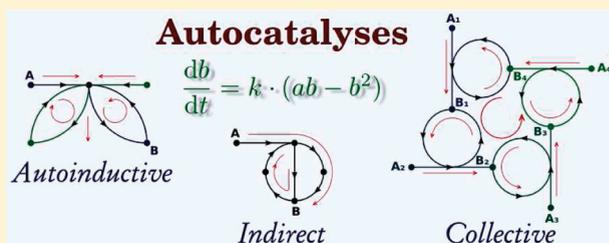


# Autocatalyses

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**ABSTRACT:** Autocatalysis is a fundamental concept, used in a wide range of domains. From the most general definition of autocatalysis, 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. With the notion of autocatalysis covering a large variety of mechanistic realizations with very similar behaviors, it is proposed that the key signature of autocatalysis is its kinetic pattern expressed in a mathematical form.



## 1. INTRODUCTION

The notion of “autocatalysis” was introduced by Ostwald in 1890 for describing reactions showing a rate acceleration as a function of time.<sup>1</sup> It is, for example, the case of esters hydrolysis, which is at the same time acid catalyzed and produces an organic acid.<sup>2</sup> Defined as a chemical reaction that is catalyzed by its own products, it has quickly been described on the basis of a characteristic differential equation.<sup>3,4</sup> Typically used to describe complex behaviors of chemical systems, like oscillatory patterns,<sup>5</sup> it has immediately appeared to be essential for the description of biological systems: growth of individual living beings,<sup>6</sup> population evolution,<sup>7</sup> or gene evolution.<sup>8</sup>

Extending this concept from a chemical description to a more open context was initially carefully described as an analogy, sometimes qualified by the more general notion of “autocatakinesis”.<sup>9,10</sup> However, this eventually leads to an overgeneralization of the term of autocatalysis, tending to be assimilated to the notion of “positive feedback”, for example, in economics.<sup>11</sup>

The notion of autocatalysis is now actively being used for describing self-organizing systems, namely in the field of emergence of life and artificial life. For example, the emergence of a stable nonracemic state in prebiotic systems can be described by a spontaneous symmetry breaking process. This relies on the destabilization of the racemic state, and the stabilization of nonracemic states.<sup>12,13</sup> Autocatalytic processes are at the core of such mechanisms.<sup>14</sup> Initially describing an open irreversible system,<sup>15</sup> this bifurcation model has been extended to reversible<sup>16</sup> and closed<sup>17,18</sup> systems. Several such experimental systems have been described.<sup>19,20</sup> However, how autocatalytic processes shall manifest is still under heavy debate.<sup>21,22</sup> If such chemical systems can easily be described mathematically, they are much more difficult to be implemented

in the physical world. Requiring either complex macromolecules or complex mechanisms, autocatalysis is rather rare in abiotic chemistry, while being ubiquitous in biosystems.

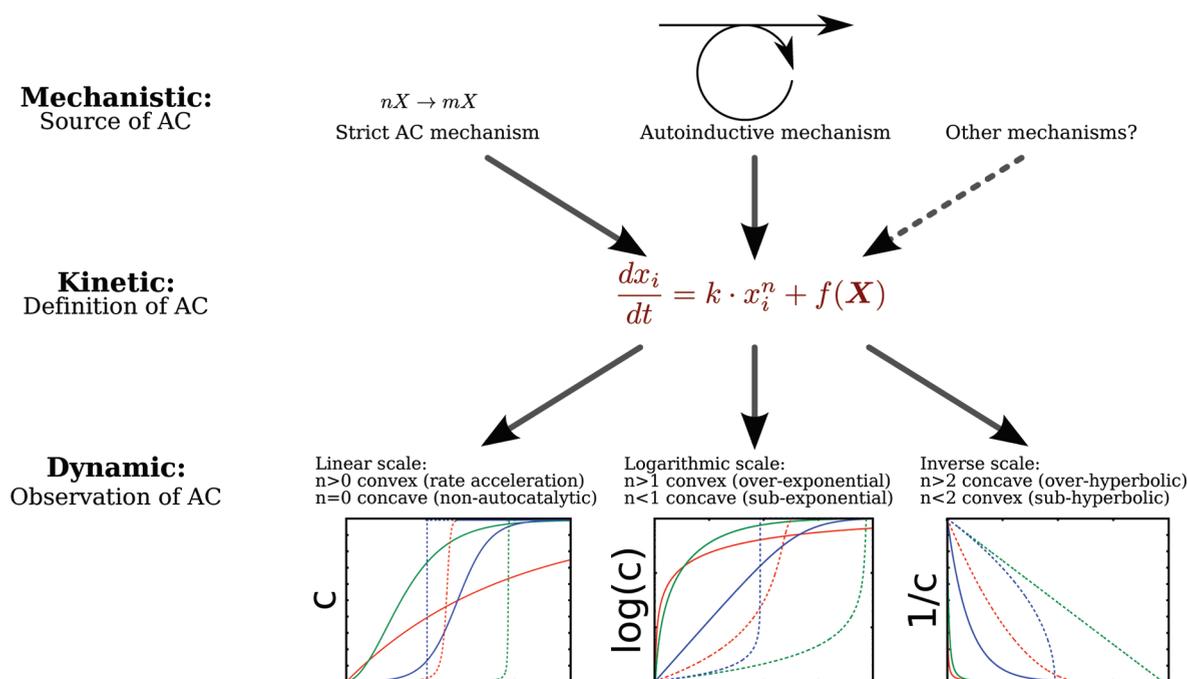
The purpose of this article is thus to clarify the meaning of chemical autocatalysis, and this effort will be undertaken by covering these following points:

- 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 observable is the direct consequence of the kinetic pattern, rather than the underlying mechanism.
- What is the role of autocatalysis? Embedded in the non-equilibrium reaction network, the competition between autocatalytic processes allows the onset of chemical selection, which is the existence of bifurcation phenomena allowing the extinction of some compounds in favor of others.

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**Figure 1.** Classification of the concepts of autocatalysis (AC) depending on their descriptions (mechanistic, kinetic, and dynamic). The graphs represent the time evolution of a nonautocatalytic reaction ( $n = 0$ , red), and of autocatalytic reactions of order  $n = 1/2$  (green), 1 (blue),  $3/2$  (dotted red), 2 (dotted green), and 3 (dotted blue).

## 2. AUTOCATALYSIS: A PRACTICAL DEFINITION

**2.1. A Kinetic Signature.** From its origin, the notion of autocatalysis has focused on the kinetic pattern of the chemical evolution.<sup>3</sup> The general definition of autocatalysis as a chemical process in which one of the products catalyzes its own formation can be mathematically generalized as

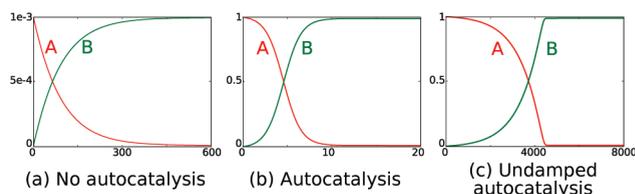
$$\frac{dx_i}{dt} = k(\mathbf{X}) \cdot x_i^n + f(\mathbf{X}), \quad k > 0; \quad n > 0; \quad |k| \gg |f| \quad (1)$$

$\mathbf{X}$  is the vector of all the concentrations  $x_j$ . An autocatalysis for the compound  $x_i$  exists when the conditions of eq 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, searching what mechanism is responsible for the autocatalytic term. This leads to the discovery of a series of different kinds of autocatalysis processes, and their respective effect, describing what observable behavior is generated by the autocatalytic term (see Figure 1).

