An assessment of stoichiometric autocatalysis across element groups

Authors: Zhen Peng[1,2]*, Betül Kaçar[1], Albert C. Fahrenbach[3], Zachary R. Adam[2]

[1]Department of Bacteriology, University of Wisconsin–Madison, Madison, Wisconsin, 53706, U.S.A.

[2]Department of Geoscience, University of Wisconsin–Madison, Madison, Wisconsin, 53706, U.S.A.

[3]School of Chemistry, Australian Centre for Astrobiology and the UNSW RNA Institute, University of New South Wales, Sydney, NSW 2052, Australia.

*Correspondence to: zhen.peng@wisc.edu

Abstract

Autocatalytic chemical reaction systems have been proposed to play critical roles during the transition from an abiotic world to one that contains living systems. These proposals are at odds with a limited number of known examples of abiotic (and in particular, inorganic) autocatalytic systems that might reasonably function in a prebiotic environment. In this study, we broadly assess the occurrence of stoichiometries that can support autocatalytic chemical systems through comproportionation reactions. If the product of a comproportionation process can be coupled with an auxiliary oxidation or reduction pathway that furnishes a reactant, then a candidate comproportionation-based autocatalytic cycle (CompAC) structure can exist. Using this strategy, we surveyed the literature and chemical databases for reactions that can be organized into CompACs that consume some chemical species as food to synthesize more autocatalysts. 226 CompACs and 44 Broad-sense CompACs were documented, and it was found that each of the 18 groups, lanthanoid series, and actinoid series in the periodic table has at least two CompACs. Our findings demonstrate that stoichiometric relationships underpinning abiotic autocatalysis could broadly exist across a range of geochemical and cosmochemical conditions, some of which are substantially different from the modern Earth. At the same time, the observation of some autocatalytic systems requires effective spatial or temporal separation between the food chemicals while allowing comproportionation and auxiliary reactions to proceed, which may explain why naturally occurring autocatalytic systems are not frequently observed. The collated CompACs and the conditions in which they might plausibly support complex, "life-like" chemical dynamics, can directly aid an expansive assessment of life's origins and provide a compendium of alternative hypotheses concerning false-positive biosignatures.

Keywords

Autocatalysis, Comproportionation, Inorganic Biosignatures, Origins of life, Elements

1. Introduction

Autocatalysis is usually defined as the phenomenon where the product of a single- or multi-step reaction also catalyzes that same reaction (IUPAC, 1997a), and is a shared feature of all living organisms. Reproduction is by definition a form of autocatalysis, and there are numerous examples of autocatalytic relationships that underpin metabolic processes (Kun et al., 2008; Roy et al., 2021), all of which are regulated by highly specialized organic polymers, e.g., proteins. Considering the similarity of dynamic behaviors afforded by biotic and abiotic autocatalytic systems, multiple studies have suggested that abiotic autocatalysis played critical roles prior to the establishment of life's characteristic sequence-specific, polymer-regulated autocatalysis (Blokhuis et al., 2020; Breslow, 1959; Colón-Santos et al., 2019; DeAngelis et al., 1986; Hunding et al., 2006; Kahana and Lancet, 2021; Kauffman, 1986; Liu et al., 2022; Peng et al., 2022, 2020; Sousa et al., 2015; Steel et al., 2020; Ulanowicz et al., 2014; Weber et al., 1989; Xavier et al., 2020).

Attributes typically associated with living organisms such as multistability, competition, mutualism, predation, the priority effect, gradual complexification, and adaptive responses to selection, can readily emerge from interacting abiotic autocatalytic reaction systems that do not involve macromolecules (Cornish-Bowden and Cárdenas, 2020; Gánti, 2003; Hunding et al., 2006; Peng et al., 2023, 2022, 2020). The Belousov-Zhabotinsky reaction is a classic example of an autocatalytic reaction network generated from the aqueous combination of a few simple organic and inorganic reagents that yields bistability and chemical oscillations (Zhabotinsky, 2007). Epstein and Huskey demonstrated in 1989 an apparent bistability in the formose reaction, a well-known example of autocatalysis relying on the simple feedstock molecule formaldehyde, and is a reaction often cited as a source of ribose being implicated in a variety of reported prebiotic nucleotide syntheses (Huskey and Epstein, 1989; Tran et al., 2020). The Grzybowski group in 2010 harnessed the pH oscillations of the autocatalytic formaldehyde-sulfite-gluconolactone (FSG) reaction to induce temporal and spatial periodic transitions between fatty acid vesicles and micelles (Lagzi et al., 2010). The Whitesides group in 2016 engineered an autocatalytic reaction network capable of bistability and oscillatory behavior based on simple α-aminothioesters, disulfides, electron-deficient olefins and the auto-amplification of cysteamine (Semenov et al., 2016). A recent study in 2022 by Muñuzuri and Pérez-Mercader demonstrated that a number of these behaviors become apparent in systems with as few as three unique molecular compounds, provided there are both Hopf and Turing instabilities present (Muñuzuri and Pérez-Mercader, 2022).

