Autocatalysis: At the Root of Self-Replication

Raphaël Plasson*,**
Keio University

Axel Brandenburg†,‡
Nordita
Stockholm University

Ludovic Jullien§
École Normale Supérieure

Hugues Bersini¶
Université Libre de Bruxelles

Abstract Autocatalysis is a fundamental concept, used in a wide range of domains. From its most general definition, that is, a process in which a chemical compound is able to catalyze its own formation, several different systems can be described. We detail the different categories of autocatalyses, and compare them on the basis of their mechanistic, kinetic, and dynamic properties. It is shown how autocatalytic patterns can be generated by different systems of chemical reactions. The notion of autocatalysis covers a large variety of mechanistic realizations with very similar behaviors; it is proposed that its key signature is its kinetic pattern expressed in a mathematical form. This notion, while describing dynamic behaviors at the most fundamental level, is at the basis for developing higher-level concepts towards life: autocatalytic sets and autopoietic systems.

Keywords
Chemical network, autoinduction, template, competition, mechanism, autopoiesis

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1 Introduction

The notion of *autocatalysis* was introduced by Ostwald in 1890 for describing reactions showing a rate acceleration as a function of time [33]. An example is the case of ester hydrolysis, which at the same time is acid catalyzed and produces an organic acid [20]. Defined as a chemical reaction that is catalyzed by its own products, it was soon been described on the basis of a characteristic differential equation [34, 35]. Typically used to describe complex behaviors of chemical systems, such as oscillatory patterns [23], it was immediately found to be essential for the description of biological systems, including the growth of individual living beings [40], population evolution [24], and gene evolution [30].

The extension of this concept from a chemical description to a more general context was initially carefully described as an analogy, sometimes qualified as the more general notion of autocatakinesis [25, 55]. However, it eventually led to an overgeneralization of the term autocatalysis, tending to assimilate it to the notion of *positive feedback*, for example, in economics [26]. The notion of autocatalysis is now,

* Contact author.
** Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1, Hiyoshi, Yokohama, 223-8852 Japan. E-mail: plasson@applc.keio.ac.jp
† Nordita, Roslagstullsbacken 23, 10691 Stockholm, Sweden.
‡ Department of Astronomy, Stockholm University, 10691 Stockholm, Sweden.
§ École Normale Supérieure, Département de Chimie, UMR8640, 24 rue Lhomond, 75231 Paris Cedex 05, France.
¶ Iridia, Université Libre de Bruxelles, 50 Av. F. Roosevelt, CP 194/6 1050 Brussels, Belgium.

however, actively being used for describing self-organizing systems, in particular in the field of emergence of life and artificial life. Autocatalytic processes are the core of the mechanisms leading to the symmetry breaking of chemical compounds towards homochirality [11, 39], and can be identified in several experimental systems [19, 45]. However, how such autocatalytic processes are to be regarded is still under heavy debate [37, 3].

Artificial life has always been more interested in the structural characterization of biochemical reaction networks rather than on its dynamic behavior (which results from it). This can be explained through the logical and computational roots of ALife. Consequently, a first interest for autocatalysis in the artificial life literature owes more to its intrinsic homeostatic character, that is, the ability to keep producing all chemicals of the system and to stabilize their concentrations despite continuous extinction and external perturbation. This homeostasis naturally is supposed to emerge from the structural closure of the reaction network.

ALife researchers think that in order to appear and maintain itself inside a soup of molecules entering various reactions, such a reactive system must form an internally cycled network or a closed organization, in which every molecule is consumed and produced again by the network. Above all, in order for life to begin, all of the components must have been able to stabilize themselves in time. These closed networks of chemical reactions are thus perfect examples of systems that, although heterogeneously composed, are capable of maintaining themselves indefinitely despite the shocks that tend to destabilize them. This comes about through a subtle self-regeneration mechanism, where the molecules end up producing those molecules that have produced them.

The purpose of this article is to clarify the meaning of chemical autocatalysis, and to explain how this dynamic concept is linked to the structural concept used in artificial life. This effort will be undertaken by covering the following points:

- What is autocatalysis for a chemical system? On the basis of the general description of a process allowing a chemical compound to enhance the rate of its own formation, autocatalysis is defined by a kinetic signature, expressed in a mathematical form.
- How can an autocatalytic process be realized? As many mechanisms can reduce to the same macroscopic kinetic laws exhibiting autocatalysis, the focus is put on several mechanistic realizations of autocatalytic processes, based on simple models further illustrated by concrete chemical examples.
- How can autocatalysis be observed and characterized? The focus is put on the dynamic properties, showing that this phenomenon is the direct consequence of the kinetic pattern, rather than the underlying mechanism.
- What is the role of autocatalysis? Embedded in a nonequilibrium reaction network, the competition between autocatalytic processes allows the onset of chemical selection, that is, the existence of bifurcation phenomena allowing the extinction of some compounds in favor of others.

2 Autocatalysis: A Practical Definition

2.1 A Kinetic Signature

From its origin, the notion of autocatalysis has focused on the kinetic pattern of chemical evolution [34]. The general definition of autocatalysis as a chemical process in which one of the products catalyzes its own formation can be mathematically generalized as

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = k(\mathbf{X}) \cdot x_i^n + f(\mathbf{X}), \qquad k > 0, \quad n > 0, \quad |k| \gg |f| \tag{1}$$

where **X** is the vector of all the concentrations x_j. An autocatalysis for the compound x_i exists when the conditions of Equation 1 are fulfilled. The term $k(\mathbf{X}) \cdot x_i^n$ describes the autocatalytic process itself, while $f(\mathbf{X})$ describes the sum of all other contributions coming from the rest of the chemical system.

We have an effective practical definition of the concept of autocatalysis, based on a precise mathematical formulation. The causes of this kinetic signature can be investigated, seeking the mechanism responsible for the autocatalytic term. This leads to the discovery of a series of different kinds of autocatalysis processes, and their respective effects, describing what observable behavior is generated by the autocatalytic term (see Figure 1).

2.2 Potential versus Effective Autocatalysis

The kinetic definition of potential versus effective autocatalysis is purely structural. As a matter of fact, a system may contain potential autocatalysis, that is, an autocatalytic core may exist in the reaction network. However, in the absence of some specific conditions necessary for this autocatalysis to be effective, the potential autocatalysis may be hidden by other kinetic effects, and thus not manifest its behavior in practice.

Possibly, in Equation 1, the term $f(\mathbf{X})$ may simply overwhelm the autocatalytic process. This is typically the case when an autocatalysis is present together with the noncatalyzed version of the same reaction, which may not be negligible in all conditions. A simple example is a system simultaneously containing a direct autocatalysis $A + B \rightarrow 2\ B$, concurrent with the nonautocatalytic reaction $A \rightarrow B$. The autocatalytic process follows a bimolecular kinetics, and will be more efficient in a concentrated than in a dilute solution. The dynamic profile of the reaction is thus sigmoidal for high initial concentration of A, but not for low initial concentration (see Figure 2a, b).

