SI Correction

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Correction to Supporting Information for "Universal motifs and the diversity of autocatalytic systems," by Alex Blokhuis, David Lacoste, and Philippe Nghe, which was first published September 28, 2020; 10.1073/pnas.2013527117 (*Proc. Natl. Acad. Sci. U.S.A.* **117**, 25230–25236).

The authors note that Fig. S4 in the *SI Appendix* appeared incorrectly. Specifically, the green arrow in panel *A* appeared in the wrong location. The *SI Appendix* has been corrected online.

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Universal motifs and the diversity of autocatalytic systems

Alex Blokhuis[a,b,c,d,1], **David Lacoste**[a], **and Philippe Nghe**[b,1]

[a]Gulliver Laboratory, UMR CNRS 7083, Paris Sciences et Lettres University, Paris F-75231, France; [b]Laboratoire de Biochimie, UMR CNRS 8231, Chimie Biologie et Innovation, Ecole Supérieure de Physique et de Chimie Industrielles de la ville de Paris, PSL University, Paris F-75231, France; [c]Groningen Institute for Evolutionary Life Sciences, University of Groningen, 9747 AG Groningen, The Netherlands; and [d]Centre for Systems Chemistry, Stratingh Institute, University of Groningen, 9747 AG Groningen, The Netherlands

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Autocatalysis is essential for the origin of life and chemical evolution. However, the lack of a unified framework so far prevents a systematic study of autocatalysis. Here, we derive, from basic principles, general stoichiometric conditions for catalysis and autocatalysis in chemical reaction networks. This allows for a classification of minimal autocatalytic motifs called cores. While all known autocatalytic systems indeed contain minimal motifs, the classification also reveals hitherto unidentified motifs. We further examine conditions for kinetic viability of such networks, which depends on the autocatalytic motifs they contain and is notably increased by internal catalytic cycles. Finally, we show how this framework extends the range of conceivable autocatalytic systems, by applying our stoichiometric and kinetic analysis to autocatalysis emerging from coupled compartments. The unified approach to autocatalysis presented in this work lays a foundation toward the building of a systems-level theory of chemical evolution.

autocatalysis | origin of life | chemical reaction networks

The capacity of living systems to replicate themselves is rooted in a chemistry that makes more of itself, that is, an autocatalytic system. Autocatalysis appears to be ubiquitous in living systems from molecules to ecosystems (1). It is also likely to have been continually present since the beginning of life and is invoked as a key element in prebiotic scenarios (2–5). Surprisingly, autocatalysis is considered to be a rarity in chemistry (6). Developments in systems chemistry are changing this view, with an increasing number of autocatalytic systems synthesized de novo (7–9). Chemical replicators have been endowed with biomimetic properties such as protein-like folding (10) and parasitism (11). Autocatalysis has also found technological applications, for example, enantiomer enrichment and acid amplification (12–14).

Understanding autocatalysis represents a primary challenge for theory. Models based on autocatalysis were first built to explain a diversity of dynamical behaviors in so-called dissipative structures, such as bistable reactions (15), oscillating reactions, and chemical waves (16). Autocatalysis then became a central topic in the study of self-replication dynamics in biological and prebiotic systems (3, 17–19) (see refs. 20–22 for recent reviews).

Despite this history, a unified theory of autocatalysis is still lacking. Such a theory is needed to understand the origins, diversity, and plausibility of autocatalysis. It would also provide design principles for artificial autocatalytic systems. Here, we present a framework that unifies the different descriptions of autocatalysis and is based on reaction network stoichiometry (23–27).

Let us start from basic definitions in chemistry as established by the International Union of Pure and Applied Chemistry (28) (see *SI Appendix*, section I for full definitions), where autocatalysis is a particular form of catalysis: "A substance that increases the rate of a reaction without modifying the overall standard Gibbs energy change (ΔG°) in the reaction; the process is called catalysis. The catalyst is both a reactant and product of the reaction. Catalysis brought about by one of the products of a (net) reaction is called autocatalysis."

From this definition, we derive conditions to determine whether a subnetwork embedded in a larger chemical network can be catalytic or autocatalytic. These conditions provide a mathematical basis to identify minimal motifs, called autocatalytic cores. We found that cores have five fundamental categories of motifs. They allow classification of all previously described forms of autocatalysis, and also reveal hitherto unidentified autocatalytic schemes. We then study the kinetic conditions, which we call viability conditions, under which autocatalytic networks can appear and be maintained on long timescales. We find that networks have different viabilities depending on their core structure, and, notably, that viability is increased by internal catalytic cycles. Finally, we expand the repertoire of autocatalytic systems, by demonstrating a general mechanism for their emergence in multicompartment systems (e.g., porous media, vesicles, multiphasic systems). This mechanism strongly relaxes chemical requirements for autocatalysis, making the phenomenon much more diverse than previously thought.

