematic cybernetics approach aimed to create robotic agents (figure 14a) [168-171] and the term *synthetic animals* to refer to this class of automata capable of autonomous behaviour [172]. These simple autonomous robots were capable of some complex behavioral responses, including unexpected ones, as it occurred

when facing mirrors [170]. These and later [173] synthetic animals revealed an interesting (and largely unappreciated) feature, namely that the complexity of embodied agents was not just the result of its cognitive complexity, but of its interaction with the environment [174].

One of the most active area within robotics is grounded in a combination of designed and evolved agents [175-177]. Evolutionary robotics takes advantage of the search over parameter spaces by means of artificial Darwinian selection, which allows the synthesis of autonomous agents [176]. This field has clearly confirmed that behaviour is the emergent outcome of the interactions between the agent and its environment. The subsequent development of behavior-based robotics has also been very useful as a pathway to approach relevant evolutionary questions [175]. An example is the transition from swimming to walking, which was required in the transition from sea to land. Inspired in the anatomy and behaviour of salamanders, a model of the central pattern generator of synchronized neurons controlling locomotion was used as a starting point for evolving its architecture and parameters to allow a switch to walking gait of a tetrapod consistent with available information [178,179]. This is a powerful illustration of this field as an alternative path to uncover evolutionary innovations.

Collective intelligence and its potential synthetic counterparts needs to be considered separately. The emergence of the *superorganism* requires crossing the so called eusociality threshold, which involves overlapped generations, division of labor into reproductive and non-reproductive subsets and the maintenance of genetic relatedness [180,181]. Interestingly, Oster and Wilson [181] explicitly mention the potential relevance of phase transitions to understand the organisation of castes in social insects. What about the synthetic counterparts? Is it possible to evolve or engineer synthetic swarms? It has been pointed out that one precondition for the origin of societies of insects was a "get together" rule that should operate once individuals are born. This is a key requirement in order to achieve a cohesive group. However, less importance has been given to the fact that, once

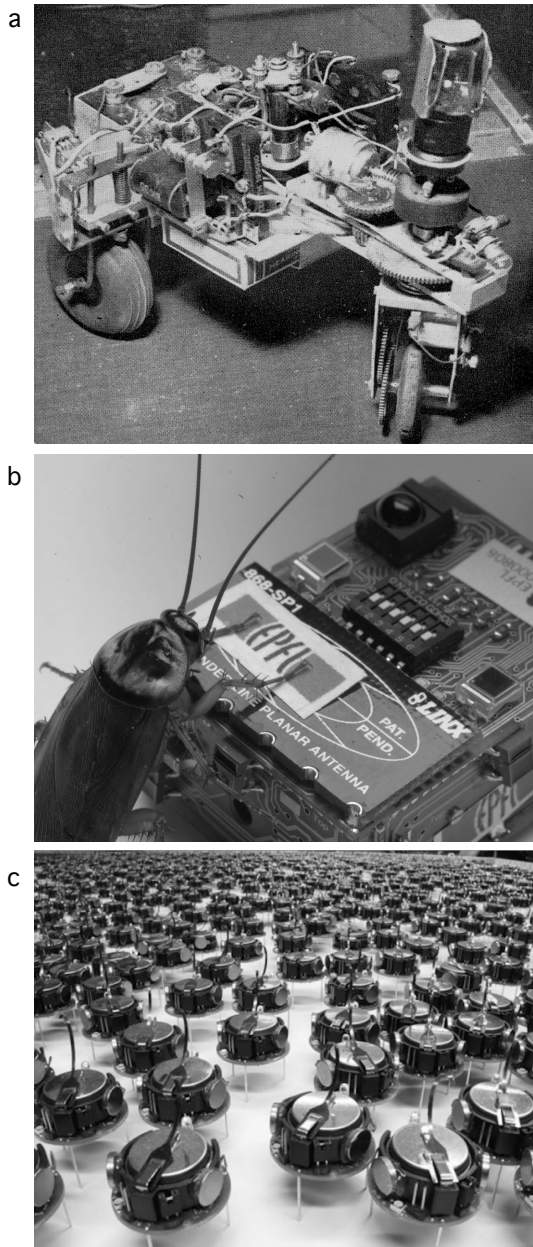


FIG. 14 One of the first "synthetic animals" (a) was built by Grey Walter. It involved a simple wheeled robot with sensors and actuators and reacting to light in different ways. Mixed synthetic swarms have been created by communicating cockroaches and their robotic counterparts (b) in order to solve problems collectively. Robotic swarms (c) made of many small robots following simple rules of interaction, can self-organise using self-assembly rules.

