

Article

Mathematical Analysis of a Prototypical Autocatalytic Reaction Network

Ekaterina V. Skorb ¹ and Sergey N. Semenov ^{2,*} ¹ ITMO University, Lomonosova St. 9, Saint Petersburg 191002, Russia; skorb@corp.ifmo.ru² Department of Organic Chemistry, Weizmann Institute of Science, Rehovot 76100, Israel

* Correspondence: sergey.semenov@weizmann.ac.il

Received: 15 April 2019; Accepted: 18 May 2019; Published: 20 May 2019



Abstract: Network autocatalysis, which is autocatalysis whereby a catalyst is not directly produced in a catalytic cycle, is likely to be more common in chemistry than direct autocatalysis is. Nevertheless, the kinetics of autocatalytic networks often does not exactly follow simple quadratic or cubic rate laws and largely depends on the structure of the network. In this article, we analyzed one of the simplest and most chemically plausible autocatalytic networks where a catalytic cycle is coupled to an ancillary reaction that produces the catalyst. We analytically analyzed deviations in the kinetics of this network from its exponential growth and numerically studied the competition between two networks for common substrates. Our results showed that when quasi-steady-state approximation is applicable for at least one of the components, the deviation from the exponential growth is small. Numerical simulations showed that competition between networks results in the mutual exclusion of autocatalysts; however, the presence of a substantial noncatalytic conversion of substrates will create broad regions where autocatalysts can coexist. Thus, we should avoid the accumulation of intermediates and the noncatalytic conversion of the substrate when designing experimental systems that need autocatalysis as a source of positive feedback or as a source of evolutionary pressure.

Keywords: Autocatalysis; reaction networks; origin of life; Michaelis-Menten kinetics; numerical simulations; self-replication

1. Introduction

Autocatalytic reactions are of profound importance for at least three problems in the chemical sciences: (i) chemical evolution and the origin of life, [1–6] (ii) dissipative chemical systems [7–9], and (iii) chemical signaling and information processing systems [10]. Autocatalytic self-replication is an element needed for Darwinian selection. Biological evolution is driven by cellular division and life most likely originates from prebiotic reactions that involve some form of self-replication and autocatalysis [1,11–14]. Dissipative systems, such as chemical and biological oscillators and Turing structures [15–18], often require autocatalytic reactions as a source of positive feedback. Finally, biochemical signaling systems need autocatalysis for signal amplification [10].

The importance of autocatalysis for determining the origin of life is twofold [19]. At the initial stages of prebiotic evolution, where organic building blocks accumulated, autocatalysis is a possible solution for the “mixtures” problem [20–22], which involves a low abundance of any particular reaction product from diverse starting materials because of the statistical distribution of the reaction products. Autocatalysis would accelerate the formation of a limited set of products and consume starting materials for forming these products, thus avoiding the formation of the complex mixture. At later stages of prebiotic evolution, autocatalysis serves as a driving force for the natural selection of information carriers [2,12,14,23]. It amplifies the fittest carriers against others. Many variations of information carriers have been proposed such as rybozimes [24], autocatalytic sets of polypeptides [1,2,12,14,22],

or vesicles carrying compositional information [23], but autocatalysis is always a driving force behind the evolution of these species.

Direct autocatalysis, which is a process whereby a product directly catalyzes its own production through formation of only short-living intermediates, is often differentiated from network autocatalysis, where multiple stable products cooperatively accelerate their own production [25–29]. Because of its high mechanistic versatility compared with direct autocatalysis, network autocatalysis has become a basis for a variety of models for determining the origin of life [1,2,11,12,14,23,30]. Nevertheless, the functional properties (e.g., the ability to evolve) of a particular network depend on their kinetic behavior which [31,32], consequently, depend on the structure of the network [33]. Therefore, it is important to analyze the kinetics of specific and chemically plausible autocatalytic reaction networks [34–36].

Semenov, Whitesides, and coworkers have recently published two autocatalytic reactions that can be reduced to a catalytic cycle, followed by the noncatalytic conversion of one product of this catalytic cycle to the catalyst itself (Figure 1) [37,38].

