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An ecological framework for the analysis of prebiotic chemical reaction networks

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ABSTRACT

It is becoming widely accepted that very early in life's origin, even before the emergence of genetic encoding, reaction networks of diverse small chemicals might have manifested key properties of life, namely self-propagation and adaptive evolution. To explore this possibility, we formalize the dynamics of chemical reaction networks within the framework of chemical ecosystem ecology. To capture the idea that life-like chemical systems are maintained out of equilibrium by fluxes of energy-rich food chemicals, we model chemical ecosystems in well-mixed compartments that are subject to constant dilution by a solution with a fixed concentration of input chemicals. Modelling all chemical reactions as fully reversible, we show that seeding an autocatalytic cycle with tiny amounts of one or more of its member chemicals results in logistic growth of all member chemicals in the cycle. This finding justifies drawing an instructive analogy between an autocatalytic cycle and a biological species. We extend this finding to show that pairs of autocatalytic cycles can exhibit competitive, predator-prey, or mutualistic associations just like biological species. Furthermore, when there is stochasticity in the environment, particularly in the seeding of autocatalytic cycles, chemical ecosystems can show complex dynamics that can resemble evolution. The evolutionary character is especially clear when the network architecture results in ecological precedence, which makes a system's trajectory historically contingent on the order in which cycles are seeded. For all its simplicity, the framework developed here helps explain the onset of adaptive evolution in prebiotic chemical reaction networks, and can shed light on the origin of key biological attributes such as thermodynamic irreversibility and genetic encoding.

1. Introduction

Empirical and theoretical analyses during the past few decades have converged on the view that the origin of life might entail spontaneous, life-like behavior emerging in networks of relatively simple chemical reactions (Hordijk et al., 2010; Kauffman, 1986; Liu and Sumpter, 2018; Ruiz-Mirazo et al., 2014; Shapiro, 2006; Walker and Davies, 2013). However, despite a growing body of theory, it is still unclear how simple chemical rules can give rise to systems manifesting the basic properties of life, namely self-propagation and the capacity for adaptive evolution (Joyce, 1994; Luisi, 1998). While abstract models have shown that autocatalysis, the chemical equivalent of self-propagation, is likely to be a common feature of chemical networks underlying the origin of life (Hordijk et al., 2012; Hordijk and Steel, 2016, 2004; Virgo et al., 2016; Virgo and Ikegami, 2013; Xavier et al., 2020), these models have, by-and-large, lacked realistic chemical kinetics, making it difficult to connect their theory of autocatalysis to plausible prebiotic settings. Furthermore, although autocatalytic reaction networks are shown to have some level of "evolvability" without linear polymers for genetic information storage (Goldford and Segrè, 2018; Hordijk, 2016; Hordijk et al., 2012; Hordijk and Steel, 2014; Vasas et al., 2012, 2010), it is largely unclear whether, how, and under what conditions such evolvability can lead to systems that sustain, grow and evolve similarly to known life. Additionally, these models, depending on their primary foci, interpret autocatalysis in different ways and thus sometimes induce ambiguities (Hordijk, 2017).

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Among the first attempts to bring ecological thinking to the origin of life problem was by Odum (Odum, 1971), who articulated the view that life began as an ecosystem of cooperating molecular components that collectively exploited energy fluxes, and only later gave rise to cells and genetic systems. An ecosystem-first view of life was also adopted by subsequent authors (Baum, 2018; Baum and Vetsigian, 2017; Fiscus, 2002; Gatti et al., 2017; Hunding et al., 2006; Lee et al., 1997; Wieczorek, 2012), but has yet to provide explicit models to explain how chemical ecosystems could form and complexify to yield systems as complex as cellular life. Here we attempt to formalize the notion of a chemical ecosystem as a set of actively interacting autocatalytic subsystems (cycles), and use tools from ecological theory (e.g., Ulanowicz, 1997) to explain how these ecosystems maintain themselves using chemical disequilibria and how they change over time as a function of their internal dynamics, stochastic perturbation, and environmental filtering. Although, we only analyze the earliest stages of self-organization, with small numbers of potentially interacting autocatalytic subsystems, we believe that this basic model of prebiotic chemical ecosystems can be readily expanded to include polymers, specific catalysts, and other characteristic features of life as we know it.

In this paper, we develop a model of autocatalytic chemical reaction networks that differs from most existing models in the origin-of-life field (Hordijk and Steel, 2016, 2004; Kauffman, 1993, 1986; Segré et al., 1998; Steel, 2000; Vasas et al., 2012) by assuming that all reactions are reversible and by following conventional mass-action chemical kinetics, without a need for specific catalysts (though this factor can easily be incorporated into our model). Also, unlike most prior theories, our approach gives explicit and careful attention to the stoichiometric properties of autocatalytic processes. Using this model, we show that a single autocatalytic cycle exhibits dynamics similar to the population dynamics of a single biological species. Furthermore, the interactions between multiple autocatalytic cycles can be described in the framework of community ecology though anaologies to competitive, predator-prey, and mutualistic interactions. Finally, we show that rare stochastic perturbations can permanently alter the trajectory of a chemical ecosystem, meaning that the state of a system can be said to manifest a memory of environments past, as noted by Ulanowicz (Ulanowicz, 2009), a likely prerequisite for adaptive processes to result in divergent evolution.

2. Results

2.1. The basic model of an autocatalytic cycle

The concept of autocatalysis was introduced by Wilhelm Ostwald to describe the phenomenon that the rates of some reactions accelerate over time (Laidler, 1985; Plasson et al., 2011; Schuster, 2019). The term implies that the rates of these reactions are increased ("-catalysis") by the presence of some of the products of the reactions ("auto-"). Although autocatalysis was originally ascribed to single reactions, it has long been appreciated that a set of reactions can be viewed as autocatalytic insofar as there are some chemicals that (a) raise the rate of the reaction set, and (b) are present in the products of the reaction set. In this manuscript, we define autocatalysis based only on stoichiometry. For a chemical in a reaction system, if there exists a sequence of elementary reactions where this chemical is present in both the reactants and products but with a smaller stoichiometric coefficient on the reactant side, then we say the sequence of reactions is an autocatalytic process and the chemical is a member chemical (or briefly, a *member*) of this autocatalytic process (Fig. 1A, M). Among other chemicals, those with larger stoichiometric coefficients on the reactant side will be referred to as food (Fig. 1A, F), and those only present in the products will be referred to as waste (Fig. 1A, W).[1] Thus, autocatalytic systems consume food to produce more members (and, perhaps, waste). Under this stoichiometry-based definition of autocatalysis, any autocatalytic process will have some cyclical organization within its reaction network, because there must be at least one chemical that is present in both the reactants and products of the system as a whole.

Under the assumption, standard in chemistry, that all reactions are reversible, the reverse of an autocatalytic process consumes members and waste to produce more food. To avoid ambiguity, we define the "food" and "waste" based on the direction of autocatalysis, even though the "waste" for autocatalysis could be viewed as the "food" for reverse autocatalysis. We will use the food and waste designations in reference only to a specified autocatalytic process. Thus, we allow that the waste of one autocatalytic process could serve as the food of another autocatalytic process in the same ecosystem. To distinguish food provided at the ecosystem level from food generated within the ecosystem, we will call the former *input food*.

We need to emphasize that our definitions of autocatalysis and food chemicals are not equivalent to those of some other models, such as the theory developed for reflexively autocatalytic food-generated (RAF) sets (Hordijk, 2017; Hordijk et al., 2010). Here, we are primarily interested in the intrinsic link between autocatalysis, a chemical phenomenon, and growth, a necessary property of early life, and less concerned with whether a reaction is catalyzed and whether a reaction network can be fully generated from a given set of "food" chemicals. Nevertheless, it can be shown that RAF sets that do not depend on catalysts in the food set contain autocatalytic cycles, by our criteria, because reflexive catalysis entails a catalyzed reaction *R* generating a product that is ultimately converted into the catalyst (by reactions other than the reverse reaction of *R*), and this catalyst is not "used up" when it catalyzes *R*. This equivalence is illustrated in Fig. S1 and in Supplemental Materials, Section 1.

In this paper, we have opted to focus on autocatalytic processes that consist of one or more reversible second-order elementary reactions with a cyclical organization such that one member of the cycle is capable of doubling with each iteration. For example, we will analyze $M + F \leftrightarrow 2\,M$, but not $2\,M + F \leftrightarrow 3\,M$ or $M + F \leftrightarrow 2\,M + 2\,W$ (the latter type is, however, considered by some prior autocatalytic models (Field and Noyes, 1974; Prigogine and Lefever, 1968)). The autocatalytic processes we will consider can be represented by a cycle with one branching reaction (Fig. 1B, R_j) and one reunion member (Fig. 1B, M_1). Whereas more complicated, multi-branched cycles are possible according to our stoichiometry-based definition of autocatalysis, given the requirement for a cyclical structure we presume that they will show similar overall dynamics to the simple cases studied here. These single-branched cycles only rely on second-order elementary reactions, which are the most widely studied (Chang, 2005, pp. 325–328), and resemble some experimentally studied autocatalytic cycles (Boutlerow, 1861; Breslow, 1959; Morowitz et al., 2000; Muchowska et al., 2017; Orgel, 2000).

A single-branched cycle has two key nodes: the branching reaction, where, in the autocatalytic direction, one member is a reac-

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[1] A complication arises if there are multiple chemicals present in both the reactants and products, but with different stoichiometric asymmetries. For example, for a reversible reaction $X + 2Y \leftrightarrow 2X + Y$, which chemical is a member and which is food? According to our definitions, either X or Y can be the member chemical. If X is regarded as the member, then Y is the food, and *vice versa*. This example shows that the roles of member, food, and waste depend on specified stoichiometric asymmetry. Nevertheless, in the following analyses we have ignored this since our goal is to use simple examples to clarify general principles. Thus, we will only consider cases where the food chemicals are only present on the reactant side of an autocatalytic process.

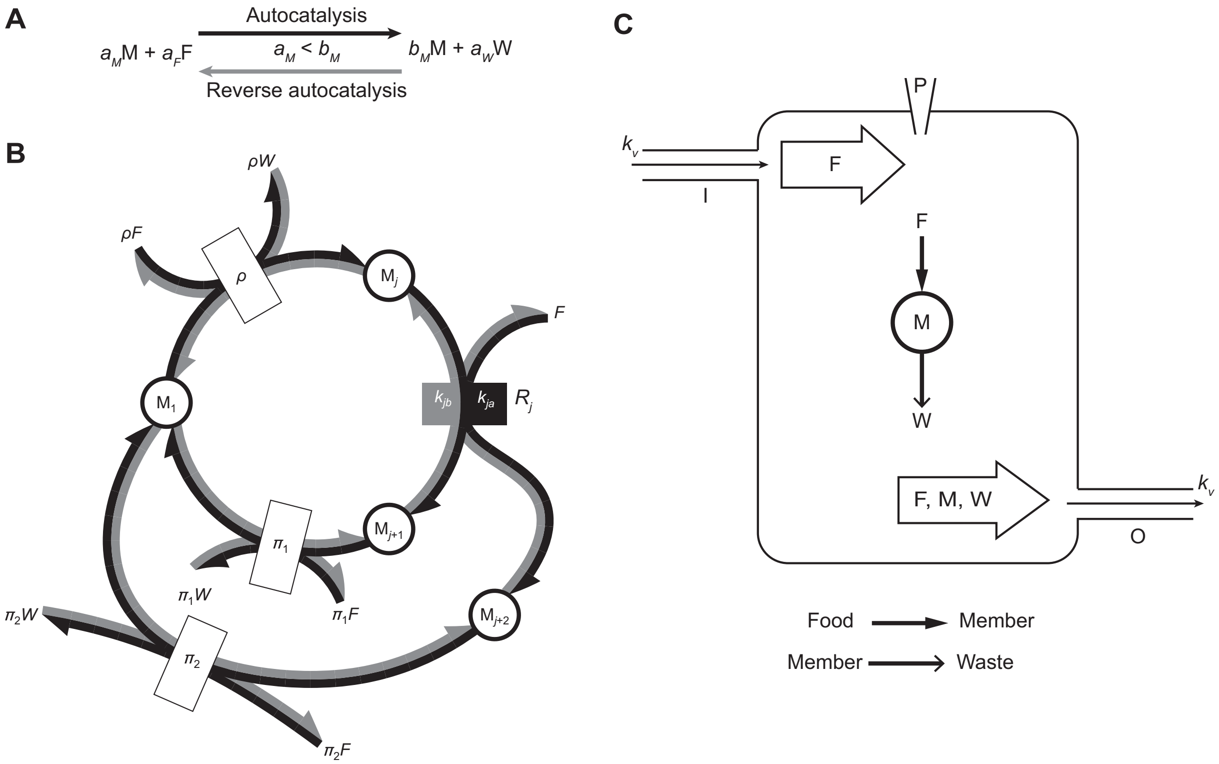


Fig. 1. Autocatalytic cycle and flow reactor. (A) Overall reaction constituting autocatalysis and reverse autocatalysis. a's and b's are stoichiometric coefficients of chemicals on the two sides of a reaction or a sequence of reactions. An autocatalytic process is characterized by at least one chemical (M) being present on both sides and its stoichiometric coefficient on the reactant side being smaller than that on the product side (i.e., $a_M < b_M$). The black arrow indicates autocatalysis; the grey arrow indicates reverse autocatalysis. **(B)** The topological structure of a simple autocatalytic cycle. Black arrows indicate the autocatalytic direction, and grey arrows indicate the reverse autocatalytic direction. Arrows accompanied by black and grey boxes represent a pair of reversible reactions, where the rate constant of a reaction indicated by arrows with a specific color is shown in the box with the same color. Arrows with an empty box (labelled ρ, π_1, or π_2) represent sequences of potential intermediate reactions. R_j is the branching reaction, where, in the autocatalytic direction, one member M_j is on the reactant side and two members M_{j+1} and M_{j+2} are on the product side. M_1 is the reunion member chemical, which is generated by both paths that split at R_j. Labels ρ, π_1, and π_2 denote the number of reactions on the three different paths: ρ for the path from M_1 to R_j, π_1 for the shorter path from R_j to M_1, and π_2 for the longer path from R_j to M_1. **(C)** Flow reactor settings. An input food solution constantly flows into the reactor through entrance I while the solution in the reactor constantly flows out through exit O. The dilution rate is k_v. Other chemicals can be added through an additional port, P, as might be needed. Inside the reactor, the set of members of an autocatalytic cycle is represented by a single circle; the triangle-headed arrow leads from food (F) to members, and the angle-headed arrow leads from members to waste (W).