It seems likely that examples of primitive "life-like" autocatalytic systems that can be generated from only small-molecule reactions will become increasingly more common, at least in the laboratory setting; but the question still remains – how probable are abiotic autocatalytic networks, especially in the context of natural environmental settings like those of early Earth? The unique capabilities of autocatalysis make a compelling case for assessing their generic pervasiveness, but searching for autocatalytic systems is an inherently difficult problem (Arya et al., 2022). It has been shown that recognizing autocatalysis in chemical reaction networks is an NP-complete problem (Andersen et al., 2012). If no autocatalytic system is detected in a given reaction network, it is also correspondingly difficult to ascertain whether some reactions are capable of forming an autocatalytic system by the inclusion of a few more reactions or the provision of new reagents. This analytical opacity presents a specific challenge towards assessing the roles and pervasiveness of autocatalysis during life's origins, or within any naturally occurring (abiotic) systems of sufficient or even mild analytical complexity.

The pervasiveness of prebiotic autocatalysis remains an open debate even after decades of study, simply in part because not many functional examples of abiotic, especially inorganic autocatalytic systems are identified (Hanopolskyi et al., 2021). Further compounding the problem is the fact that some autocatalytic reaction networks may require spatial and/or temporal separation of components in order to operate, and recognition of these unique situations may easily elude analytical scrutiny. In comparison, biochemistry is replete with autocatalytic systems that afford vital metabolic functions via enzymatically constructed substrates and reaction pathways that are themselves regulated by the autocatalytic production of co-occurring catalytic polymers (Sousa et al., 2015). As a result, some researchers have suggested that abiotic autocatalytic reaction networks, lacking the custodianship of Darwinian natural selection, must be comparatively few and far between, and are therefore sparse in the chemical probability space (Orgel, 2008; Schnitter et al., 2022).

Assessing whether abiotic autocatalysis is *i*) truly rare, or *ii*) is in some ways limited to, or more pronounced in, chemical compounds of a given composition or class, would greatly aid in the development of new experimental designs for prebiotic autocatalytic protocols in the laboratory, as well as in the estimation of the emergence of autocatalysis in yet-to-be determined exoplanetary or otherwise exotic astrochemical environments. The search for plausible prebiotic autocatalytic systems has been generally centered on carbon-mediated cycles, because biological autocatalysis largely relies on organic substrates mediated by linear polymers, e.g., proteins and nucleic acids. No reason has been unequivocally enunciated, however, to ignore wholesale other elements and inorganic compounds that might have scaffolded life's origins terrestrially or elsewhere in the cosmos (Blokhuis, 2019). For example, complex functions, though seemingly requiring diverse and highly evolved catalytic polymers, may be partially – albeit imperfectly – undertaken by inorganic catalysts (e.g., metal ions) and interactions between simple autocatalytic cycles (Cornish-Bowden and Cárdenas, 2020; Gánti, 2003; Hunding et al., 2006; Kahana and Lancet, 2021; Muchowska et al., 2020, 2017; Peng et al., 2023, 2022, 2020; Plum and Baum, 2022). It is also possible that other pathways to alternative, non-Terran examples of life-like systems can arise under laboratory or exoplanetary/astrochemical conditions that largely deviate from terrestrial environments (Kawai et al., 2013; McKay, 1998; Stevenson et al., 2015).