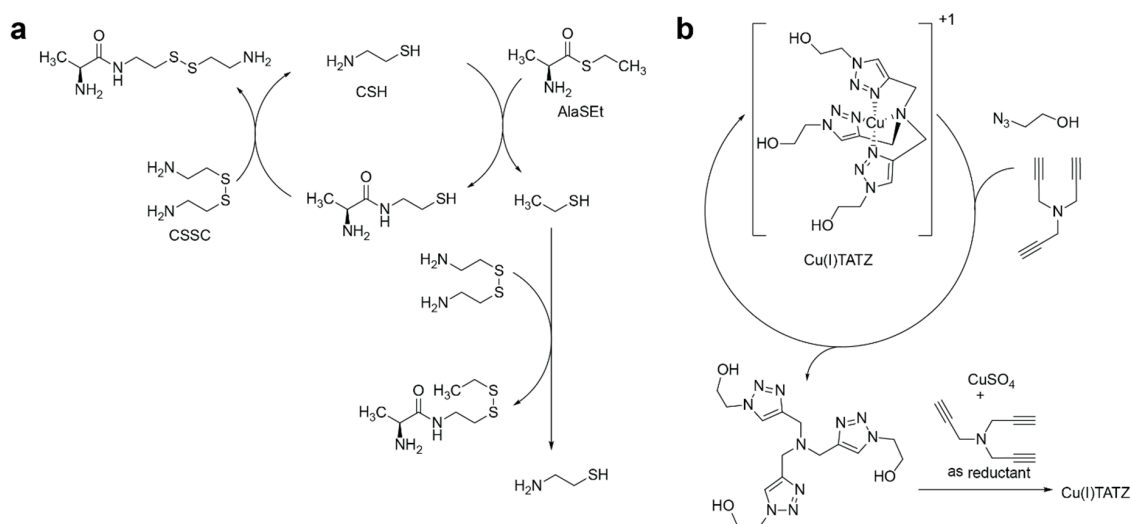


Figure 1. Schemes that represent (a) the thiol-based autocatalytic reaction and (b) the copper-catalyzed azide-alkyne cycloaddition-based autocatalytic reaction as a catalytic cycle coupled to a non-catalytic reaction that converts one of the products of catalytic transformation into the catalyst itself. Examples of autocatalysts are cysteamine (CSH) and a copper complex (Cu(I)TATZ).

In the first example, we can separate a catalytic cycle of cysteamine (CSH), which catalyzed the acylation of cysteamine (CSSC) by a thioester; this is followed by converting one of its byproducts, ethanethiol, into CSH (Figure 1a) [37]. In the second example, the catalytic cycle of the copper-catalyzed azide-alkyne cycloaddition reactions is followed by the formation of a catalytically active complex from triazole derivatives (Figure 1b) [38]. Because of the abundance of catalytic reactions in nature, we speculate that these motifs might be among the most common autocatalytic motifs in simple (i.e., non-biological) reaction networks.

Here, we would like to analyze the kinetic behavior of one type of these motifs where the Michaelis-Menten-type catalysis is coupled to one additional irreversible reaction (Figure 2).

We decided to analyze this particular motif because the Michaelis-Menten scheme can be applied to many catalytic reactions and possibility to reduce extended motifs to this motif by considering only rate-limiting steps. We would like to determine under which conditions this reaction network can be used in place of quadratic autocatalysis in experiments investigating chemical evolution and chemical systems with nonlinear kinetics and whether the kinetics of this network will always cause mutual exclusion of competing replicators.

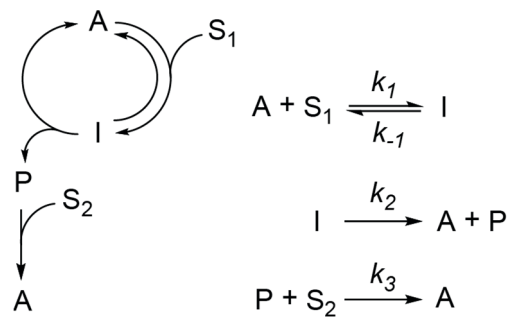


Figure 2. The autocatalytic reaction network analyzed here.

2. Results and Discussion

2.1. Analysis of Kinetics for a Network with an Infinite Supply of Substrates

Equations (1)–(3) with constant S_1 and S_2 describe the network in this approximation:

$$\frac{dA}{dt} = -k_1 S_1 A + (k_2 + k_{-1})I + k_3 S_2 P \quad (1)$$

$$\frac{dI}{dt} = k_1 S_1 A - (k_2 + k_{-1})I \quad (2)$$

$$\frac{dP}{dt} = k_2 I - k_3 S_2 P \quad (3)$$

Let us first consider two of the simplest cases: (i) when quasi-steady-state approximation (QSSA) can be applied to I ($\frac{dI}{dt} = 0$) and P ($\frac{dP}{dt} = 0$) and (ii) when QSSA can be applied to A ($\frac{dA}{dt} = 0$) and P ($\frac{dP}{dt} = 0$). Simple calculations (see the Appendix A) show that in the first case the reaction is perfectly autocatalytic with the effective rate constant $k_e = k_1 S_1 k_2 / (k_2 + k_{-1})$:

$$\frac{dA}{dt} = \frac{k_1 S_1 k_2}{(k_2 + k_{-1})} A \quad (4)$$

Obviously, in a situation with a limited amount of S_1 , the reaction will behave as quadratic autocatalysis with rate constant k_e .