tant and two members are products (Fig. 1B, R_j); and the reunion member, which is a shared product of two reaction paths (Fig. 1B, M_1). Thus, the topological structure of a simple autocatalytic cycle can be characterized by three parameters: ρ (signifying "road"), the number of reactions between the reunion member and the reactant member of the branching reaction; π_1 (signifying "path 1"), the number of reactions between a product member of the branching reaction and the reunion member along the shorter branch; and π_2 (signifying "path 2"), the number of such reactions along the longer (or equal-length) branch. Table S1 (Supplemental Materials, Section 2) shows the examples of 0-0-0, 1-0-0, 1-1-2, 2-0-0, 2-0-1, and 2-1-1 cycles. Note that the 0-0-0 cycle is a simple reversible autocatalytic reaction.

We model autocatalytic systems in a continuously stirred flow reactor (Fig. 1C). The source solution of the food is constantly added into the inflow port (I) and the solution in the reactor is constantly removed via the outflow port (O). The rates of addition, k_v, and removal are the same, meaning that k_v is the dilution rate (Fig. 1C), which is defined as the volume of the solution flowing into (or out from) the reactor per unit time divided by the volume of the solution in the reactor. To understand how such a reactor may model the prebiotic environment, we might view it as a small, well-mixed pool in a hydrothermal field receiving a constant flux of liquid from an uphill volcano and simultaneously losing a similar amount through a downhill outlet (Damer and Deame, 2015). Alternatively, we can view the reactor as a small patch of mineral at the bottom of the ocean, with chemicals held in the "reactor" by adsorption onto the mineral surface, and the "flow" representing adsorption/desorption occurring at the interface between the mineral and an ocean rich in food and poor in waste or member chemicals (Wächtershäuser, 1988).

In our models, the reactor has an additional entrance (P) for introducing additional chemicals. Such an entrance represents occasional introduction of new chemicals into the system, as might occur from rare geological events such as meteoritic impacts, long-distance import of chemicals from other chemical environments, or the occurrence of rare chemical reactions. In this paper, before adding member chemicals through entrance P, the concentration of input food in the reactor is assumed to already be the same as that of the input solution. All chemicals in these models are assumed to be soluble at all concentrations considered.

It is worth noting that although our model only considers autocatalytic processes consisting of chemical reactions, there is no reason to assume that autocatalytic cycles consist only of the breakage and formation of covalent bonds. One or more of the steps in an autocatalytic cycle can entail physical or chemical interactions that do not affect covalent bonds, such as adsorption or the formation of non-covalent supramolecular complexes (as is often involved in catalysis). Nevertheless, the mathematical treatments in this paper only apply to systems where all reactions follow rate laws, which means that some of our quantitative conclusions will not apply to all autocatalytic cycles.

2.2. The dynamics of a single autocatalytic cycle can be approximated by logistic growth model

In population ecology, the logistic growth model is widely used to describe how population size changes over time when resources are limited. The basic logistic growth model is formalized by the differential equation:

$$\frac{dN}{dt} = rN\left(\frac{K-N}{K}\right) \tag{1}$$

where N is the population size, t is time, r is the intrinsic growth rate, and K is the carrying capacity. This equation shows that N will finally become stable near K, and that the speed with which N approaches K is governed by r.

In this section, we will show that the dynamics of a single autocatalytic cycle can be approximated by the logistic model. Furthermore, we determine that there are intrinsic connections between chemical kinetic parameters such as rate constants and ecological parameters such as the intrinsic growth rate.

2.2.1. The logistic growth of the 0–0–0 cycle

First, we analyze the 0–0–0 cycle:

$$\begin{cases} \mathrm{M} + \mathrm{F} \xrightarrow{k_a} 2\mathrm{M} \\ 2\mathrm{M} \xrightarrow{k_b} \mathrm{M} + \mathrm{F} \end{cases} \tag{2}$$

where M is the sole member, F is the food, k_a and k_b are rate constants of the forward (autocatalytic) and reverse (reverse autocatalytic) reactions, respectively. When this reaction system is put in a flow reactor where the dilution rate is k_v and the concentration of food in the source solution is f, the input and output processes of the reactor are described by:

$$\begin{cases} \varnothing \xrightarrow{k_v f} \mathrm{F} \\ \mathrm{F} \xrightarrow{k_v} \varnothing \\ \mathrm{M} \xrightarrow{k_v} \varnothing \end{cases} \tag{3}$$

where Ø denotes the environment outside the reactor. It can be shown that if the initial concentration of M is much smaller than f, the dynamics of [M] (i.e., the concentration of M over time) can be approximated by the logistic model (see Supplemental Materials, Section 3):

$$\frac{d[\mathrm{M}]}{dt} = r_M[\mathrm{M}]\left(\frac{K_M - [\mathrm{M}]}{K_M}\right) \tag{4}$$

by defining:

$$\begin{cases} r_M = k_a f - k_v \\ K_M = \frac{k_a f - k_v}{k_a + k_b} \end{cases} \tag{5}$$

This implies that, provided that $k_a f$ is greater than k_v, seeding the reactor with a tiny amount of M will result in logistic growth of [M] (Fig. 2). This conclusion is not surprising and was already reported in the literature (Lloyd, 1967). Although the intrinsic growth rate and carrying capacity seem to be independent constants in the logistic equation (Eq. (1)), we can see that r_M and K_M are non-independent because they are linked directly to the underlying rate constants. Lowering the rate constant of the reverse reaction, k_b, which amounts to making the net reaction more thermodynamically favorable, raises K_M without altering r_M. In contrast, adding a catalyst, which raises both k_a and k_b without changing their ratio, increases both r_M and K_M (for details see Supplemental Materials, Sections 4 and 5).

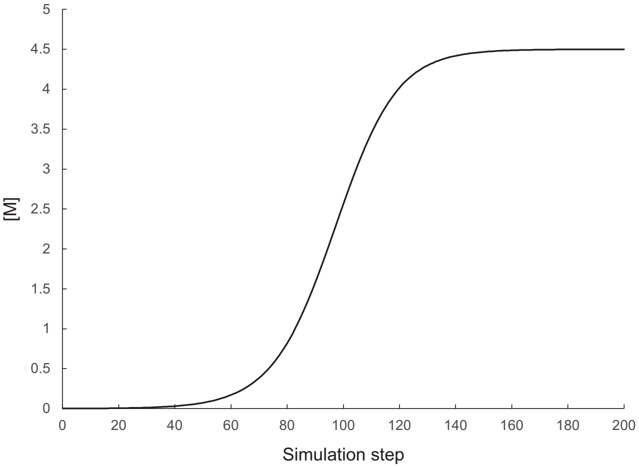


Fig. 2. The logistic growth of a 0-0-0 cycle. This logistic growth curve of a 0-0-0 cycle was generated by setting k_a = 0.01, k_b= 0.01, k_v = 0.01, f = 10, and the initial concentration of $[\mathrm{M}]_0$ = 0.001.

While increasing the dilution rate k_v can increase the amount of food flowing into the reactor per unit time, it actually decreases r_M and K_M because it also increases the loss rate of M. We can also see that maximum growth rate and carrying capacity are reached when k_v approaches zero, which corresponds to the case of a closed reactor. This shows that there is a "cost" to openness: when the rate of member production and dilution balance out, there will be more unused food in the reactor than in the case that the system had reached equilibrium without flow. However, from a chemical point of view, openness seems inevitable and necessary. This is because: (a) all systems on the planet, and even the planet itself, are open systems receiving a flux of free energies in different forms; (b) only open systems have the potential for complex, long-term dynamical changes (Wagner et al., 2019); and (c) although an autocatalytic system may achieve maximum growth and system size locally in one closed reactor, its success would not be replicable in other environments. Indeed, if the member chemicals flowing out from a reactor can later flow into new reactors, increasing k_v could be beneficial for the autocatalytic system to maximize global dispersal. Since the amount of M flowing out from a reactor per unit time is proportional to k_v[M], which can be defined as a dispersal index, it is easy to show that maximum dispersal will be achieved when $k_v/k_a = f/2$ (see Supplemental Materials, Section 6).

2.2.2. The logistic growth of the 1-0-0 cycle

Now we proceed to the 1-0-0 cycle (Fig. 3). By making the substitutions:

$$\begin{cases} S = [\mathrm{M}_1] + [\mathrm{M}_2] + [\mathrm{W}] \\ [\mathrm{M}_1] = \theta_1 S \\ [\mathrm{M}_2] = \theta_2 S \\ [\mathrm{W}] = (1 - \theta_1 - \theta_2)S \end{cases} \tag{6}$$

it can be shown that the dynamics of S can be approximated by the logistic model (see Supplemental Materials, Section 7):

$$\frac{dS}{dt} = r_S S\left(\frac{K_S - S}{K_S}\right) \tag{7}$$

by defining:

$$\begin{cases} r_S = k_{1a}\theta_1 f + k_{2a}\theta_2 f - k_v \\ K_S = \frac{k_{1a}\theta_1 f + k_{2a}\theta_2 f - k_v}{k_{1a}\theta_1 + k_{2a}\theta_2 + k_{1b}\theta_2(1-\theta_1-\theta_2) + k_{2b}\theta_1{}^2} \end{cases} \tag{8}$$

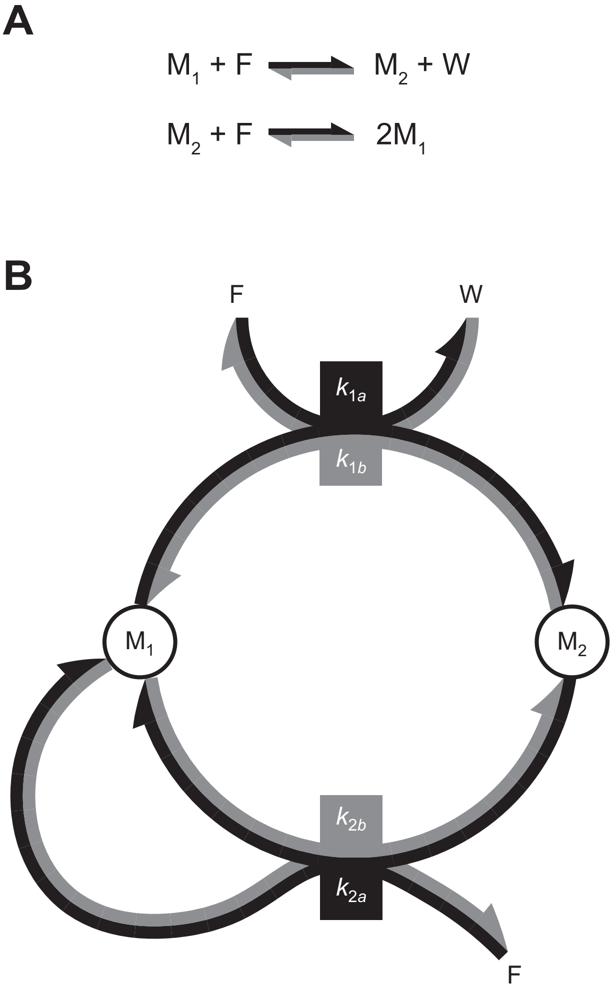


Fig. 3. The topological structure of the 1-0-0 cycle. (**A**). List of reactions. (**B**). Graphical representation. Black arrows point in the autocatalytic (forward) direction, whereas grey arrows point in the direction of reverse autocatalysis. The reaction boxes containing forward and reverse rate constants are color coded black and grey, respectively. The two forward arrows leaving the branching reaction (with the rate constant k_{2a}) indicate a stoichiometric doubling.