such step has been achieved, group responses resulting from phase transitions emerge too [18,182-184]. Here too interactions among individuals can trigger system-level responses provided that critical thresholds are reached [18,183,185].

These transitions provide the group-level dynamics required to perform different types of tasks. A specially

relevant example in our context is provided by an experiment that combined mixed societies of artificial and natural agents [186,187] including both real and robotic cockroaches (fig 14b) that have to perform a two-choice decision between two shelters. The robots were shown to modulate the collective decision process leading to a pattern that cannot occur in their absence. In other words, the artificial component of the mixture forces the proper swarm behaviour to occur and to test hypothesis concerning the origins of swarm intelligence. Moreover, the use of robot swarms or simulated agents working on a given spatial domain, provided insights into eusociality [188-191]. Novel ways of implementing large numbers of robotic swarms [192,193] capable of using self-assembly rules (fig 14c) have also been engineered.

Microbes are also capable of integrating sensory information, store memories and display different levels of behavioural control [194-196]. They thus incorporate several relevant components required to build or design complex decision-making systems. In some cases, the ways microbial colonies respond to environmental challenges can be easily classified as a swarm intelligence problem [194]. Alternatively, many well known examples of collective decision making could be engineered using modified microorganisms [197] capable of implementing computational tasks with no known counterpart from the microbial world.

An interesting outcome of the study of natural, synthetic and robotic systems is the presence of seemingly universal decision-making rules of organisation. Group responses displayed by ant colonies are based on so called *quorum sensing* (QS) mechanisms [198] also displayed by microbial populations [199]. The QS rule, as well as other amplification mechanisms pervade phase transitions between individual, disorganised behavior (ants search individually) and colony order (collective search towards a given nutrient source). Here a signal (a pheromone, for example) φ triggers its own production with constant rate μ and is proportional to the population density ρ . The signal is produced following a function $f(\varphi)$ by individuals (present at a given density ρ) and decays at a rate δ [197]. The minimal model that captures this is: $d\varphi/dt = f_\rho(\varphi) - \delta\varphi$. A common form of $f(\varphi)$ is a so-called Hill-like function⁸ namely:

$$f_\rho(\varphi) = \frac{\mu\rho\varphi^2}{\theta^2 + \varphi^2} \quad (24)$$

which gives small values for $\varphi < \theta$ and large values otherwise. Close to the threshold θ it rapidly increases. The

⁸ The quadratic terms that appear in this Hill function are characteristic of some well known regulatory controls associated to the presence of dimers as gene regulators. In other cases, saturation functions with similar shape are related to well known threshold-like phenomena exhibited by physiological and neural systems.

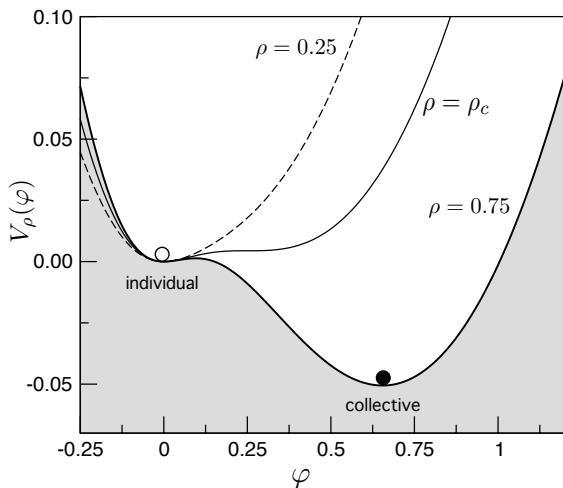


FIG. 15 Phase transitions from individual to collective response through a QS mechanism, as described by $V_\rho(\varphi)$. Here the state of the system is described by a global field φ that is proportional to the system's activity. Here we have fixed $\mu u = 1, \theta = 0.25$ and $\delta = 1$ (thus $\rho_c = 0.5$) and different ρ are used: $\rho = 0.25, 0.5, 0.75$.