Herein, we focus on a specific type of reaction – comproportionation – to outline one possible strategy for enumerating chemical reaction networks with autocatalytic motifs across the periodic table. Comproportionation (alternatively referred to as con-, sym-, or synproportionation) is typically defined as when two chemical species containing the same element with different oxidation numbers react to yield a product species with the same intermediate oxidation state (IUPAC, 1997b, 1997c) (Fig. 1A). Comproportionation reactions are a potentially interesting basis for assessing autocatalysis because they combine two general attributes of cellular biochemical systems: *i*) reactions driven by electrochemical potentials (redox reactions) to yield reduced or oxidized product(s) and *ii*) stoichiometric (potentially autocatalytic) amplification of those products. A stoichiometric autocatalytic cycle can be formed by coupling a comproportionation process with either an auxiliary oxidation (Fig. 1B) or reduction pathway (Fig. 1C) to form a loop that amplifies the intermediate-oxidation-state species and either the most oxidized- or reduced-state species, respectively. Such an autocatalytic cycle herein is termed a **Comp**roportionation-based **A**utocatalytic **C**ycle (CompAC).

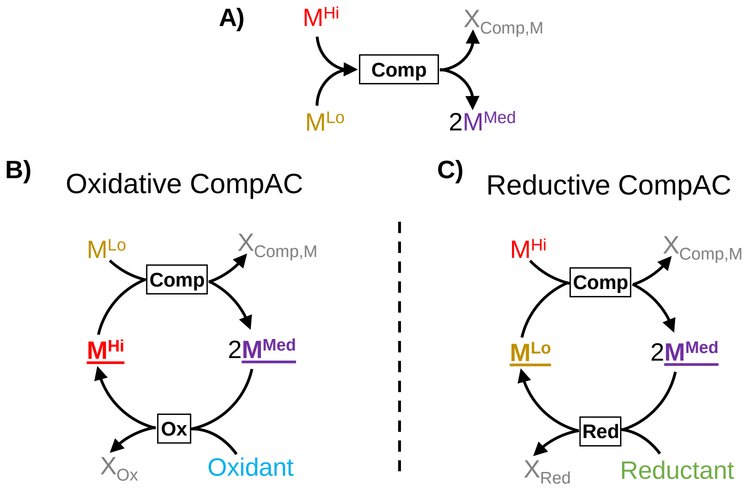

Fig. 1. Conceptualization of Comproportionation-based Autocatalytic Cycles (CompACs). **(A)** For an element/compound M that can take three or more oxidation states (Lo = lowest oxidation state, Med = intermediate oxidation state, Hi = highest oxidation state), comproportionation between oxidized M^{Hi} and reduced M^{Lo} produces two intermediate-state M^{Med} plus any associated waste products ($X_{Comp,M}$). Note that for some comproportionation reactions, the stoichiometry may be different; for example, one M^{Hi} may comproportionate with two M^{Lo} while consuming an additional food species F_{Comp}: $M^{Hi} + 2M^{Lo} + F_{Comp} \longrightarrow 3M^{Med} + X_{Comp,M}$. **(B)** An oxidative auxiliary process utilizes an oxidant to oxidize an M^{Med} to an M^{Hi}; the result is an oxidative CompAC. **(C)** A reductive auxiliary process utilizes a reductant to reduce an M^{Med} to an M^{Lo}; the result is a reductive CompAC. Autocatalysts reside on the cycles and are underlined; intermediate-state, the most oxidized, and the most reduced M's are highlighted purple, red, and gold, respectively; oxidant and reductant food of the auxiliary processes are highlighted blue and green, respectively; waste products are highlighted grey.

We developed a specific search strategy for CompACs and used this strategy to document 226 CompACs across 46 elements from the literature published during the past two centuries. Each of the 18 groups, lanthanoid series, and actinoid series in the periodic table has the potential for multiple CompACs. We also documented 44 prospective abiotic autocatalytic cycles that do not necessarily involve redox reactions but can be interpreted as Broad-sense CompACs, if an infrequent definition of "comproportionation" that only considers stoichiometry is applied (Greenwood and Earnshaw, 1997, p. 694; IUPAC, 1997c, 1997b; Schmidt and Siebert, 1973, p.

849). We demonstrate that autocatalysis is likely a broadly existing phenomenon, as it can be manifested by multiple sets of reaction rules, under a wide variety of conditions, and through the coordination of relatively small numbers of reactions between simple chemical species. Reconceptualizing the parameter space of environmental conditions under which autocatalytic dynamics are more easily observable may enable researchers to access ACs under a broader array of laboratory conditions.