It is also seen that the function $k(\mathbf{X})$ may vary during the reaction process. In a simple autocatalytic process as described above, k is proportional to the concentration of A, and is thus more important at the beginning of the reaction (leading to an initial exponential increase of the product B) than at the end

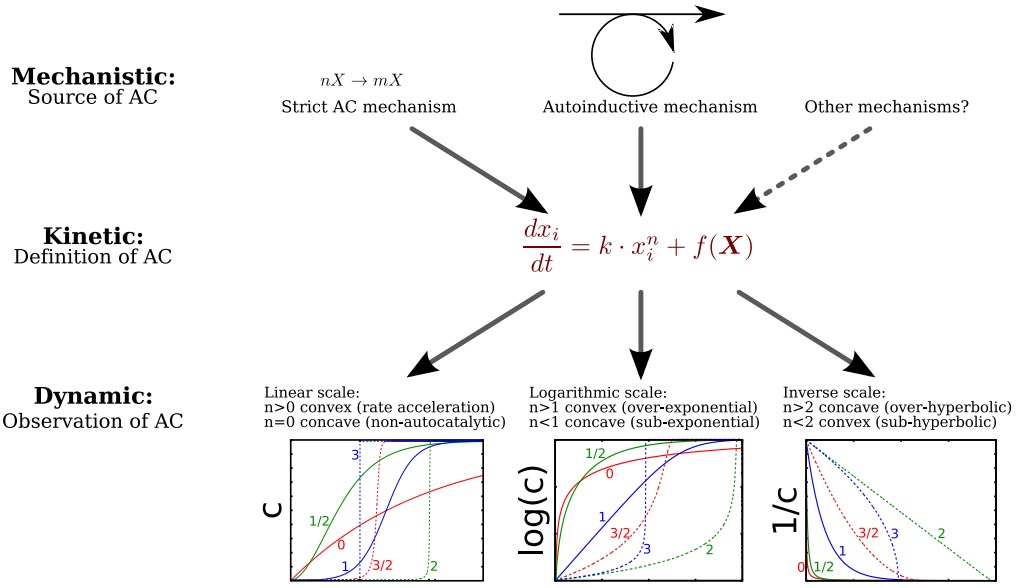


Figure 1. Classification of the concepts of autocatalysis (AC) depending on their descriptions (mechanistic, kinetic, and dynamic). The graphs represent the time evolution of autocatalytic reactions. The number close to each curve corresponds to the respective order n. The colors indicated below in parenthesis are visible on the electronic version of this article. Nonautocatalytic reaction ($n = 0$, red), and autocatalytic reactions of order $n = 1/2$ (green), 1 (blue), 3/2 (dotted red), 2 (dotted green), and 3 (dotted blue).

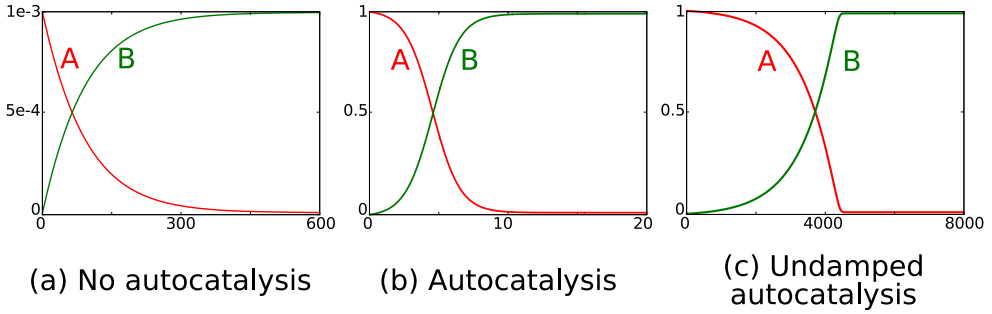


Figure 2. (a, b): First-order autocatalytic process ($\Gamma_1 = 10^2$ M·s^{-1}) in presence of a nonautocatalytic reaction ($\Gamma_2 = 10^{-2}$ M·s^{-1}) of spontaneous transformation of A into B ($K_A = 1$ M, $K_B = 10^2$ M). (a) Dilute ($a_o = 10^3$ M). (b) Concentrated ($a_0 = 1$ M). (c) Undamped autocatalysis (indirect autocatalysis, described in Figure 4b, $\Gamma_4 = 0.1$ M·s^{-1}).

(leading to a damping of the autocatalysis), so that one has a global sigmoidal evolution. In systems where the influence of A on k is weaker, as detailed further, an undamped autocatalysis will be observed, characterized by an exponential variation until the very end (see Figure 2c).

3 Building Autocatalysis

How can this kinetic pattern be realized? Different chemical systems can be built for obtaining similar dynamic behaviors. The task is thus to identify the mechanisms that can potentially generate the autocatalysis kinetic pattern of Equation 1. In this article all of them will be called autocatalytic. That status has been disputed for some patterns on account of their distinct chemical realizations. In the following, we emphasize the major mechanistic patterns to be reduced to an equivalent kinetic autocatalysis, and discuss where their differences come from.

3.1 Template Autocatalysis

The simplest autocatalysis corresponds to the direct pattern $X \rightarrow 2\,X$; one instance of a given compound gives birth to two of them, in an atomic transformation. Thus can be represented by the following chemical reaction:

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B + B \tag{2}$$

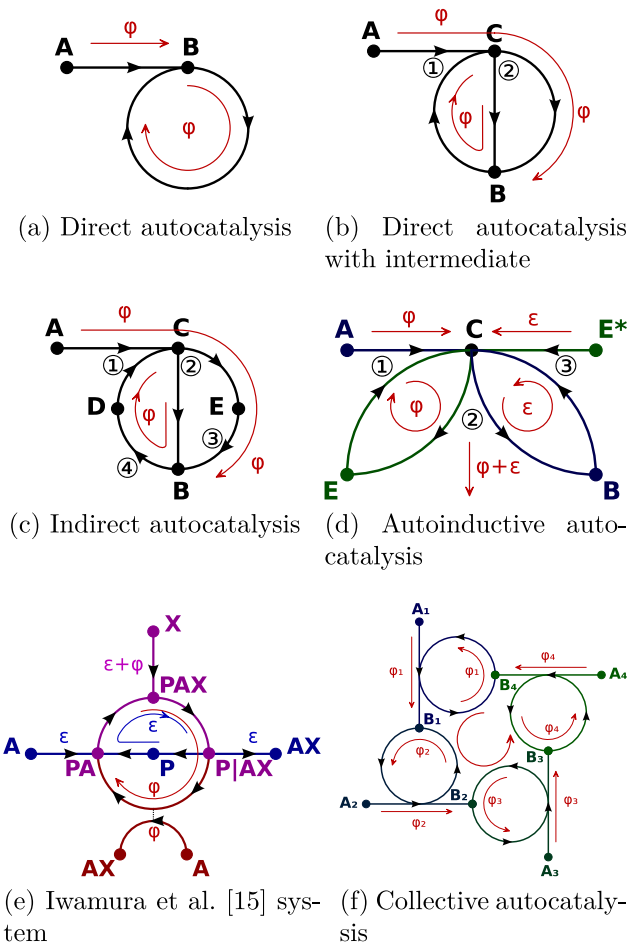
The corresponding network is given in Figure 3a.

This one-step transformation can be decomposed into a succession of two simpler transformations. The first step is the aggregation of the two reactants into an intermediate compound C, and the second step is the generation of two identical products from this intermediate:

$$A + B \overset{\Gamma_1}{\rightleftharpoons} \mathrm{C} \tag{3}$$

$$\mathrm{C} \overset{\Gamma_2}{\rightleftharpoons} B + B \tag{4}$$

The corresponding network is given in Figure 3b.



(a) Direct autocatalysis (b) Direct autocatalysis with intermediate

(c) Indirect autocatalysis (d) Autoinductive autocatalysis

(e) Iwamura et al. [15] system (f) Collective autocatalysis

Figure 3. Reaction network of different autocatalytic processes of spontaneous transformation of A into B (a–d), of $A + X$ into AX (e), and of A_i into B_i (f). The indicated fluxes correspond to what is observed within the QSSA.