Examples, Definitions, and Conventions

Catalysis and Autocatalysis. The following reactions have the same net mass balance but a different status regarding catalysis:

$$\mathrm{A} \overset{(\mathrm{I})}{\rightleftharpoons} \mathrm{B}, \qquad \mathrm{A}+\mathrm{E} \overset{(\mathrm{II})}{\rightleftharpoons} \mathrm{B}+\mathrm{E}, \qquad \mathrm{A}+\mathrm{B} \overset{(\mathrm{III})}{\rightleftharpoons} 2\mathrm{B}. \qquad [1]$$

Since no species is both a reactant and product in reaction I, it should be regarded as uncatalyzed. Reactions II and III instead contain species which are both a reactant and a product, species E in reaction II and species B in reaction III, and, following the

Significance

Autocatalysis, the ability of chemical systems to make more of themselves, is a hallmark of living systems, as it underlies metabolism, reproduction, and evolution. Here, we present a unified theory of autocatalysis based on stoichiometry. This allows us to identify essential motifs of autocatalytic networks, namely, autocatalytic cores, which come in five categories. In these networks, internal catalytic cycles are found to favor growth. The stoichiometry approach furthermore reveals that diverse autocatalytic networks can be formed with multiple compartments. Overall, these findings suggest that autocatalysis is a richer and more abundant phenomenon than previously thought.

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[1]To whom correspondence may be addressed. Email: a.w.p.blokhuis@rug.nl or philippe.nghe@espci.psl.eu.

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definition above, these species can be considered as catalysts. In reaction II, the amount of species E remains unchanged, in contrast to the case of reaction III, where the species B experiences a net production. For this reason, reaction III represents genuine autocatalysis. Although reaction II is usually referred to as simply catalyzed in the chemistry literature, we propose to call it an example of allocatalysis to contrast it with the case of autocatalysis, catalysis being common to both.

We emphasize that stoichiometric considerations are necessary but not sufficient to characterize catalysis, which, according to the definition, should also accelerate the rate of the net reaction. In the following, we will first generalize the stoichiometric conditions, then examine kinetic ones.

Stoichiometric Matrix and Reaction Vectors. Reaction networks are represented as a stoichiometric matrix $\boldsymbol{\nu}$ (23, 26), in which columns correspond to reactions and rows correspond to species. The entries in a column are the stoichiometric coefficients of the species participating in that reaction; the coefficient is negative for every species consumed and positive for every species produced. A reaction vector $\boldsymbol{g} = [g_1, .., g_r]^T$ results in a change of species numbers $\Delta \boldsymbol{n} = \boldsymbol{\nu} \cdot \boldsymbol{g}$. The support of $\boldsymbol{g}$, denoted supp($\boldsymbol{g}$), is the set of its nonzero coordinates. A reaction cycle is a nonzero reaction vector $\boldsymbol{c}$ such that no net species number change occurs: $\boldsymbol{\nu} \cdot \boldsymbol{c} = \mathbf{0}$, or, equivalently, $\mathbf{c}$ belongs to the right null space of $\boldsymbol{\nu}$. Vectors $\boldsymbol{b}^T$ belonging to the left null space of $\boldsymbol{\nu}$ induce conservation laws, because, in that case, $\boldsymbol{b} \cdot \boldsymbol{n}$ represents a conserved quantity. The case of all coefficients b_k nonnegative is referred to as a mass-like conservation law. For example, in Fig. 1*A*, conserved quantities are $n_{\mathrm{E}} + n_{\mathrm{EA}}$ (catalysts) and $n_{\mathrm{A}} + n_{\mathrm{EA}} + n_{\mathrm{B}}$ (total compounds).

Lastly, catalyzed reactions may not always be distinguished from uncatalyzed ones in the stoichiometric matrix. For instance, in reactions II and III, catalysts cancel on each side, leading to the same column vector as for reaction I. This is avoided by describing catalysis through a sequence of reactions steps from which it emerges, so that a participating species is either a reactant or a product,

$$\mathrm{A} + \mathrm{E} \overset{\mathrm{IIa}}{\rightleftharpoons} \mathrm{EA} \overset{\mathrm{IIb}}{\rightleftharpoons} \mathrm{E} + \mathrm{B}, \qquad [2]$$

$$\mathrm{A} + \mathrm{B} \overset{\mathrm{IIIa}}{\rightleftharpoons} \mathrm{AB} \overset{\mathrm{IIIb}}{\rightleftharpoons} 2\mathrm{B}. \qquad [3]$$

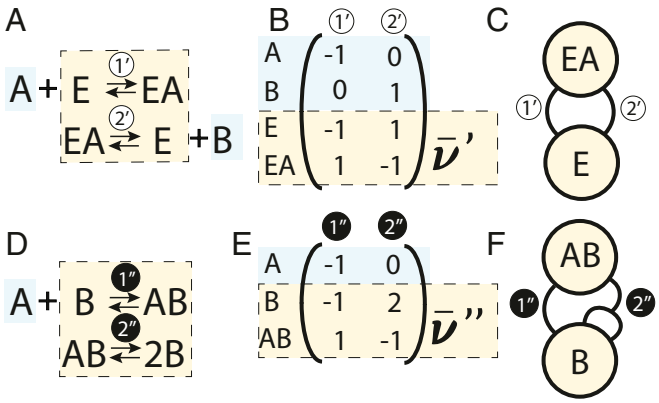

Fig. 1. Different representations for (*A*–*C*) allocatalysis and (*D*–*F*) autocatalysis. (*A*) Combining reactions 1′ + 2′ affords an allocatalytic cycle that converts A to B. (*B*) Stoichiometric matrix of *A*; the dashed square encloses the allocatalytic submatrix $\bar{\nu}'$ for network *B*. (*C*) Graph representation of the allocatalytic subnetwork. (*D*) Combining 1″ + 2″ affords an autocatalytic cycle converting A to B. (*E*) Stoichiometric matrix of *D*; the dashed square encloses the autocatalytic submatrix $\bar{\nu}''$ for network *E*. (*F*) A graph representation of the autocatalytic subnetwork.