In the second case, the reaction is entirely autocatalytic for I with k_2 as the autocatalytic constant (see the Appendix A):

$$\frac{dI}{dt} = k_2 I \quad (5)$$

Let us next look at a situation where we apply QSSA only to I . This situation is important for experimental systems because it has been shown that many catalytic reactions follow Michaelis–Menten kinetics, which implies QSSA for I . The equations (1)–(3) can be reduced to the second order Equation (6) on P :

$$\frac{d^2 P}{dt^2} + k_3 S_2 \frac{dP}{dt} - \frac{k_3 S_2 k_1 S_1 k_2}{(k_2 + k_{-1})} P = 0 \quad (6)$$

From 6, with initial conditions $P(0) = 0$ and $A(0) = A_0$, we can derive an expression for A (see the Appendix A for details).

$$A(t) = \frac{A_0}{\sqrt{k_3 S_2 (k_3 S_2 + 4k_1 S_1 k_2 / (k_2 + k_{-1}))}} ((k_3 S_2 + \lambda_1) e^{\lambda_1 t} - (k_3 S_2 + \lambda_2) e^{\lambda_2 t})$$

$$\lambda_{1/2} = \frac{-k_3 S_2 \pm \sqrt{k_3 S_2 (k_3 S_2 + 4k_1 S_1 k_2 / (k_2 + k_{-1}))}}{2} \quad (7)$$

Note that for physical (positive) rate constants and concentrations, λ_1 is always positive and λ_2 is always negative. The first term in Equation (7) has a positive exponent (λ_1) and has the higher coefficient in front of the exponent other than the second term, and therefore, it will dominate from the beginning. Chemically, this equation means that if intermediates of the catalytic cycle do not accumulate in significant amounts, the reaction will behave as exponential autocatalysis from the beginning of the experiment and any deviations from exponential growth will decay over time.

Next, we will examine a situation where we do not have an accumulated product of the catalytic cycle because of the substantially high rate of its conversion to the autocatalyst. This situation is described by QSSA with $\frac{dP}{dt} = 0$ and cannot be reduced to the second order differential equation; instead, we need to solve a system involving two equations:

$$\frac{dA}{dt} = -k_1 S_1 A + (2k_2 + k_{-1})I \quad (8)$$

$$\frac{dI}{dt} = k_1 S_1 A - (k_2 + k_{-1})I \quad (9)$$

For the initial conditions, $A(0) = A_0$ and $I(0) = 0$; this system has a solution:

$$A(t) = A_0(C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t})$$

$$\lambda_{1/2} = \frac{-k_1 S_1 - k_2 - k_{-1} \pm \sqrt{(k_1 S_1 + k_2 + k_{-1})^2 + 4k_1 S k_2}}{2} \quad (10)$$

Both the C_1 and C_2 coefficients are positive and $C_1 + C_2 = 1$ (for an exact expression of C_1 and C_2 , see the Appendix A). The value λ_1 is always positive and λ_2 is always negative for any positive rate constants. Therefore, the value of the decaying term, $A_0 C_2 e^{\lambda_2 t}$, will not exceed that of A_0 . These calculations indicate that if in an experimental system the product P does not accumulate and A_0 is much smaller than the concentration of the substrate, S_1 , this system will behave as an almost perfect quadratic autocatalysis.

Finally, we will briefly examine a situation where we do not apply any QSSA. For an autocatalyst A, the solution has a general form:

$$A(t) = C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t} + C_3 e^{\lambda_3 t} \quad (11)$$

If any part of λ_{1-3} is positive, then A will grow exponentially after an initial lag period (the term with a positive exponent will dominate in Equation (11)). As we show in the Appendix A, because rate constants are positive, one of the λ_{1-3} values must be positive. Thus, independently of rate constants and after some lag period, this reaction network will produce exponential growth. Experimental systems are limited by the amounts of the substrates S_1 and S_2 and might not have time to reach an exponential phase, especially with a high initial concentration of A.

2.2. Competition of the Autocatalysts of Two Different Autocatalytic Networks for Common Substrates

To describe a practically interesting situation, we analyzed the competition between two autocatalytic networks in a continuously stirred tank reactor (CSTR). Network 1 consists of A_1 , I_1 , and P_1 and network 2 consists of A_2 , I_2 , and P_2 ; they compete for common substrates S_1 and S_2 . Here, the system is defined by:

$$\frac{dA_1}{dt} = -k_1 S_1 A_1 + (k_2 + k_{-1})I_1 + k_3 S_2 P_1 - k_0 A_1 \quad (12)$$

$$\frac{dI_1}{dt} = k_1 S_1 A_1 - (k_2 + k_{-1} + k_0)I_1 \quad (13)$$

$$\frac{dP_1}{dt} = k_2 I_1 - (k_3 S_2 + k_0)P_1 \quad (14)$$

$$\frac{dA_2}{dt} = -k'_1 S_1 A_2 + (k'_2 + k'_{-1}) I_2 + k'_3 S_2 P_2 - k_0 A_2 \quad (15)$$

$$\frac{dI_2}{dt} = k'_1 S_1 A_2 - (k'_2 + k'_{-1} + k_0) I_2 \quad (16)$$

$$\frac{dP_2}{dt} = k'_2 I_1 - (k'_3 S_2 + k_0) P_2 \quad (17)$$

$$\frac{dS_1}{dt} = -(k_1 A_1 + k'_1 A_2 + k_0) S_1 + k_{-1} I_1 + k'_{-1} I_2 + k_0 S_{10} \quad (18)$$

$$\frac{dS_2}{dt} = -(k_3 P_1 + k'_3 P_2 + k_0) S_2 + k_0 S_{20}, \quad (19)$$

where S_{10} and S_{20} are the concentrations at which S_1 and S_2 are supplied to the reactor.