**2.2. Potential versus Effective Autocatalysis.** This kinetic definition is purely structural. As a matter of fact, a system may contain *potential* autocatalysis, i.e., an autocatalytic core exists 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 eq 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



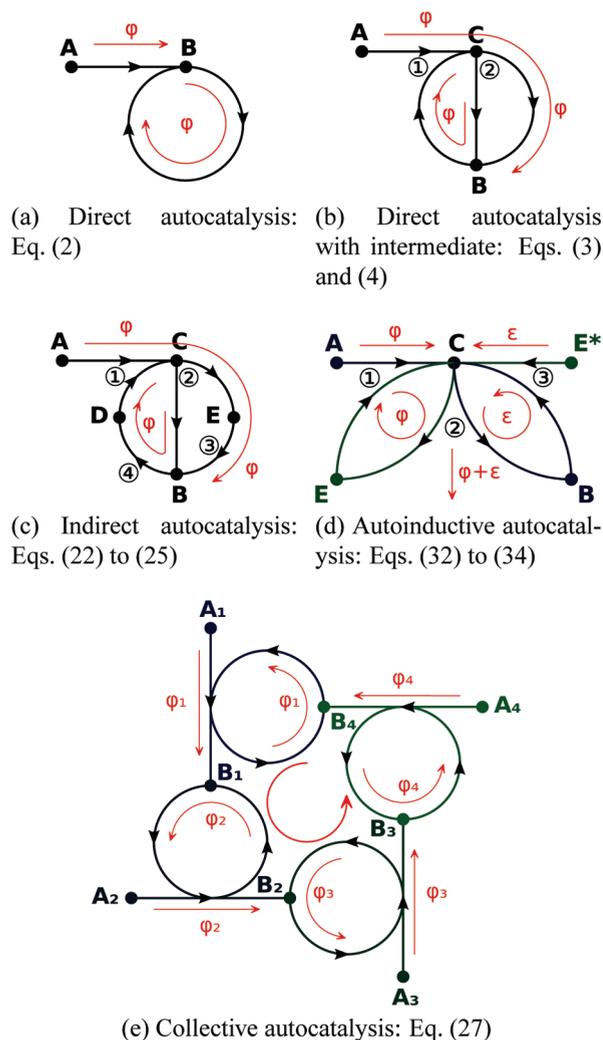
**Figure 2.** (a,b) First-order autocatalytic process ( $\Gamma_1 = 10^2 \text{ M} \cdot \text{s}^{-1}$ ) in the presence of a non-autocatalytic reaction ( $\Gamma_2 = 10^{-2} \text{ M} \cdot \text{s}^{-1}$ ) of spontaneous transformation of A into B ( $K_A = 1 \text{ M}$ ,  $K_B = 10^2 \text{ M}$ ): (a) diluted ( $a_0 = 10^{-3} \text{ M}$ ); (b) concentrated ( $a_0 = 1 \text{ M}$ ). (c) Undamped autocatalysis (indirect autocatalysis, described in Figure 4b,  $\Gamma_4 = 0.1 \text{ M} \cdot \text{s}^{-1}$ ).

autocatalysis  $A + B \rightarrow 2B$ , concurrent with the non-autocatalytic reaction  $A \rightarrow B$ . The autocatalytic process follows a bimolecular kinetics, and will be more efficient in a concentrated rather than in a diluted solution. The dynamic profile of the reaction is thus sigmoidal for high initial concentration of A, but no more for low initial concentration<sup>23</sup> (see Figure 2a,b).

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

How can this kinetic pattern be realized? Let us now detail several types of mechanisms. They can all be reduced, in some conditions, to the autocatalysis kinetic pattern of eq 1. All of them



**Figure 3.** Reaction network of different autocatalytic processes of spontaneous transformation of A into B (a–d), and of  $A_i$  into  $B_i$  (e). The equations given for each system correspond to the corresponding mechanism. The indicated fluxes correspond to what is observed within the QSSA.

will be equally defined in the paper as autocatalytic, while this status may have been disputed in the past on account of the distinct chemical realizations. In the following, we emphasize the major mechanistic pattern to eventually be reduced to an equivalent kinetic autocatalysis, and discuss where their difference comes from.

**3.1. Template Autocatalysis.** The simplest autocatalysis is obtained by the  $X \rightarrow 2X$  pattern. It can be represented by:



The corresponding network is given in Figure 3a. It can further be decomposed through the introduction of an intermediate compound C:



The corresponding network is given in Figure 3b.

The first mechanism entails the following kinetic evolution:

$$\frac{db}{dt} = -\frac{da}{dt} \quad (5)$$

$$= k_1 ab - k_{-1} b^2 \quad (6)$$

This can be expressed as a chemical flux  $\varphi = db/dt$ , by relying on the Mikulecky formalism:<sup>24–26</sup>

$$\varphi = \Gamma_1(V_A V_B - V_B^2) \quad (7)$$

$$V_A = \frac{a}{K_A} \quad (8)$$

$$V_B = \frac{b}{K_B} \quad (9)$$

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

$k_1$  and  $k_{-1}$  are the kinetic constant rates of the reaction 1 in the direct and reverse direction.  $K_A$  and  $K_B$  are the thermodynamic constants of formation of compounds A and B. Formally there is a linear flux  $\varphi$  of transformation of A into B, coupled to a circular flux of same intensity from B back to B (see Figure 3a,b).

This formalism directly gives a normalization of the equations: all the kinetic parameters  $\Gamma_i$  possess the same unit ( $M \cdot s^{-1}$ ) whatever the order of the corresponding reaction, and the equilibrium state corresponds to the equality between the  $V_x$  parameters. Indeed, the equilibrium state corresponds to the state where all fluxes are zero, which leads in this case to  $\varphi = 0$ , that is, to  $V_A V_B = V_B^2$ . Either  $V_B$  is zero, that is, the systems contains only A and no reactions are possible, or  $V_A = V_B$ , which is the equilibrium state between A and B:

$$\frac{a}{b} = \frac{K_A}{K_B} = K_{eq} \quad (11)$$

Focusing on reaction fluxes, this formalism also directly gives access to the nonequilibrium steady-states. If a continuous nonzero flux  $\varphi$  is maintained in this system (for example, by imposing an input flux of A and an output flux of B), then we have

$$\frac{V_A}{V_B} = 1 + \frac{\varphi}{\Gamma_1 V_B^2} \quad (12)$$

$$\frac{a}{b} = K_{eq} \left( 1 + \frac{\varphi}{k_{-1} b^2} \right) \quad (13)$$

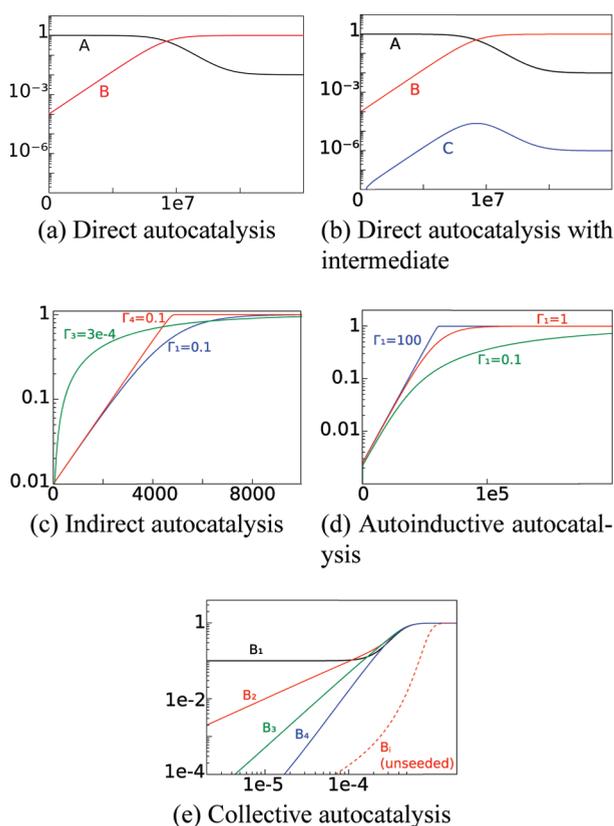
The steady-state corresponds to the equilibrium state corrected by a factor equal to  $1 + \varphi/(k_{-1} b^2)$ .