potential function reads now:

$$V_\rho(\varphi) = \frac{\delta}{2}\varphi^2 - \mu\rho \left[\varphi - \theta \arctan\left(\frac{\varphi}{\theta}\right) \right] \quad (25)$$

and in figure 15 we show three examples for subcritical, critical ($\rho_c = 0.5$) and supercritical densities. For $\rho < \rho_c$ we can see that the only stable state is the $\varphi^* = 0$ point, as expected, but the shape of $V_\rho(\varphi)$ is clearly deforming as we approach ρ_c .

Ant colonies have been often compared to brains and neural networks [200,201]. The analogy is approximate but useful, since allows finding universal laws too. Both ant colonies and brains process, store and use information about their environments while monitoring internal colony states. However, ant colonies are made of agents in movement, thus defining a different state of matter compared with grey matter: insect colonies are fluid neural networks [202-204] and thus some of the crucial features of a standard neural network are not present in the swarm. Is the fluid state a constraint for developing more complex cognitive capacities? Are "solid" and "fluid" neural systems the only two solutions available? Future work might shed some light into the invention of eusociality [205] and the implications for defining universality classes of cognitive complexity.

IX. SYNTHETIC LANGUAGES

The transition towards a complex language is a recent one and had an enormous relevance to human evolution. It is also a hard problem [206]. One of the obvious facts is the gap between the complexity of human language and any other known biological communication system. The

gap is due to the presence of a grammar that allows the generation of recursive structures of potentially infinite complexity [1,207]. Another crucial observation concerns language acquisition in children. Around two years of age, when the sequence babbling-one word-to words utterances is replaced by full sentences [208] and children develop grammatical competence, suggesting that this is an indication of an innate capacity of language [209,210]. Grammar effectively defines the mapping between linguistic forms and meanings. In its original formulation, Chomsky introduced the concept of *Universal Grammar* (UG) to describe the hardwired 'linguistic theory' that is shared by all human brains and allows children to search the (large) space of possible human grammars [211].

Two main avenues have been followed to study the transition to language using artificial systems. One involves theoretical and computational models including (a) standard replicator equations [212,123] (b) information theoretic approaches [214,215], (c) statistical physics [216,217] or (d) the simulation of discrete agents [218,219]. The second class deals with physically embodied, robotic agents capable of sensing and tracking their environments while naming and sharing objects and actions [220-222]. In most of these artificial models, qualitative (phase) transitions are also at work.

Several transitions are involved in language complexity [223]. First, consider the evolutionary dynamics associated to the emergence of language coherence [224]. Let us assume that a set of possible rules $\mathcal{G} = \{G_k\}$ (with $k = 1, \dots, n$). Each G_k that can generate "valid" messages. These have been identified as "grammars" in previous studies [224] but the general approach can be applied to other features of language, including the inventory of shared words. Different G 's can have similar rules, and thus are capable of generating some common sentences. How can a search over a very large space \mathcal{G} end in a common, shared grammar? We will define $A = (a_{ij})$, where a_{ij} indicates the similarity between G_i and G_j . If two individuals are communicating by means of two different grammars, the payoff associated to this exchange will be $F(G_i, G_j) = (a_{ij} + a_{ji})/2$ and the frequency of agents using the i -th grammar follows a replicator-mutator equation:

$$\frac{dx_i}{dt} = \sum_{j=1}^n x_j f_j(\mathbf{x}) Q_{ij} - x_i \Phi(\mathbf{x}) \quad (26)$$

where $\sum_{j=1}^n x_j = 1$. Moreover, we have $\Phi = \sum_k f_k x_k$ and the matrix Q_{ij} is the probability that an agent learning G_i from an individual ends using G_j instead. This introduces a noise in the model. If we assume the simplest, super-symmetric model where $a_{ij} = a$, and such that $Q_{ij} = \delta_{ij}(q/n - 1) + (1 - \delta_{ij})(1 - q)$ with $\delta_{ij} = 1$ if $i = j$ and zero otherwise. Here, q is a learning parameter and one solution is $x_i = x$ and $x_{j \neq i} = (1 - x)/(n - 1)$. Assuming that $n \gg 1$ (a crude approximation, since $x \sim O(1/n)$)