We call this convention *nonambiguity* and assume henceforth that it is respected.

Catalysis and Autocatalysis in Stoichiometric Matrices

In this section, we will consider any possible submatrix $\bar{\nu}$ of $\boldsymbol{\nu}$, the stoichiometric matrix of a reaction network, and ask whether the stoichiometry of the corresponding subnetwork, called a motif, is compatible with the definitions of allocatalysis or autocatalysis. Note that such identification makes a priori assumptions neither on the values and signs of reaction vector coefficients nor on kinetics, nor on which species are catalytic or not. A matrix $\bar{\nu}$ is a restriction of $\boldsymbol{\nu}$ to certain rows and columns, which respectively correspond to the species and reactions of the motif under consideration.

The restriction of the rows means that the species of $\boldsymbol{\nu}$ are separated into internal species of the motif (rows of $\bar{\nu}$) and external species (remaining rows of $\boldsymbol{\nu}$). These external species could be, in some cases, chemostatted (26), and represent feedstock compounds, also called the food set (29), and waste from the point of view of internal species of the motif. In Fig. 1, external species have been colored in blue, while stoichiometric submatrices have been boxed in yellow. Fig 1 *A* and *D* represents examples of allocatalysis and autocatalysis, respectively, with their respective submatrices $\bar{\nu}'$ and $\bar{\nu}''$, and hypergraph representations Fig. 1 *C* and *F*.

Restriction of columns separates reactions which are part of the motif and those which occur outside of it. A motif such that each of its reactions has at least one reactant and at least one product is called *autonomous*. This means that every column of $\bar{\nu}$ contains a positive and a negative coefficient. Below, we pose autonomy as a condition for catalysis. Indeed, it ensures that the production of any species of the motif is conditional on the presence of other chemical species of the motif. Otherwise, rate acceleration would be allowed unconditionally on an already present substance, in opposition to the definition of catalysis. Autonomy is less restrictive than former conditions for autocatalysis (24), and is similar to the siphon concept in Petri Nets (30), but without assumption on reaction signs (*SI Appendix*, section 1). Note that it does not forbid that reactions outside the motif produce species of the motif.

Criterion for Allocatalysis. By definition, allocatalysis is an ensemble of reactions by which a set of species remain conserved in number (the catalysts) while other external species undergo a turnover which changes their numbers. This leads to the conditions below.

There exists a set of species $\boldsymbol{S}$, a submatrix $\bar{\nu}$ of $\boldsymbol{\nu}$ restricted to $\boldsymbol{S}$, and a nonzero reaction vector $\boldsymbol{c}$ such that 1) $\bar{\nu}$ is autonomous; 2) supp($\boldsymbol{c}$) is included in the columns of $\bar{\nu}$; 3) $\boldsymbol{c}$ is a reaction cycle of $\bar{\nu}$ ($\bar{\nu} \cdot \boldsymbol{c} = \mathbf{0}$); and 4) $\boldsymbol{\nu} \cdot \boldsymbol{c} \neq 0$. The members of $\boldsymbol{S}$ which participate in $\boldsymbol{c}$ (i.e., that are consumed and produced) are called allocatalysts: $\boldsymbol{c}$, an allocatalytic cycle and $\bar{\nu}$, an allocatalytic matrix.

Condition 1 has been discussed above. Condition 2 expresses the involvement of the catalysts in the reactions $\boldsymbol{c}$, where all columns of $\bar{\nu}$ are nonzero due to condition 1, so that all reactions of $\boldsymbol{c}$ involve catalysts. Condition 3 expresses the conservation of catalysts, and condition 4 expresses the net reaction. Since the reaction cycle $\boldsymbol{c}$ is a cycle of the reduced matrix but not of the original matrix, some authors have qualified it as emergent and shown that it can establish a nonequilibrium steady state driven by the turnover of the external species (26). Note that being allocatalytic is not a property of the submatrix $\bar{\nu}$ alone but involves the larger matrix $\boldsymbol{\nu}$ as imposed by condition 4.

Criterion for Autocatalysis. By definition, autocatalysis is the process by which a combination of reactions involves a set of species which all increase in number conditional on species in the set

itself (the autocatalysts), while other species undergo a turnover. This leads to the following conditions.