In the presence of an intermediate compound, the equations become

$$\varphi_1 = \Gamma_1(V_A V_B - V_C) \quad (14)$$

$$\varphi_2 = \Gamma_2(V_C - V_B^2) \quad (15)$$

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,



**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), computed without the QSSA, in a logarithmic scale for concentrations (a–c), or logarithmic scales for both time and concentrations (d).  $K$  and concentrations are in M, times in s, and  $\Gamma$  in  $M \cdot s^{-1}$ . (a) Figure 3a,  $\Gamma_1 = 10^{-4}$ ; (b) Figure 3b,  $\Gamma_1 = 1$ ,  $\Gamma_2 = 10^{-4}$ ,  $K_C = 0.01$ ; (c) Figure 3c,  $\Gamma_1 = \Gamma_2 = \Gamma_3 = \Gamma_4 = 10$  (except the values indicated on the graph),  $K_C = K_D = K_E = 0.01$ ; (d) Figure 3d,  $\Gamma_2 = \Gamma_3 = 100$ ,  $K_C = K_E = 1$ ,  $K_{E^*} = 10$ ; (e) Figure 3e,  $\Gamma_1 = 100$ ,  $\Gamma_2 = 1$ .

hereafter QSSA), so that

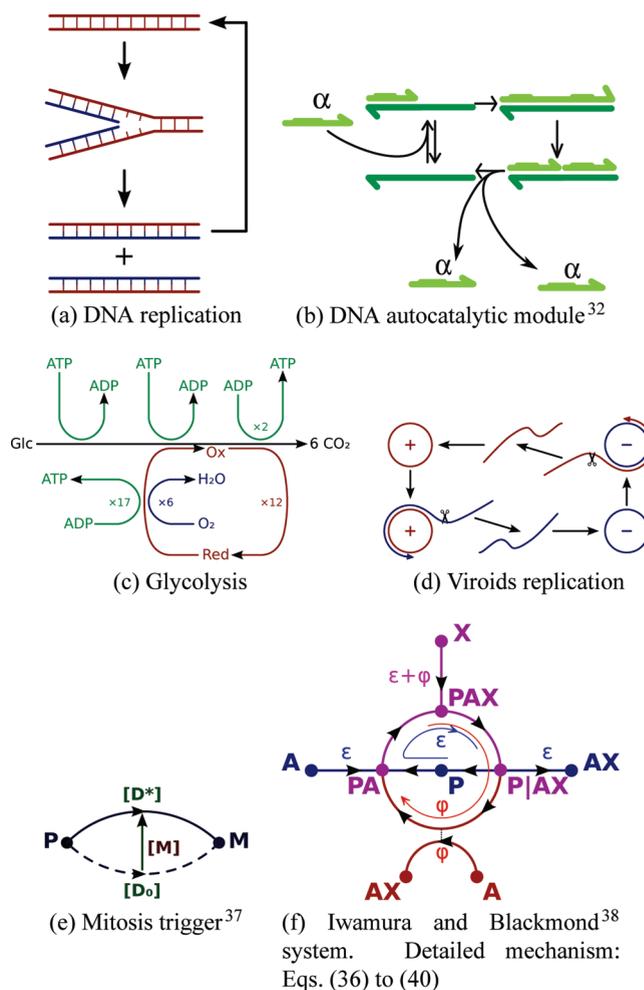
$$\varphi_1 \approx \varphi_2 \quad (16)$$

$$= \varphi \quad (17)$$

$$\Rightarrow \varphi = \frac{\Gamma_1 \Gamma_2}{\Gamma_1 + \Gamma_2} (V_A V_B - V_B^2) \quad (18)$$

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 are in the presence of the perfect kinetic signature of an autocatalytic system, following a sigmoidal evolution. In the examples given in Figure 4a, b, the same evolution of A and B is obtained, whether the reaction is performed via an intermediate compound C or not.<sup>27</sup> This equivalence is guaranteed as long as the compound C remains unstable, i.e.,  $K_C \ll K_A K_B$ . When it is not the case, the dimeric intermediate C hardly liberates the final compound B, which eventually leads to an autocatalytic process on the order of 1/2 rather than 1.<sup>28,29</sup>

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 (see Figure 5a).



**Figure 5.** Experimental examples of autocatalyses. (a) Template autocatalysis: a double strand of DNA is used directly as a template for generating two identical double strands of DNA, each one being able to be newly replicated. (b) Template autocatalysis with intermediate: a DNA template possessing two identical sites for an oligonucleotide  $\alpha$ , able to generate a new  $\alpha$  when activated by a first one. (c) Indirect autocatalysis: the glycolysis consist in transforming one molecule of glucose into six molecules of  $CO_2$ . The process requires the initial consumption of two molecules of ATP, for generating compounds that are then oxidized into  $CO_2$ . These latter processes generate in turn a much larger number of ATP molecules than initially consumed. (d) Collective autocatalysis: a  $\oplus$  circular RNA strand can be used as a catalyst for generating several complementary RNA strands, in a “rolling circle” mechanism. These new strands can then be cyclized in a  $\ominus$  circular RNA strand, that can be used with a similar mechanism to generate several new  $\oplus$  circular RNA strands. (e) Simple autoinductive autocatalysis: the catalyst of a  $P \rightarrow M$  transformation is activated in the presence of the product M. (f) Autoinductive autocatalysis. The  $A + X \rightarrow AX$  reaction can be catalyzed by P, if it has been first activated by the product AX.

More simple examples can be found in some biological mechanisms that require autocatalytic processes, for example, for the generation of chemical oscillation inducing circadian rhythmicity in cells. The system described by Mehra et al. is based on a nonequilibrium system of association/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 adenosine triphosphate (ATP) consumption, one cycle consuming and freeing A and B.<sup>30</sup> The oscillations are generated by coupling this chemical flux to an autocatalytic

process of phosphorylation obeying the reaction scheme<sup>31</sup>  $A + C + AC^* \rightarrow 2AC^*$ .

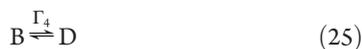
An example of template autocatalysis via intermediate compounds has recently been designed.<sup>32</sup> It is based on the in vitro formation of short DNA strands. A simplified mechanism is



In this system, the template strand T is not the simple complementary strand of the autocatalytic compound A; it actually possesses 2 times this sequence. This implies the prior formation of a duplex between A and T on the first site, which initiates the formation of a second instance of A on the second site. The result is a reaction  $A \rightarrow 2A$  catalyzed by T (see Figure 5b).

**3.2. Network Autocatalysis.** The direct mechanism of template autocatalysis is conceptually the simplest framework. It may actually not 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 reactant and products never directly interact:



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

The QSSA for compounds C, D, and E, justified if these compounds are unstable, allows one to express the reaction flux as

$$\varphi = \frac{1}{\frac{1}{\Gamma_1} + \frac{1}{\Gamma_2} + \frac{V_A}{\Gamma_4} + \frac{V_B}{\Gamma_3}} (V_A V_B - V_B^2) \quad (26)$$

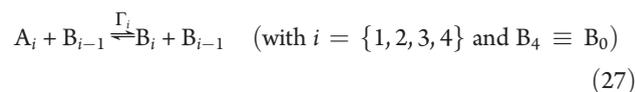
The details of the calculations are given in the Appendix.