The first mechanism entails the following kinetic evolution:

$$\frac{\mathrm{d}b}{\mathrm{d}t} = -\frac{\mathrm{d}a}{\mathrm{d}t} \tag{5}$$

$$= k_1 ab - k_{-1} b^2 \tag{6}$$

This can be expressed as a chemical flux $\varphi = \frac{\mathrm{d}b}{\mathrm{d}t}$, by relying on the Mikulecky formalism [29, 36, 38]:

$$\varphi = \Gamma_1 \left(V_A V_B - V_B^2 \right) \tag{7}$$

$$V_A = \frac{a}{K_A} \tag{8}$$

$$V_B = \frac{b}{K_B} \tag{9}$$

$$\Gamma_1 = k_1 \cdot K_A K_B = k_{-1} \cdot K_B^2 \tag{10}$$

where k_1 and k_{-1} are the kinetic constant rates of the first reaction in the direct and reverse directions, and K_A and K_B are the thermodynamic constants of formation of compounds A and B.

Formally, there is a unidirectional flux φ of transformation of A into B, coupled to a cyclic flux of the same intensity from B back to B (see Figure 3a, b). In the presence of an intermediate compound, the equations become

$$\varphi_1 = \Gamma_1(V_A V_B - V_C) \tag{11}$$

$$\varphi_2 = \Gamma_2\left(V_C - V_B^2\right) \tag{12}$$

Under the hypothesis that C is an unstable intermediate (i.e., $K_C \ll K_B, K_A$), the variation of C can be neglected compared to the variations of A and B (quasi-steady-state approximation, hereafter QSSA), so that

$$\varphi_1 \approx \varphi_2 \tag{13}$$

$$= \varphi \tag{14}$$

$$\Rightarrow \quad \varphi = \frac{\Gamma_1\Gamma_2}{\Gamma_1 + \Gamma_2}\left(V_A V_B - V_B^2\right) \tag{15}$$

The system is strictly equivalent to the direct autocatalysis, with an apparent rate $\Gamma_1\Gamma_2/(\Gamma_1 + \Gamma_2)$. With these two systems, we have the perfect kinetic signature of an autocatalytic system, following a sigmoidal evolution (see Figure 4a). This equivalence is guaranteed as long as the compound C remains unstable. When that is not the case, the dimeric intermediate C very slowly liberates the final compound B, which eventually leads to an autocatalytic process of order 1/2 rather than 1 [51, 54].

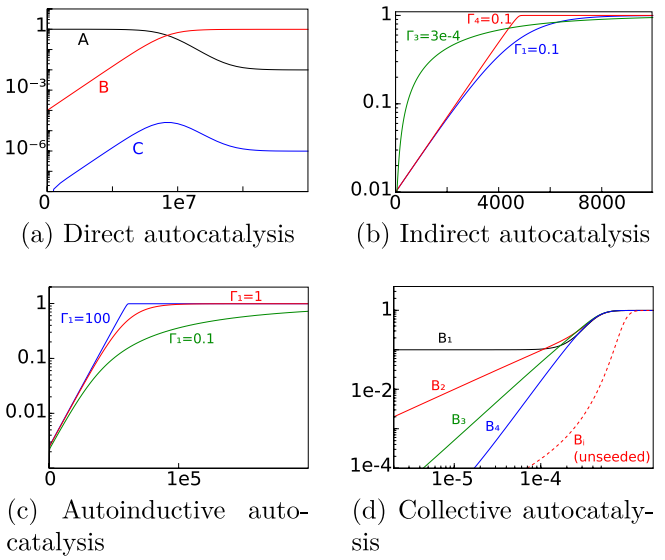


Figure 4. Time evolution of compound concentrations for different autocatalytic processes of spontaneous transformation of A into B ($K_A = 1$ M and $K_B = 100$ M) on a logarithmic scale for concentrations (a–c), and on logarithmic scales for both time and concentrations (d). K and concentrations are in molarities, times in seconds, and Γ in $M \cdot s^{-1}$. (a) Figure 3b, $\Gamma_1 = 1$, $\Gamma_2 = 10^{-4}$, $K_C = 0.01$; (b) Figure 3c, $\Gamma_1 = \Gamma_2 = \Gamma_3 = \Gamma_4 = 10$ (except the values indicated on the graph), $K_C = K_D = K_E = 0.01$; (c) Figure 3d, $\Gamma_2 = \Gamma_3 = 100$, $K_C = K_E = 1$, $K_{E^*} = 10$; (d) Figure 3f, $\Gamma_1 = 100$, $\Gamma_2 = 1$.

Template autocatalysis requires a direct association between the reactants and the products. This is typically the case of DNA replication, one double strand molecule giving birth to two identical double strand molecules, thanks to the very selective association of complementary nucleotides along each strand. More simple examples can be found in some biological mechanisms that require autocatalytic processes, for example, for the generation of the chemical oscillations inducing circadian rhythm in cells. The system described by Mehra et al. is based on a nonequilibrium system of association and dissociation of proteins forming a large chemical cycle [$C \rightarrow AC \rightarrow AC^* \rightarrow ABC^* \rightarrow BC^* \rightarrow C^* \rightarrow C$], maintained by a flux of ATP consumption, one cycle consuming and freeing A and B [28]. The oscillations are generated by coupling this chemical flux to an autocatalytic process of phosphorylation obeying the reaction scheme [53] $A + C + AC^* \rightarrow 2\,AC^*$.

3.2 Network Autocatalysis

The direct mechanism of template autocatalysis is conceptually the simplest framework. It may not actually be the most representative class of autocatalysis, and a similar kinetic signature can result from more complex reaction networks.

3.2.1 Indirect Autocatalysis

The autocatalytic effect can be indirect when reactants and products never directly interact. A simple framework can be built from the previous system by adding intermediate compounds:

$$A + D \overset{\Gamma_1}{\rightleftharpoons} C \tag{16}$$

$$C \overset{\Gamma_2}{\rightleftharpoons} B + E \tag{17}$$

$$E \overset{\Gamma_3}{\rightleftharpoons} B \tag{18}$$

$$B \overset{\Gamma_4}{\rightleftharpoons} D \tag{19}$$

There is no direct A–B coupling, nor any direct $2B$ formation, but a dimeric compound C is present. The network decomposition of this system (see Figure 3c) implies once again a noncyclical flux of transformation of A into B, linked to a large reaction cycle transforming B back to B. This system is still reducible to an $X \rightarrow 2\,X$ pattern.

The QSSA for compounds C, D, and E comes down to expressing the equality of the fluxes expressed by Equations 16 to 19, which leads to

$$\varphi = \frac{1}{\frac{1}{\Gamma_1} + \frac{1}{\Gamma_2} + \frac{V_A}{\Gamma_4} + \frac{V_B}{\Gamma_3}} \left(V_A V_B - V_B^2\right) \tag{20}$$

Though the same autocatalytic signature expressed by the factor $V_A V_B - V_B^2$ is obtained, it is now multiplied by a nonconstant factor. Depending on the numerical values of the system parameters, the same mechanistic pattern will thus generate different dynamic properties.

When the terms V_A/Γ_4 and V_B/Γ_3 are small compared to either Γ_1^{-1} or Γ_2^{-1} (i.e., when at least one of the two reactions (16), (17) is kinetically limiting), the system behaves like a simple autocatalytic system, with $\varphi \propto a \cdot b$ before the reaction completion, and with progressive damping of the exponential growth as long as A is consumed. When the term V_A/Γ_4 is predominant (i.e., when reaction (19) is kinetically limiting), the flux $\varphi \propto b$: The profile remains exponential up to the reaction completion, with no damping due to A consumption. When the term V_B/Γ_3 is predominant

(i.e., when reaction (18) is kinetically limiting), the flux $\varphi \propto a$: The autocatalytic effect is lost (see Figure 4b).

Network autocatalysis is probably the most common such mechanism. A typical biochemical example is the presence of autocatalysis in glycolysis [1, 31]. In this system, there is a net balance following the $X \rightarrow 2\,X$ pattern. ATP must be consumed to initiate the degradation of glucose, but many more molecules of ATP are produced during the whole process. While these systems are effectively autocatalytic, there is obviously no possible templating effect of one molecule of ATP to generate another one.