2. Results

Following the formalism of CompACs described above (Fig. 1), we collated comproportionation reactions on an element-by-element basis from literature and databases, including primary literature that reported experimentally confirmed reactions as well as secondary literature such as reviews, textbooks, handbooks of chemical reactions and substances, and the Reaxys database (https://www.reaxys.com/). Specifically, all candidate reactions retrieved from the Reaxys database were cross-checked with primary literature sources. Auxiliary reaction pathways that lead from the intermediate-oxidation-state product of comproportionation to one of the reactants of comproportionation were similarly collected and collated. Although all of these reactions are known to occur, only a very limited number of combinations of them, such as the Belousov-Zhabotinsky reaction (Zhabotinsky, 2007), the chlorite-iodide reaction (De Kepper et al., 1990), and the formation of colloidal mercury in a Hg^{2+}-Fe^{2+} system (Raposo et al., 2000), have been explicitly reported as cases of autocatalysis. This search strategy for CompACs brings the advantage of providing a simple and generalized framework for identifying stoichiometric autocatalytic motifs across different elements, according to current knowledge, without explicit reference to terrestrial prebiotic plausibility.

We documented 226 CompACs across the periodic table (Table 1, Table S1, Supplemental Information 3). At least two CompACs are documented for each of the 18 groups, lanthanoid series, and actinoid series in the periodic table. Of these, most CompACs are composed of two reactions, and only eight CompACs consist of four or more reactions.

Table 1. Representative examples of Comproportionation-based Autocatalytic Cycles (CompACs). The arrows in this table do not mean that the reactions are irreversible, but are intended to indicate the autocatalytic direction. Autocatalysts are shown in bold. For the extended list of CompACs, please refer to Table S1 and Supplemental Information 3. Comproportionation reactions are shown by the upper equations, while the auxiliary oxidation or reduction reactions are shown by the lower equations.

Group or Series	Count of CompACs	Representative CompAC	References

Group 1	8	$NaH + \mathbf{HCl} \rightarrow NaCl + \mathbf{H_2}$ $2\,CuCl + \mathbf{H_2} \rightarrow 2\,Cu + \mathbf{2\,HCl}$	(Törndahl et al., 2004; 马 et al., 2003, p. 10)
Group 2	2	$\mathbf{Ca} + CaF_2 \rightarrow \mathbf{2\,CaF}$ $\mathbf{3\,CaF} + Sc \rightarrow \mathbf{3\,Ca} + ScF_3$	(Walters et al., 1928; Zmbov and Margrave, 1967)
Lanthanoid	3	$\mathbf{2\,EuCl_3} + Eu \rightarrow \mathbf{3\,EuCl_2}$ $\mathbf{2\,EuCl_2} + Cl_2 \rightarrow \mathbf{2\,EuCl_3}$	(Da Silva et al., 2001; Kuznetsov et al., 2001)
Actinoid	5	$ThO_2 + \mathbf{Th} \rightarrow \mathbf{2\,ThO}$ $\mathbf{ThO} + Si \rightarrow \mathbf{Th} + SiO$	(Hildenbrand and Murad, 1974; Hoch and Johnston, 1954)
Group 3	2	$\mathbf{2\,YF_3} + Y \rightarrow \mathbf{3\,YF_2}$ $\mathbf{YF_2} + CaF \rightarrow \mathbf{YF_3} + Ca$	(Knight and Wise, 1980; Zmbov and Margrave, 1967)
Group 4	4	$TiBr_2 + \mathbf{TiBr_4} \rightarrow \mathbf{2\,TiBr_3}$ $\mathbf{2\,TiBr_3} + 2\,HBr \rightarrow \mathbf{2\,TiBr_4} + H_2$	(Stebler et al., 1989; Young et al., 1946)
Group 5	18	$\mathbf{2\,VCl_3} + V \rightarrow \mathbf{3\,VCl_2}$ $\mathbf{2\,VCl_2} + 2\,HCl \rightarrow \mathbf{2\,VCl_3} + H_2$	(Лидин et al., 2007, pp. 594, 595)
Group 6	11	$\mathbf{Cr_2O_7^{2-}} + 6\,Cr^{2+} + 14\,H^+ \rightarrow \mathbf{8\,Cr^{3+}} + 7\,H_2O$ $\mathbf{2\,Cr^{3+}} + 3\,MnO_2 + 2\,H_2O \rightarrow \mathbf{2\,HCrO_4^-} + 3\,Mn^{2+} + 2\,H^+$ $\mathbf{2\,HCrO_4^-} \rightarrow \mathbf{Cr_2O_7^{2-}} + H_2O$	(Liang et al., 2021; Szabó et al., 2018; Topich et al., 2004, p. 59; Zintl and Schloffer, 1928)
Group 7	21	$2\,MnO_4^- + \mathbf{3\,Mn^{2+}} + 2\,H_2O \rightarrow \mathbf{5\,MnO_2} + 4\,H^+$ $\mathbf{MnO_2} + 2\,Fe^{2+} + 4H^+ \rightarrow \mathbf{Mn^{2+}} + 2\,Fe^{3+} + 2\,H_2O$	(Li et al., 2017; Tekin and Bayramoğlu, 1993)
Group 8	5	$Fe + \mathbf{2\,Fe^{3+}} \rightarrow \mathbf{3\,Fe^{2+}}$ $\mathbf{2\,Fe^{2+}} + Cl_2 \rightarrow \mathbf{2\,Fe^{3+}} + 2\,Cl^-$	(Bühler and Schwarz, 2012; Crabtree and Schaefer, 1966; Thorpe, 1882)
Group 9	6	$\mathbf{Co_3O_4} + Co \rightarrow \mathbf{4\,CoO}$ $\mathbf{6\,CoO} + O_2 \rightarrow \mathbf{2\,Co_3O_4}$	(Kalmus, 1914; Sakka, 1991; 马 et al., 2003, p. 480)
Group 10	7	$NiS_2 + \mathbf{Ni_3S_2} \rightarrow \mathbf{4\,NiS}$ $\mathbf{3\,NiS} + H_2 \rightarrow \mathbf{Ni_3S_2} + H_2S$	(Delafosse et al., 1962; Delafosse and Barret, 1961)