When the terms  $V_A/\Gamma_4$  and  $V_B/\Gamma_3$  are small compared to either  $\Gamma_1^{-1}$  or  $\Gamma_2^{-1}$  (i.e., when at least one of the two reactions of eqs 22 and 23 is kinetically limiting), the system behaves like a simple autocatalytic system, with  $\varphi \propto a \cdot b$  before the reaction completion, with a progressive damping of the exponential growth as long as A is consumed. When the term  $V_A/\Gamma_4$  is predominant (i.e., when the reaction of eq 25 is kinetically limiting), the flux is  $\varphi \propto b$ : the profile remains exponential up to the reaction completion, with no damping due to A consumption. When the term  $V_B/\Gamma_3$  is predominant (i.e., when the reaction of eq 24 is kinetically limiting), the flux is  $\varphi \propto a$ : the autocatalytic effect is lost (see Figure 4c).

Network autocatalysis is probably the most common kind of mechanisms. A typical biochemical example is the presence of autocatalysis in glycolysis.<sup>33,34</sup> In this system, there is a net balance following the  $X \rightarrow 2X$  pattern. ATP must be consumed to initiate the degradation of glucose, but much more molecules of ATP are produced during the whole process (see Figure 5c). 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 the Eigen’s hypercycles,<sup>35</sup> are responsible of even more indirect autocatalysis. No compound influences its own formation rate, but rather 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 3e):



There are four independent systems, only connected 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

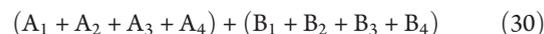
$$\varphi_i = \Gamma_i V_{B_{i-1}} (V_{A_i} - V_{B_i}) \quad (28)$$

$$\varphi = \Gamma V_B (V_A - V_B) \quad (29)$$

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 4e, 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 sub-exponential, 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  $\varphi_i \propto t^{i-1}$ . Seeding with  $B_1$ , the compound  $B_2$  evolves in  $t^2$ . Its impact on compound  $B_3$  induces an evolution in  $t^3$ . In its turn, the impact of compound  $B_3$  on compound  $B_4$  induces an evolution in  $t^4$ . The compound  $B_1$  at first remains constant, and it is only following a given delay that it gets catalyzed by  $B_4$  (see Figure 4e).

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:



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 for the replication of viroids.<sup>36</sup> 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 (see Figure 5d).

3.2.3. *Template versus Network Autocatalysis.* All the preceding systems can be reduced to a  $X \rightarrow 2X$  pattern. This is characterized by a linear flux of chemical transformations, coupled to 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. They can be considered as mechanistically equivalent: a seemingly direct autocatalysis may really be an indirect autocatalysis once its precise mechanism is known, 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 such a template complex is never formed, we preferentially speak of network autocatalysis, in which the  $X \rightarrow 2X$  pattern only results from the reaction balance.

**3.3. Autoinductive Autocatalysis.** Some reactions are not characterized by an  $X \rightarrow 2X$  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 eq 1, but are sometime referred as “autoinductive” instead of “autocatalytic”.<sup>22</sup>

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 under two forms  $E/E^*$ ,  $E^*$  being the more stable one. These two forms of the catalyst interact differently with the product B (see Figure 3d):



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  $\varphi$ , and the transformation of  $E^*$  into E catalyzed by B of intensity  $\varepsilon$ , with  $\varphi \gg \varepsilon$ . Assuming that  $E^*$  is very stable compared to E and C, this decomposition gives (see Appendix for details)

$$\varphi = \frac{\Gamma_1 \Gamma_2 V_{E^*}^0}{\Gamma_1 V_A + \Gamma_2 V_B} (V_B V_A - V_B^2) \quad (35)$$

The autoinduction is kinetically equivalent to the indirect autocatalysis mechanism:

- When  $\Gamma_2 \gg \Gamma_1(K_B/K_A)$ , the flux  $\varphi$  is  $\Gamma_1 V_{E^*}^0 (V_A - V_B)$ : the system is nonautocatalytic.
- When  $\Gamma_2 \approx \Gamma_1(K_B/K_A)$ , the flux  $\varphi$  is  $\Gamma_2 (V_{E^*}^0/V_A^0) (V_A V_B - V_B^2)$ : the system is simply autocatalytic.
- When  $\Gamma_2 \ll \Gamma_1(K_B/K_A)$ , the flux  $\varphi$  is  $\Gamma_2 V_{E^*}^0 (V_B - (V_B^2/V_A))$ : the system presents an undamped autocatalysis.

Following the kinetic analysis, the behavior is similar to the time evolution of autocatalytic systems (see Figure 4d). The behavioral equivalence of these two systems (kinetically equivalent but

mechanistically very different) will be investigated in more detail in the next section.

This simple framework was used for describing the activation of a maturation promoting factor (MPF) in eucaryotes.<sup>37</sup> This process is known to be autocatalytic, namely, generating chemical oscillations leading to repeated mitosis. The simple autocatalytic core of the process relies on the presence of a slow activation of the unactivated form of the MPF (P) into the active one (M), catalyzed by a compound  $D_0$ . This catalyst can in turn be activated into a  $D^*$  form by M,  $D^*$  being a much more efficient catalyst than  $D_0$  for the MPF activation (see Figure 5e).

A more complex example of autoinductive autocatalysis was proposed for explaining the mechanism of the proline-catalyzed  $\alpha$ -aminoxylation of aldehydes.<sup>38</sup> If the chemical relevance of this theoretical framework is debated,<sup>39</sup> it is a good example for understanding how such process may be implemented. It corresponds to the following mechanism:



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 5f). 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  $\varepsilon$ . The second one only contains fast reactions, and corresponds to a fast flux  $\varphi$ . In an ideal case (see Appendix for details), the flux of production of AX is equal to

$$\varphi = \Gamma_5 V_P^0 \left( V_A V_{AX} - \frac{V_{AX}^2}{V_X} \right) \quad (41)$$

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

3.3.2. *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 linear 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<sup>38</sup> but can also be explained by network autocatalytic mechanisms, when the consumption of the reactant does not limit the kinetics of the network.

## 4. EMBEDDED AUTOCATALYSES

One interest of autocatalysis resides in its ability to give birth to rich nonlinear behaviors such as 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 chemical and biochemical competitive systems,<sup>40,41</sup> leading to different stable or multistable states.<sup>42</sup> They are classically studied in population evolution.<sup>43,44</sup> A simple model for the evolution of a species  $x_i$  is

$$\frac{dx_i}{dt} = k_i x_i^n \quad (42)$$

Depending on the order  $n$ , this leads to the following variation of  $x$ :

$$0 < n < 1 \Rightarrow x_i = ((1-n)k_i t + x_{i,0}^{1-n})^{1/(1-n)} \quad (43)$$

$$n = 1 \Rightarrow x_i = x_{i,0} e^{k_i t} \quad (44)$$

$$n > 1 \Rightarrow x_i = \frac{x_0}{(1 - (n-1)x_{i,0}^{n-1} k_i t)^{1/(n-1)}} \quad (45)$$

These equations are describing the unlimited growth in an infinite environment of the species  $x_i$ . In the case  $0 < n < 1$ , the evolution is polynomial with an evolution in  $t^{1/(1-n)}$ , the degree of the evolution is  $1/(1-n) > 1$ . In the case  $n = 1$ , the evolution is exponential. In the case  $n > 1$ , the evolution is superexponential; the species grows to infinity in a finite time.

If two species  $x_1$  and  $x_2$  grow simultaneously, the ratio  $x_1/x_2$  will indicate whether the two species grow at a similar rate, or if one overwhelms the other. In the case of  $0 < n < 1$ , this ratio is

$$\frac{x_1}{x_2} = \left( \frac{(1-n)k_1 t + x_{1,0}^{1-n}}{(1-n)k_2 t + x_{2,0}^{1-n}} \right)^{1/(1-n)} \quad (46)$$

For large values of  $t$ , this ratio converges to

$$\lim_{x \rightarrow +\infty} \frac{x_1}{x_2} = \left( \frac{k_1}{k_2} \right)^{1/(1-n)} \quad (47)$$

This is described as a “survival of all” behavior, as both species can coexist.