There exists a set of species $\boldsymbol{S}$, a submatrix $\bar{\boldsymbol{\nu}}$ of $\boldsymbol{\nu}$ restricted to $\boldsymbol{S}$, and a reaction vector $\boldsymbol{g}$ such that 1) $\bar{\boldsymbol{\nu}}$ is autonomous and 2) all coordinates of $\Delta \boldsymbol{n} = \bar{\boldsymbol{\nu}} \cdot \boldsymbol{g}$ are strictly positive, or equivalently, $\bar{\boldsymbol{\nu}}$ has no mass-like conservation laws. The members of $\boldsymbol{S}$ consumed (and produced) by $\boldsymbol{g}$ are called autocatalysts, $\boldsymbol{g}$ is an autocatalytic mode, and $\bar{\boldsymbol{\nu}}$ is an autocatalytic matrix.

Condition 1 ensures the conditionality of the reactions on autocatalysts, as it forbids cases where species of $\boldsymbol{S}$ are produced from external reactants only, thus playing the role of conditions 1 and 2 in the definition of allocatalysis. Condition 2 expresses the increase in autocatalyst number. The equivalence between the two formulations of condition 2 is an immediate consequence of Gordan's theorem (31). Importantly, the second formulation of condition 2 does not involve an autocatalytic mode $\boldsymbol{g}$, so that conditions 1 and 2 can be expressed as properties of a matrix itself, in contrast with allocatalysis. This allows us to look for minimal autocatalytic motifs, which we do next. Note that external species must feed the autocatalytic system in order to guarantee the net mass increase imposed by condition 2.

Autocatalytic Cores. An autocatalytic core is an autocatalytic motif which is minimal because it does not contain any smaller autocatalytic motif. Consequently, an autocatalytic system is either a core or it contains one or several cores. The stoichiometric conditions show that characterizing cores is equivalent to finding all autonomous matrices whose images contains vectors with only strictly positive components. This well-posed formulation allowed us to show that the stoichiometric matrix $\bar{\boldsymbol{\nu}}$ of an autocatalytic core must verify a number of nonobvious properties reported below and demonstrated in *SI Appendix*, sections 2 and 3.

First, $\bar{\boldsymbol{\nu}}$ must be square (the number of species equals the number of reactions) and invertible. The inverse has a chemical interpretation. By definition of the inverse, the kth column of $\bar{\boldsymbol{\nu}}^{-1}$ is a reaction vector such that species k increases by one unit, making it an elementary mode of production. Likewise, the reaction vector obtained by summing the columns of $\bar{\boldsymbol{\nu}}^{-1}$ leads to a net increase by one unit of every autocatalyst, which thus represents an elementary mode of autocatalysis. This shows how stoichiometry informs on fundamental modes of autocatalysis (27).

Second, every forward reaction of a core involves only one core species as a reactant. While this excludes reactions between two different core species, a single core species may react with itself. As $\bar{\boldsymbol{\nu}}$ is square, this also implies that every species of a core is consumed (none is only produced), and thus is an autocatalyst. Furthermore, every species is the reactant of a single reaction. Overall, every species is uniquely associated with a reaction as being its reactant, so that $\bar{\boldsymbol{\nu}}$ admits a representation with a negative diagonal and zero or positive coefficients elsewhere, at least one coefficient of each column being strictly positive to ensure autonomy.

These properties are constraining enough to allow an exhaustive enumeration of reaction graphs that are cores. Autocatalytic cores are found to belong to five categories, denoted as type I to type V. Fig. 2*A* represents typical members of each category as reaction hypergraphs (see *SI Appendix*, Fig. S1 for general cases). As can be seen in these graphs, all minimal motifs contain a fork, which is a reaction with a single reactant and two products. The presence of at least one fork is consistent with the intuition that autocatalysis requires reaction steps that amplify the amount of autocatalysts. In type I cores, the fork ends with two copies of the same compound, whereas, in types II to V, forks end with different compounds. Note that type I cores can be seen as a particular case of type II if one formally allows different nodes to represent a same chemical species. It is obligatory for types II and III to contain one fork with two distinct products, for type IV to contain two such forks, and for type V to contain three. In Fig. 2*A*, the orange squares on the links between the nodes indicate that these links could contain further nodes and reactions in series, provided certain rules on cycles given in the next paragraph.