Group 11	9	$Cu + \mathbf{Cu^{2+}} \rightarrow \mathbf{2\ Cu^{+}}$ $\mathbf{Cu^{+}} + Fe^{3+} \rightarrow \mathbf{Cu^{2+}} + Fe^{2+}$	(Bjergbakke et al., 1976; Ciavatta et al., 1980; Orth et al., 1989)
Group 12	7	$\mathbf{Hg} + Hg^{2+} \rightarrow \mathbf{Hg_2^{2+}}$ $\mathbf{Hg_2^{2+}} + 2\ Fe^{2+} \rightarrow \mathbf{2\ Hg} + 2\ Fe^{3+}$	(Kozin and Hansen, 2013; Raposo et al., 2000)
Group 13	14	$2\ B_2O_3 + \mathbf{2\ B} \rightarrow \mathbf{3\ B_2O_2}$ $\mathbf{B_2O_2} + 2\ H_2 \rightarrow \mathbf{2\ B} + H_2O$	(Inghram et al., 1956; Sommer et al., 1963; Wang et al., 2008)
Group 14	22	$C + \mathbf{CO_2} \rightarrow \mathbf{2\ CO}$ $\mathbf{CO} + FeO \rightarrow Fe + \mathbf{CO_2}$	(Wilson and Bremner, 1948)
Group 15	25	$\mathbf{HNO_2} + HNO_3 \rightarrow \mathbf{2\ NO_2} + H_2O$ $\mathbf{2\ NO_2} + Cu + 2\ H^{+} \rightarrow \mathbf{2\ HNO_2} + Cu^{2+}$	(Abd El Aal et al., 1992; Evans, 1944)
Group 16	32	$\mathbf{SO_2} + 2\ H_2S \rightarrow \mathbf{3\ S} + 2\ H_2O$ $\mathbf{S} + O_2 \rightarrow \mathbf{SO_2}$	(Patnaik, 2003, p. 892; Steudel, 2003; Uzun et al., 2016)
Group 17	21	$\mathbf{HCl} + HOCl \rightarrow \mathbf{Cl_2} + H_2O$ $\mathbf{Cl_2} + H_2 \rightarrow \mathbf{2\ HCl}$	(Lister, 1952; Patnaik, 2003, p. 210)
Group 18	4	$\mathbf{XeF_4} + Xe \rightarrow \mathbf{2\ XeF_2}$ $\mathbf{XeF_2} + F_2 \rightarrow \mathbf{XeF_4}$	(Claassen et al., 1962; Weinstock et al., 1966; 马 et al., 2003, p. 332)