In the case of  $n = 1$ , this ratio is

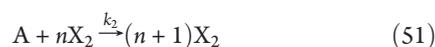
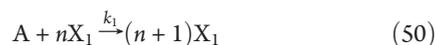
$$\frac{x_1}{x_2} = e^{(k_1 - k_2)t} \quad (48)$$

The ratio increases to infinity (that is,  $x_1$  overwhelms  $x_2$ ) when  $k_1 > k_2$ , and it decreases to 0 (that is,  $x_2$  overwhelms  $x_1$ ) when  $k_2 > k_1$ . This is described as a “survival of the fittest” behavior, as the fastest species floods the slowest one.

In the case of  $n > 1$ , the evolution is especially fast, as the species can reach infinity in a finite time. If  $k_1 x_{1,0}^{n-1} > k_2 x_{2,0}^{n-1}$ , the species  $x_1$  totally conquers the infinite space before  $x_2$  at  $t = 1/(k_1 x_{1,0}^{n-1})$ . If  $k_2 x_{2,0}^{n-1} > k_1 x_{1,0}^{n-1}$ , the species  $x_2$  totally conquers the infinite space before  $x_1$  at  $t = 1/(k_2 x_{2,0}^{n-1})$ . In contrast to the cases of  $n \leq 1$ , a species can overwhelm the other one not only because of its intrinsic property ( $k_i$ ), but also because of the initial conditions ( $x_{i,0}$ ). This is described as a “survival of the first” behavior (or “survival of the common”), as the species with a higher initial population can overwhelm a faster species.

This extremely simplified model actually does not introduce direct competition between the species, and only evaluates their

relative ability to grow. More realistic systems can be described, typically by limiting the growth rate by the consumption of a common food, available in restricted quantity. Behavior similar to that in the previous ideal case is observed, while avoiding the artifact of infinite growth in finite time. This can be illustrated by the following simple chemical system:

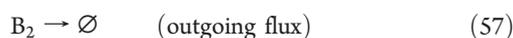
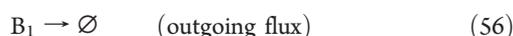
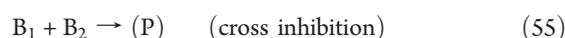
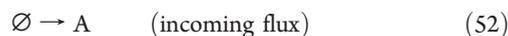


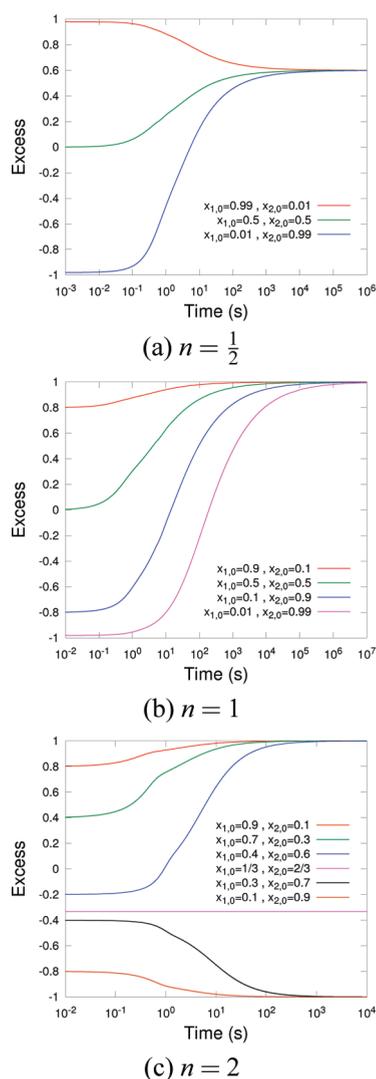
In this case, competition is introduced between  $X_1$  and  $X_2$  through the consumption of  $A$ , the quantity of which is limited by the incoming flux intensity, which is supposed to be constant. The analytical resolution of this system is more complex than that for the previous one, but it can be easily solved numerically.

An example has been calculated in the cases of  $n = 1/2$ ,  $n = 1$ , and  $n = 2$ , with a compound  $X_1$  that is 2 times faster than compound  $X_2$  (see Figure 6). For  $n = 1/2$ , the system reaches a steady state containing both compounds, independently of the initial conditions. The ratio  $x_1/x_2$  is equal to the ratio  $k_1/k_2$ , in accordance with eq 47. For  $n = 1$ , the system reaches a steady state containing essentially  $X_1$ , that is, the faster compound, independently of the initial conditions. For  $n > 1$ , the system reaches a state containing only the faster compound  $X_1$  only if  $k_2 x_{2,0} < k_1 x_{1,0}$ , that is,  $X_2$  is able to overwhelm the faster compound if it starts with at least 2 times the concentration of  $X_1$ .

The case of  $0 < n < 1$  is the least interesting one, as it hardly leads to a clear selectionist process. However, real mechanisms that seem 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.<sup>28,29,45</sup> This turns out to be a fundamental problem for understanding the emergence of the first replicative molecules.<sup>46–48</sup> More complex mechanisms may lead to higher orders, typically by the formation of dimeric autocatalysts.<sup>49</sup> This is the case of the Soai reaction whose high sensitivity to initial conditions may potentially be explained by the formation of trimeric<sup>50</sup> or even hexameric complexes.<sup>51</sup>

**4.2. Comparative Efficiency of Direct and Autoinductive Autocatalyses.** The relative efficiency of two different autocatalytic mechanisms can be evaluated by having them competing with each other. Two different steady states can appear when these two autocatalytic processes are placed in a nonequilibrium open-flow system, both being fed by the same incoming compound and with cross-inhibition between them:

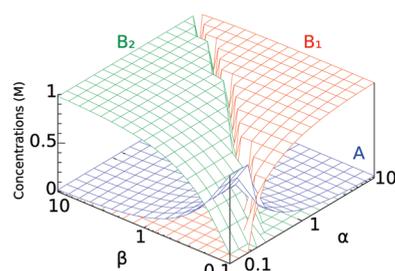




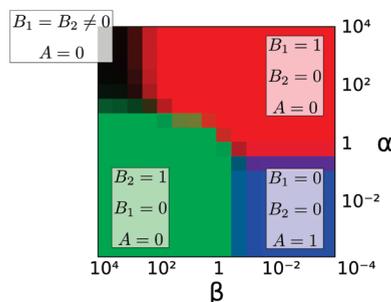
**Figure 6.** Evolution of the excess of  $X_1$  over  $X_2$ , for the competitive autocatalysis described in eqs 49–51. The excess is defined by  $(x_1 - x_2)/(x_1 + x_2)$ ; it is equal to 1 for a system containing exclusively  $X_1$ , 0 for a system containing the same quantity of  $X_1$  and  $X_2$ , and  $-1$  for a system containing exclusively  $X_2$ . Computed for  $f = 1 \text{ M} \cdot \text{s}^{-1}$ ,  $k_1 = 2 \text{ M}^{-n} \cdot \text{s}^{-1}$ ,  $k_2 = 1 \text{ M}^{-n} \cdot \text{s}^{-1}$ ,  $x_{1,0} + x_{2,0} = 1 \text{ M}$ , and different initial values of excess (indicated inside the graph for each curve).