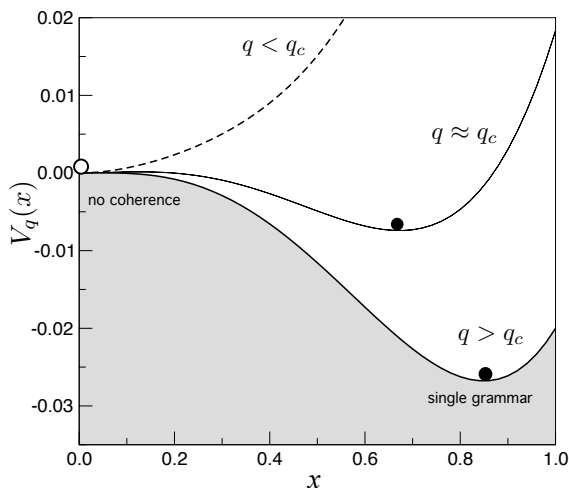


FIG. 16 Phase transitions in grammar evolution. Here the potential function $V_q(x)$ is represented for three different q values of the learning parameter, namely $q = 0.5, 0.8, 0.9$ which are below, close and beyond the critical value q_c separating multiple grammars (with $a = 0.3$ and $f_0 = 0$) (here since $n \gg 1$ it corresponds to $x = 0$).

solutions are replaced by a zero) that the SSM follows:

$$\frac{dx}{dt} = (1-a)x^2(q-x) - \eta(1-q)(x-1) \quad (27)$$

where $\eta = (a + f_0)(1-q)$. This model involves a phase transition between a state associated to multiple coexisting grammars and one single, universally adopted one. The shape of the potential function is given by:

$$V_q(x) = \eta(1-q)\frac{x^2}{2} - (1-a)x^3\left(\frac{q}{3} - \frac{x}{4}\right) \quad (28)$$

and is shown in figure 16 for different values of the learning parameter q . As we can appreciate, there is a regime where many different grammars coexist ($x^* = 0$) whereas after a threshold q_c is reached, a stable state is given by a single dominant grammar for $q > q_c$. In general terms, we can use this model to represent the emergence of language coherence within populations of communicating agents. As soon as the critical threshold is reached, a sudden jump to the single-language solution occurs.

The previous strategy neither takes into account most structural and computational complexity of syntax nor the relevance of meaning [225]. An alternative approach to the problem incorporates a system capable of perception, programmed to label objects and actions. The use of embodied robotic agents (Figure 17a-b) revealed several remarkable things. One is that embodiment is a key requirement to evolve complex communication [226]. Secondly, evolutionary experiments showed that, along with a lexicon, rudimentary forms of grammar also emerge [227] thus indicating that a grammatical network organisation (figure 17b) should be expected also in artificially evolved languages. The complexity of the

evolved networks of word interactions has been analysed by means of fluid construction grammars [228].

Finally, another avenue to synthetic languages is grounded in a statistical physics approach that seeks to explain some key universal traits such as Zipf's law, which establishes that the frequency of any word is inversely proportional to its rank [229]. Specifically, if we rank all the occurrences of words in a text from the most common word to the least one, the probability $p(s_i)$ that in a random trial we find the i -th most common word S_i (with $i = 1, \dots, n$) falls off as

$$p(s_i) = \frac{1}{Z} i^{-\gamma} \quad (29)$$

with $\gamma \approx 1$ and Z the normalisation constant. This law indicates that most words are rare whereas a few are very common, and this abundance is also connected with the frequency of connections between words within sentences [230]. Does Zipf's law define a universal feature of complex languages, natural and synthetic?