We should mention at this point that if networks compete only for substrate S_1 and S_2 is considered to be in an unlimited supply (i.e., we consider Equations (12)–(18) with S_2 being constant), autocatalysts A_1 and A_2 cannot coexist at a steady state if any difference between the rate constants of the reactions of the networks exists (see the Appendix A). The model with constant S_2 describes experimental systems where S_2 is in a big excess in relation to S_1 or where conversion of P to A is a monomolecular reaction.

If S_2 is variable, we cannot draw a simple conclusion about coexistence and need to use numerical analysis. We analyzed 12–19 using Mathematica script (see the Appendix A). Figure 3a shows concentrations of A_1 and A_2 at $t = 2000$ where, in most cases, the system reaches a steady state. We set all constants to unity, the initial concentrations of A_1 and A_2 to 0.001, k_0 to 0.1, and varied k_1 and k_3 , which characterize reactions with substrates. The graph has two characteristic features: (i) autocatalysts A_1 and A_2 do not coexist, if one has a nonzero concentration and another falls to zero; (ii) competition is not sensitive to k_3 as soon as k_3 is sufficiently high. These features mean that these networks can undergo Darwinian evolution and that this evolution will be more sensitive to improvements in k_1 than in k_3 .

An important difference between model 12–19 and plausible chemical systems is the presence of the noncatalytic conversion of substrates to autocatalysts in many experimental systems. To consider these reactions, we have to add $k_4 S_1$ and $k'_4 S_1$ to Equations (12) and (13) correspondingly, and subtract both these terms from Equation (18). We performed a numerical analysis of the modified equations with the same parameters as in Figure 3a and with k_4 and k'_4 set to 0.01 (Figure 3b). The graph shows that autocatalysts can coexist and the region of coexistence is higher for low k_3 values. Thus, we should avoid accumulating P in experimental systems with noncatalytic background reactions. We also explored how k_2 and k_{-1} influence the competition between two replicators (Figure 3c,d). The plots demonstrate that k_2 , which represents k_{cat} in a classical Michaelis-Menten scheme, has a stronger influence on the competition than k_3 does, but it is less important than k_1 . Interestingly, simultaneously varying k_2 and k_{-1} produces almost a symmetrical plot, which indicates their equal contribution to the competition between replicators (Figure 3d). Overall, the data indicate that k_1 , which is responsible for initiating the catalytic cycle, has the greatest effect on the competition, whereas k_3 , which is responsible for an auxiliary reaction that produces an extra molecule in the catalyst, has a minimum effect.