In addition, the use of the term “comproportionation” in published literature is sometimes not necessarily associated with redox reactions following the pattern shown in Fig. 1A, but only emphasizes a specific stoichiometric relationship (IUPAC, 1997b, 1997c). For example, $O_2SCl_2 + O_2SF_2 \rightarrow 2O_2SFCl$ is sometimes referred to as a comproportionation reaction because atoms of the same element in different reactant species appear in the same product species with stoichiometric excess (Greenwood and Earnshaw, 1997, p. 694; Schmidt and Siebert, 1973, p. 849), while none of the involved atom change their oxidation numbers. In this regard, we also formalize a “Broad-sense CompAC” by combining this broader definition of a comproportionation reaction with an auxiliary process. For example, $O_2SCl_2 + \mathbf{O_2SF_2} \rightarrow \mathbf{2O_2SFCl}$ can be combined with $\mathbf{O_2SFCl} + KSO_2F \rightarrow \mathbf{O_2SF_2} + KCl + SO_2$ (Seel et al., 1967) to form a Broad-sense CompAC (autocatalysts are shown in bold). Consequently, we documented 44 Broad-sense CompACs (Table S2) that are stoichiometrically capable of autocatalysis. Again, most Broad-sense CompACs consist of two reactions, and no Broad-sense CompAC consists of four or more reactions. In addition, some other classic examples of abiotic autocatalysis, such as the formose reaction (Boutlerow, 1861; Breslow, 1959), pyrite oxidation in an aqueous environment (Osborne et al., 2010), and the oxidation of oxalic acid by permanganate (Adler and Noyes, 1955; Kovács et al., 2004; Ladbury and Cullis, 1958), may also be enumerated as Broad-sense CompACs. Taken together, CompACs do not reflect an isolated or particularly specialized attribute of elements of any particular group.

3. Discussion

Based on experimentally confirmed chemical reactions compiled from almost two centuries of literature, we documented empirically testable CompACs in all groups, the lanthanoid series and the actinoid series in the periodic table. The size distribution of the CompACs (the overwhelming majority of which contain only two reactions, and none more than five) indicate that it would be relatively easy to experimentally test them and couple multiples of them together to form a more complex, ecosystem-like network, setting aside the possibility of side-reactions. These findings suggest that, although computationally searching for autocatalysis in any given reaction network is a highly challenging task, there may exist generic chemical circumstances or attributes that are correlated with a potential for autocatalytic behavior.

The composition of many of these CompACs (Table 1, Tables S1 and S2) seem only tangentially relevant to living organisms. Some CompACs center around the chemical elements that are absent or very rare in most organisms (e.g., Th and Hg) (Lecroq et al., 2009; Smith and Huyck, 1997); some are unlikely to occur under ambient terrestrial pressure or temperature conditions; and some produce chemicals that are deleterious or lethal to most living organisms. They are nevertheless potentially relevant for exploring the origins of life and the distribution of complex chemical dynamics in various astrochemical and exoplanetary locales. First, the conditions under which life originated could be dramatically different from what living organisms are dealing with today, and extraterrestrial life – if it exists – could be very different from life as we know it. Coupling of CompACs to organic chemistry, in a variety of different environmental contexts, could encompass a subset of reactions suitable for the sustenance of alternative life-like chemical systems. Secondly, abiotic CompACs might have played critical roles during life's emergence but were subsequently lost from living organisms later, becoming the "missing links," analogous to how construction scaffolds are removed after houses are built (Blokhuis, 2019). Third, even if some CompACs are completely irrelevant to life either as we know it or in a form yet to be known, they may nevertheless generate secondary or tertiary chemical effects that may be misinterpreted as false positive biosignatures (Meadows et al., 2022). Any and all of these conditions may be leveraged to engineer life-like chemical systems with useful chemosynthetic and information-processing properties.

Emergent patterns from interactions between CompACs

Being based on redox reactions, different CompACs may be coupled to form complexes of autocatalytic networks (Fig. 2) (Peng et al., 2020). For example, the auxiliary processes of two oxidative CompACs may consume the same oxidant, making these CompACs compete for food (Fig. 2A). The auxiliary process of an oxidative CompAC and that of a reductive CompAC may recycle a shared oxidant-reductant pair, making these CompACs mutualistic (Fig. 2B).