A toy model can be defined by considering a set of symbols $S = \{s_k\}$ and a set of objects of reference $R = \{r_j\}$ that are shared by a hearer and a speaker. A given toy language can be described by the graph that connects the two sets, as the one shown in figure 17(b-d). Here two efforts are defined, namely the one for the speaker, Ω_s and one for the hearer, Ω_h . Here Ω_s will be minimal by using one or a few words to refer to all objects (fig 17b) whereas Ω_h would be minimised if the speaker uses one signal (word) for each object (meaning) i. e. a one-to-one mapping (fig 17d). Clearly, minimal effort for one implies maximal effort for the second. A conjecture [231] suggested that language complexity might be a consequence of the simultaneous minimisation of both efforts. This *least effort principle* was formalised using information theory [232]. One way of defining the global effort is to consider a linear (energy) function $\Omega(\lambda)$ to be minimised:

$$\Omega(\lambda) = \lambda\Omega_h + (1-\lambda)\Omega_s \quad (30)$$

with $\lambda \in [0, 1]$. This parameter tunes the relative contribution of each effort. If $p(s_i)$ is the probability of using s_i , the hearer's effort is defined by the entropy

$$\Omega_h = H(S) = - \sum_{i=1}^n p(s_i) \log(p(s_i)) \quad (31)$$

measuring symbol diversity. Similarly, the uncertainty of properly retrieving the right objects associated to each signal, gives:

$$\Omega_s = H(R|S) = - \sum_i p(s_i) \sum_j p(r_j|s_i) \log p(r_j|s_i) \quad (32)$$

where $p(r_j|s_i)$ is the probability of associating the signal s_i to the reference object r_j . It can be shown that minimal effort is achieved at $H(S) = H(R|S)$ (when

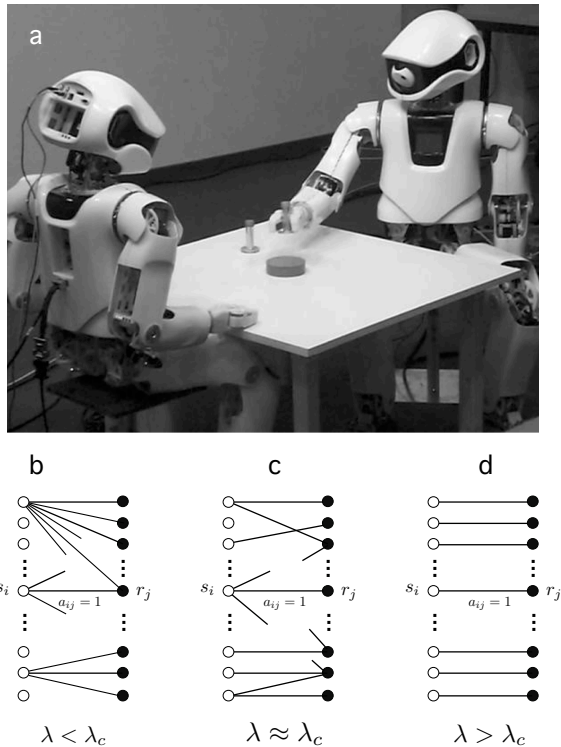


FIG. 17 Emergent synthetic languages. By using embodied robotic agents (a) a protogrammar can emerge (image from the Neurocybernetics group at Osnabrück) that can be traced through the analysis of the underlying synthetic language network developed by the agents. A formal model of language (c) is described as an evolvable bipartite signal-object graph (b-d) whose topology depends of the specific trade-offs associated to the efforts of communicating agents, as described by equation (30) as weighted by a control parameter λ .

$\lambda_c = 1/2$) and that a phase transition occurs at this critical value (fig 17c). Zipf's law could be the outcome of criticality [232,233]. Indeed, the heterogeneous distribution of word use defined by Zipf's law seem to occur close to λ_c , where ambiguity is a key trait. The presence of ambiguity is a specially relevant property here, largely absent in embodied communicating agents, in order to avoid combinatorial explosions [234]. Since a heterogeneous distribution of words might automatically lead to an efficient navigation [230] the least effort scenario suggests a unified framework to account for some crucial features, including the roots of a proto-syntax [235].