Because θ_1 and θ_2 are not necessarily constants, r_S and K_S may vary with θ_1 and θ_2 across different stages of the growth dynamics. This suggests that the [M_1]-to-[M_2] ratio of the initially added members may have a significant impact on the growth dynamics, at least initially. On the other hand, numerical simulations show that θ_1 and θ_2 are nearly constant after the early stage of growth (Fig. 4B), so we can approximately treat r_S, K_S, θ_1, and θ_2 as constants. Thus, according to Eqs. (6) and (7), each of the growth dynamics of [M_1], [M_2], and [W] can also be approximated by a logistic model (Fig. 4A). In addition, the fact that r_S and K_S are related to θ values shows that the growth dynamics of an autocatalytic cycle will be affected by the choice of members to seed the cycle. Indeed, numerical simulations show that the seed choice does impact the initial growth rate, but without affecting the carrying capacity (see Supplemental Materials, Section 8). The initial growth rate is the highest if the seed member is the reactant of the branching reaction, and the lowest if it is the reactant of the first reaction on the π_2 branch (Fig. S3).

Following the same logic, the growth dynamics of other autocatalytic cycles of this basic form in a flow reactor are likely to be approximated by logistic models provided that the starting concentrations of members are much smaller than the food concentration, and/or the starting ratios of the members' concentrations are close to the ratio that they will attain at steady state. This general logistic form supports a general analogy between an autocatalytic cycle and a population of organisms. To link the two together, we may imagine that the chemical cycle represents the life cycle of a single individual. For example, a 1-0-0 cycle can be seen as an egg becoming an adult and that adult producing two eggs and dying, with food needed to convert an egg into an adult and an adult into two new eggs. There are, of course, major differences between autocatalytic chemical cycles and biological organisms, most notably the reversibility of the former. You cannot feed organisms waste and see them shrink while spitting out food! We will return to biological irreversibility in the Discussion.

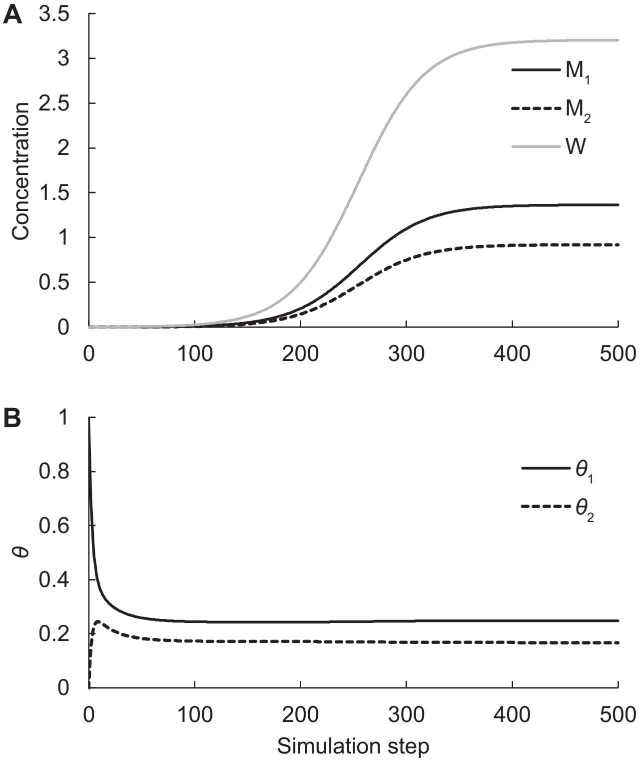


Fig. 4. Logistic growth dynamics of the 1-0-0 cycle. (A) The dynamics of waste (W) and members (M_1 and M_2). **(B)** The dynamics of θ values. θ_j is the proportion of member M_j in the total concentration of waste and all members. This simulation was run by setting reaction rate constants to 0.01, $f = 10$, $k_v = 0.01$, $[M_1]_0 = 0.001$, and $[M_2]_0 = 0$.

2.3. Numerical analyses of more complicated cycles

Although analytical treatment can generate exact descriptions of the growth dynamics, it is not always feasible to obtain such solutions, especially when the autocatalytic cycle consists of more chemicals and reactions. Thus, hereafter, we use numerical simulations to explore factors that affect the dynamics of more complicated cycles and chemical ecosystems containing more than one autocatalytic cycle. First, we use numerical analyses to examine how chemical kinetic parameters affect the growth dynamics of single autocatalytic cycles.

We considered the 2-0-0, 2-0-1, and 2-1-1 cycles (Table S1, Fig. S4-6) and ran multiple simulations with the same (symmetrical) rate constants (0.01), but different k_v and f. This allowed us to explore the relationship between the parameters determining food flux, namely the dilution rate k_v and the input food concentration f, and the parameters describing growth (the intrinsic growth rate

r_M, the carrying capacity K_M) and maximal potential dispersal (k_vK_M). We explored $k_v \in [0, 0.012]$ and $f \in [0, 4]$ (Fig. S7).

Not surprisingly, for the same combinations of f and k_v, networks with more members have lower values of r_M (Fig. S7A, D, G), K_M (Fig. S7B, E, H), and k_vK_M (Fig. S7C, F, I). This follows since a larger cycle requires more food for each iteration of the full cycle. It is also intuitive that larger cycles have a higher threshold flux rate (f / k_v) needed for the cycle to grow and sustain itself (i.e., K_M exceeding the tiny initial concentration of members). In addition, if we define the threshold of f / k_v as η, then for f / $k_v > \eta$, r_M and K_M are generally positively correlated to $(f - \eta k_v)/\sqrt{1+\eta^2}$ (see Supplemental Materials, Section 9, Fig. S8). Concerning the potential dispersal, for a given f, the maximal k_vK_M is achieved when k_v is approximately f / (2η) (Fig. S7C, F, I), which is consistent with the well-known principle that the maximum sustainable yield of a logistically growing population is achieved when the population size is half its carrying capacity.

2.4. Chemical interactions between autocatalytic cycles mimic ecological interactions between biological species

The prior sections showed that an autocatalytic cycle in a flow reactor has many similarities to a population of organisms. This suggests that if multiple autocatalytic cycles can chemically interact within a flow reactor, their dynamics might be similar to those of ecological interactions between populations. To investigate this explicitly, we examined different types of interactions between pairs of autocatalytic cycles. The scenarios examined below are only a subset of the possible interactions among autocatalytic cycles. Also, the mechanisms shown below are only a subset of all possible mechanisms underlying the examined ecological interactions; for example, we will show that recycled waste can mediate mutualisms, but mutualisms may also be mediated by reflexive catalysis.

A

Reactions	Annotation
$M + F \leftrightarrow 2M$	M cycle
$\mu + F \leftrightarrow 2\mu$	μ cycle

B

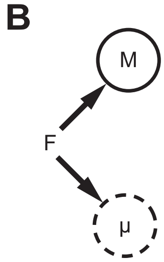
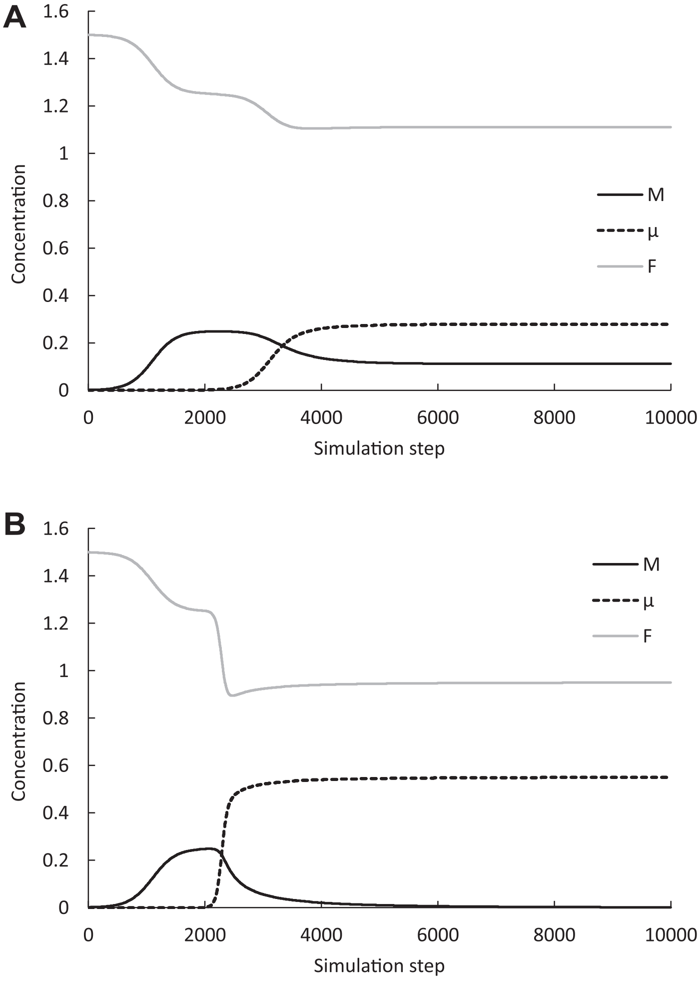


Fig. 5. A possible reaction network underlying competition of two 0-0-0 cycles. **(A)** Reactions in the network. See Figure S9 for graphical representation. **(B)** Summary diagram of the interaction between M (shown by the solid circle) and μ (shown by the dashed circle). M and μ compete for the same food F.

2.4.1. Competition

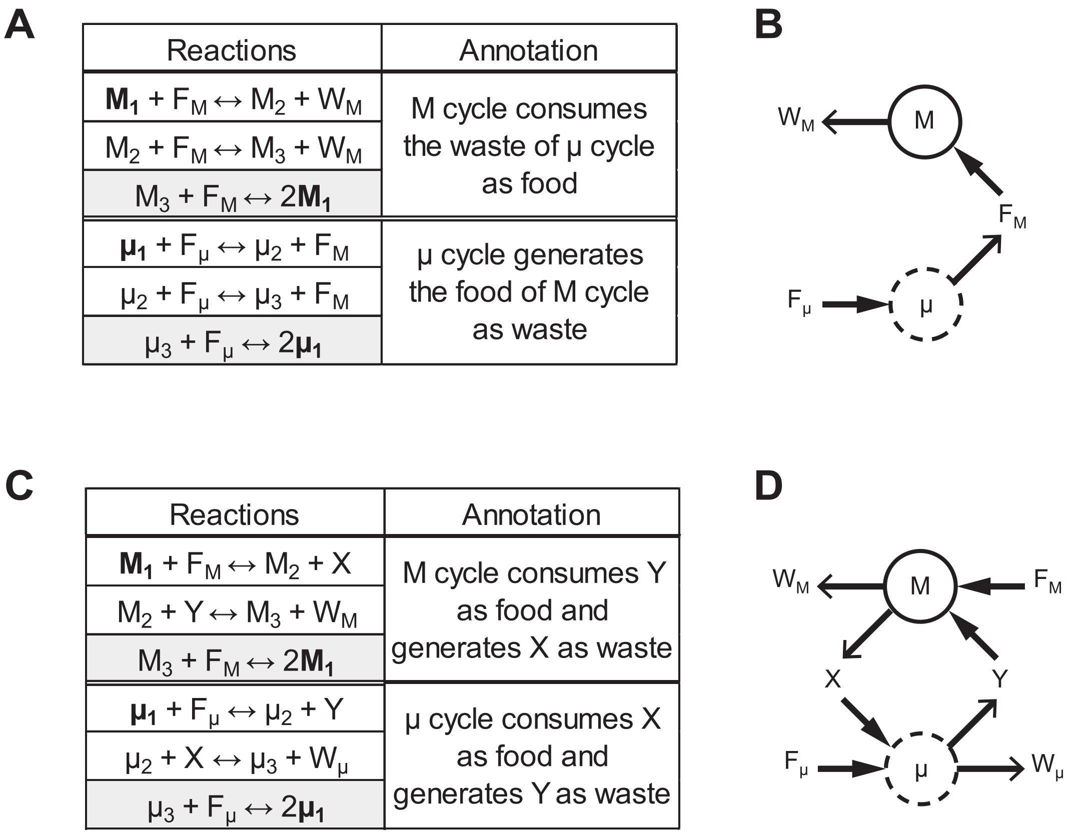
In ecology, competition arises when multiple species compete for the same resources and those resources are limited (Neill et al., 2009; Passarge et al., 2006; Sommer, 1999). For example,



k_a	0.01
k_b	0.01
k_α	0.012
k_β	0.012
k_v	0.01
f	1.5
$[M]_0$	0.001
$[\mu]_{2000}$	0.001

k_a	0.01
k_b	0.01
k_α	0.025
k_β	0.025
k_v	0.01
f	1.5
$[M]_0$	0.001
$[\mu]_{2000}$	0.001

Fig. 6. Simulations of competition. **(A)** Competitive coexistence. **(B)** Competitive exclusion. Parameters used to generate the dynamics are shown next to the dynamics. In both cases, M was seeded at the beginning and μ was seeded at the 2000th step.