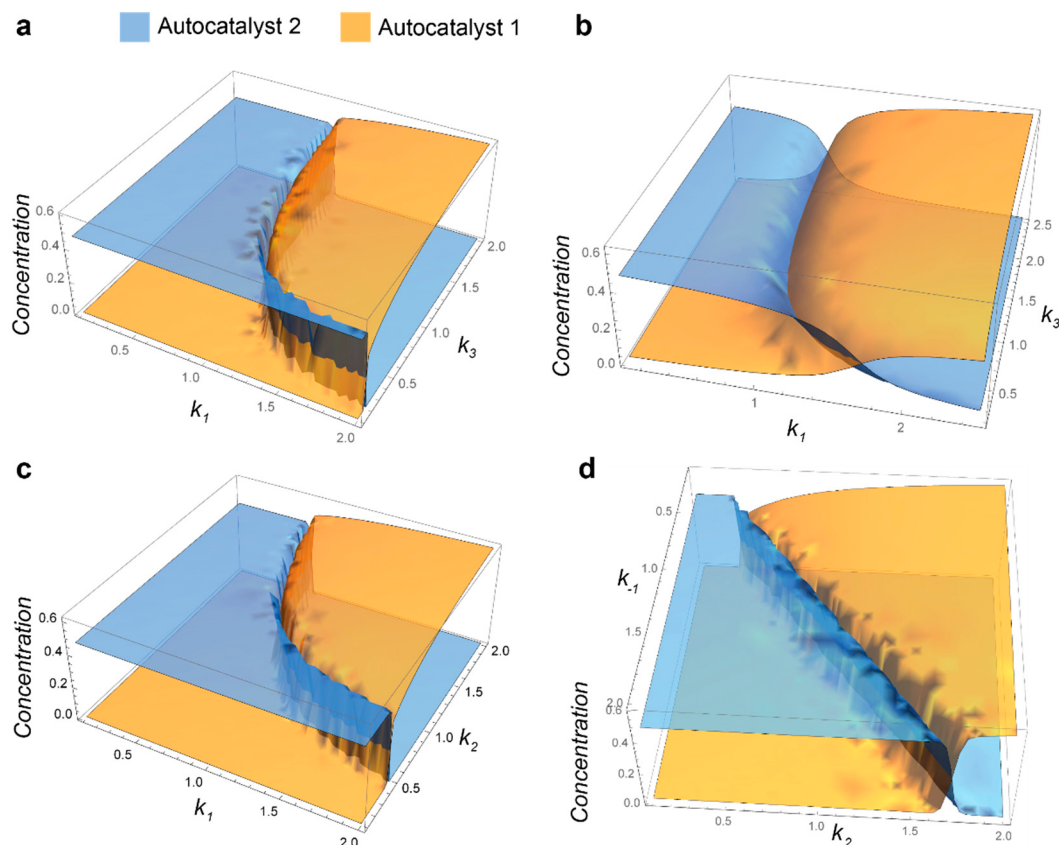


Figure 3. Competition between replicators A_1 and A_2 in continuously stirred tank reactor (CSTR). (a) The system is based on Equations (12)–(19). All reaction rate constants except k_1 and k_3 are set to 1; k_0 is set to 0.1, S_{10} and S_{20} are set to 1, and k_1 and k_3 are varied from 0.1 to 2. (b) When considering the noncatalytic formation of A_1 and A_2 with $k_4 = k_4' = 0.01$, other parameters are identical to a. (c) The system is based on Equations (12)–(19). All reaction rate constants except k_1 and k_2 are set to 1; k_0 is set to 0.1, S_{10} and S_{20} are set to 1, and k_1 and k_2 are varied from 0.1 to 2. (d) The system is based on Equations (12)–(19). All reaction rate constants except k_{-1} and k_2 are set to 1; k_0 is set to 0.1, S_{10} and S_{20} are set to 1, and k_{-1} and k_2 are varied from 0.1 to 2. In all plots, the concentrations of replicators A_1 and A_2 are plotted at $t = 2000$, $A_1(0) = 0.001$, $A_2(0) = 0.001$.

3. Conclusions

In this work, we determined, as precisely as possible, where and how to use reactions in experimental systems, which are based on the scheme shown in Figure 2. The results provide two main conclusions: (i) As soon as an intermediate of catalytic I or an intermediate product P does not accumulate in the reaction (at least one of them can be described by QSSA), the reaction kinetics does not deviate from exponential autocatalysis after a short lag period. (ii) The competition between these networks results in the mutual exclusion of autocatalysts if the noncatalytic formation of autocatalysts is negligible. Therefore, although these networks are not direct autocatalysts from a mechanistic perspective, they will behave as simple quadratic autocatalysts in most experimental systems.

Finally, if some variable information in autocatalyst A is transferred to product P and then retained during conversion of P to A, the network fulfills the conditions for Darwinian evolution. Interestingly, an experimental system from Otto's group is [39,40], in a way, already following this mechanism. The growth of the supramolecular stacks, which is catalyzed by the terminus of the stack, is the catalytic step with information transfer; breaking the stack, which generates an extra terminus, is a P to A step that retains the information.

Author Contributions: Both authors generated an idea, discussed it and wrote the paper. S.N.S. performed the computations.

Acknowledgments: E.V.S. acknowledges the Russian Government support Grant 08-08.

Conflicts of Interest: There are no conflicts of interest.

Appendix A

I. Equations (2)–(3) at $\frac{dI}{dt} = 0$ and $\frac{dP}{dt} = 0$ give:

$$k_1 S_1 A - (k_2 + k_{-1}) I = 0 \quad (\text{A1})$$

$$k_2 I - k_3 S_2 P = 0 \quad (\text{A2})$$

$$I = \frac{k_1 S_1 A}{k_2 + k_{-1}} \quad (\text{A3})$$

$$P = \frac{k_2 k_1 S_1 A}{k_3 S_2 (k_2 + k_{-1})} \quad (\text{A4})$$

Substitution of (A3) and (A4) into (1) gives Equation (4)

Equations (1) and (3) at $\frac{dA}{dt} = 0$ and $\frac{dP}{dt} = 0$ give:

$$-k_1 S_1 A + (k_2 + k_{-1}) I + k_3 S_2 P = 0 \quad (\text{A5})$$

$$P = \frac{k_2 I}{k_3 S_2} \quad (\text{A6})$$

$$A = -\frac{(2k_2 + k_{-1}) I}{k_1 S_1} \quad (\text{A7})$$

Substitution of (A7) into (2) gives Equation (5)

II. Equation (6) at $P(0) = 0$ and $A(0) = A_0 \Rightarrow \frac{dP}{dt}(0) = \frac{k_1 S_1 k_2}{(k_2 + k_{-1})} A_0$ has a solution:

$$P(t) = \frac{A_0 k_1 S_1 k_2}{(k_2 + k_{-1}) \sqrt{k_3 S_2 (k_3 S_2 + 4k_1 S_1 k_2 / (k_2 + k_{-1}))}} (e^{\lambda_1 t} - e^{\lambda_2 t});$$

$$\lambda_{1/2} = \frac{-k_3 S_2 \pm \sqrt{k_3 S_2 (k_3 S_2 + 4k_1 S_1 k_2 / (k_2 + k_{-1}))}}{2} \quad (\text{A8})$$

Considering that:

$$A(t) = \frac{(k_2 + k_{-1})}{k_1 S_1 k_2} (k_3 S_2 P + \frac{dP}{dt}) \quad (\text{A9})$$

A(t) is described by Equation (7).