X. SYNTHETIC MINDS

The human brain experienced an accelerated expansion and differentiation through a series of events associated to successive additions of neural microcircuits [234]. Part of these processes deal with simple but key mechanisms that are common to humans and our ancestors. But some circuits seem to incorporate distinctive traits that are related to our human condition [235]. The

evolutionary dynamic of neural networks within complex brains has unfolded over millions of years, eventually allowing the rise of the human mind capable of symbolic thinking and self-awareness. Here consciousness defines a special and specially puzzling property. It has been the focus of scholar efforts [236-238] and Darwin himself asked "How does consciousness commence?" [239]. Despite its importance and implications for understanding general anesthesia, coma or minimal consciousness, it remains an unsolved problem [240]. Different paths have been followed in search for the evolutionary origin of consciousness or even potential definitions or classes [241]. These include finding evolutionary homologies [242] and developing quantitative measures of neural correlates of consciousness [243]. In this context, it has been suggested that a parameter Φ can be defined that measures the capacity of a system to integrate information. Using a set of postulates under an information theory framework, $\Phi = 0$ for non-conscious agents whereas $\Phi > 0$ otherwise, thus aiming at measuring consciousness levels [244]. A relevant question is: when and how did consciousness evolve? which necessarily requires to assume that some kind of consciousness is present in some metazoans. As pointed out by Gerald Edelman, a scientific approach to this problem might "necessarily require the synthesis of artifacts" [245].

Can a machine be conscious? A crucial precursor to this question has to be found in Turing's classical paper *Computing machinery and intelligence* [246]. Although not explicitly addressing the problem of consciousness, Turing was the first to explore the problem of how to detect (using natural language) intelligence in a machine. The pursuit of cognitively complex machines pervades many scientific and philosophical debates since the 1950s [247,248]. The field of Artificial Intelligence soon started to develop some systematic approaches based on the construction of ever more complex programmed machines, sometimes emulating cognitive tasks using neural networks but most of the time following an algorithmic approach. The field experienced a major shift since the rise of new approaches to machine learning known as *deep learning* which is on convolutional neural networks [249]. Beyond the impressive success of their practical implementation [250] they have also raised relevant questions concerning the workings of natural and synthetic minds [251,252].

In previous sections we have mentioned the importance of defining the preconditions for different major synthetic transitions. What would be the key conditions predating the emergence of consciousness? [205,253,254] Some advances within robotic agents suggest that key features of the problem might be achievable by using the proper architectures. A specially interesting examples is provided by robots capable of mirror recognition [255,256]. Since a self-aware robot would be more capable of dealing with novel situations, several studies have been focused towards developing robots involving internal self-models [257]. Here the embodied nature of robotic agents and

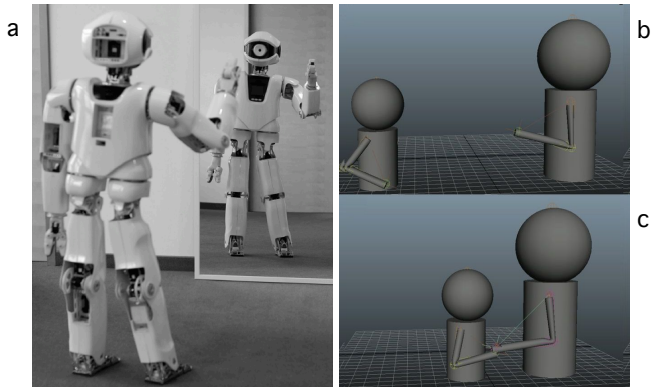


FIG. 18 Transitions to self-awareness. Robotic agents can be used (a) to explore the problem of mirror recognition (image provided by Luc Steels). When equipped with an internal representation of their internal states, they can pass the so called mirror test. Modelling agent interactions (b-c) incorporating a mirror system in their architecture (d) allows developing behavioural patterns (adapted from [263]).