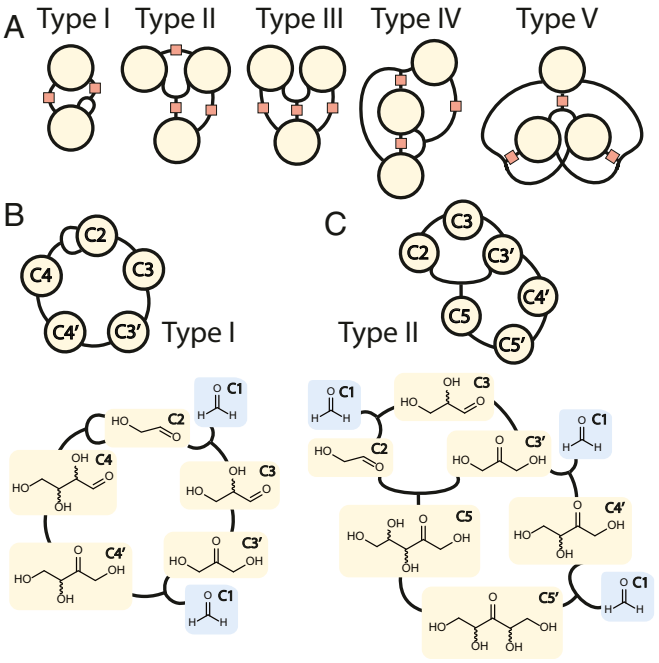

Fig. 2. (*A*) Five minimal motifs. Orange squares indicate where further nodes and reactions may be added, provided this preserves the motif type (I, II, III, IV, V) and minimality. (*B* and *C*) Examples of chemical networks, along with their autocatalytic cores. Blue, external species; yellow, autocatalysts. (*B*) Type I: Breslow's 1959 mechanism for the formose reaction (32). (*C*) Type II: Another autocatalytic cycle in the formose reaction. Species denoted as *Cx* inside the nodes refer to molecules containing *x* carbon atoms, which are shown below in standard chemical representation.

The five types differ in their number of graph cycles and the way these cycles overlap.* Type I consists of a single graph cycle that is weight asymmetric, defined as the product of the stoichiometric coefficients of its reaction products being different than that of its reactants. Types II and III comprise two distinct but overlapping graph cycles, Type IV comprises three, and Type V more than three, where any such graph cycle involving a strict subset of the core species must be an allocatalytic cycle, that is, weight symmetric (it would otherwise be of type I, contradicting minimality).

Unification of Autocatalytic Schemes. The stoichiometric characterization of autocatalysis provides a unified approach to autocatalytic networks reported in the literature. The examples below are further detailed in *SI Appendix*, section 4. The formose reaction is a classic example of autocatalysis known to contain many autocatalytic cycles (33). Fig. 2 *B* and *C* shows types I and III cores both found in the formose reaction. Similarly, autocatalytic cores of types I and III can be found in the Calvin cycle and reverse Krebs cycle (*SI Appendix*, Fig. S4). Some reaction steps in Fig. 2*B* may be catalyzed externally (e.g., by enzymes, base, ions), but external catalysis, in general, does not alter the core. By the same token, proposed examples of autoinduction

Graph cycles are closed paths in the reaction hypergraph and should not be confounded with *reaction cycles* which are right null vectors of the stoichiometric matrix.

introduced in refs. 21 and 34 contain type I and III cores (*SI Appendix*, Fig. S3).

In the GARD (Graded Autocatalysis Replication Domain) model for self-enhancing growth of amphiphile assemblies (4, 5), all underlying autocatalysis is described (*SI Appendix*, Fig. S6) by type I cycles with one fork and type II cycles built up from sequential nonoverlapping allocatalytic cycles (cross-incorporation, such as N_3 in Fig. 3). More generally, when such catalytic cycles are compactly written as single reactions as in Eq. **1**, they can be treated in the RAF (Reflexively Autocatalytic and Food-generated) framework (29), where they form irreducible RAF sets (35). This formally establishes the recently suggested link (5, 36) between these models.

Another reported form of autocatalysis is "chemical amplification" due to cavitands (37). The mechanism involves a reactive compound in a molecular cage, whose free counterpart can react to form two species that exchange with the caged species, thus amplifying its release. We find that this process can be described within our framework and corresponds to a type III core (*SI Appendix*, Fig. S5).

Overall, previously described autocatalytic schemes comprise types I, II, and III. We have not yet found examples of types IV and V.

Viability of Autocatalytic Networks. Stoichiometric conditions do not guarantee that autocatalysts within motifs amplify. Whether an initial autocatalyst amplifies or degrades depends on kinetic considerations. To address this so-called fixation problem (17, 22), we examined the probability P_{ex} of extinction (or $1-P_{ex}$ of fixation) of species within autocatalytic motifs, as a function of transition probabilities of reaction steps.

Considering a homogeneous system with a steady supply of reactants, several authors have noted that, in the highly dilute autocatalyst regime, appreciable rates require first-order autocatalysis (17, 22, 38); that is, each forward reaction step only involves one autocatalyst. Among first-order order networks, fixation models have so far focused on type I networks (e.g., Fig. 2*B*), which have a single graph cycle containing n species. In a transition step, a given species may either proceed irreversibly to the next species or disappear as a result of degradation. King (38) found that, if every reaction step k among n steps of the cycle has a success probability Π_k^+ ($1-\Pi_k^+$ being the degradation probability), fixation is possible for a doubling probability $p_2=\prod_{k=1}^{n}\Pi_k^+\geq 1/2$. This minimum value of p_2 above which fixation is possible is called the decay threshold (19, 39). Bagley et al. (17) used birth–death processes to derive P_{ex} for an autocatalytic loop containing one species ($n=1$). Schuster (22) reported detailed time-dependent statistics for such networks in various contexts.