III. In Equation (10) coefficients C_1 and C_2 are expressed by:

$$C_1 = \frac{k_1 S_1 - k_2 - k_{-1} + \sqrt{(k_1 S_1 + k_2 + k_{-1})^2 + 4k_1 S_1 k_2}}{2 \sqrt{(k_1 S_1 + k_2 + k_{-1})^2 + 4k_1 S_1 k_2}}$$

$$C_2 = \frac{k_2 + k_{-1} - k_1 S_1 + \sqrt{(k_1 S_1 + k_2 + k_{-1})^2 + 4k_1 S_1 k_2}}{2 \sqrt{(k_1 S_1 + k_2 + k_{-1})^2 + 4k_1 S_1 k_2}} \quad (\text{A10})$$

IV. Equations (1)–(3) are linear and a solution for this linear system of ODE has the following form:

$$\begin{pmatrix} A \\ I \\ P \end{pmatrix} = C_1 e^{\lambda_1 t} \tilde{v}_1 + C_2 e^{\lambda_2 t} \tilde{v}_2 + C_3 e^{\lambda_3 t} \tilde{v}_3 \quad (\text{A11})$$

where λ_1 , λ_2 , and λ_3 are eigenvalues, and v_{1-3} are the corresponding eigenvectors of the matrix:

$$\begin{pmatrix} -k_1 S_1 & k_2 + k_{-1} & k_3 S_2 \\ k_1 S_1 & -k_2 - k_{-1} & 0 \\ 0 & k_2 & -k_3 S_2 \end{pmatrix} \quad (\text{A12})$$

λ_1 , λ_2 , and λ_3 are roots of the equation:

$$\lambda^3 + (k_1 S_1 + k_2 + k_{-1} + k_3 S_2) \lambda^2 + k_3 S_2 (k_1 S_1 + k_2 + k_{-1}) \lambda - k_1 S_1 k_3 S_2 k_2 = 0 \quad (\text{A13})$$

From Vieta's formula:

$$\lambda_1 \lambda_2 \lambda_3 = k_1 S_1 k_3 S_2 k_2 \quad (\text{A14})$$

Because k_1 , k_2 , k_3 , S_1 , S_2 are positive, one of the λ_{1-3} values must be positive.

V. Steady-state conditions for 12-19 are as follows:

$$A_1(-k_1 S_1 + \frac{(k_2 + k_{-1})k_1 S_1}{k_2 + k_{-1} + k_0} + \frac{k_2 k_1 S_1 k_3 S_2}{(k_3 S_2 + k_0)(k_2 + k_{-1} + k_0)} - k_0) = 0 \quad (\text{A15})$$

$$A_2(-k'_1 S_1 + \frac{(k'_2 + k'_{-1})k'_1 S_1}{k'_2 + k'_{-1} + k_0} + \frac{k'_2 k'_1 S_1 k'_3 S_2}{(k'_3 S_2 + k_0)(k'_2 + k'_{-1} + k_0)} - k_0) = 0 \quad (\text{A16})$$

If we consider S_2 to be constant and the reaction rates are different for two networks, this system of equations does not have solutions where both A_1 and A_2 are nonzero.

VI. Mathematic script that generates the plot 3A. Plots 3B-C were generated by modifying this script. $k_0 = 0.1$; $k_1 = 1$; $k_{1r} = 1$; $k_2 = 1$; $k_3 = 1$; $k_{1z} = 1$; $k_{1rz} = 1$; $k_{2z} = 1$; $k_{3z} = 1$; $S_{01} = 1$; $S_{02} = 1$; $s = \text{ParametricNDSolve}[\{a'[t] == -a[t]*(i*k_1*s_1[t] + k_0) + b[t]*(k_2 + k_{1r}) + h*k_3*s_2[t]*p[t]$, $b'[t] == i*k_1*a[t]*s_1[t] - b[t]*(k_2 + k_{1r} + k_0)$, $p'[t] == k_2*b[t] - (h*k_3*s_2[t] + k_0)*p[t]$, $a_1'[t] == -a_1[t]*(k_{1z}*s_1[t] + k_0) + b_1[t]*(k_{2z} + k_{1rz}) + k_3*s_2[t]*p_1[t]$, $b_1'[t] == k_{1z}*a_1[t]*s_1[t] - b_1[t]*(k_{2z} + k_{1rz} + k_0)$, $p_1'[t] == k_{2z}*b_1[t] - (k_3*s_2[t] + k_0)*p_1[t]$, $s_1'[t] == -i*k_1*a[t]*s_1[t] - k_{1z}*a_1[t]*s_1[t] + k_{1r}*b[t] + k_{1rz}*b_1[t] - k_0*s_1[t] + k_0*S_{01}$, $s_2'[t] == -h*k_3*p[t]*s_2[t] - k_3*p_1[t]*s_2[t] - k_0*s_2[t] + k_0*S_{02}$, $a[0] == 0.001$, $a_1[0] == 0.001$, $b[0] == p[0] == b_1[0] == p_1[0] == 0$, $s_1[0] == s_2[0] == 1$ }, {a, b, p, a1, b1, p1, s1, s2}, {t, 0, 2000}, {i, h}]; $\text{Plot3D}[\{a[i, h][2000] / . s, a_1[i, h][2000] / . s\}, \{i, 0.1, 2\}, \{h, 0.1, 2\}, \text{PlotStyle} \rightarrow \text{Opacity}[0.7], \text{Mesh} \rightarrow \text{None}, \text{AxesStyle} \rightarrow 16]$