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 for the emergence of homochirality.<sup>15</sup> Because of the system symmetry, the same probability to end 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 to compete, replacing eq 53 and eq 54 by the corresponding mechanism. Kinetic parameters have first been normalized so that each reaction leads on their own to the same kinetic behavior (sigmoidal evolution, half-reaction at  $10^5 \text{ s}$ ), and then multiplied by  $\alpha$  and  $\beta$  parameters, respectively, in order to tune the respective velocity of each mechanism. The result is actually symmetrical between the two processes, and only the fastest product is maintained in the system:  $B_1$  when  $\alpha > \beta$ , and  $B_2$  when  $\alpha < \beta$  (see Figure 7a). As a consequence, while



(a) Sharp transition between two steady states depending on the relative values of  $\alpha$  and  $\beta$  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 7.** Competition between template and autoinductive autocatalysis, respectively generating  $B_1$  and  $B_2$  compounds from the same  $A$  compound. Incoming flux of  $A$ , and outgoing fluxes of  $B_1$  and  $B_2$ ,  $10^{-5} \text{ M} \cdot \text{s}^{-1}$ .  $K_A = 1$ ,  $K_{B_1} = K_{B_2} = 100$ . Direct autocatalysis:  $\Gamma_{AC} = 10^{-2} \cdot \alpha$ ,  $\Gamma_{NC} = 10^{-6} \cdot \alpha$ . Autoinduction, according to Figure 3d:  $\Gamma_1 = \beta$ ,  $\Gamma_2 = \Gamma_3 = 100 \cdot \beta$ ,  $K_C = K_E = 1$ ;  $K_{E^*} = 10$ .

mechanistically different, these two autocatalysis 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 7b). Such a result is well-known for open-flow Frank systems.<sup>52</sup>

**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. Network autocatalysis must not, however, be confused with autocatalytic sets. The first notion of “network autocatalysis” indicates, as detailed above, that an autocatalytic behavior can be generated within a more or less complex reaction network. The latter notion of an “autocatalytic set” describes a subset of reaction that is not only able to generate autocatalytically a set of compounds, but that is able to generate and sustain *all* of its components.

This is a rather popular notion in the field of artificial life literature, but relies much more on the cooperation between autocatalytic mechanisms than on the competition that has just been detailed here. This implies a notion of material closure of the system and of self-maintenance of the whole network by crossing fluxes.<sup>53–55</sup> More than a mechanism allowing some compounds to accelerate their own formation, an autocatalytic set is a chemical network that is able to generate and maintain all of his internal components.

This has been illustrated in the literature by the study of several theoretical reaction networks.<sup>22</sup> While several of the studied systems possess an autocatalytic mechanism, only one of them succeeds in maintaining a steady-state production of its components in an open-flow environment. This behavior does not originate from the nature of the autocatalyses: as shown above, this should lead to equivalent dynamic properties. By contrast, it evidences the important role of the system closure for its ability to be self-sustained. This can be understood by studying the chemical exchanges between the systems and their surroundings. This topological analysis is detailed in the Appendix. It appears that the nonsustainable networks possess a common property: some of their components are connected to an outgoing flux, but miss a connection to an incoming flux. They are ineluctably eliminated from the system, and the network is doomed to collapse. Whether this network contains an autocatalytic mechanism is unimportant, as this feature will not be able to manifest itself in the long term. By contrast, all the elements of the sustainable network are involved in both incoming and outgoing fluxes. They can thus exist in a nonzero steady-state concentration, and the network can be maintained. In this case, the autocatalytic mechanism can be effective, and the dynamics of the system may lead to the continuous production of its internal elements.

## 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. Indeed, experimental chemical systems with a self-amplification behavior show a large variety of reaction networks. Thus, a pragmatic definition of autocatalysis has to be based on a kinetic signature, in order to classify the systems according to 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. However, the problem of the evolvability of such systems must be kept in mind.<sup>56</sup> If a system evolves toward a stable attractor, no evolution turns out to be possible. There is the necessity of “open-ended” evolution,<sup>57</sup> i.e., 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”, redounding upon the concept originally introduced by Muller<sup>8</sup> for the autocatalytic power linked to mutability of genes. This concept leads to the more general notion of replicators.<sup>58</sup> 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.<sup>59</sup>

## 6. APPENDIX

The kinetic behaviors of three different mechanisms for autocatalytic transformations have been studied in detail. The methodology consists in establishing the different chemical fluxes of the network. The relationship between these fluxes can be simplified by assuming the QSSA for relevant compounds. The purpose is then to establish the expression of the transformation flux  $\varphi$  as a function of the concentration of the reactants and the products.

**6.1. Indirect Autocatalysis.** The four fluxes of Figure 3c can be written as

$$\varphi_1 = \Gamma_1(V_A V_D - V_C) \quad (58)$$

$$\varphi_2 = \Gamma_2(V_C - V_B V_E) \quad (59)$$

$$\varphi_3 = \Gamma_3(V_E - V_B) \quad (60)$$

$$\varphi_4 = \Gamma_4(V_B - V_D) \quad (61)$$

The QSSA for D comes down to  $\varphi_1 \approx \varphi_4$ :

$$\Gamma_1 V_A V_D - \Gamma_1 V_C = \Gamma_4 V_B - \Gamma_4 V_D \quad (62)$$

$$(\Gamma_1 V_A + \Gamma_4) V_D = \Gamma_4 V_B + \Gamma_1 V_C \quad (63)$$

$$V_D = \frac{\Gamma_4 V_B + \Gamma_1 V_C}{\Gamma_1 V_A + \Gamma_4} \quad (64)$$

Replacing  $V_D$  by eq 64 in eq 58 gives

$$\varphi_1 = \Gamma_1 \left( V_A \frac{\Gamma_4 V_B + \Gamma_1 V_C}{\Gamma_1 V_A + \Gamma_4} - V_C \right) \quad (65)$$

$$= \frac{\Gamma_1 \Gamma_4}{\Gamma_1 V_A + \Gamma_4} V_A V_B + \Gamma_1 V_C \frac{-\Gamma_4}{\Gamma_1 V_A + \Gamma_4} \quad (66)$$

$$= \frac{\Gamma_1 \Gamma_4}{\Gamma_1 V_A + \Gamma_4} (V_A V_B - V_C) \quad (67)$$

The QSSA for E comes down to  $\varphi_2 \approx \varphi_3$ :

$$\Gamma_2 V_C - \Gamma_2 V_B V_E = \Gamma_3 V_E - \Gamma_3 V_B \quad (68)$$

$$V_E = \frac{\Gamma_2 V_C + \Gamma_3 V_B}{\Gamma_3 + \Gamma_2 V_B} \quad (69)$$

Replacing  $V_E$  by eq 69 in eq 59 gives

$$\varphi_2 = \Gamma_2 \left( V_C - V_B \frac{\Gamma_2 V_C + \Gamma_3 V_B}{\Gamma_3 + \Gamma_2 V_B} \right) \quad (70)$$

$$= \Gamma_2 V_C \frac{\Gamma_3}{\Gamma_3 + \Gamma_2 V_B} - \Gamma_2 V_B \frac{\Gamma_3 V_B}{\Gamma_3 + \Gamma_2 V_B} \quad (71)$$

$$= \frac{\Gamma_2 \Gamma_3}{\Gamma_3 + \Gamma_2 V_B} (V_C - V_B^2) \quad (72)$$

At last, the QSSA for C comes down to  $\varphi_1 \approx \varphi_2 = \varphi$ . Combining eq 67 and eq 72 gives

$$V_C = \frac{\Gamma'_1 V_A V_B + \Gamma'_2 V_B^2}{\Gamma'_1 + \Gamma'_2} \quad (73)$$

$$\text{with } \Gamma'_1 = \frac{\Gamma_1 \Gamma_4}{\Gamma_1 V_A + \Gamma_4} \quad (74)$$

$$\text{and } \Gamma'_2 = \frac{\Gamma_2 \Gamma_3}{\Gamma_3 + \Gamma_2 V_B} \quad (75)$$

Replacing  $V_C$  by eq 73 in eq 67 gives

$$\varphi = \Gamma'_1 V_A V_B - \Gamma'_1 \frac{\Gamma'_1 V_A V_B + \Gamma'_2 V_B^2}{\Gamma'_1 + \Gamma'_2} \quad (76)$$

$$= \left( \Gamma'_1 - \frac{\Gamma_1^2}{\Gamma'_1 + \Gamma'_2} \right) V_A V_B - \frac{\Gamma'_1 \Gamma'_2}{\Gamma'_1 + \Gamma'_2} V_B^2 \quad (77)$$

$$= \frac{\Gamma'_1 \Gamma'_2}{\Gamma'_1 + \Gamma'_2} (V_A V_B - V_B^2) \quad (78)$$