their capacity for visual recognition of their environment (fig 18a) has been the key to develop robots capable of passing the mirror test with high accuracy. By incorporating an internal model, artificial agents internally simulate their own actions and their sensory effects. In this way they can achieve behavioural advantages, particularly if these can be generated by the robot itself [259]. These features provide the basis for the emergence of emotional states and what some authors name *functional imagination*, i. e. the manipulation of information that is not directly available to an agent's sensors [260]. Related work involves modelling the neural basis of mirror neuron systems [261] within artificial agents [262-264] and include explicit embodied modelling of interactions and the emergence of ritualised gestures (fig 18b). Such connections open novel avenues towards a synthetic ethology.

Is the emergence of consciousness a phase transition phenomenon? Explicit suggestions of a tipping point [265] propose that once some brain complexity thresholds are overcome (but not below) consciousness might be inevitable. On the other hand, consciousness requires a neural substrate that provides a compromise between integration and segregation [243,266] and the right trade-off might need a brain poised at a critical (transition) point [267]. The transition might need specific architectural changes, as suggested by the reentry hypothesis [268] incorporated within artificial systems as multiple positive loops [237,245]. It is interesting that research in this area also considers the potential repertoire of levels of consciousness in the anesthetized brain [266,269] which reveal the presence of sharp transitions between aware and unconscious states.

As a final point, we also need to consider potential departures of synthetic minds (either evolved or designed) from real brains. This includes the fluid neural networks

(virtual or natural) associated to collective intelligence systems [201,203]: would an ant colony or a termite nest have a $\Phi > 0$ consciousness level? On the other hand, some artificial life models have shown how artificial agents evolve highly integrated "brains" while evolving in complex environments [270]. But a major difference between artificial and biological candidates to a "mind" is the potential of the former for gathering massive data from non-local sources [271]. Given the relevance played by embodiment in shaping minds [272,273] we should also expect major differences associated to the distributed nature of synthetic minds grounded in the use of non-local sources of information. Similarly, we should expect new classes of minds emerging in the future as a result from interactions between human and embodied communication robots equipped with learning and memory [274].

XI. SYNTHETIC ECOSYSTEMS

As a final example in our hierarchy, let us consider the problem of designing and/or evolving synthetic ecosystems. Ecosystems are complex adaptive systems, and in many ways they can be described, under a systems approach, as far from equilibrium structures. Synthetic ecosystems include [275]: (a) those ecosystem that result from the evolution of communities under laboratory-constrained conditions, (b) special species assemblies evolved in human-created environments which often display overabundance of extremophiles and (c) engineered communities of multiple interacting microbial organisms resulting from partial or total designed strains from synthetic biology techniques [276]. All these systems represent departures from their natural counterparts in several ways. Moreover, we can include in this list those synthetic ecosystems resulting from artificial life experiments [159, 160,277,278] where a more or less sophisticated set of physical constraints are introduced along with evolvable genomes [279].

The canonical example of long-term evolution experiments using microorganisms is provided by Lenski's work with *E. coli*, involving thousands of generations of population transfers [280]. Many other selection experiments have been shown to create novel adaptations not present in our current biosphere, such as the low-pressure conditions found in Mars [281]. A somewhat similar class of unintentional evolution experiments occurs in special contexts related to specific artificial environments, such as solar panels [282] or coffee machines [283]. Ecosystems adapted to these "alien" conditions are dominated by extremophiles evolved under strong selection towards specific adaptations to -for example- high temperatures or caffeine abundance. These artificial ecosystems can be helpful to gain insight into the evolution of extreme communities but also for future designed ecosystems (see below).

The rise of synthetic biology allows to create novel ecosystems where interacting species or their niches are

engineered, with or without further artificial evolution. Understanding the patterns of organisation of these communities is a much needed task, since no species within a given community live in isolation [284,285]. Examples of synthetic ecosystems include different microbial consortia in liquid or spatial environments involving different forms of communication [286-289]. These ecosystems will offer valuable information about the stability of artificial communities of interacting species, and this might be relevant for the engineering of the human microbiome and its alternative states [290,291] as well in potential approaches to ecosystem bioengineering [292,293].