References

1. Eigen, M. Selforganization of matter and the evolution of biological macromolecules. *Naturwissenschaften* **1971**, *58*, 465–523. [\[CrossRef\]](#)
2. Eigen, M.; Schuster, P. Hypercycle—Principle of Natural Self-Organization. B. Abstract Hypercycle. *Naturwissenschaften* **1978**, *65*, 7–41. [\[CrossRef\]](#)
3. Sievers, D.; Von Kiedrowski, G. Self Replication of Complementary Nucleotide-Based Oligomers. *Nature* **1994**, *369*, 221–224. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Li, T.; Nicolaou, K.C. Chemical self-replication of palindromic duplex DNA. *Nature* **1994**, *369*, 218–221. [\[CrossRef\]](#)
5. Lee, D.H.; Granja, J.R.; Martinez, J.A.; Severin, K.; Ghadiri, M.R. A self-replicating peptide. *Nature* **1996**, *382*, 525–528. [\[CrossRef\]](#)
6. Ashkenasy, G.; Jagasia, R.; Yadav, M.; Ghadiri, M.R. Design of a directed molecular network. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 10872–10877. [\[CrossRef\]](#)
7. Whitesides, G.M.; Grzybowski, B. Self-assembly at all scales. *Science* **2002**, *295*, 2418–2421. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Nicolis, G.; Prigogine, I. *Self-Organization in Nonequilibrium Systems: From Dissipative Structures to Order Through Fluctuations*; Wiley: New York, NY, USA, 1977; pp. 40–233.