A

Reactions	Annotation
$\mathbf{M_1} + F_M \leftrightarrow M_2 + W_M$	M cycle consumes the waste of μ cycle as food
$M_2 + F_M \leftrightarrow M_3 + W_M$	
$M_3 + F_M \leftrightarrow 2\mathbf{M_1}$	
$\boldsymbol{\mu_1} + F_\mu \leftrightarrow \mu_2 + F_M$	μ cycle generates the food of M cycle as waste
$\mu_2 + F_\mu \leftrightarrow \mu_3 + F_M$	
$\mu_3 + F_\mu \leftrightarrow 2\boldsymbol{\mu_1}$	

C

Reactions	Annotation
$\mathbf{M_1} + F_M \leftrightarrow M_2 + X$	M cycle consumes Y as food and generates X as waste
$M_2 + Y \leftrightarrow M_3 + W_M$	
$M_3 + F_M \leftrightarrow 2\mathbf{M_1}$	
$\boldsymbol{\mu_1} + F_\mu \leftrightarrow \mu_2 + Y$	μ cycle consumes X as food and generates Y as waste
$\mu_2 + X \leftrightarrow \mu_3 + W_\mu$	
$\mu_3 + F_\mu \leftrightarrow 2\boldsymbol{\mu_1}$	

Fig. 7. Sample reaction networks underlying mutualism. (A)(B) Facultative mutualism or unidirectionally obligate mutualism. **(C)(D)** Reciprocally obligate mutualism. **(A)(C)** List of reactions and verbal summary. See Figure S10 for graphical depictions. **(B)(D)** Summary diagrams with the M and μ cycles shown in circles. Input of food is shown with triangle-headed arrows whereas output of waste is shown with angle-headed arrows.

plants compete for sunlight and predators compete for prey. In ecology, in cases where at least one of the species is viable in a certain ecosystem, possible results of pairwise competition are: (a) competitive coexistence, where competitors exist in the same environment and (b) competitive exclusion, where one competitor survives and one goes extinct. Using two simple 0-0-0 cycles that share the same food (Fig. 5, Fig. S9), it can be shown that there are three possible steady states (see Supplemental Materials, Section 10), one corresponding to coexistence and two to exclusion, as follows.

$$\begin{cases} [\mathrm{M}] = \frac{k_a k_\beta f - k_v\left(k_\alpha + k_\beta - k_a\right)}{k_a k_\beta + k_\alpha k_b + k_b k_\beta} \\ [\mu] = \frac{k_\alpha k_b f - k_v (k_a + k_b - k_\alpha)}{k_a k_\beta + k_\alpha k_b + k_b k_\beta} \end{cases} \tag{9}$$

$$\begin{cases} [\mathrm{M}] = \frac{k_a f - k_v}{k_a + k_b} \\ [\mu] = 0 \end{cases} \tag{10}$$

$$\begin{cases} [\mathrm{M}] = 0 \\ [\mu] = \frac{k_\alpha f - k_v}{k_\alpha + k_\beta} \end{cases} \tag{11}$$

To visually present the dynamics of competition, we numerically simulated two representative scenarios (Fig. 6). For both scenarios, the M cycle is assumed to have lower rate constants than the μ cycle, making μ a better competitor. In each scenario, M was introduced at the beginning, with μ introduced later. When the rate constants are close in magnitude, competitive coexistence occurs, where μ suppresses M but M can still persist (Fig. 6A). In contrast, when the competitive ability of μ relative to M exceeds a threshold, competitive exclusion occurs, where the introduction of μ results in M declining towards zero concentration (Fig. 6B).

In the scenarios shown in Fig. 6, the ratio between the rate constants of the forward and reverse reactions is kept constant. Therefore, these results illustrate that catalyzing reactions in one autocatalytic cycle increases the competitiveness of that cycle relative to other cycles, even though catalysis accelerates both the forward and reverse reactions. This implies that cycles that happen to be able to utilize environmental chemicals (e.g., metal ions) as their catalysts, are more likely to persist than equivalent cycles that do not have such an ability. In addition, if the reaction network is more complex such that the members or waste of a cycle can be converted into the catalysts of the cycle, the network as a whole is likely to have higher competitiveness.

It is worth noting that when an ecosystem is taken over by a better competitor with higher rate constants, the efficiency with which the food flux is exploited generally increases, as seen by a significant decline in the concentration of food in the reactor (Fig. 6A,B). Although the decline in [F] is not strictly monotonic since matter stored in M may be converted back to food as μ establishes (Fig. 6A,B), the food concentration in the M-dominating phase is markedly higher than in the μ-dominating stage. This aligns with the intuition that there is a tendency for chemical ecosystems to become progressively better at exploiting food over time. However, this only follows when both cycles have similar standard Gibbs energy changes and when there is no disturbance. It is easy to imagine (and confirm by simulation) that in cases where there is frequent disturbance or forced dispersal, a rapidly growing but thermodynamically less favored autocatalytic cycle can outcompete a slower growing but thermodynamically more favored cycle.

In the case of competition between larger autocatalytic cycles, it is possible for competition to be for food, or waste, or both. This follows because the accumulation of waste can facilitate reverse autocatalysis, which means that for an autocatalytic cycle, if there are other competitor cycles generating the same waste, its growth will be suppressed. Numerical simulations (not shown) confirmed that the range of possible outcomes is the same when competition is for waste rather than food.

2.4.2. Mutualism

Since metabolic networks of living organisms consist of a large number of chemicals and reactions that appear to cooperate, "co-operation" between chemicals and reactions has long been considered as an important factor in the origin of life (Ehrenfreund et al., 2006; Herschy et al., 2014; Lanier et al., 2017; Mathis et al., 2017; Pereira et al., 2012; Vaidya et al., 2012). Before the origin of metabolic control via the encoded production of specific catalysts, cofactors, and inhibitors, mutualistic interactions among autocatalytic systems could explain the emergence of metabolic complexity (Gatti et al., 2017). Indeed, it has been shown that a replicating system of cooperating molecules can outcompete "selfish" replicators (Hordijk and Steel, 2013), suggesting that mutualistic interactions are important drivers of the complexification. In facultative mutualism, different species can survive without each other but nonetheless gain a benefit from each other's presence. For example, many insect pollinators can exploit multiple alternative food sources, and plants can utilize multiple different pollinators. In obligate mutualism, cooperating species require one another for survival or reproduction. For example, figs and fig wasps form reciprocally obligate mutualism, as figs require fig wasps to reproduce and *vice versa*. In this section, we will show how the interactions between two 2–0-0 cycles can generate the dynamics of facultative mutualism, unidirectionally obligate mutualism, and reciprocally obligate mutualism.

Facultative and obligate mutualisms can be generated between the cycles where the food of one is the waste of the other (Fig. 7, Fig. S10). In our model of facultative mutualism (Fig. 7A,B, Fig. 8A–C), when reactions are initiated just by M_1 (Fig. 8A) or μ_1 (Fig. 8B), the M cycle or μ cycle, respectively, can survive in the reactor. However, the carrying capacities of both cycles are higher when both cycles are initiated (Fig. 8C). This is because the production of F_M by the μ cycle provides additional food for the M cycle and the consumption of F_M by the M cycle helps remove waste from the μ cycle, promoting reactions in the autocatalytic direction. Therefore, the interaction between these two cycles is a facultative mutualism.

To model unidirectionally obligate mutualism, the only modification needed is to no longer add F_M through the entrance I as input food (Fig. 1C) such that $f_M = 0$. Thus, the M cycle completely relies on the F_M produced by the μ cycle, whereas the μ cycle can survive without the M cycle. In this case, if the reactions are initiated by both M_1 and μ_1, the M cycle can survive as the μ cycle produces F_M (Fig. 8D). Furthermore, the μ cycle achieves a higher carrying capacity as its waste is consumed by the M cycle (Fig. 8D). In this scenario, the presence of the μ cycle is necessary for the survival of the M cycle. However, the presence of μ is not sufficient to guarantee that M persists: f_μ could be low enough that it can support the growth of μ but results in the production of too little F_M to support the growth of M.

To increase the benefits of cooperation still further, we can consider a case where the waste of one cycle is an indispensable food (i.e., one not provided from the external sources) for

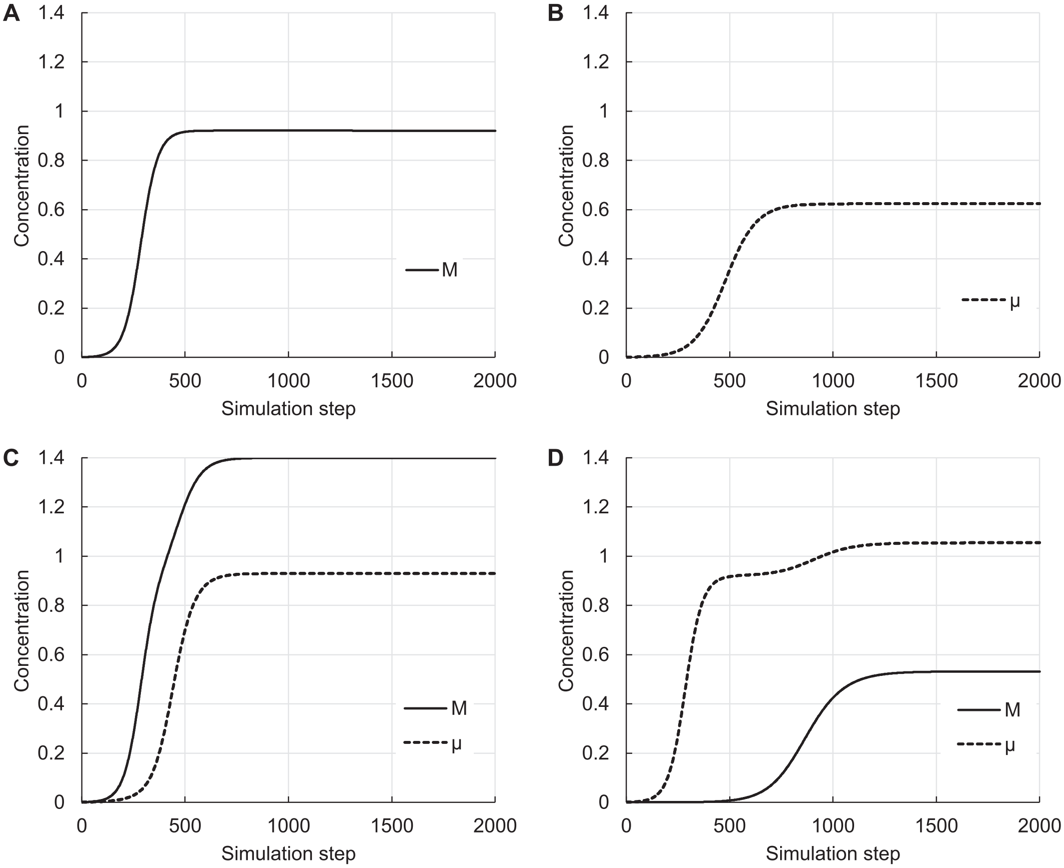


Fig. 8. Simulations of facultative and unidirectionally obligate mutualisms due to recycled waste. The vertical axis shows the total concentration of members for the M and/or μ cycles. All rate constants are 0.02, and k_v = 0.001. **(A-C)** correspond to facultative mutualism because food for both cycles is provided ($f_M = f_\mu = 5$), whereas **(D)** corresponds to unidirectionally obligate mutualism because only F_μ is provided ($f_M = 0$; $f_\mu = 5$). Simulations **A-C** differ in whether they are seeded with M only (**A:**$[M_1]_0$ = 0.001), μ only (**B:**$[\mu_1]_0$ = 0.001), or both (**C:**$[M_1]_0 = [\mu_1]_0$ = 0.001).