Here, we extend the treatment of the fixation problem so as to include reversible reactions and networks beyond type I using the theory of branching processes (40). In these stochastic processes, an autocatalytic species $\mathrm{X_s}$ is, after a sequence of reaction steps in the network, replaced by k copies. Reaction sequences yielding k copies happen with a probability p_k, such that

$$\mathrm{X_s}\xrightarrow{p_0}\emptyset,\quad \mathrm{X_s}\xrightarrow{p_1}\mathrm{X_s},\quad \ldots\quad \mathrm{X_s}\xrightarrow{p_k}k\mathrm{X_s},\quad \ldots. \qquad [4]$$

The probability P_{ex} that $\mathrm{X_s}$ goes extinct is then the probability that its k descendants independently go extinct,

$$P_{ex}=p_0+p_1P_{ex}+p_2P_{ex}^2+\ldots=\sum_{k=0}^{\infty}p_kP_{ex}^k. \qquad [5]$$

The main difficulty here is to derive p_k from transition probabilities Π_k. A procedure for this is given in *SI Appendix*, section 5, where branching processes are constructed from reaction networks. Below, we exemplify this method by generalizing known results for type I networks, solutions for other networks being detailed in *SI Appendix*, section 5. We then apply it to compare the P_{ex} of autocatalytic motifs which differ in their core structures.

Reversible Type I Cycles. Consider a type I cycle consisting of n reaction steps, such as N_1 in Fig. 3*B*, and let us start at the first step with species $\mathrm{X_1}$ (marked node). Ultimately, $\mathrm{X_1}$ will either be successfully converted and yield $2\mathrm{X_1}$ or be degraded prematurely, which simplifies Eq. **4** to

$$\emptyset\xleftarrow{p_0}\mathrm{X_1}\xrightarrow{p_2}2\mathrm{X_1}, \qquad [6]$$

with $p_0+p_2=1$. The overall outcome described by Eq. **6** corresponds to the simplest type of branching process: a birth–death process. Eq. **5** then becomes a quadratic equation that yields

$$P_{ex}=\begin{cases}\frac{1}{p_2}-1, & p_2\geq\frac{1}{2},\\ 1, & p_2<\frac{1}{2}.\end{cases} \qquad [7]$$

This generalizes Bagley et al.'s (17) observation for type I networks to $n>1$ and reversible reactions. For reversible reactions, p_2 is found by considering all possible sequences of forward and backward reactions along the cycle. From $\mathrm{X_k}$, let Π_k^- be the transition probability to revert to X_{k-1}, and Π_k^+ to convert to X_{k+1}. We have

$$p_2=\prod_{k=1}^{n}\Pi_k^+\Gamma_k, \qquad [8]$$

$$\Gamma_{k+1}=\sum_{s=0}^{\infty}(\Pi_{k+1}^-\Gamma_k\Pi_k^+)^s=\frac{1}{1-\Pi_{k+1}^-\Gamma_k\Pi_k^+}, \qquad [9]$$

where Γ_k recursively ($\Gamma_1=1$) counts the statistical weight of all back-and-forth trajectories from $\mathrm{X_k}$ to itself, in terms of Π_k^-

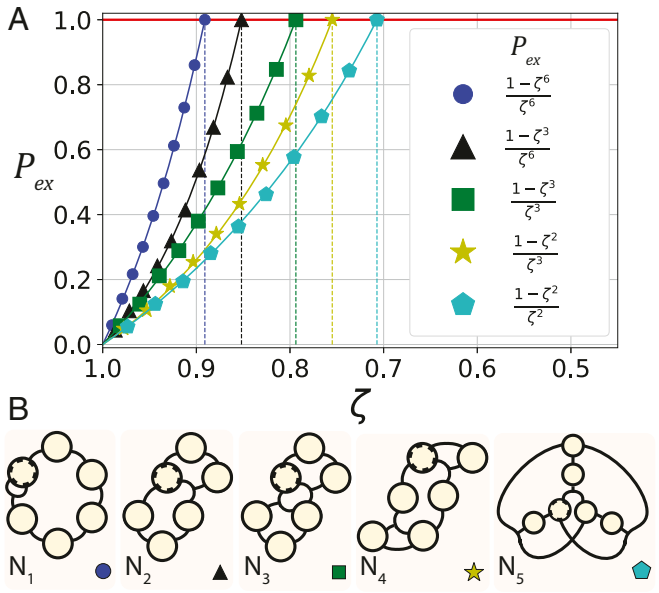

Fig. 3. (*A*) P_{ex} as function of ζ (legend: $P_{ex}(\zeta)$ for $P_{ex}<1$) for (*B*) five autocatalytic networks of similar size, starting at the dashed node. N_1: type I cycle. N_2: type II with one fork. N_3: type II, two nonoverlapping allocatalytic cycles, a common motif in GARD with a first-order RAF representation. N_4: type II, allocatalytic cycles connected by intermediate steps. N_5: type V. P_{ex} after 1,000 simulated trials, detailed in *SI Appendix*, section 8; lines are exact solution, derived in *SI Appendix*, section 6.

and Π_k^+. In the irreversible reaction limit $\Pi_k^- \to 0, \Gamma_k \to 1$, King's expression for p_2 is recovered (38).