3.2.2 Collective Autocatalysis

More general systems, reminiscent of Eigen's hypercycles [7], are responsible for even more indirect autocatalysis. No compound influences its own formation rate, rather, each influences the formation of other compounds, which in turn influence other reactions, in such a way that the whole set of compounds collectively catalyzes its own formation.

A simple framework can be built from the association of several systems of transformation $A_i \rightarrow B_i$, each B_i catalyzing the next reaction (see Figure 3f):

$$A_i + B_{i\text{-}1} \overset{\Gamma_i}{\rightleftharpoons} B_i + B_{i\text{-}1} \qquad (\text{with } i = \{1,2,3,4\} \text{ and } B_4 \equiv B_0) \tag{21}$$

There are four independent systems, connected only by catalytic activities.

If the system is totally symmetric, then all b_i are equal and all a_i are equal, so that the rates become

$$\varphi_i = \Gamma_i V_{B_{i\text{-}1}}(V_{A_i} - V_{B_i}) \tag{22}$$

$$\varphi = \Gamma V_B(V_A - V_B) \tag{23}$$

This leads to a *collective* autocatalysis with all compounds present. They mutually favor their formation, which results in an exponential growth of each compound (see Figure 4d, dotted curve).

With symmetrical initial conditions (i.e., identical for the four systems), the system strictly behaves autocatalytically. If the symmetry is broken (e.g., by seeding only one of the B_i), the system acts with delays. The evolution laws are subexponential, of increasing order; at the very beginning of the reaction, considering that A_i do not significantly change and that B_i are in low concentrations, we obtain $\varphi_i \propto t^{i\text{-}1}$. On seeding with B_1, the compound B_2 evolves as t^2. Its influence on compound B_3 induces an evolution as t^3. In its turn, the influence of compound B_3 on compound B_4 induces an evolution as t^4. Compound 1 at first remains constant, and it is only following a given delay that it is catalyzed by B_4 (see Figure 4d).

This system is actually not characterized by a direct cyclic flux, but by a cycle of fluxes influencing each other and resulting in a cooperative collective effect:

$$(A_1 + A_2 + A_3 + A_4) + (B_1 + B_2 + B_3 + B_4) \tag{24}$$

$$\rightarrow \quad 2(B_1 + B_2 + B_3 + B_4) \tag{25}$$

The simultaneous presence of all different compounds is needed to observe a first-order autocatalytic effect. Given asymmetric initial conditions, a transitory evolution of lower order is first observed, until the formation of the full set of compounds.

A typical example of collective autocatalysis is observed in the replication of viroids [9]. Each opposite strand of cyclic RNAs can catalyze the formation of the other one, leading to the global growth of the viroid RNA in the infected cell.

3.2.3 Template versus Network Autocatalysis

All the preceding systems can be reduced to an $X \rightarrow 2\,X$ pattern. This is characterized by a noncyclical flux of chemical transformations, coupled with an internal loop flux: For each molecule (or set of molecules) A transformed into B, one B is transformed and goes back to B, following a more or less complex pathway. Such systems can be considered as mechanistically equivalent: A seemingly direct autocatalysis may turn out to be an indirect autocatalysis once its precise mechanism is found by decomposing the global reaction into several elementary reactions.

Practically, autocatalysis will be considered to be direct (or template) when a dimeric complex of the product is formed (i.e., allowing the "imprint" of the product onto the reactant). If no such template complex is ever formed, we preferentially speak of network autocatalysis, in which the $X \rightarrow 2\,X$ pattern only results from the reaction balance.

3.3 Autoinductive Autocatalysis

Some reactions are not characterized by an $X \rightarrow 2\,X$ pattern, but still exhibit a mechanism for the enhancement of the reaction rate by the products. This is typically the case for systems where the products increase the reactivity of the reaction catalyst rather than directly influencing their reaction production itself. These systems still possess the kinetic signature of Equation 1, but are sometimes referred to as autoinductive instead of autocatalytic [3].

3.3.1 Simple Network

Let us take a simple reaction network of a transformation $A \rightarrow B$ catalyzed by a compound that can exist in two forms E and E^*, E^* being the more stable one. These two forms of the catalyst interact differently with the product B (see Figure 3d):

$$A + E \overset{\Gamma_1}{\rightleftharpoons} C \tag{26}$$

$$C \overset{\Gamma_2}{\rightleftharpoons} B + E \tag{27}$$

$$C \overset{\Gamma_3}{\rightleftharpoons} B + E^* \tag{28}$$

There is no dimeric compound in the system, even indirectly formed.

Provided the catalyst, present in C, E, and E^*, is in low total concentration, the QSSA implies the presence of two fluxes: the transformation of A into B catalyzed by E, of intensity φ, and the transformation of E^* into E catalyzed by B, of intensity ε, with $\varphi \gg \varepsilon$. Assuming that E^* is very stable compared to E and C, this decomposition eventually leads to

$$\varphi = \frac{\Gamma_1 \Gamma_2 V^0_{E^*}}{\Gamma_1 V_A + \Gamma_2 V_B}\left(V_B V_A - V_B^2\right) \tag{29}$$

Once again, the same kinetic signature is obtained, but multiplied by a nonconstant factor. Interestingly, while the mechanism is fundamentally different, the same patterns that were observed for indirect autocatalysis are obtained:

- When $\Gamma_2 \gg \Gamma_1 K_B / K_A$, the flux φ is $\Gamma_1 V^0_{E^*}(V_A - V_B)$: The system is nonautocatalytic.
- When $\Gamma_2 \approx \Gamma_1 K_B / K_A$, the flux φ is $\Gamma_2\ (V^0_{E^*}/V^0_A)\ (V_A V_B - V_B^2)$: The system is simply autocatalytic.

- When $\Gamma_2 \ll \Gamma_1 K_B/K_A$, the flux φ is $\Gamma_2 V^0_{E^*}(V_B - V_B^2/V_A)$: The system presents an undamped autocatalysis.

Following the kinetic analysis, the behavior is found to be similar to the time evolution of autocatalytic systems (see Figure 4c). The behavioral equivalence of these two systems (kinetically equivalent but mechanistically very different) will be investigated in more detail in the next section.

3.3.2 Iwamura's Model

An example of autoinductive autocatalysis is the α-aminoxylation of aldehydes catalyzed by proline [15]. The core principle is a reaction $A + X \rightarrow AX$, catalyzed by P, the product AX catalyzing the first catalytic step $P + A \rightarrow PA$ (see Figure 3e). This chemical system can be decomposed into two different fluxes $A + X \rightarrow AX$: one coupled to a catalytic cycle $[P \rightarrow PA \rightarrow PAX \rightarrow P|AX \rightarrow P]$, and one coupled to a catalytic cycle $[PA \rightarrow PAX \rightarrow P|AX \rightarrow PA]$. The first one contains the slow reaction of A on P, and corresponds to a slow flux ε. The second one only contains fast reactions, and corresponds to a fast flux φ. In an ideal case, and following the same analytical methodology, the flux of production of AX can be shown to be equal to

$$\varphi = \Gamma_5 V_P^0 \left(V_A V_{AX} - \frac{V_{AX}^2}{V_X} \right). \tag{30}$$

The kinetic signature of an undamped autocatalysis is once again obtained.

3.3.3 Network versus Autoinductive Autocatalysis

Autoinductive autocatalysis is mechanistically different from network or template autocatalysis. The balance equation is rather of the form $A + \alpha B \rightarrow (1 + \alpha)B$, with $\alpha \ll 1$. The noncyclical transformation $A \rightarrow B$ is only weakly coupled to the cycle of B back to itself, this latter one being subject to a much lower flux than the linear flux. However, autoinduction is kinetically and dynamically equivalent to network autocatalysis, leading to the same kind of differential equation, and thus of behavior. It must be noted that the undamped exponential profile—due to a flux only proportional to the products and not to the reactant—is not characteristic of autoinductive processes [15], but can also be explained by network autocatalytic mechanisms, when the consumption of the reactant is not limiting the kinetics of the network.