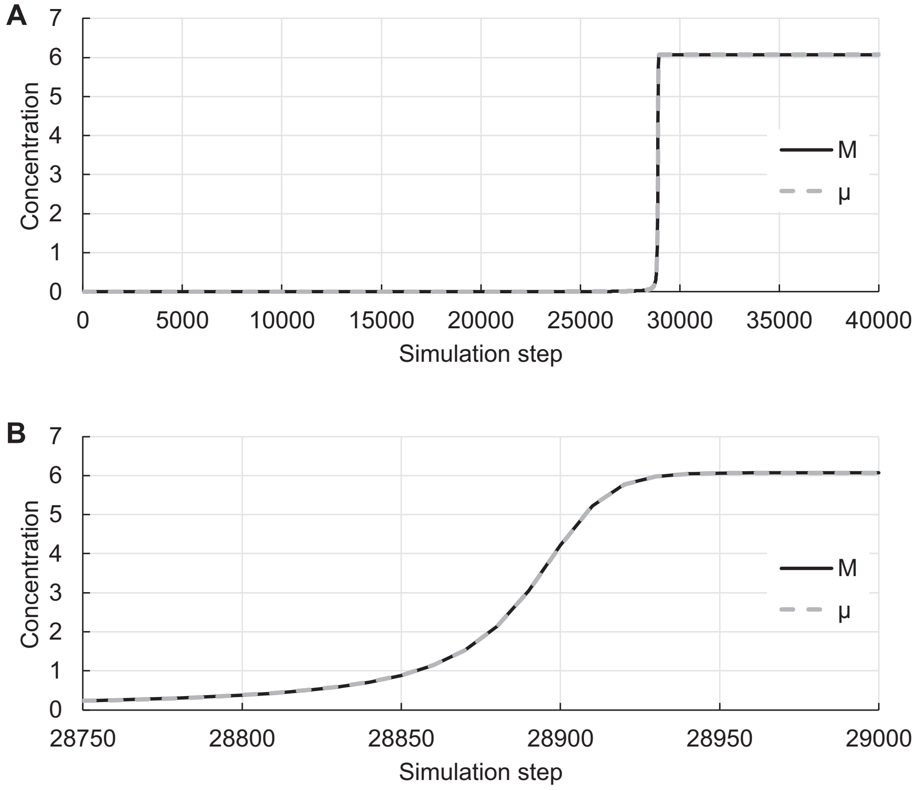


Fig. 9. Simulation of reciprocally obligate mutualism due to recycled waste. **(A)** The dynamics of the total concentration of members for the M and μ cycles. The concentration of M and μ members follow the same trajectory. **(B)** A zoomed-in view of the growth phase of the dynamics shown in **A**. The simulation was run by setting all rate constants to 0.04, $k_v = 10^{-5}$, $f_M = f_\mu = 20$, $[M_1]_0 = [\mu_1]_0 = 0.001$.

A

Reactions	Annotation
$\mathbf{M_1} + F \leftrightarrow M_2 + W_M$	M cycle is the prey
$M_2 + F \leftrightarrow M_3 + W_M$	
$M_3 + F \leftrightarrow 2\mathbf{M_1}$	
$\boldsymbol{\mu_1} + M_1 \leftrightarrow \mu_2 + W_\mu$	μ cycle is the predator
$\mu_2 + M_2 \leftrightarrow \mu_3 + W_\mu$	
$\mu_3 + M_3 \leftrightarrow 2\boldsymbol{\mu_1}$	

B

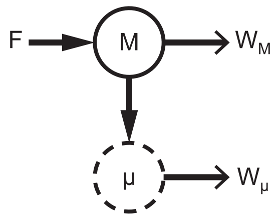


Fig. 10. Possible reaction network underlying predation. **(A)** Reactions in the network. Figure S11 provides a graphical representation. **(B)** Summary diagram of the interaction between M and μ. The μ cycle consumes the members of the M cycle as food. Input of food is shown with triangle-headed arrows whereas output of waste is shown with angle-headed arrows.

the other, and *vice versa* (Fig. 7C,D). Such a strong, reciprocally obligate mutualism ties the two cycle's fate together closely (Fig. 9). In these conditions, the growth curves (Fig. 9) differ from a typical logistic curve (e.g., Fig. 2) in that there is a long waiting time before the onset of fast simultaneous growth of [M] and [μ].

Mutualisms allow autocatalytic cycles to exploit food chemicals that they cannot directly use. Thus, in these examples, the M cycle has access to the energy stored in F_μ (Fig. 7B,D), and the μ cycle has access to the energy stored in F_M (Fig. 7D), allowing each cycle to more efficiently use energy sources and achieve higher carrying capacity in the presence of the mutualist (Figs. 8, 9). This feature of mutualism underlies the centripetality of a chemical ecosystem, which is also an important property of biological ecosystems (Ulanowicz, 1997).

2.4.3. Predation

Predation, in which predators kill and feed on prey species, is a common way for many organisms to obtain food. Pathogenesis and parasitism are similar to predation; pathogens and parasites also feed on host species but usually consume only part of the host, not killing the host immediately. Classically, the population dynamics of predator–prey systems is modelled using the Lotka-Volterra equations (Lotka, 1927, 1920; Volterra, 1927, 1926), which allow that predation may lead to diverse dynamics, including stable oscillation, damped oscillation, and establishment of a steady state without oscillation. In this section, we will show that if the members of one 2-0-0 cycle are the food of another (Fig. 10, Fig. S11), dynamics resemble the Lotka-Volterra model.

In numerical simulations, the parameters of the prey cycle, M (Fig. 10), were held constant, with equal forward and reverse rate

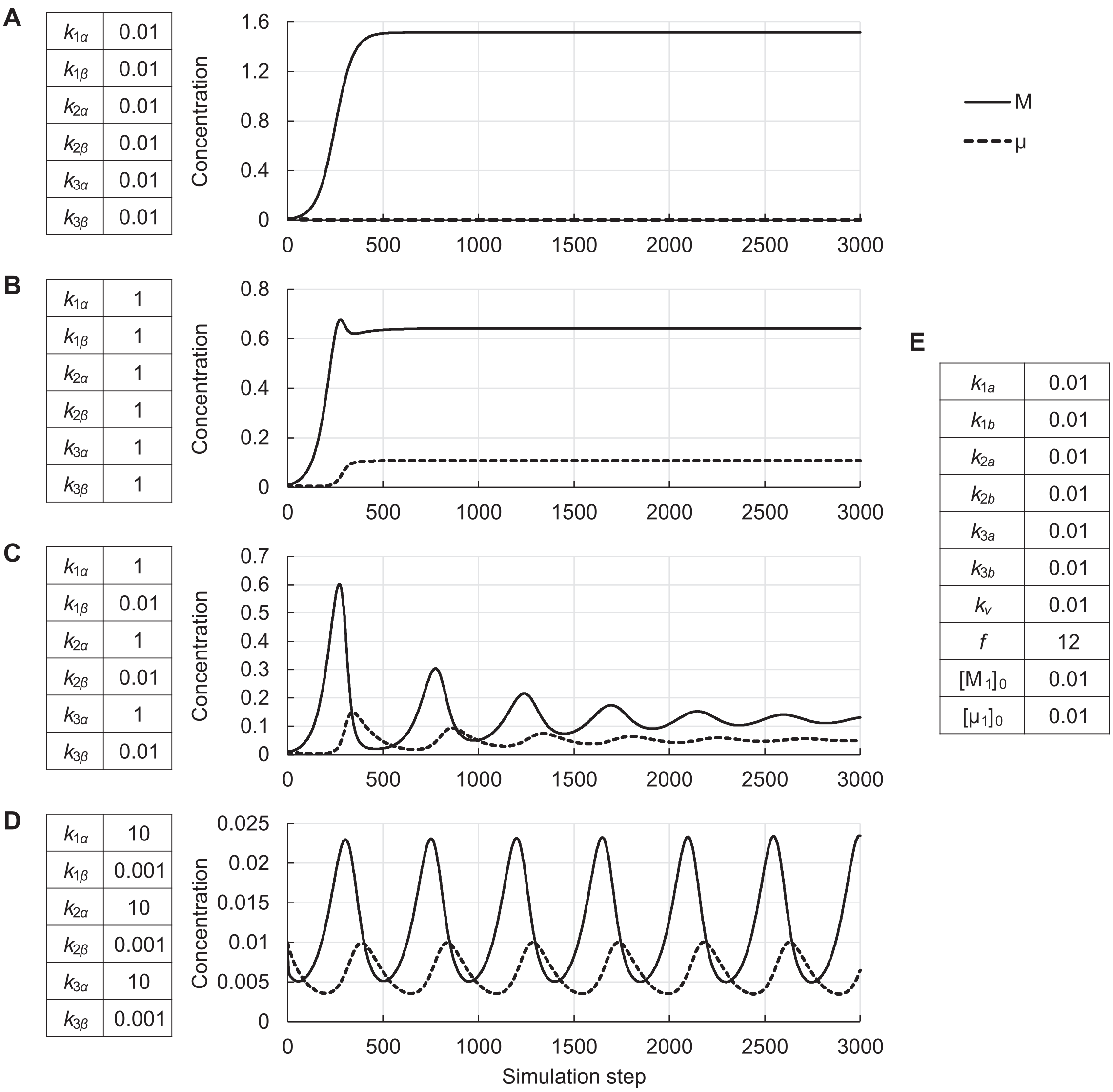


Fig. 11. Alternative outcomes of simulations of predation. The dynamics of the total concentration of members for the M and μ cycles, when the M cycle is the prey cycle and the μ cycle is the predator cycle. The parameters specific to a simulation are shown to the left of panels **A-D**, while panel **E** shows parameters shared by all simulations. **(A)** Extinction of the predator cycle. **(B)** Steady state coexistence of the prey and predator cycle. **(C)** Damped oscillation of the prey and predator cycles. **(D)** Stable oscillation of the prey and predator cycles.

constants (Fig. 11E), and we examined how the dynamics varied with different rate constants for the predator cycle, μ (Figs. 10, 11A–D). If the predator rate constants are the same as the prey rate constants, the predator cycle cannot survive in the reactor (Fig. 11A). If the predator rate constants are larger but equal in the forward (autocatalytic) and reverse directions, the predator cycle can survive in the reactor at steady state (Fig. 11B). When the predator's rate constants for autocatalysis exceeds those of reverse autocatalysis, resulting in what we might think of as a higher predation efficiency, the dynamics can display damped (Fig. 11C) or stable oscillations (Fig. 11D). However, higher predation efficiency decreases the concentrations of both the predators and prey in the reactor (Fig. 11B–D).

2.5. Ecosystem dynamics and the transition to evolution

We have shown that individual autocatalytic cycles show behavior similar to populations of individual species in an ecosystem and that pairs of cycles can exhibit interactions similar to those previously studied in ecology. How might our understanding of the origins of life, and especially the origins of adaptive evolution, be clarified by such a chemical ecosystems perspective? We will attempt to show here that the dynamical behavior of even simple ecosystems can come to resemble evolution in two ways. First, long-term dynamical patterns can be observed. Second, the order in which different potential autocatalytic cycles become actualized can be sensitive to the history of seeding, which can result in historical contingency. We will not attempt, here, to extend the model to include transitional steps towards more familiar genetics-based evolution, though we believe that this is quite feasible within a chemical ecosystem ecology framework.

In ecology, succession refers to changes in species composition within a geographical range over time (Connell and Slatyer, 1977; Morin, pp. 319–339, 2011; Prach and Walker, 2011). Although such changes are gradual, the entire process can sometimes be separated into distinct stages, each with different dominating species (Morin, 2011, pp. 319–339). Insofar as these changes are autogenic, driven by the properties of the species in the ecosystem rather than

A

Reactions	Annotation
$\mathbf{M_1} + F_M \leftrightarrow M_2 + W_M$	M cycle
$M_2 + F_M \leftrightarrow M_3 + W_M$	
$M_3 + F_M \leftrightarrow 2\mathbf{M_1}$	
$2F_\mu + W_M \leftrightarrow X$	Mutual inhibition is mediated by restricting food availability
$2F_M + W_\mu \leftrightarrow Y$	
$\boldsymbol{\mu_1} + F_\mu \leftrightarrow \mu_2 + W_\mu$	μ cycle
$\mu_2 + F_\mu \leftrightarrow \mu_3 + W_\mu$	
$\mu_3 + F_\mu \leftrightarrow 2\boldsymbol{\mu_1}$	

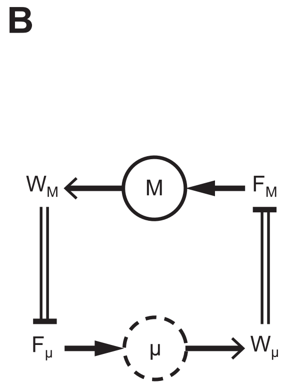


Fig. 12. A possible reaction network underlying occupancy advantage. **(A)** Reactions in the network (see Figure S12 for a graphical representation). The waste of each cycle reacts with the food of the other cycle to form a compound that cannot be directly utilized by either cycle. **(B)** Summary of the interaction. Input of food is shown with triangle-headed arrows, output of waste is shown with angle-headed arrows, and inhibitory reactions are indicated with flat-ended double lines (the double lines reflect that the ratio of the food stoichiometric coefficient to that of waste is 2:1 in this model).

changes in the external environment itself, which is commonly the case (Connell and Slatyer, 1977), the changes have an evolutionary character. The current state of an ecosystem in a particular area is a heritable phenotype because that state is self-sustained for at least a period of time due to constant regeneration of the species present. While not sufficient for adaptive evolution, the heritability of a successional stage, rather similar to the epigenetic maintenance of cell type during the development of multicellular organisms, provides the first necessary ingredient for evolution.