9. Field, R.J.; Noyes, R.M. Oscillations in chemical systems. IV. Limit cycle behavior in a model of a real chemical reaction. *J. Chem. Phys.* **1974**, *60*, 1877–1884. [[CrossRef](#)]
10. Kholodenko, B.N. Cell-signalling dynamics in time and space. *Nat. Rev. Mol. Cell Bio.* **2006**, *7*, 165–176. [[CrossRef](#)]
11. Dyson, F.J. A Model for the Origin of Life. *J. Mol. Evol.* **1982**, *18*, 344–350. [[CrossRef](#)]
12. Vasas, V.; Fernando, C.; Santos, M.; Kauffman, S.; Szathmary, E. Evolution before genes. *Biol. Direct* **2012**, *7*. [[CrossRef](#)]
13. Nghe, P.; Hordijk, W.; Kauffman, S.A.; Walker, S.I.; Schmidt, F.J.; Kemble, H.; Yeates, J.A.M.; Lehman, N. Prebiotic network evolution: Six key parameters. *Mol. Biosyst.* **2015**, *11*, 3206–3217. [[CrossRef](#)]
14. Kauffman, S.A. Autocatalytic sets of proteins. *J. Theor. Biol.* **1986**, *119*, 1–24. [[CrossRef](#)]
15. Epstein, I.R.; Pojman, J.A. *An Introduction to Nonlinear Chemical Dynamics: Oscillations, Waves, Patterns, and Chaos*; Oxford University Press: New York, NY, USA, 1998; pp. 17–324.
16. Dekepper, P.; Epstein, I.R.; Kustin, K. A Systematically Designed Homogeneous Oscillating Reaction - the Arsenite-Iodate-Chlorite System. *J. Am. Chem. Soc.* **1981**, *103*, 2133–2134. [[CrossRef](#)]
17. Lengyel, I.; Epstein, I.R. Modeling of Turing Structures in the Chlorite Iodide Malonic-Acid Starch Reaction System. *Science* **1991**, *251*, 650–652. [[CrossRef](#)] [[PubMed](#)]
18. Turing, A.M. The Chemical Basis of Morphogenesis. *Philos. T. Roy. Soc. B* **1952**, *237*, 37–72.
19. Lifson, S. On the crucial stages in the origin of animate matter. *J. Mol. Evol.* **1997**, *44*, 1–8. [[CrossRef](#)]
20. Hordijk, W.; Hein, J.; Steel, M. Autocatalytic Sets and the Origin of Life. *Entropy* **2010**, *12*, 1733–1742. [[CrossRef](#)]
21. Eschenmoser, A. Etiology of potentially primordial biomolecular structures: From vitamin B12 to the nucleic acids and an inquiry into the chemistry of life's origin: A retrospective. *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 12412–12472. [[CrossRef](#)]
22. Hordijk, W.; Steel, M. Chasing the tail: The emergence of autocatalytic networks. *Biosystems* **2017**, *152*, 1–10. [[CrossRef](#)]
23. Markovitch, O.; Lancet, D. Excess Mutual Catalysis Is Required for Effective Evolvability. *Artif. Life* **2012**, *18*, 243–266. [[CrossRef](#)] [[PubMed](#)]
24. Lincoln, T.A.; Joyce, G.F. Self-Sustained Replication of an RNA Enzyme. *Science* **2009**, *323*, 1229–1232. [[CrossRef](#)] [[PubMed](#)]
25. Plasson, R.; Brandenburg, A.; Jullien, L.; Bersini, H. Autocatalyses. *J. Phys. Chem. A* **2011**, *115*, 8073–8085. [[CrossRef](#)]
26. Hinshelwood, C.N. On the Chemical Kinetics of Autosynthetic Systems. *J. Chem. Soc.* **1952**, 745–755. [[CrossRef](#)]
27. Blackmond, D.G. An examination of the role of autocatalytic cycles in the chemistry of proposed primordial reactions. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 386–390. [[CrossRef](#)]
28. Bisette, A.J.; Fletcher, S.P. Mechanisms of Autocatalysis. *Angew. Chem. Int. Ed.* **2013**, *52*, 12800–12826. [[CrossRef](#)]
29. Hordijk, W.; Steel, M.; Dittrich, P. Autocatalytic sets and chemical organizations: Modeling self-sustaining reaction networks at the origin of life. *New J. Phys.* **2018**, *20*, 015011. [[CrossRef](#)]
30. Hordijk, W.; Steel, M.; Kauffman, S. The structure of autocatalytic sets: Evolvability, enablement, and emergence. *Acta Biotheor.* **2012**, *60*, 379–392. [[CrossRef](#)]
31. Szathmary, E. The origin of replicators and reproducers. *Philos. Trans. R. Soc. Lond B Biol. Sci.* **2006**, *361*, 1761–1776. [[CrossRef](#)]
32. Szathmáry, E. Simple growth laws and selection consequences. *Trends in Ecology & Evolution* **1991**, *6*, 366–370.
33. Wagner, N.; Ashkenasy, G. How Catalytic Order Drives the Complexification of Molecular Replication Networks. *Isr. J. Chem.* **2015**, *55*, 880–890. [[CrossRef](#)]
34. Ashkenasy, G.; Hermans, T.M.; Otto, S.; Taylor, A.F. Systems chemistry. *Chem. Soc. Rev.* **2017**, *46*, 2543–2554. [[CrossRef](#)] [[PubMed](#)]
35. Ludlow, R.F.; Otto, S. Systems chemistry. *Chem. Soc. Rev.* **2008**, *37*, 101–108. [[CrossRef](#)]
36. Dadon, Z.; Wagner, N.; Alasibi, S.; Samiappan, M.; Mukherjee, R.; Ashkenasy, G. Competition and cooperation in dynamic replication networks. *Chemistry* **2015**, *21*, 648–654. [[CrossRef](#)]

37. Semenov, S.N.; Kraft, L.J.; Ainla, A.; Zhao, M.; Baghbanzadeh, M.; Campbell, C.E.; Kang, K.; Fox, J.M.; Whitesides, G.M. Autocatalytic, bistable, oscillatory networks of biologically relevant organic reactions. *Nature* **2016**, *537*, 656–660. [[CrossRef](#)] [[PubMed](#)]
38. Semenov, S.N.; Belding, L.; Cafferty, B.J.; Mousavi, M.P.S.; Finogenova, A.M.; Cruz, R.S.; Skorb, E.V.; Whitesides, G.M. Autocatalytic Cycles in a Copper-Catalyzed Azide-Alkyne Cycloaddition Reaction. *J. Am. Chem. Soc.* **2018**, *140*, 10221–10232. [[CrossRef](#)]
39. Carnall, J.M.A.; Waudby, C.A.; Belenguer, A.M.; Stuart, M.C.A.; Peyralans, J.J.P.; Otto, S. Mechanosensitive Self-Replication Driven by Self-Organization. *Science* **2010**, *327*, 1502–1506. [[CrossRef](#)]
40. Sadownik, J.W.; Mattia, E.; Nowak, P.; Otto, S. Diversification of self-replicating molecules. *Nat. Chem.* **2016**, *8*, 264–269. [[CrossRef](#)]



© 2019 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).