4 Embedded Autocatalyses

Autocatalysis is not so important per se, but as a way of giving birth to rich nonlinear behaviors like bifurcation, multistability, or chemical oscillations. It is crucial to study the interaction of autocatalytic mechanisms and their ability to generate such behaviors when embedded in a larger chemical network.

4.1 Dynamical Distinctions

Different behaviors depending on the order n of the autocatalysis can be observed in biochemical competitive systems. They are classically studied in population evolution [32, 46] and described as survival of all in the case of $0 < n < 1$ (characterized by the coexistence of all compounds), as survival of the fittest in the case of $n = 1$ (when the only stable solution retains the fittest, or most reproducible, compound), and as survival of the first in the case of $n > 1$ (when the final solution just retains the product initially present in the highest concentration).

The case $0 < n < 1$ is the least interesting one, as it never leads to a clear selection process. However, a real mechanism that seems to possess a first-order autocatalysis may actually present

a lower autocatalytic order. This is typically the case for direct template autocatalysis, in which the order falls to 1/2 on account of the high stability of the dimeric intermediate—which is actually a necessary condition for the selectivity of template replication [50, 51, 54]. This turns out to be a fundamental problem for understanding the emergence of the first replicative molecules [22, 42, 47].

More complex mechanisms may lead to higher orders, typically by the formation of dimeric autocatalysts [52]. This is the case of the Soai reaction, whose high sensitivity to initial conditions may potentially be explained by the formation of trimeric [13] or even hexameric complexes [43].

4.2 Comparative Efficiency of Direct and Autoinductive Autocatalyses

The relative efficiency of two autocatalytic mechanisms can be evaluated by having them compete which each other. Bifurcations appear when these two autocatalytic processes are placed in a non-equilibrium open-flow system, both being fed by the same incoming compound and with cross-inhibition between them:

$$\rightarrow A \qquad \text{(incoming flux)} \tag{31}$$

$$A \overset{\alpha}{\rightleftharpoons} B_1 \qquad \text{(direct AC)} \tag{32}$$

$$A \overset{\beta}{\rightleftharpoons} B_2 \qquad \text{(autoinduced AC)} \tag{33}$$

$$B_1 + B_2 \rightarrow P \qquad \text{(cross-inhibition)} \tag{34}$$

$$B_1 \rightarrow \qquad \text{(outgoing flux)} \tag{35}$$

$$B_2 \rightarrow \qquad \text{(outgoing flux)} \tag{36}$$

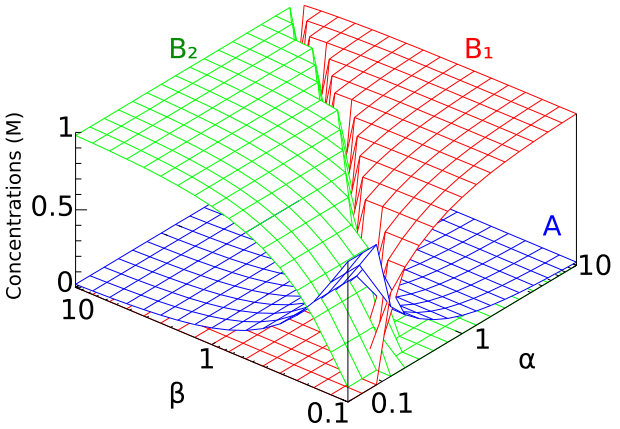
In the case of total symmetry between B_1 and B_2, with the same direct autocatalytic mechanism, this system would correspond to the classical Frank model [11] describing processes for the emergence of homochirality. Because of the system symmetry, the same probability of ending up with either B_1 or B_2 is observed.

The kinetic equivalence between template autocatalysis and autoinductive autocatalysis can be shown by making these two mechanisms compete, replacing Equations 32 and 33 with the corresponding mechanisms. The kinetic parameters have first been normalized so that each reaction leads on its own to the same kinetic behavior (sigmoidal evolution, half-reaction at 10^5 s), and then multiplied by the parameters α and β, respectively, in order to tune the velocities of the mechanisms. The result is then symmetrical between the two processes, and only the faster product is maintained in the system: B_1 when $\alpha > \beta$, and B_2 when $\alpha < \beta$ (see Figure 5a). As a consequence, while mechanistically different, these two autocatalyses are shown to be dynamically equivalent.

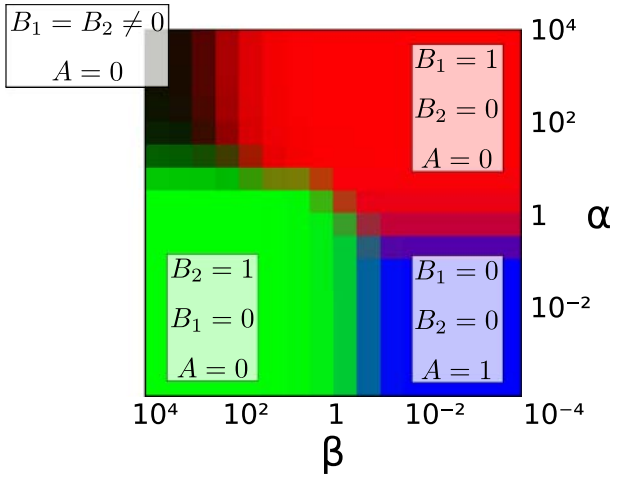
This selectivity is independent of the relative stability of B_1 and B_2, but is only possible for kinetics that are well adapted to the global influx of matter. For slow kinetics, there is a flush of the system, and neither B_1 nor B_2 can be maintained. For fast kinetics, the system is close to equilibrium, the compounds B_1 and B_2 both being present in proportion to their respective stability (see Figure 5b). Such a result is well known for open-flow Frank systems [4].

4.3 From Autocatalytic Processes Toward Autocatalytic Sets

These competitive systems are able to dynamically maintain a set of components, to the detriment of others. These autocatalytic *networks* must however not be confused with autocatalytic *sets*. This latter notion is rather popular in the artificial life literature, but relies much more on the cooperation between autocatalytic mechanisms than on the competition that has just been detailed here. It implies a notion of material closure of the system and of self-maintenance of the whole network by crossing



(a) Sharp bifurcation depending on the relative values of α and β for moderate reactivities.



(b) Different zones of behaviors: majority of A for $\alpha, \beta \ll 1$, majority of B_1 for $\alpha > \beta$, majority of B_2 for $\alpha < \beta$, and coexistence of B_1 and B_2 for $\alpha, \beta \gg 1$.

Figure 5. Competition between template and autoinductive autocatalysis, generating, respectively, compounds B_1 and B_2 from the same compound A. Incoming flux of A and outgoing fluxes of B_1 and B_2 are 10^{-5} M·s^{-1}. We have $K_A = 1$, $K_{B_1} = K_{B_2} = 100$. Direct autocatalysis: $\Gamma_{AC} = 10^2 \cdot \alpha$, $\Gamma_{NC} = 10^6 \cdot \alpha$. Autoinduction, according to Figure 3d: $\Gamma_1 = \beta$, $\Gamma_2 = \Gamma_3 = 100 \cdot \beta$, $K_C = K_E = 1$; $K_{E^*} = 10$.

energy fluxes [2, 14, 17]. Confusion among these different phenomena can be found in the literature [3], when the failure of autoinductive sets to be maintained does not originate from a difference of behavior between autocatalytic and autoinductive mechanisms, but from a defect in the closure of the system (e.g., induced by the leakage of some components).