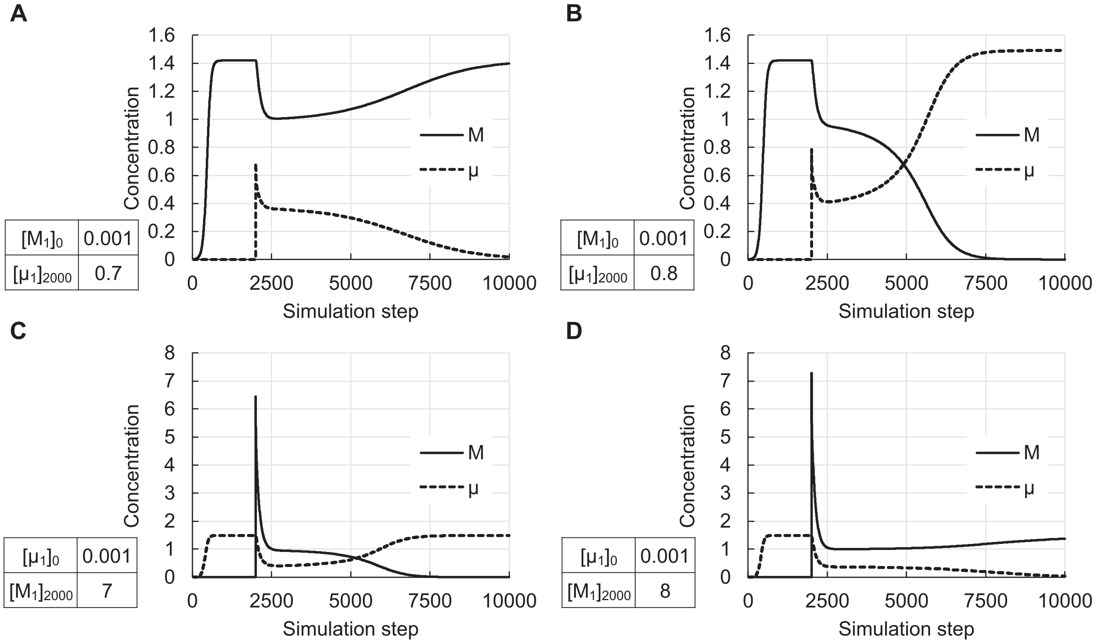
Successional dynamics have two key components: a delay in the invasion of late successional species and (perhaps) the decline and/or eventual extinction of early successional species. The former feature could involve early successional species facilitating the later establishment of late successional species. Of these potential mechanisms, we have already described some of the possible mechanisms. Trophic level climbing applies when the establishment of early successional prey can support the later establishment of a predator. Unidirectional, obligate mutualism, where an early successional cycle/species produces waste that serves as essential food for a late successional cycle/species, can also explain this pattern. Similarly, although we have not modelled it here, it should be obvious that niche amelioration can occur, in which an early successional cycle/species removes an inhibitory factor from the environment that would otherwise make the late successional cycle/species inviable. Putting these together it seems clear that networks composed of many potential autocatalytic cycles have the potential to show long-term dynamical changes.

Succession-like dynamics could result from deterministic factors, such as earlier-activated cycles facilitating later cycles and more competitive cycles tending to drive less-competitive cycles to extinction. In biological ecosystems, while the trajectory of succession is influenced by stochastic factors such as the arrival of seeds or other propagules, deterministic factors can dominate late in succession as communities converge to more predictable compositions (Måren et al., 2018). This contrasts with long-term evolutionary dynamics, which are subject to historical contingency, where chance events alter the potential for further evolution. This allows for the amplification of differences over time such that evolving lineages can diverge almost indefinitely. Could such historical contingency also come in to play in chemical ecosystems?

The obvious place to look for historical contingency is occupancy advantage, in which an established occupant of an environment has an advantage over potential invaders merely by virtue of having established first (Wright and Vetsigian, 2016). Such a "survival of the first" or "priority effect" phenomenon is important to explore because it establishes cases in which, depending on which cycles are actualized by rare seeding events first, different trajectories can be established. Or, to put it another way, an ecosystem can be said to remember prior chemical exposures, at least for a time. In this section, we will show how the mutual inhibition of two 2-0-0 cycles can result in occupancy advantage (Fig. 12, Fig. S12). The inhibition is mediated by the waste of one cycle reacting with the food of the other cycle to form a compound, X or Y, that cannot be directly utilized by either cycle.

In our simulations we assumed that each cycle has equal rate constants for forward and reverse reactions, but the μ cycle has 10% higher rate constants than the M cycle. Nonetheless, if the M cycle is the first occupant, it can still dominate the reactor and prevent establishment of the μ cycle (Fig. 13A). Only if the amount of introduced μ_1 is higher than a threshold can the μ cycle take over the reactor (Fig. 13B). In other words, the reaction network described in Fig. 12 specifies a bistable system, where the non-trivial steady states are either M-dominated or μ-dominated, and the switch between the steady states requires a large-enough trigger. The same holds when the μ cycle is the occupant and the M cycle is the invader (Fig. 13C,D), but the threshold amount of M_1 for switching the state is much higher.

In some cases, when the seeding is rare and stochastic, ecosystems can "remember" whether they were first seeded by M or μ. Suppose that a reactor starts to run without any of the members, with occasional seeding events bringing in either the M_1 or μ_1. Depending on the frequency and magnitude of the seeding events, the outcome would be different. In a case where one cycle (μ) has a higher carrying capacity and can more efficiently utilize the environment and suppress the other (Fig. 13, $K_M \approx 1.42$, $K_\mu \approx 1.49$), and the magnitude of each seeding event is below the threshold for switching the M-dominated state to the μ-dominated state, the extent of historical contingency is determined by the frequency of seeding events. If seeding events are frequent enough, the system will tend to end up μ-dominated because μ will eventually accumulate enough members to trigger the M-to-μ switch, but if



E

k_{1a}	0.01
k_{1b}	0.01
k_{2a}	0.01
k_{2b}	0.01
k_{3a}	0.01
k_{3b}	0.01
$k_{1\alpha}$	0.011
$k_{1\beta}$	0.011
$k_{2\alpha}$	0.011
$k_{2\beta}$	0.011
$k_{3\alpha}$	0.011
$k_{3\beta}$	0.011
k_{xa}	0.01
k_{xb}	0.01
k_{ya}	0.01
k_{yb}	0.01
k_v	0.01
f_M	10
f_μ	10

Fig. 13. Simulations of occupancy advantage due to mutual inhibition. **(A)(B)** The dynamics of the total concentration of members for the M and μ cycles, when the M cycle is the occupant and the μ cycle is the invader. If the amount of μ_1 introduced at the 2000th timestep is below the threshold then it cannot invade (**A**), but if it is above the threshold, it can (**B**). **(C)(D)** The dynamics of the total concentration of members for the M and μ cycles, when the μ cycle is the occupant and the M cycle is the invader. In this case the concentration of M_1 needed to supersede the μ cycle (**C**, **D**) is about ten times higher than that of μ_1 to supersede the M cycle (**A**, **B**). **(E)** Parameters shared by all simulations (variable parameters provided in panels **A-D**).

seeding is very rare, the system will converge to whichever state was triggered by the first seeding event (Fig. S13).[2] This shows that the ability of a system to capture information about history (which seeding event happened first) depends on the system's dynamics.

3. Discussion

3.1. An ecological perspective clarifies the expected dynamics of autocatalytic chemical systems

It has long been appreciated that there are parallels between chemical reaction systems and ecology (Lloyd, 1967). Flux balance analysis, a method designed for studying metabolic pathways (Khandelwal et al., 2013), and the RAF theory (Gatti et al., 2017) have both been applied to ecological communities. Here we have explored these parallels in more detail, focusing on one particular chemical motif, the autocatalytic cycle.

We show that simple autocatalytic cycles exhibit logistic growth in a flow reactor when the reactor is seeded with a small quantity of a member and the ratio of the food concentration to the dilution rate is above a threshold. In such cases, the growth rate and carrying capacity can be connected back to flow parameters and reaction kinetics. This result demonstrates that individual autocatalytic cycles have conceptual equivalence to populations of individual species and implies that chemical reaction networks composed of multiple autocatalytic cycles that are actualized in a specific environment can be equated with a chemical ecosystem.

Diverse interactions among autocatalytic cycles, combined with the potential for rare seeding of previously inactive cycles, allow chemical ecosystem to show complex, long-term dynamics. Among other patterns, it is possible for a chemical ecosystem to transition between a series of transiently steady states, each characterized by a different set of active and viable cycles (together with their peripheral reactions). We would argue that this phenomenon, which is driven by both stochastic and deterministic forces, can validly be equated with ecological succession and exhibits some evolutionary features.

Using a series of numerical simulations, we have demonstrated that autocatalytic cycles can negatively affect one another, via predation on member chemicals, production of cross-inhibitors, or competition for food or waste. Likewise, autocatalytic cycles can form reciprocal mutualisms, for example by cross-feeding or removal of waste. Indeed, sets of cooperating autocatalytic cycles can be seen to show autocatalysis at a higher hierarchical level in much the same way that biological ecosystems can show autocatalysis among multiple individual species (Gatti et al., 2017; Ulanowicz, 1997). Consequently, our results suggest the possibility of using ecological theory to help model and understand the behavior of complex chemical reaction networks, such as those seen in cellular metabolism. If a network includes multiple discrete autocatalytic cycles whose pairwise positive and negative interactions can be quantified, it may be possible to predict ecosystem behavior using approaches from ecosystem ecology, where each autocatalytic cycle is treated as a species. For example, one can use ecosystem matrix methods (Delmas et al., 2019; Ulanowicz, 2004) at a coarse-grained level and apply concepts such as trophic levels, food webs, and guilds. This might be a useful approach for studying chemical reaction networks in cases where the rate constants of individual reactions are largely unknown.

A complication that would likely arise in a coarse-graining procedure is the existence of more complex architectures than the simple, single-branched autocatalytic cycles that we investigated in this paper. Autocatalytic cycles can overlap (Fig. S1), for example, when there are multiple alternative branching reactions, reunion members, and reaction paths. In much the same way that it can be unclear whether to treat obligate mutualists, such as an endosymbiont and its host, as one composite species or two, it

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[2] When the magnitude of seeding events is larger, the resulting dynamics will be less affected by the frequency of seeding events. If the magnitude is between the threshold for the M−to-μ switch and that of the μ-to-M switch, the system tends to end up μ-dominated because the μ cycle can always invade the M−dominated state but not *vice versa*. If the magnitude is higher than the threshold for the μ-to-M switch, the system tends to keep switching between the M−dominated and μ-dominated states because the μ cycle can always invade the M−dominated state and *vice versa*.

can also be ambiguous whether mutualistic cycles ought to be treated as a set of cooperating cycles or as a single, larger autocatalytic cycle. Further work is needed to understand the diversity of autocatalytic motifs in real chemical reaction systems and to evaluate the extent of applicability of ecological methods.

The development of models of network autocatalysis is not only of theoretical importance but is needed to guide the development of experimental strategies for detecting autocatalysis (Baum and Vetsigian, 2017; Semenov et al., 2016; Vincent et al., 2019). A characteristic of all the ACs studied here is periods during which chemical concentrations show exponential growth or decline. However, further work with more complex networks is needed to understand whether this feature can serve as a failsafe indicator of autocatalytic processes.

3.2. During the origin of life, chemical ecosystems evolved adaptively before the emergence of polymer-based digital genetics

A key challenge in origin-of-life research is that most evolutionary models require genetic polymers, but such chemicals are energetically expensive, unlikely to form by chance, and seem to require the simultaneous existence of metabolic systems for the continuous formation of their constituent monomers. An emerging view is that heritability in early life was encoded by chemical concentrations, or analog inheritance, with a later transition to sequence-based encoding in linear polymers, or digital inheritance (Walker and Davies, 2013). The framework developed here confirms prior work supporting the plausibility of analog inheritance and adaptive evolution before digital genetic encoding (Goldford and Segrè, 2018; Hordijk, 2016; Hordijk et al., 2012; Hordijk and Steel, 2014; Liu and Sumpter, 2018; Vasas et al., 2012, 2010).