Mutualism is also possible if the auxiliary process of an oxidative CompAC and that of a reductive CompAC happen to be the same reaction (Fig. 2C). The comproportionation or auxiliary process of a CompAC may consume an autocatalyst of another CompAC as food, synonymizing these CompACs to a predator-prey relationship (Fig. 2D,E) (Cornish-Bowden and Cárdenas, 2020; Gánti, 2003). Bistability and the priority effect are also possible, if autocatalysts of different CompACs dimerize to form a new chemical species (Fig. 2F) (Peng et al., 2023).

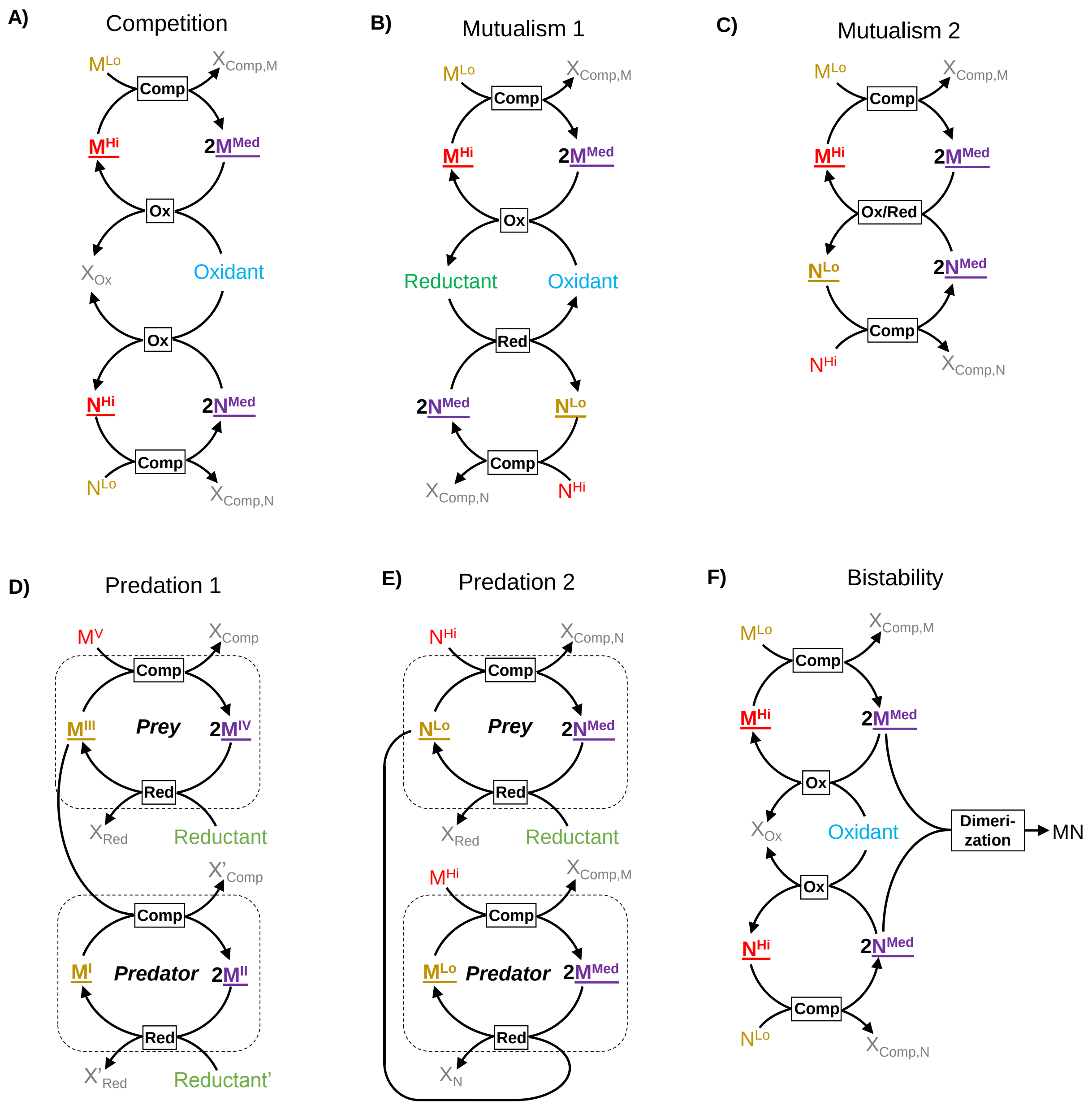

Fig. 2. Possible mechanisms of ecological interactions between abiotic CompACs. Abiotic CompACs can be coupled through an array of chemical reaction types. Depending on how a pair of CompACs are coupled, the relationship between CompACs can be interpreted as different ecological interactions. Note that these examples are not the only mechanisms for these ecological interactions among abiotic autocatalytic systems. Autocatalysts reside on the cycles

and are underlined; intermediate-state, the most oxidized, and the most reduced M/N's are highlighted purple, red, and gold, respectively; oxidant and reductant food of the auxiliary processes are highlighted blue and green, respectively; waste products are highlighted grey. **(A)** If two oxidative CompACs consume the same oxidant as food for their auxiliary processes, then the CompACs compete for a shared food species. **(B)** An oxidative CompAC and a reductive CompAC can be mutualistic, if the auxiliary process of the oxidative CompAC (M^{Hi}-M^{Med}) and the auxiliary process of the reductive CompAC (N^{Lo}-N^{Med}) recycle the shared oxidant-reductant pair. **(C)** An oxidative CompAC and a reductive CompAC can also be mutualistic if the auxiliary process of one happens to also be the auxiliary process of the other. **(D)** A predator CompAC (M^{I}-M^{II}) can prey on another CompAC (M^{III}-M^{IV}), if the autocatalyst of the latter (M^{III}) is consumed as food by the comproportionation process of the former ($M^{I} + M^{III} \rightarrow 2M^{II} + X'_{Comp}$). **(E)** A predator CompAC (M^{Med}-M^{Lo}) can also prey on another CompAC (N^{Lo}-N^{Med}), if the autocatalyst of the latter (N^{Lo}) is consumed as food by the auxiliary process of the former ($M^{Med} + N^{Lo} \rightarrow M^{Red} + X_N$). **(F)** If the autocatalysts (M^{Med} and N^{Med}) of different CompACs (M^{Hi}-M^{Med} and N^{Hi}-N^{Med}) dimerize to form a new chemical species (MN), then these two CompACs may form a bistable system wherein either the M-dominated or N-dominated state is locally stable.