Such autocatalytic sets may be ultimately based on a perfectly reversible chemical reaction, but can be obtained more subtly in the presence of a lot of intermediary molecules and catalysts, providing a more complex reaction network. By this reaction-based roundabout in which all molecules participate, they all contribute to maintaining themselves at a constant concentration, compensating and repairing any disruption in concentration undergone by any one of them. The bigger the network, the more stable it should be, and the more molecules it will contribute to maintain the concentrations in a zone that should vary very little, despite external disruptions.

A network of this kind will be materially closed, but have to be energetically open if none of the molecules appears in or disappears from the network as a result of external factors. Energy, originating in external sources, is necessary for the reactions to start and be sustained. The presence of such an energy flux, maintaining the network far from thermodynamic equilibrium, is needed because, without it, no reactive flow circulating through the entire network would be possible. A molecular end of the cycle must be re-energized in order to restart the whole cyclical reaction process. This cycle thus acts as a chemical machine, energetically driven from the outside. As soon as one of the molecules is being produced in the network without, in turn, producing one of the molecules making up the network, it absorbs and thus destroys the network. In the presence of molecules of this kind, produced but nonproductive, the only way of maintaining the network consists of feeding it materially and thus making it open to material influx.

A chemical network acts on the flow of material and energy, playing the role of an intermediate ongoing stabilization zone, made up of molecules that may be useful to other vital functions (such as the assembly of enclosing membranes or the catalysis of self-replication). It transforms, as well as preserving, all the chemical agents which it recruits. Biologists generally agree that a reactive network must exist prior to the appearance of life, at least to catalyze and make possible the other life processes such as genetic reading and coding; it is open to external influences in the form of matter and energy, but necessarily contains a series of active cycles. They are most often designated as either metabolism or protometabolism. The most popular and active advocates of this metabolism-first hypothetical scenario of the origin of life are Kauffman [18], Maynard-Smith and Szathmáry [27], Dyson [6], De Duve [5], Gánti [12], and Shapiro [44]. The ALife pioneers Kauffman [16, 18] and Fontana [10] were the forerunners in the study of the appearance and properties of these closed networks. Figure 6 illustrates this work, dedicated to the study of prebiotic chemistry, limiting the reactions studied to polymerization, such as $aa + bb \rightarrow aabb$, or inversely, depolymerization or hydrolysis: $abaa \rightarrow ab + aa$.

The analysis of Kauffman is only of a structural type. He showed that provided the probability that a reaction takes place is affected by the presence of a catalyst that is itself produced by the network (in such a case the whole network is called by him an autocatalytic set), a process of percolation or phase transition, characteristic of this type of simulation, is produced. For probabilities too low, the network does not pop up, because the reactions are too improbable; but as soon as these probabilities reach a threshold value, the network percolates, giving rise to multiple molecules produced by multiple reactions. Kauffman grants a privileged status to this threshold value and to the giant explosive network resulting from it in his scenario of the origin of life, without really arguing the reason such a status should exist, but extending to the world of biology the immense interest and enthusiasm that phenomena of phase transition arouse among physicists. Fontana for his part is concerned with the inevitable appearance of reaction cycles (such as that illustrated in Figure 1). All the molecules produced by these cycles in the network in turn produce molecules of the network. He is among those many biologists who see these closed networks, or organizations, as forming a key stage in the appearance of life, due both to their stability and to the fact that they form structural and dynamic attractors for the system. They induce a stabilization and internal regulation zone together with an energetic motor in a chemical soup that is continually crossed by a flow of matter and energy. Fontana went on to show how these networks are also capable of self-regeneration and self-replication.

What both Fontana and Kauffman completely underestimate, along with most of the ALife researchers in their footsteps, is indeed the interesting dynamic consequences of such a structurally closed autocatalytic set. As has been shown in the preceding kinetic and dynamic analysis, these mechanisms, based on loops of reactions, can generate dynamic patterns of sigmoid form, with possible reaction delays among the members of the network. As a matter of fact, autocatalysis goes well beyond this stabilization mechanism, since these reaction schemes, more than just cycling, must further be really autocatalytic—namely, when a product of the reaction network doubles the concentration of one of the reactants: $a + b \rightarrow a + a$. As was shown, this can happen in either a direct or a very indirect way. Definitely the first ALife researcher who perceived the interest of such

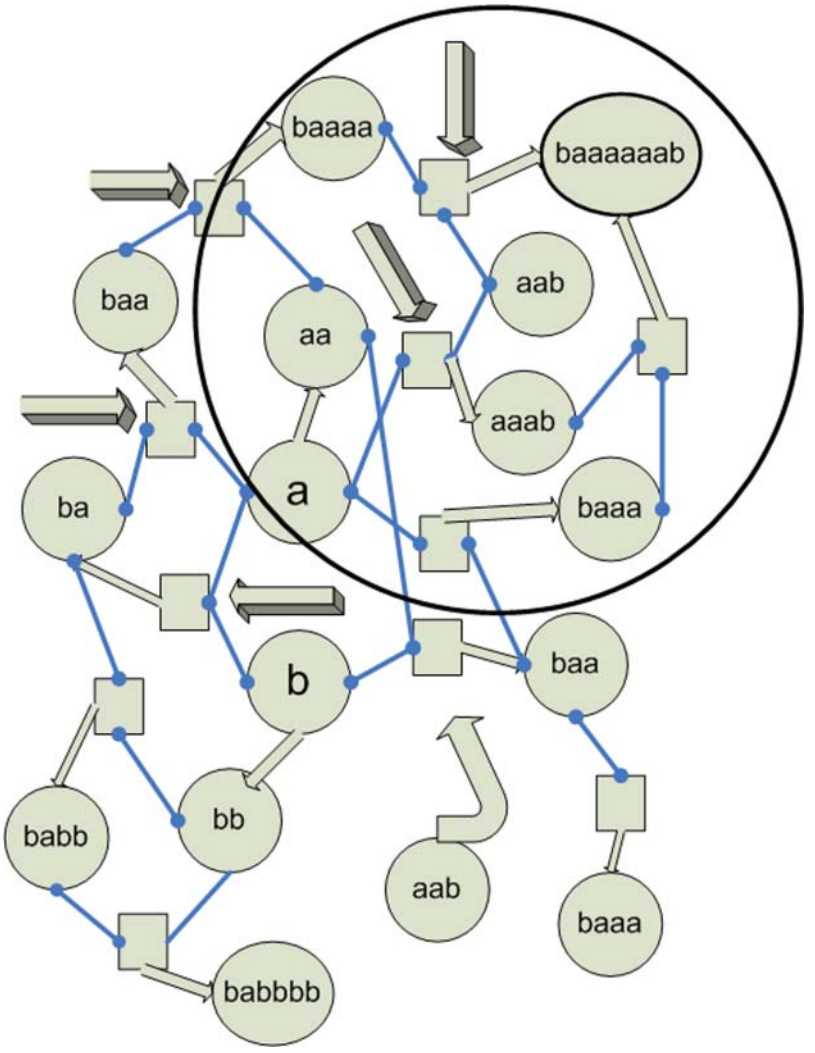


Figure 6. Representation of a network of chemical reactions of polymerization ($a + b \rightarrow ab$) and depolymerization ($ab \rightarrow a + b$) taking place in a simulated chemical reactor. Molecules are represented by circles, and reactions by squares. Each reaction can be catalyzed, as the arrows pointing to the squares show, by a molecule of the network (giving rise to an autocatalytic network). Some molecules can appear (like the molecule *aab*) or simply disappear from the network. Reaction cycles can appear, like the one circled in the figure ($aa \rightarrow baaaa \rightarrow baaaaaab \rightarrow baaa \rightarrow aa$).

exponential growth was Gánti [12]. He studied at large the so-called *formose* reaction, during which a two-carbon molecule, reacting twice with a carbon monomer, leads to a four-carbon molecule, which subsequently splits, thus duplicating the original molecule. Gánti was thus the first to connect and synchronize the several replication processes—chemical, genetic, and in the surrounding membrane—in order for the cell to simultaneously duplicate its boundary, its metabolism, and its informational support.