Our model focuses on simple autocatalytic cycles, which are numerous in extant metabolism (Sousa et al., 2015; Xavier et al., 2020), known in experimental organic chemistry (Boutlerow, 1861; Breslow, 1959), common in random chemical networks (Liu and Sumpter, 2018; Virgo and Ikegami, 2013), and, thus, likely to have been seeded spontaneously in chemically diverse environments like the early Earth. Unlike some previous frameworks, we model these cycles using rate laws and standard, reversible chemical reactions. Our model confirms that an autocatalytic cycle consisting of reversible reactions can be triggered by import or local production of one of its members, a seed, and then show logistic growth of member and waste chemicals, and a corresponding decline in food chemical, bringing the ecosystem as a whole to a new transiently steady state. At this quasi-steady state, the ecosystem can be said to manifest heritability in that the flux out of a reactor, which can be thought of as the ecosystem's offspring, have the same concentrations of member chemicals as the reactor itself and would be expected, therefore, to convert downstream reactors to a similar state.

In addition to the deterministic forces which cause chemical ecosystems to manifest heritability, stochastic phenomena have the potential to alter a reactor's trajectory. Seeding of a new autocatalytic cycle, which might establish a new transient steady state (Kreyssig et al., 2012), can be triggered by even a single molecule of a member chemical, which means that the activation of a new cycle might be rare and highly unpredictable. In this regard, as noted by Vasas et al. (Vasas et al., 2012), the seeding of new autocatalytic cycles resembles mutation. Moreover, some of these chemical mutations can irreversibly change future dynamics. For example, our model of occupancy advantage shows that whichever of two mutually inhibitory cycles is seeded first can suppress the other cycle indefinitely (if seeds are small enough and rare enough). This is significant because, depending on which cycle is established, alternative future paths could become more or less discoverable, resulting in a tendency for alternative ecosystems to diverge over time by constantly opening new "adjacent possibles" (Kauffman, 2014).

This conceptual framework suggests that chemical ecosystems receiving an ongoing flux of potential input food would be expected to show dynamics that are basically identical to evolution despite lacking any digitally encoded genetic information. A chemical ecosystem would presumably spend most time at quasi-steady states, where deterministic forces tend to keep all the activated autocatalytic cycles at carrying capacity. However, over longer periods, systems will tend to explore the local chemical space due to stochastic fluctuations and seeding events, resulting, occasionally, in a transition to a new quasi-steady state. These may include the addition of new autocatalytic cycles that are able to coexist with the old cycles, for example through mutualistic or competitive or predatory coexistence. Alternatively, new cycles can snuff out preexisting cycles, for example through competitive or predatory exclusion, or inhibition.

In an actual spatial environment, rather than the idealized well-mixed reactors modelled here, we believe that long-term ecosystem dynamics deserve to be viewed through the lens of evolution. If there were multiple spatial locations housing loosely connected reactor-analogs, for example a network of pores in a rock matrix or a cluster of mineral grains to which member chemicals are adsorbed, then different ecosystems could readily compete for invasion of new space. While much more work and spatially explicit models are needed, our simple simulations here suggest some of the factors that might shape such adaptive evolution.

Although we were able to show that a sufficient flux of food can drive a system out of equilibrium regardless of the standard Gibbs energy change of the chemical reactions, we also observed that autocatalytic systems that are thermodynamically favored, having higher rate constants in the autocatalytic direction, tend to grow faster and achieve higher carrying capacity, resulting in a competitive advantage. This implies that, if competing cycles were seeded over time, and those cycles could exploit different food and/or generate different waste chemicals, the cycles that persist will tend to be those that are most thermodynamically favored, using food that is further from thermodynamic equilibrium and producing lower-energy waste. We would go so far as to speculate that the irreversibility of modern life is not an indication that the life state *requires* truly irreversible chemistry but that there has been a persistent tendency for less and less reversible cycles to have become enriched in metabolic systems over the eons due to adaptive evolution.

We also show that, regardless of thermodynamics, autocatalytic cycles with overall higher rate constants are favored. Since catalysts, by definition, raise reaction rate constants, this implies that catalyzed cycles will also tend to predominate. Catalysts may be obtained directly from the environment (i.e., environmental catalysts, such as metal ions) or derived from members or waste of autocatalytic cycles. Our framework suggests that, all things being equal, an autocatalytic cycle that is catalyzed will outcompete one that is not, implying that selection will favor cycles that are better able to synthesize and utilize catalysts. This insight may shed some light on how and why digital genetic encoding evolved in chemical ecosystems on the path to life.

The precursors of both amino acids and nucleobases can be derived from members of the reductive citric acid cycle (Morowitz et al., 2000), an autocatalytic cycle whose reactions can, to some degree, proceed with transition metal catalysts rather than the enzymes used in modern life (Muchowska et al., 2017). Generally, we would expect polymers to behave like predators or parasites of monomer-producing cycle(s) since they would siphon off member chemicals and reduce growth. However, if some polymers provided a benefit to the monomer-producing cycle through catalysis, the polymers and the monomer-producing cycle could both increase in abundance, making them collectively more competitive and more extinction-resistant. It is even possible to imagine that selection would favor ecosystems producing a second kind of polymer that aided the ecosystem by promoting the production of catalytic sequences of the first polymer type, for example by promoting template-guided synthesis. Thus, while much more work is needed, there are reasons to suspect that adaptive evolution could begin in analog chemical ecosystems and gradually transition to a polymer-based digital genetic system such as that seen in cellular life.

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CRediT authorship contribution statement

Zhen Peng: Conceptualization, Methodology, Software, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Alex M. Plum:** Methodology, Software, Visualization, Writing - review & editing. **Praful Gagrani:** Methodology, Writing - review & editing. **David A. Baum:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Materials and methods

Simulation algorithm

For a chemical κ, its concentration in the reactor is $[\kappa]$. The instantaneous change in $[\kappa]$ may be due to three processes: addition, dilution, and reaction.

If κ is added constantly through the entrance I (Fig. 1C), we have

$$\left.\frac{\mathrm{d}[\kappa]}{\mathrm{d}t}\right|_{\mathrm{addition,I}} = k_v f_\kappa \tag{12}$$

where k_v is the dilution rate and f_κ is the concentration of κ in the source solution.

If κ is added through the port P (Fig. 1C) at time t', we have

$$\left.\frac{\mathrm{d}[\kappa]}{\mathrm{d}t}\right|_{\mathrm{addition,P};t=t'} = I_{\kappa;t=t'} \tag{13}$$

where $I_{\kappa;t=t'}$ is the instantaneous growth rate of $[\kappa]$ only due to the addition of κ through the entrance P at t'.

As κ is constantly diluted and removed from the reactor through the exit O (Fig. 1C), we have

$$\left.\frac{\mathrm{d}[\kappa]}{\mathrm{d}t}\right|_{\mathrm{dilution};t=t'} = -k_v[\kappa]_{t=t'} \tag{14}$$

Also, κ is constantly produced and consumed by chemical reactions. For a reversible reaction R_j consisting of the forward reaction R_{ja} and the reverse reaction R_{jb}, we have

$$\left.\frac{\mathrm{d}[\kappa]}{\mathrm{d}t}\right|_{R_j;t=t'} = v_{ja;t=t'}\left(-\omega_{ja,\kappa}+\omega_{jb,\kappa}\right) + v_{jb;t=t'}\left(-\omega_{jb,\kappa}+\omega_{ja,\kappa}\right) \tag{15}$$

where v_{ja} and v_{jb} are respectively the reaction rates of R_{ja} and R_{jb} calculated according to rate laws, $\omega_{ja,\kappa}$ and $\omega_{jb,\kappa}$ are respectively the stoichiometric coefficients of κ on the reactant and product sides of R_{ja}. Specifically, if κ is only on the reactant side of R_{ja}, then $\omega_{jb,\kappa} = 0$; if κ is only on the product side of R_{ja}, then $\omega_{ja,\kappa} = 0$; if κ is not involved in R_{ja}, then $\omega_{ja,\kappa} = \omega_{jb,\kappa} = 0$.

Thus, for the flow reactor where there are Z possible reversible reactions, the instantaneous change rate in $[\kappa]$ at t' is given by

$$\left.\frac{\mathrm{d}[\kappa]}{\mathrm{d}t}\right|_{t=t'} = \left.\frac{\mathrm{d}[\kappa]}{\mathrm{d}t}\right|_{\mathrm{addition,I}} + \left.\frac{\mathrm{d}[\kappa]}{\mathrm{d}t}\right|_{\mathrm{addition,P};t=t'} + \left.\frac{\mathrm{d}[\kappa]}{\mathrm{d}t}\right|_{\mathrm{dilution};t=t'} + \sum_{j=1}^{Z}\left.\frac{\mathrm{d}[\kappa]}{\mathrm{d}t}\right|_{R_j;t=t'} \tag{16}$$

Equation (16) needs to be applied to every chemical involved in at least one of the Z reversible reactions.

To run numerical simulations, the instantaneous change in $[\kappa]$ from t_i to t_{i+1} is approximated by

$$\Delta[\kappa]_{t_i\to t_{i+1}} = \Delta t\cdot\left.\frac{\mathrm{d}[\kappa]}{\mathrm{d}t}\right|_{t=t_i} \tag{17}$$

where the time step size $\Delta t = t_{i+1} - t_i$. For simplification, in all the simulations reported in this paper, $\Delta t = 1$.

The simplification that $\Delta t = 1$ would cause errors when $\mathrm{d}[\kappa]/\mathrm{d}t$ is too large. When such an error was detected, we decreased the rate constants and dilution rates proportionally to circumvent the error.

The Python code that we used to perform the simulations is in Supplemental Materials.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtbi.2020.110451.

References

Baum, D.A., 2018. The origin and early evolution of life in chemical complexity space. Journal of Theoretical Biology 456, 295–304. https://doi.org/10.1016/j.jtbi.2018.08.016.

Baum, D.A., Vetsigian, K., 2017. An experimental framework for generating evolvable chemical systems in the laboratory. Orig. Life Evol. Biosph. 47 (4), 481–497.

Boutlerow, A.M., 1861. Formation synthétique d'une substance sucrée. Compt. Rend. Sean. l'a Acad. Sci. 53, 145–147.

Breslow, R., 1959. On the mechanism of the formose reaction. Tetrahedron Lett. 1 (21), 22–26.

Chang, R., 2005. Physical Chemistry for the Biosciences. University Science Books.

Connell, J.H., Slatyer, R.O., 1977. Mechanisms of succession in natural communities and their role in community stability and organization. Am. Nat. 111 (982), 1119–1144.

Damer, B., Deamer, D., 2015. Coupled Phases and Combinatorial Selection in Fluctuating Hydrothermal Pools: A Scenario to Guide Experimental Approaches to the Origin of Cellular Life. Life 5, 872–887. https://doi.org/10.3390/life5010872.

Delmas, E., Besson, M., Brice, M.-H., Burkle, L.A., Dalla Riva, G.V., Fortin, M.-J., Gravel, D., Guimarães Jr., P.R., Hembry, D.H., Newman, E.A., Olesen, J.M., Pires, M.M., Yeakel, Poisot, T., . Analysing ecological networks of species interactions: analyzing ecological networks. Biol. Rev. 94 (1), 16–36.

Ehrenfreund, P., Rasmussen, S., Cleaves, J., Chen, L., 2006. Experimentally tracing the key steps in the origin of life: the aromatic world. Astrobiology 6 (3), 490–520.

Field, R.J., Noyes, R.M., 1974. Oscillations in chemical systems. IV. Limit cycle behavior in a model of a real chemical reaction. J. Chem. Phys. 60 (5), 1877–1884.

Fiscus, D.A., 2002. The Ecosystemic Life Hypothesis III: The Hypothesis and Its Implications. Bull. Ecol. Soc. Am. 83, 146–149.

Gatti, R.C., Hordijk, W., Kauffman, S., 2017. Biodiversity is autocatalytic. Ecol. Model. 346, 70–76. https://doi.org/10.1016/j.ecolmodel.2016.12.003.

Goldford, J.E., Segrè, D., 2018. Modern views of ancient metabolic networks. Curr. Opin. Syst. Biol. 8, 117–124. https://doi.org/10.1016/j.coisb.2018.01.004.