Replacing  $\Gamma'_1$  and  $\Gamma'_2$  by their expression given in eq 74 and eq 75 then gives

$$\varphi = \frac{V_A V_B - V_B^2}{\frac{1}{\Gamma_1} + \frac{1}{\Gamma_2} + \frac{V_A}{\Gamma_4} + \frac{V_B}{\Gamma_3}} \quad (79)$$

**6.2. Autoinductive Autocatalysis.** The three fluxes of Figure 3d are

$$\varphi_1 = \Gamma_1 (V_A V_E - V_C) \quad (80)$$

$$\varphi_2 = \Gamma_2 (V_C - V_B V_E) \quad (81)$$

$$\varphi_3 = \Gamma_3 (V_B V_{E^*} - V_C) \quad (82)$$

The QSSA for C comes down to  $\varphi_1 + \varphi_3 \approx \varphi_2$ , and the QSSA for E comes down to  $\varphi_1 \approx \varphi_2$ . This implies that  $\varphi_3 \ll \varphi_1$ , so that with  $\varphi_3 = \varepsilon$  and  $\varphi_1 = \varphi$  we obtain

$$\varphi_2 = \varphi + \varepsilon \approx \varphi \quad (83)$$

In that context, eq 82 gives

$$V_C = V_B V_{E^*} - \frac{\varepsilon}{\Gamma_3} \quad (84)$$

Combining eqs 80 and 81 in eq 83 then gives

$$\Gamma_2 V_C - \Gamma_2 V_B V_E = \Gamma_1 V_A V_E - \Gamma_1 V_C + \varepsilon \quad (85)$$

$$V_E = \frac{(\Gamma_1 + \Gamma_2) V_C - \varepsilon}{\Gamma_1 V_A + \Gamma_2 V_B} \quad (86)$$

Replacing  $V_C$  by its value given in eq 84 leads to

$$V_E = \frac{(\Gamma_1 + \Gamma_2) V_{E^*} V_B - \frac{\Gamma_1 + \Gamma_2 + \Gamma_3}{\Gamma_3} \varepsilon}{\Gamma_1 V_A + \Gamma_2 V_B} \quad (87)$$

$$V_E \approx \frac{(\Gamma_1 + \Gamma_2) V_{E^*} V_B}{\Gamma_1 V_A + \Gamma_2 V_B} \quad (88)$$

The flux of destruction of A can be computed by replacing  $V_E$  in eq 80 by eq 88 (computing the flux of formation of B from eq 81 would of course give the same result):

$$\varphi = \Gamma_1 \left( V_A \frac{(\Gamma_1 + \Gamma_2) V_{E^*} V_B}{\Gamma_1 V_A + \Gamma_2 V_B} - V_B V_{E^*} \right) \quad (89)$$

$$= \Gamma_1 \frac{(\Gamma_1 + \Gamma_2) V_{E^*} V_B V_A - V_B V_{E^*} (\Gamma_1 V_A + \Gamma_2 V_B)}{\Gamma_1 V_A + \Gamma_2 V_B} \quad (90)$$

$$= \Gamma_1 \Gamma_2 V_{E^*} \frac{V_B V_A - V_B^2}{\Gamma_1 V_A + \Gamma_2 V_B} \quad (91)$$

The law of conservation of E compounds leads to

$$\varphi = \frac{\Gamma_1 \Gamma_2 V_{E^*}^0 (V_B V_A - V_B^2)}{(\Gamma_1 V_A + \Gamma_2 V_B)(1 + r_C V_C + r_E V_E)} \quad (92)$$

with  $r_C = K_C/K_{E^*}$  and  $r_E = K_E/K_{E^*}$ . Assuming that  $E^*$  is much more stable than C and E,  $r_C$  and  $r_E \ll 1$ , so that we finally obtain<sup>60</sup>

$$\varphi = \frac{\Gamma_1 \Gamma_2 V_{E^*}^0}{\Gamma_1 V_A + \Gamma_2 V_B} (V_B V_A - V_B^2) \quad (93)$$

**6.3. Iwamura and Blackmond Model.** The five fluxes of Figure 3e are

$$\varphi_1 = \Gamma_1 (V_A V_P - V_{PA}) \quad (94)$$

$$\varphi_2 = \Gamma_2 (V_{PA} V_X - V_{PAX}) \quad (95)$$

$$\varphi_3 = \Gamma_3 (V_{PAX} - V_{P|AX}) \quad (96)$$

$$\varphi_4 = \Gamma_4 (V_{P|AX} - V_P V_{AX}) \quad (97)$$

$$\varphi_5 = \Gamma_5 (V_{P|AX} V_A - V_{PA} V_{AX}) \quad (98)$$

The QSSA for P leads to  $\varphi_1 = \varphi_4$ ; for PA, it leads to  $\varphi_2 = \varphi_1 + \varphi_5$ ; for PAX it leads to  $\varphi_3 = \varphi_2$ ; for P|AX, it leads to  $\varphi_3 = \varphi_4 + \varphi_5$ . The fluxes can thus be decomposed into two elementary fluxes:

$$\varphi_1 = \varepsilon \quad (99)$$

$$\varphi_2 = \varphi + \varepsilon \quad (100)$$

$$\varphi_3 = \varphi + \varepsilon \quad (101)$$

$$\varphi_4 = \varepsilon \quad (102)$$

$$\varphi_5 = \varphi \quad (103)$$

$\varphi$  is the flux of the catalytic reaction, and  $\varepsilon$  is the flux of the non-catalytic reaction, so that  $\varepsilon \ll \varphi$ . This would typically be characterized by  $\Gamma_1 \ll \Gamma_5$ .

$\varphi_2 = \varphi_3$  leads to

$$V_{P|AX} = \frac{\Gamma_2}{\Gamma_{23}} V_{PAX} - \frac{\Gamma_2}{\Gamma_3} V_{PA} V_X \quad (104)$$

with  $\Gamma_{23} = \Gamma_2 \Gamma_3 / (\Gamma_2 + \Gamma_3)$ .

$\varphi_3 \approx \varphi_5$  leads to

$$V_{P|AX} = \frac{\Gamma_{23}}{\Gamma_2} V_{PAX} + \frac{\Gamma_5}{\Gamma_3 + \Gamma_5 V_A} V_{PA} V_{AX} \quad (105)$$

Combining eqs 104 and 105, and thereby eliminating  $V_{P|AX}$ , leads to

$$V_{PAX} = \frac{\frac{\Gamma_5}{\Gamma_2} V_{AX} + V_X + \frac{\Gamma_5}{\Gamma_3} V_A V_X}{\Gamma_5 V_A + \Gamma_{23}} \Gamma_{23} V_{PA} \quad (106)$$

Combining eq 106 with eq 104 leads to

$$V_{P|AX} = \frac{\Gamma_5 V_{AX} + \Gamma_{23} V_X}{\Gamma_5 V_A + \Gamma_{23}} V_{PA} \quad (107)$$

$\varphi_1 = \varphi_4$  leads to

$$V_P = \frac{\Gamma_4 V_{P|AX} + \Gamma_1 V_{PA}}{\Gamma_1 V_A + \Gamma_4 V_{AX}} \quad (108)$$

Combining eqs 108 and 107 leads to

$$V_P = \frac{\Gamma_4(\Gamma_5 V_{AX} + \Gamma_{23} V_X) + \Gamma_1(\Gamma_5 V_A + \Gamma_{23})}{(\Gamma_1 V_A + \Gamma_4 V_{AX})(\Gamma_5 V_A + \Gamma_{23})} V_{PA} \quad (109)$$

The flux of production of AX can be computed from eq 95, eq 96, or eq 98, which leads to

$$\varphi = \Gamma_5 \Gamma_{23} V_{PA} \frac{V_A V_X - V_{AX}}{\Gamma_5 V_A + \Gamma_{23}} \quad (110)$$