Artificial life researchers only focus on the cooperative type of autocatalytic set and leave aside the competitive type, which might indeed turn out to be of even greater interest. When various autocatalytic cycles enter into antagonistic interaction, they turn out to be responsible for symmetry breaking (one of the cycles, randomly favored initially, wins and takes it all). And indeed, it is crucial to take into account the unavoidable interactions between autocatalytic systems, responsible for an even

richer zoology of behaviors. The early origin of life should not be studied without taking into account the self-organization of chemical networks, the emergence and antagonism of autocatalytic cycles, and how energy flows drive the whole process.

Such chemical networks are, for instance, interesting for understanding the onset of biological homochirality as the destabilization of the racemic state resulting from the competition between enantiomers and from amplification processes relating to both autocatalytic competitors (one left-oriented and the other right-oriented [39]). Interestingly enough, the chemical reaction network under study is made up of the same type of polymerization and depolymerization reactions as the one studied by Fontana [10] and Farmer et al. [8]. In the additional presence of epimerization reactions allowing the transformation of a right-hand monomer to a left-hand one and vice versa, the concentration of one family of monomers (for instance the left one) vanishes in favor of the other. The flux of energy is transferred and efficiently distributed through the system, leading to competitions between right and left reaction sets, and to the stabilization of one them to the detriment of the other one.

4.4 From Autocatalytic Sets Toward Autopoietic Systems

The emergence of a reaction network of this kind undeniably creates the stability necessary for exploiting its constituents in many reactive systems, such as the ones dedicated to the construction of membranes or the replication of molecules carrying the genetic code. This network also acts as a primary filter, as it can accept new molecules within it, but can equally well reject other molecules seeking to be incorporated within it. They would be rejected because they do not participate in any of the reactions making up the network. However, such a system would still miss a primary form of individuation: By definition it can only be unique, as no spatial frontier allows it to be individuated from another network. Although it is perhaps possible to conceive of an interpenetration of several chemical networks, establishing a clear separation between them would remain a problem.

A fundamental property of all living organisms is that they can be differentiated from one another. The production of a second organism from a first one is a mechanism of life that can only operate if the clone elaborates something to spatially distinguish itself from its original. The best way of successfully completing this individuation and of being able to distinguish between these networks is to revert to a spatial divide, which can only be produced by some form of container capable of enclosing these networks in a given space. Biochemists are well acquainted with an ideal type of molecule, a raw material for these membranes, in the form of lipidic (amphiphilic) molecules or fatty acids, the two extremities of which behave in antagonistic ways—the first hydrophilic (attracted to water), and the second hydrophobic (repelled by it). Quite naturally, these molecules tend to assemble in a double layer (placing the two opposing extremities opposite to each other), formed by the molecules lining up and resulting in the shape of a sphere, which protects the hydrophobic extremities from water. Like soap bubbles, these lipid spheres are semipermeable. They imprison the many chemical components trapped during their formation. They do, however, actively channel in and out the most appropriate chemicals for maintaining themselves.

In assimilating living organisms to autopoietic systems, Varela et al. [48] were the first who insisted that this membrane should be endogenously produced by the elements and the reactions making up the network (for example, lipids would come from the reactions of the network themselves) and would in return promote the emergence and self-maintenance of the network. The membrane can help with the appearance of the reactive and growing network by the frontiers that it sets up, through the concentrations of certain molecules trapped in it, or by acting as a catalyst to some of the reactions due to its geometry or its makeup. Basically, autopoiesis requires a cogeneration of the membrane and of the reactive network that it walls up. The network presents a double closure: one chemical, linked to the cycle of its reactions, and another physical, due to the frontiers produced by the membrane.

So both Varela and Gánti further saw in the cooperative coupling of two autocatalytic processes—the internal metabolism and the surrounding membrane—the underlying road toward chemical individuation and self-replication. While Gánti also required the informational template as a third autocatalytic system to be coupled with the two previous ones, Varela defended the idea that the genetic template was

not a key ingredient in the definition of life. For him and his definition of autopoiesis, the first two connected systems were substantially enough for life to appear.

5 Conclusion

Important distinctions need to be made between mechanistic and dynamic aspects of autocatalysis. One single mechanism can produce different dynamics, while identical dynamics can originate from different mechanisms. Thus, a pragmatic definition of autocatalysis has to be based on a kinetic signature, in order to classify the systems according their observable behavior, rather than on a mechanistic signature, which would instead classify the systems according to the origin of their behavior. All the different autocatalytic processes described in this work are able to generate autocatalytic kinetics. They can constitute a pathway toward the onset of *self-sustaining autocatalytic sets* (as chemical attractors in nonequilibrium networks) and further toward the onset of *autopoietic systems* (as enclosed systems of mutually maintaining reaction networks, constituting a complex autocatalytic set that is guaranteeing not only its own sustenance, but also its individuation).

However, these systems, autocatalytic in a broad sense, still lack a fundamental dynamic property for encompassing the whole concept of life. The problem of the evolvability of such systems must be kept in mind [49]. If a system evolves toward a stable attractor, no evolution turns out to be possible. There is the necessity of *open-ended* evolution [41]—that is, the possibility for a dynamic set to not only maintain itself (i.e., as a strict autocatalytic system) but also to act as a general autocatalytic set, recovering the concept originally introduced by Muller [30] for the autocatalytic power linked to mutability of genes. For example, insights can be gained by a deeper and renewed study of the evolution of prions as a simple mechanism of mutable autocatalytic systems [21].

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References

1. Ashkenazi, M., & Othmer, H. G. (1977). Spatial patterns in coupled biochemical oscillators. *Journal of Mathematical Biology*, *5*(4), 305–350.
2. Benkö, G., Centler, F., Dittrich, P., Flamm, C., Stadler, B. M. R., & Stadler, P. F. (2009). A topological approach to chemical organizations. *Artificial Life*, *15*(1), 71–88.
3. Blackmond, D. (2009). An examination of the role of autocatalytic cycles in the chemistry of proposed primordial reactions. *Angewandte Chemie International Edition*, *48*(2), 386–390.
4. Cruz, J. M., Parmananda, P., & Buhse, T. (2008). Noise-induced enantioselection in chiral autocatalysis. *Journal of Physical Chemistry A*, *112*, 1673–1676.
5. De Duve, C. (2002). *Life evolving: Molecules, mind, and meaning*. Oxford, UK: Oxford University Press.
6. Dyson, F. (1999). *Origins of life*. Cambridge, UK: Cambridge University Press.
7. Eigen, M., & Schuster, P. (1977). The hypercycle, a principle of natural self-organization. *Naturwissenschaften*, *64*, 541–565.
8. Farmer, J. D., Kauffman, S. A., & Packard, N. H. (1986). Autocatalytic replications of polymers. *Physica D: Nonlinear Phenomena*, *22*(1–3), 50–67.
9. Flores, R., Delgado, S., Gas, M.-E., Carbonell, A., Molina, D., Gago, S., & la Peña, M. D. (2004). Viroids: The minimal non-coding RNAs with autonomous replication. *FEBS Letters*, *567*(1), 42–48.
10. Fontana, W. (1991). Algorithmic chemistry. *Artificial Life II*, *11*, 159–209.
11. Frank, F. C. (1953). Spontaneous asymmetric synthesis. *Biochem Biophys Acta*, *11*, 459–463.
12. Gánti, T. (2003). *The principles of life*. Oxford, UK: Oxford University Press.

13. Gridnev, I., Serafimov, J., Quiney, H., & Brown, J. (2003). Reflections on spontaneous asymmetric synthesis by amplifying autocatalysis. *Organic & Biomolecular Chemistry*, *1*(21), 3811–3819.