Viability of Autocatalytic Cores. To investigate how autocatalytic motif structure affects survival, we calculated P_{ex} for five different cores (N_1 to N_5; Fig. 3): They are of equal size (six reaction steps, six species), and all reactions proceed irreversibly with the same success probability ζ, which plays a similar role as the transition probability Π_k^+ in the example above and is sometimes called specificity (19, 38, 39).†

Fig. 3 highlights how P_{ex} depends on ζ for each core structure. The highest ζ for extinction ($P_{ex} = 1$) is observed for the type I cycle N_1, and progressively lower values are found for N_2 to N_4, which are all of type II. Type V network N_5 tolerates the lowest specificity ζ before extinction, sustaining almost 3 times higher failure rates $1 - \zeta$ than N_1. These differences can be qualitatively understood by counting the minimum number of steps needed to produce more autocatalysts. In respective order, networks N_1 to N_5 in Fig. 3*B* do so in six, four, three, three, and two steps. In particular, given their symmetries, the P_{ex} of N_3 and N_5 have the same dependence on ζ as a three- and two-membered type I cycles, respectively.

It has been suggested that large networks are disfavored in general (38). The examples of Fig. 3 indicate that this can be counterbalanced by the presence of more allocatalytic cycles in the network. This is, in particular, the case for autocatalytic sets, as every net reaction must participate in an allocatalytic cycle.

Extensions: Multicompartment Autocatalysis

We finally show how stoichiometric criteria allow the identification of autocatalysis that emerges from compartments coupled via selective exchange, as found in systems comprising vesicles, pores, emulsions, and complex coacervates (41). The reaction network in Fig. 4*A* is incapable of autocatalysis, as it does not contain any autocatalytic core. However, when we place this network in two compartments α and β coupled by a membrane permeable to A and A_2B only, a type II core emerges (Fig. 4*B*).

The core identification indicates a possible setting for autocatalysis: U and V are chemostatted in α, and AB is chemostatted in β (Fig. 4*C*). The reaction involving U and V may, in principle, also take place in β, but it is not required for autocatalysis, as it is not part of the type II core. In Fig. 4 *C* and *D*, it is assumed that U and V are absent.

We now apply our viability analysis to this autocatalytic network in the presence of degradation reactions (r_6 and r_7 in Fig. 4*C*). Let us introduce a characteristic rate k for reactions r_2, r_4 and r_5, a degradation rate k^d for reactions r_6 and r_7, and an exchange rate k^{ex} for reactions r_1 and r_3. Fig. 4*D* shows the extinction probability as a function of the degradation rate k^d and exchange rate k^{ex}, both normalized by k. To overcome the degradation threshold ($P_{ex} < 1$), the ratio k^d/k must lie above a certain threshold (vertical black dotted line in Fig. 4*D*), and the rate of exchange k^{ex} should outpace the rate of degradation (black slanting dotted line in Fig. 4*D*). Stochastic simulations (*SI Appendix*, section 8 and Fig. S9) confirm autocatalytic growth in these conditions.

In this example of coupled compartments, compounds are no longer restricted to one role: AB is an autocatalyst in α and a feedstock in β. Chemical reactions are no longer restricted to one direction: The reaction used for reproduction in α is reused in β to provide the missing step to close the cycle. Such multicompartment autocatalysis is, however, more general. For instance, a single reaction $A \rightleftharpoons B + C$ can give rise to type III motifs, given three compartments coupled by selective exchange as detailed in *SI Appendix*, section 9 and Fig. S9.