Combining eqs 110 and 109 leads to

$$\varphi = \frac{\Gamma_5 \Gamma_{23} V_P (V_A V_X - V_{AX}) \left( \frac{\Gamma_1}{\Gamma_4} V_A + V_{AX} \right)}{\Gamma_5 \left( \frac{\Gamma_1}{\Gamma_4} V_A + V_{AX} \right) + \Gamma_{23} \left( \frac{\Gamma_1}{\Gamma_4} + V_X \right)} \quad (111)$$

This can be simplified in an ideal case, assuming that the compound P is the most stable compound among P, PA, PAX, and P|AX, so that  $V_P \approx V_P^0$ , and that the reactivities are so that  $\Gamma_1 \ll (\Gamma_4, \Gamma_5) \ll \Gamma_{23}$  (i.e., assuming that reaction 1 is very slow, and that reactions 2 and 3 are very fast), which leads to

$$\varphi \approx \Gamma_5 V_P^0 \left( V_A V_{AX} - \frac{V_{AX}^2}{V_X} \right) \quad (112)$$

**6.4. Closure of Autocatalytic Networks.** The self-sustaining ability of several autocatalytic networks has been studied by Blackmond.<sup>22</sup> This property can be deduced from a simple topological analysis, upon investigating the closure of the different systems.

Case i (as represented in Scheme 3 in ref 22) is the following system of reactions:



It is the simple catalysis of the reaction  $A + B \rightleftharpoons C$  by the catalyst E. There is an incoming flux of A and B, and the continuous destruction of C and E.

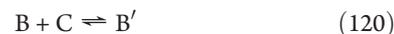
The decomposition of the chemical elements into elementary moieties can be obtained from the computation of the left null space of the corresponding stoichiometric matrix.<sup>26,61</sup> For this system, this leads to (the zeroes are represented by dots, for more clarity):

$$\nu_1 = \begin{pmatrix} -1 & \cdot \\ \cdot & -1 \\ \cdot & +1 \\ -1 & +1 \\ +1 & -1 \end{pmatrix} \Rightarrow \text{Null}(\nu_1) = \begin{matrix} A \\ B \\ C \\ E \\ I \end{matrix} \begin{pmatrix} 1 & \cdot & \cdot \\ \cdot & 1 & \cdot \\ 1 & 1 & \cdot \\ \cdot & \cdot & 1 \\ 1 & \cdot & 1 \end{pmatrix} \quad (119)$$

The compounds can be decomposed into three moieties  $\alpha$ ,  $\beta$  and  $\varepsilon$ , with  $A = \alpha$ ,  $B = \beta$ ,  $C = \alpha\beta$ ,  $E = \varepsilon$  and  $I = \alpha\varepsilon$ . For example, the reaction  $A + E \rightleftharpoons I$  comes down to  $\alpha + \varepsilon \rightleftharpoons \alpha\varepsilon$ .

The input flux only brings the moieties  $\alpha$  and  $\beta$  via A and B, while the three moieties are expelled outside the system via the destruction of C and E. As all the compounds containing the moiety  $\varepsilon$  are connected to fluxes leading to the destruction of E, their concentrations in the steady state are zero. The steady state of this system can thus only contain the reactions that do not involve the compounds containing the moiety  $\varepsilon$  (i.e., the compounds E and I). The reaction network becomes reduced to eqs 113, 114, and 117, that is, the sole fluxes and no reaction: the system cannot be self-sustained because of the  $\varepsilon$  leak.

Case ii adds the following reactions to the set of eqs 113–118:



The moiety decomposition becomes:

$$\nu_2 = \begin{pmatrix} -1 & \cdot & \cdot & \cdot \\ \cdot & -1 & -1 & \cdot \\ \cdot & \cdot & +1 & -1 \\ \cdot & +1 & -1 & +2 \\ -1 & +1 & \cdot & +1 \\ +1 & -1 & \cdot & -1 \end{pmatrix} \Rightarrow \text{Null}(\nu_2) = \begin{matrix} A \\ B \\ B' \\ C \\ E \\ I \end{matrix} \begin{pmatrix} 1 & \cdot & \cdot \\ \cdot & 1 & \cdot \\ 1 & 2 & \cdot \\ 1 & 1 & \cdot \\ \cdot & \cdot & 1 \\ 1 & \cdot & 1 \end{pmatrix} \quad (122)$$

The same decomposition as in case i is obtained, with the addition of the compound  $B' = \alpha\beta_2$ . Here again, there is a leak of  $\varepsilon$  destroying E and I. The steady-state network can be solely composed of the reaction, eq 120, plus the fluxes, eqs 113, 114, and 117. This is not sufficient to sustain a reaction flux, as the reaction eq 120 cannot connect the incoming fluxes of A and B to the outgoing flux of C.

Case iii adds the following reactions to the set of eqs 113–118:



The moiety decomposition becomes:

$$\nu_3 = \begin{pmatrix} -1 & \cdot & \cdot & -1 & \cdot \\ \cdot & -1 & \cdot & \cdot & -1 \\ \cdot & +1 & -1 & \cdot & +1 \\ -1 & +1 & -1 & \cdot & \cdot \\ \cdot & \cdot & +1 & -1 & +1 \\ +1 & -1 & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & +1 & -1 \end{pmatrix} \Rightarrow \text{Null}(\nu_3) = \begin{matrix} A \\ B \\ C \\ E \\ E' \\ I \\ I' \end{matrix} \begin{pmatrix} 1 & \cdot & \cdot \\ \cdot & 1 & \cdot \\ 1 & 1 & \cdot \\ \cdot & \cdot & 1 \\ 1 & 1 & 1 \\ 1 & \cdot & 1 \\ 2 & 1 & 1 \end{pmatrix} \quad (126)$$

The same decomposition as in case i is obtained, with the addition of the compounds  $E' = \alpha\beta\varepsilon$  and  $I' = \alpha_2\beta\varepsilon$ . Here again, there is a leak of  $\varepsilon$ , now destroying the compounds E,  $E'$ , I and  $I'$ . The steady-state network can only contain the fluxes, eqs 113, 114, and 117; the system is not self-sustainable.

At last, case iv adds the following reactions to the set of eqs 113–118:



The moiety decomposition becomes:

$$v_4 = \begin{pmatrix} -1 & \cdot & -1 & \cdot \\ \cdot & -1 & \cdot & -1 \\ \cdot & +1 & -1 & +2 \\ -1 & +1 & \cdot & \cdot \\ +1 & -1 & \cdot & \cdot \\ \cdot & \cdot & +1 & -1 \end{pmatrix} \Rightarrow \text{Null}(v_4) = \begin{matrix} A \\ B \\ C \\ E \\ I \\ I'' \end{matrix} \begin{pmatrix} 1 & \cdot & \cdot \\ \cdot & 1 & \cdot \\ 1 & 1 & \cdot \\ \cdot & \cdot & 1 \\ 1 & \cdot & 1 \\ 2 & 1 & \cdot \end{pmatrix} \quad (129)$$

The same decomposition as in case i is obtained, with the addition of the compound  $I'' = \alpha_2\beta$ . This time, the leak of  $\varepsilon$  eliminates E and I, but not  $I''$ . The steady-state network can be reduced to eqs 127 and 128, with the addition of the fluxes, eqs 113, 114, and 117. A global flux of reaction can be obtained by eq 127 + eq 128 + eq 113 + eq 114 + eq 117, corresponding to  $\emptyset \rightarrow A + B \rightleftharpoons C \rightarrow \emptyset$ . This last system can thus be self-sustained, as all its components can be maintained in non-zero concentrations. The failure of the systems i, ii, and iii is simply explained by a defect in the closure of the networks. The three systems ii, iii, and iv are autocatalytic, but only iv is an autocatalytic set.

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