14. Hordijk, M., & Steel, M. (2004). Detecting autocatalytic, self-sustaining sets in chemical reaction systems. *Journal of Theoretical Biology*, *227*(4), 451–461.

15. Iwamura, H., Wells, D. H., Mathew, S. P., Klussmann, M., Armstrong, A., & Blackmond, D. G. (2004). Probing the active catalyst in product-accelerated proline-mediated reactions. *Journal of the American Chemical Society*, *126*(50), 16312–16313. doi: 10.1021/ja0444177.

16. Kauffman, S. (1995). *At home in the universe: The search for laws of self-organization and complexity*. Oxford, UK: Oxford University Press.

17. Kauffman, S. A. (1986). Autocatalytic sets of proteins. *Journal of Theoretical Biology*, *119*, 1–24.

18. Kauffman, S. A. (1993). *The origin of order*. Oxford, UK: Oxford University Press.

19. Kondepudi, D. K., Kaufman, R. J., & Singh, N. (1990). Chiral symmetry breaking in sodium chlorate crystallization. *Science*, *250*(4983), 975–976.

20. Laidler, K. J. (1986). The development of theories of catalysis. *Archive for History of Exact Sciences*, *35*(4), 345–374.

21. Li, J., Browning, S., Mahal, S. P., Oelschlegel, A. M., & Weissmann, C. (2010). Darwinian evolution of prions in cell culture. *Science*, *327*(5967), 869–872.

22. Lifson, S., & Lifson, H. (1999). A model of prebiotic replication: Survival of the fittest versus extinction of the unfittest. *Journal of Theoretical Biology*, *199*(4), 425–433.

23. Lotka, A. J. (1910). Contribution to the theory of periodic reactions. *The Journal of Physical Chemistry*, *14*(3), 271–274.

24. Lotka, A. J. (1920). Analytical note on certain rhythmic relations in organic systems. *Proceedings of the National Academy of Sciences of the United States of America*, *6*(7), 410.

25. Lotka, A. J. (1925). *Elements of physical biology*. Baltimore, MD: Williams & Wilkins Company.

26. Malcai, O., Biham, O., Richmond, P., & Solomon, S. (2002). Theoretical analysis and simulations of the generalized Lotka-Volterra model. *Physical Review E*, *66*(3), 031102.

27. Maynard-Smith, J., & Szathmáry, E. (2000). *The origins of life: From the birth of life to the origin of language*. Oxford, UK: Oxford University Press.

28. Mehra, A., Hong, C. I., Shi, M., Loros, J. J., Dunlap, J. C., & Ruoff, P. (2006). Circadian rhythmicity by autocatalysis. *PLoS Computational Biology*, *2*(7), e96.

29. Mikulecky, D. C. (2001). Network thermodynamics and complexity: A transition to relational systems theory. *Computational Chemistry*, *25*, 369–391.

30. Muller, H. J. (1922). Variation due to change in the individual gene. *The American Naturalist*, *56*(642), 32–50.

31. Nielsen, K., Sørensen, P. G., & Hynne, F. (1997). Chaos in glycolysis. *Journal of Theoretical Biology*, *186*(3), 303–306.

32. Nowak, M. A. (2006). *Evolutionary dynamics: Exploring the equations of life*. Cambridge, MA: The Belknap Press of Harvard University Press.

33. Ostwald, W. (1890). Über autokatalyse. *Berichte über die Verhandlungen der Königlich-Sächsischen Gesellschaft der Wissenschaften zu Leipzig, Mathematisch-Physische Klasse*, *42*, 189–191.

34. Ostwald, W. (1902). *Lehrbuch der Allgemeinen Chemie* (2nd ed., p. 263). Leipzig: Engelmann.

35. Ostwald, W. (1912). *Outlines of general chemistry* (W. W. Taylor, Transl.) (Chapter XI.1, p. 301). Macmillan and Co.

36. Peusner, L., Mikulecky, D. C., Bunow, B., & Caplan, S. R. (1985). A network thermodynamic approach to Hill and King-Altman reaction-diffusion kinetics. *Journal of Chemical Physics*, *83*(11), 5559–5566.

37. Plasson, R. (2008). Comment on "re-examination of reversibility in reaction models for the spontaneous emergence of homochirality." *Journal of Physical Chemistry B*, *112*(31), 9550–9552.

38. Plasson, R., & Bersini, H. (2009). Energetic and entropic analysis of mirror symmetry breaking processes in a recycled microreversible chemical system. *Journal of Physical Chemistry B*, *113*(11), 3477–3490.

39. Plasson, R., Kondepudi, D. K., Bersini, H., Commeyras, A., & Asakura, K. (2007). Emergence of homochirality in far-from-equilibrium systems: Mechanisms and role in prebiotic chemistry. *Chirality*, *19*(8), 589–600.

40. Robertson, T. (1908). Further remarks on the normal rate of growth of an individual, and its biochemical significance. *Development Genes and Evolution*, *26*(1), 108–118.

41. Ruiz-Mirazo, K. (2007). Enabling conditions for "open-ended evolution." *Biology & Philosophy*, *23*(1), 67.

42. Scheuring, I., & Szathmáry, E. (2001). Survival of replicators with parabolic growth tendency and exponential decay. *Journal of Theoretical Biology*, *212*(1), 99–105.

43. Schiaffino, L., & Ercolani, G. (2008). Unraveling the mechanism of the Soai asymmetric autocatalytic reaction by first-principles calculations: Induction and amplification of chirality by self-assembly of hexamolecular complexes. *Angewandte Chemie*, *120*(36), 6938–6941.

44. Shapiro, R. (2006). Small molecule interactions were central to the origin of life. *Quarterly Review of Biology*, *81*(2), 105–125.

45. Soai, K., Shibata, T., Morioka, H., & Choji, K. (1995). Asymmetric autocatalysis and amplification of enantiomeric excess of a chiral molecule. *Nature*, *378*, 767–768.

46. Szathmáry, E. (1991). Simple growth laws and selection consequences. *Trends in Ecology & Evolution*, *6*(11), 366–370.

47. Szathmáry, E., & Gladkih, I. (1989). Sub-exponential growth and coexistence of non-enzymatically replicating templates. *Journal of Theoretical Biology*, *138*(1), 55–58.

48. Varela, F., Maturana, H., & Uribe, R. (1974). Autopoiesis: The organization of living systems, its characterization and a model. *Biosystems*, *5*(4), 187–196.

49. Vasas, V., Szathmáry, E., & Santos, M. (2010). Lack of evolvability in self-sustaining autocatalytic networks constraints metabolism-first scenarios for the origin of life. *Proceedings of the National Academy of Sciences*, *107*(4), 1470–1475.

50. von Kiedrowski, G. (1986). A self-replicating hexadeoxynucleotide. *Angewandte Chemie International Edition in English*, *25*(10), 932–935.

51. von Kiedrowski, G. (1993). Minimal replicator theory I: Parabolic versus exponential growth. *Bioorganic Chemistry Frontiers*, *3*, 115–146.

52. Wagner, N., & Ashkenasy, G. (2009). Symmetry and order in systems chemistry. *The Journal of Chemical Physics*, *130*(16), 164907.

53. Wang, Z.-X., & Wu, J.-W. (2002). Autophosphorylation kinetics of protein kinases. *Biochemical Journal*, *368*(3), 947–952.

54. Wills, P. R., Kauffman, S. A., Stadler, B. M. R., & Stadler, P. F. (1998). Selection dynamics in autocatalytic systems: Templates replicating through binary ligation. *Bulletin of Mathematical Biology*, *60*(6), 1073–1098.

55. Witzemann, E. J. (1933). Mutation and adaptation as component parts of a universal principle: II. The autocatalysis curve. *The American Naturalist*, *67*(710), 264–275.