Herschy, B., Whicher, A., Camprubi, E., Watson, C., Dartnell, L., Ward, J., Evans, J.R.G., Lane, N., 2014. An origin-of-life reactor to simulate alkaline hydrothermal vents. J. Mol. Evol. 79 (5-6), 213–227. https://doi.org/10.1007/s00239-014-9658-4.

Hordijk, W., 2017. Autocatalytic confusion clarified. J. Theor. Biol. 435, 22–28. https://doi.org/10.1016/j.jtbi.2017.09.003.

Hordijk, W., 2016. Evolution of autocatalytic sets in computational models of chemical reaction networks. Orig. Life Evol. Biosph. 46 (2-3), 233–245. https://doi.org/10.1007/s11084-015-9471-0.

Hordijk, W., Hein, J., Steel, M., 2010. Autocatalytic sets and the origin of life. Entropy 12, 1733–1742. https://doi.org/10.3390/e12071733.

Hordijk, W., Steel, M., 2016. Autocatalytic sets in polymer networks with variable catalysis distributions. J. Math. Chem. 54 (10), 1997–2021. https://doi.org/10.1007/s10910-016-0666-z.

Hordijk, W., Steel, M., 2014. Conditions for evolvability of autocatalytic sets: a formal example and analysis. Orig. Life Evol. Biosph. 44 (2), 111–124. https://doi.org/10.1007/s11084-014-9374-5.

Hordijk, W., Steel, M., 2013. A formal model of autocatalytic sets emerging in an RNA replicator system. J. Syst. Chem. 4 (1). https://doi.org/10.1186/1759-2208-4-3.

Hordijk, W., Steel, M., 2004. Detecting autocatalytic, self-sustaining sets in chemical reaction systems. J. Theor. Biol. 227 (4), 451–461.

Hordijk, W., Steel, M., Kauffman, S., 2012. The structure of autocatalytic sets: evolvability, enablement, and emergence. Acta Biotheor. 60 (4), 379–392.

Hunding, A., Kepes, F., Lancet, D., Minsky, A., Norris, V., Raine, D., Sriram, K., Root-Bernstein, R., 2006. Compositional complementarity and prebiotic ecology in the origin of life. BioEssays 28 (4), 399–412.

Joyce, G.F., 1994. Foreword. In: Deamer, D.W., Fleischaker, G.R. (Eds.), Origins of Life: The Central Concepts. Jones and Bartlett Publishers.

Kauffman, S.A., 2014. Prolegomenon to patterns in evolution. Biosystems 123, 3–8. https://doi.org/10.1016/j.biosystems.2014.03.004.

Kauffman, S.A., 1993. The Origins of Order: Self-Organization and Selection in Evolution. Oxford University Press.

Kauffman, S.A., 1986. Autocatalytic sets of proteins. J. Theor. Biol. 119 (1), 1–24. https://doi.org/10.1016/S0022-5193(86)80047-9.

Khandelwal, R.A., Olivier, B.G., Röling, W.F.M., Teusink, B., Bruggeman, F.J., 2013. Community flux balance analysis for microbial consortia at balanced growth. PLOS ONE 8, e64567. https://doi.org/10.1371/journal.pone.0064567.

Kreyssig, P., Escuela, G., Reynaert, B., Veloz, T., Ibrahim, B., Dittrich, P., 2012. Cycles and the Qualitative Evolution of Chemical Systems. PLoS ONE 7 (10), e45772. https://doi.org/10.1371/journal.pone.0045772.

Laidler, K.J., 1985. Chemical kinetics and the origins of physical chemistry. Arch. Rational Mech. 32 (1), 43–75.

Lanier, K.A., Petrov, A.S., Williams, L.D., 2017. The central symbiosis of molecular biology: molecules in mutualism. J. Mol. Evol. 85 (1-2), 8–13.

Lee, D.H., Severin, K., Ghadiri, M.R., 1997. Autocatalytic networks: the transition from molecular self-replication to molecular ecosystems. Curr. Opin. Chem. Biol. 1 (4), 491–496.

Liu, Y.u., Sumpter, D.J.T., 2018. Mathematical modeling reveals spontaneous emergence of self-replication in chemical reaction systems. J. Biol. Chem. 293 (49), 18854–18863.

Lloyd, P.J., 1967. American, German and British antecedents to pearl and Reed's Logistic Curve. Population Studies 21 (2), 99. https://doi.org/10.2307/2172714.

Lotka, A.J., 1927. Fluctuations in the Abundance of a Species considered Mathematically. Nature 119, 12–12. https://doi.org/10.1038/119012a0.

Lotka, A.J., 1920. Analytical note on certain rhythmic relations in organic systems. PNAS 6 (7), 410–415.

Luisi, P.L., 1998. About various definitions of life. Orig. Life Evol. Biosph. 28, 613–622. https://doi.org/10.1023/A:1006517315105.

Måren, I.E., Kapfer, J., Aarrestad, P.A., Grytnes, J.-A., Vandvik, V., 2018. Changing contributions of stochastic and deterministic processes in community assembly over a successional gradient. Ecology 99 (1), 148–157.

Mathis, C., Ramprasad, S.N., Walker, S.I., Lehman, N., 2017. Prebiotic RNA network formation: a taxonomy of molecular cooperation. Life 7, 38. https://doi.org/10.3390/life7040038.

Morin, P.J., 2011. Community Ecology. John Wiley & Sons.

Morowitz, H.J., Kostelnik, J.D., Yang, J., Cody, G.D., 2000. The origin of intermediary metabolism. Proc. Natl. Acad. Sci. 97 (14), 7704–7708.

Muchowska, K.B., Varma, S.J., Chevallot-Beroux, E., Lethuillier-Karl, L., Li, G., Moran, J., 2017. Metals promote sequences of the reverse Krebs cycle. Nat. Ecol. Evol. 1 (11), 1716–1721. https://doi.org/10.1038/s41559-017-0311-7.

Neill, C., Daufresne, T., Jones, C.G., 2009. A competitive coexistence principle? Oikos 118 (10), 1570–1578.

Odum, H.T., 1971. Environment, Power, and Society. Wiley-Interscience, New York, NY.

Orgel, L.E., 2000. Self-organizing biochemical cycles. Proc. Natl. Acad. Sci. 97 (23), 12503–12507.

Passarge, J., Hol, S., Escher, M., Huisman, J., 2006. Competition for nutrients and light: stable coexistence, alternative stable states, or competitive exclusion? Ecol. Monogr. 76 (1), 57–72.

Pereira, L., Rodrigues, T., Carrapiço, F., 2012. A symbiogenic way in the origin of life. In: Seckbach, J. (Ed.), Genesis – In The Beginning: Precursors of Life, Chemical Models and Early Biological Evolution, Cellular Origin, Life in Extreme Habitats and Astrobiology. Springer, Netherlands, Dordrecht, pp. 723–742. https://doi.org/10.1007/978-94-007-2941-4_36.

Plasson, R., Brandenburg, A., Jullien, L., Bersini, H., 2011. Autocatalysis: at the root of self-replication. Artif. Life 17 (3), 219–236. https://doi.org/10.1162/artl_a_00033.

Prach, K., Walker, L.R., 2011. Four opportunities for studies of ecological succession. Trends Ecol. Evol. 26 (3), 119–123. https://doi.org/10.1016/j.tree.2010.12.007.

Prigogine, I., Lefever, R., 1968. Symmetry breaking instabilities in dissipative Systems. II. J. Chem. Phys. 48 (4), 1695–1700. https://doi.org/10.1063/1.1668896.

Ruiz-Mirazo, K., Briones, C., de la Escosura, A., 2014. Prebiotic systems chemistry: new perspectives for the origins of life. Chem. Rev. 114 (1), 285–366. https://doi.org/10.1021/cr2004844.

Schuster, P., 2019. What is special about autocatalysis?. Monatsh. Chem. 150 (5), 763–775. https://doi.org/10.1007/s00706-019-02437-z.

Segré, D., Lancet, D., Kedem, O., Pilpel, Y., 1998. Graded autocatalysis replication domain (gard): kinetic analysis of self-replication in mutually catalytic sets. Orig Life Evol. Biosph., 28, 501–514. https://doi.org/10.1023/A:1006583712886.

Semenov, S.N., Kraft, L.J., Ainla, A., Zhao, M., Baghbanzadeh, M., Campbell, V.E., Kang, K., Fox, J.M., Whitesides, G.M., 2016. Autocatalytic, bistable, oscillatory networks of biologically relevant organic reactions. Nature 537 (7622), 656–660. https://doi.org/10.1038/nature19776.

Shapiro, R., 2006. Small molecule interactions were central to the origin of life. Q. Rev. Biol. 81 (2), 105–126. https://doi.org/10.1086/506024.

Sommer, U., 1999. Competition and coexistence. Nature 402 (6760), 366–367. https://doi.org/10.1038/46453.

Sousa, F.L., Hordijk, W., Steel, M., Martin, W.F., 2015. Autocatalytic sets in E. coli metabolism. J. Syst. Chem. 6 (1). https://doi.org/10.1186/s13322-015-0009-7.

Steel, M., 2000. The emergence of a self-catalysing structure in abstract origin-of-life models. Appl. Math. Lett. 13 (3), 91–95. https://doi.org/10.1016/S0893-9659(99)00191-3.

Ulanowicz, R.E., 2009. A Third Window: Natural Life Beyond Newton and Darwin. Templeton Foundation Press, West Conshohocken, Pa.

Ulanowicz, R.E., 2004. Quantitative methods for ecological network analysis. Comput. Biol. Chem. 28 (5-6), 321–339. https://doi.org/10.1016/j.compbiolchem.2004.09.001.

Ulanowicz, R.E., 1997. Ecology, the Ascendent Perspective, Complexity in Ecological Systems Series. Columbia University Press, New York.

Vaidya, N., Manapat, M.L., Chen, I.A., Xulvi-Brunet, R., Hayden, E.J., Lehman, N., 2012. Spontaneous network formation among cooperative RNA replicators. Nature 491 (7422), 72–77. https://doi.org/10.1038/nature11549.

Vasas, V., Fernando, C., Santos, M., Kauffman, S., Szathmáry, E., 2012. Evolution before genes. Biol. Direct 7 (1), 1. https://doi.org/10.1186/1745-6150-7-1.

Vasas, V., Szathmary, E., Santos, M., 2010. Lack of evolvability in self-sustaining autocatalytic networks constraints metabolism-first scenarios for the origin of life. Proc. Natl. Acad. Sci. 107 (4), 1470–1475.

Vincent, L., Berg, M., Krismer, M., Saghafi, S., Cosby, J., Sankari, T., Vetsigian, K., Cleaves, H. J. III, and Baum, D. A., 2019. Chemical ecosystem selection on mineral surfaces reveals long-term dynamics consistent with the spontaneous emergence of mutual catalysis. Life 9, 80. https://doi.org/10.3390/life9040080.

Virgo, N., Ikegami, T., 2013. Autocatalysis before enzymes: the emergence of prebiotic chain reactions. Artif. Life Conf. Proceed. 25, 240–247. https://doi.org/10.1162/978-0-262-31709-2-ch036.

Virgo, N., Ikegami, T., McGregor, S., 2016. Complex autocatalysis in simple chemistries. Artif. Life 22 (2), 138–152. https://doi.org/10.1162/ARTL_a_00195.

Volterra, V., 1927. Fluctuations in the abundance of a species considered mathematically. Nature 119 (2983), 12–13. https://doi.org/10.1038/119012b0.

Volterra, V., 1926. Fluctuations in the abundance of a species considered mathematically1. Nature 118 (2972), 558–560. https://doi.org/10.1038/118558a0.

Wächtershäuser, G., 1988. Before enzymes and templates: theory of surface metabolism. Microbiol. Rev. 52, 452–484

Wagner, N., Hochberg, D., Peacock-Lopez, E., Maity, I., Ashkenasy, G., 2019. Open prebiotic environments drive emergent phenomena and complex behavior. Life 9, 45. https://doi.org/10.3390/life9020045.

Walker, S.I., Davies, P.C.W., 2013. The algorithmic origins of life. J. R. Soc. Interface 10, 20120869. https://doi.org/10.1098/rsif.2012.0869.

Wieczorek, R., 2012. On prebiotic ecology, supramolecular selection and autopoiesis. Orig. Life Evol. Biosph., 42, 445–452. https://doi.org/10.1007/s11084-012-9306-1.

Wright, E.S., Vetsigian, K.H., 2016. Inhibitory interactions promote frequent bistability among competing bacteria. Nat. Commun. 7, 1–7. https://doi.org/10.1038/ncomms11274.

Xavier, J.C., Hordijk, W., Kauffman, S., Steel, M., Martin, W.F., 2020. Autocatalytic chemical networks at the origin of metabolism. Proc. R. Soc. B 287 (1922), 20192377. https://doi.org/10.1098/rspb.2019.2377.