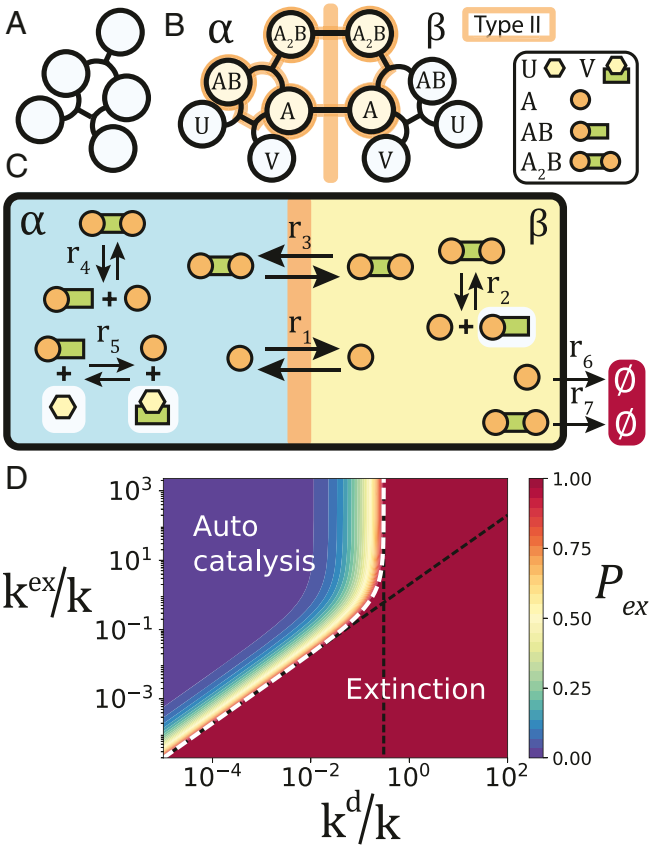

Fig. 4. Multicompartment autocatalysis. (*A*) Reaction network with two reactions and five species in a single compartment. The network does not contain any autocatalytic core, and thus cannot perform autocatalysis. (*B*) Same reaction network as in *A*, but duplicated in two compartments α and β, coupled by the selective exchange of species A and A_2B. A type II core, highlighted in orange, emerges. (*C*) Open reactor with two compartments, a semipermeable membrane, degradation, and exchange reactions. Chemostatted species have a lighter background: U and V in α and AB in β. (*D*) Extinction probability P_{ex} for multicompartment autocatalysis in *C*, starting from a single A_α, as a function of exchange rate k^{ex} and degradation rate k^d, relative to other relevant reaction rates fixed at k. Slanting asymptote: exchange-limited survival $k_{ex} = 2k^d$. Vertical asymptote: reaction-limited survival $k^d/k = \sqrt{13} - 3/2$. Dashed white line: transition between extinction and potential fixation ($P_{ex} < 1$). Expressions for P_{ex} and asymptotes are derived in *SI Appendix*, section 7.

Discussion

We presented a theoretical framework for autocatalysis based on stoichiometry, which allows a precise identification of the different forms of autocatalysis. Starting with a large stoichiometric matrix, we provide criteria for reaction network motifs that allow allocatalysis and autocatalysis. A detailed analysis of the graph structure contained in these reduced stoichiometric matrices reveals that they contain only five possible recurrent motifs, which are minimal in the sense that they do not contain smaller motifs. Fundamental modes of production of minimal autocatalytic cores are encoded in the column vectors of the inverse of the autocatalytic core submatrix. Autocatalytic cores are found to have a single reactant species for each reaction. This means that autocatalytic networks require the availability of certain chemical species in their cores to operate properly, but also implies that the proper functioning of an autocatalytic

†Note that, in general, the calculation of P_{ex} may involve reactions that are not in the core. Here, we consider cases where this is not necessary.

network will guarantee the stable supply of certain products, a definitive advantage when these products are key enzymes or metabolites.

We identified these minimal motifs in known examples of autocatalysis such as the formose reaction, central metabolic cycles, the GARD model, and RAF sets. Autocatalytic cores also provide a basis for algorithms to identify these recurring autocatalytic motifs in large chemical networks (24, 42, 43), as has been done for gene regulatory networks (44). In this way, we may be able to break the complexity of large chemical networks into smaller, more manageable structures (45). Additionally, autocatalytic cores are the building block of evolution in prebiotic chemistries (35); thus their identification paves the way to a systematic exploration of the possible modes of chemical evolution (46, 47).

Autocatalytic motifs provide different degrees of robustness, which we evaluated using the notion of viability. Viability can be computed as a survival probability in an appropriately defined branching process. This approach is generally applicable to autocatalytic models upon identification of their cores, highlighting the interest of a unified framework. Viability results from a competition between reactions that produce autocatalysts and side reactions such as degradation. This is intimately related to the "paradox of specificity" (19, 39): Autocatalytic motifs are more likely to be found in large networks with many different chemical components engaging in many different reactions, but putting many components together favors side reactions, leading to extinction.

Multicompartment autocatalysis introduced here offers a way around this problem: Coupled compartments effectively enlarge the number of species without requiring new reactions. In multicompartment autocatalysis, cycles rely on the environmental coupling of reaction networks, which allows access to conditions unattainable in a single compartment. In this way, autocatalysis can emerge from reaction schemes as simple as a bimolecular reaction, provided certain semipermeability conditions are met for the exchange of compounds between compartments. In the example shown here (Fig. 4), this allowed us to reuse the compounds and reactions to complete autocatalytic cycles. The principle is more general, however: Autocatalysis may also emerge from coupling phases with physical–chemical conditions conducive to different reactions, as observed in liquid–solid (48) and solid–gas (49) interfaces. Liquid–liquid interfaces in cellular organization and multiphase coacervates (41) are promising places to further explore such principles.

Overall, our framework shows that autocatalysis comes in a diversity of forms and can emerge in unexpected ways, indicating that autocatalysis in chemistry must be more widespread than previously thought. This invites a search for further extensions of autocatalysis, which provides new vistas for understanding how chemistry may complexify toward life (50).

Materials and Methods

Theoretical methods and derivation of results are detailed in *SI Appendix* comprising the following sections: 1) terminology and definitions; 2) derivation of autocatalytic cores from graph theory; 3) their chemical interpretation and 4) application to formose, autoinduction, metabolic cycles, chemical amplification, RAF sets, and GARD; 5) branching process derivation and determination of P_{ex}; 6) determination of P_{ex} for Fig. 3; 7) determination of P_{ex} for Fig. 4*D*; 8) stochastic simulations; and 9) autocatalysis from one bimolecular reaction and three compartments.

Data Availability. There are no data underlying this work.

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