Since the microbiome seems to follow universal ecological patterns [294] these manipulations can shed some light into the resilience of future synthetic ecosystems resulting from the release of modified organisms. In this context, transitions between alternative states have been also recognised as a fundamental part of their robustness and fragility [295, 296]. Here some species, known as *ecosystem engineers* play a crucial role in shaping the ecology and evolution of communities and their potential modification [297,298]. Finally, the possibility that learning can be incorporated as part of our understanding of evolution, particularly within the context of ecosystems [299,300] opens novel forms of thinking in evolutionary transitions and further levels of informational complexity to be designed or artificially evolved.

XII. DISCUSSION

What drives the emergence of major novelties in evolution? In this paper we have explored the parallel path followed by artificial versions of those transitions that have been identified in the historical record of life. In some cases, the main difference involves the presence of developmental processes that are an inevitable part of biological complexity but are absent in most artificial systems. An exception here are those based on synthetic biology and thus using cells and their interactions as part of the engineering toolkit. Development, as well as constraints associated to genetic similarity and other features of real biology are largely absent in most artificial designs grounded in hardware but also in simulated scenarios, with some exceptions. Since development defines the mapping between genotype and phenotype in biological systems, it also incorporates a big deal of complexity that results from the tinkered nature of evolution.

Some of the transitions that have repeatedly occurred in evolution have been also achieved in the artificial context, including multicellularity, symbiosis or different forms of cognitive complexity. In most cases, the basic logic is shared by the living and the designed systems, thus reflecting seemingly universal rules of organisation. The universality has to be understood in terms of fundamental principles and minimal requirements and in this context we suggest that phase transitions might be a specially relevant framework here. We have illustrated

this in different case studies where simple models capture the nature of the transition, where the qualitative nature of the change can be seen as an instance of a phase change not very different from those described by statistical physics models. This view has been defended within the context of origins of life studies [301] and future theoretical work will be needed to substantiate this conjecture but it might also require to rethink the framework of physical theories by incorporating the emergence of generative rules. This is specially important when we think in the nature of the rules allowing the open-ended nature of evolutionary change. In other words, novel "phases" come with new properties but also with internal grammars that describe their computational complexity. Such a generalised theory is still missing.

Among the examples described above, novel forms of communication or hybrid systems also illustrate the idea that synthetic transitions might incorporate qualitative features not present in biology. In most cases, the differences also arise due to the lack of a natural selection process, where cost constraints and competition for resources should play a leading role. Molecular systems can display growth and replication processes not grounded in the standard template-based mechanism. Genetic codes with lower and higher combinatorial repertoires have been constructed and replicating protocells created by means of a mixture of growth-instability cycles and external triggers with no genetic control. Similarly, the non-local nature of information processing exhibited by robotic agents clearly departs from the limits imposed by the embedded neural system carried with by every individual in the natural world. Similarly, the goal of creating self-aware machines typically ignores the social context and developmental path where natural minds arise. These examples not only stress the differences, but also suggest that in some cases (such as protocells or machine intelligence and consciousness) the path towards the transition might be more difficult to achieve, both in the biological and the artificial contexts.

A final point to be made is that evolution, as pointed out by the french biologist Francois Jacob [302] does not operate as an engineer. Evolution does not foresee the future and requires existing materials and rules to build new structures. Novelties thus necessarily arise through reuse and rewiring⁹. The engineer is not (in principle) limited by such constraints, and can overcome the messy and often non-modular nature of biological circuits. However, it is not less true that, because of the tinkered nature of evolution, biological structures often incorporate levels of robustness and integration that clearly depart from their artificial counterparts. The underlying landscape of evolved designs might contain properties that are not captured by the engineering-driven

⁹ Charles Darwin himself already stated the presence of tinkering as part of the evolutionary process, see [303], p. 348.

version where some simplifying assumptions are made. If that is the case, achieving some of the METs using synthetic paths might need to incorporate evolutionary dynamics as an essential part of the process.

Acknowledgments

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