In contrast to autocatalytic cycles observed in biochemistry that may involve dozens of reaction steps and/or biomacromolecules (e.g., the Calvin cycle and DNA replication), CompACs are much simpler since they usually consist of only two or three reactions. Such simplicity could be important for a primitive life-like autocatalytic system to emerge and persist. An autocatalytic cycle with fewer reaction steps tends to have a higher "carrying capacity" (Peng et al., 2020), and it is arguably easier to find naturally occurring or laboratory-generated conditions that allow every reaction in a smaller autocatalytic cycle to occur.

Separation between food species facilitates the observation of autocatalytic dynamics

Although we have detailed many small-reaction-number CompACs, real chemical reaction systems are rarely this simple. Real systems, even those under controlled laboratory conditions, should be expected to be "messy," with multiple side reactions and alternative pathways. For this reason, the existence of a CompAC does not necessarily mean that it will be easily observable, nor that it will generate complex dynamics between and amongst species in a chemical system. There are systemic constraints that are known to facilitate complicated autocatalytic dynamics within representative examples of the described reaction sets. For example, the Belousov-Zhabotinsky reaction can exhibit bursting and chaotic oscillations in a continuous-flow stirred tank reactor but not in a closed one (Zhabotinsky, 2007).

Although the acceleration of a reaction over time is neither sufficient nor necessary for autocatalysis, it is usually the phenomenon that is most easily measured in experimental protocols. Another method of observing autocatalysis is to check whether a tiny amount of candidate autocatalysts can be used as a "seed" to trigger a reaction system that produces much more autocatalysts (Peng et al., 2022). A CompAC is more likely to exhibit reaction acceleration or seed-dependence when direct reactions between the complementary reductive and oxidative food of the comproportionation and auxiliary steps are suppressed. Based on the CompACs we documented, there are generally three ways to suppress the direct reaction between oxidative food and reductive food: kinetic, spatial, and temporal separations.

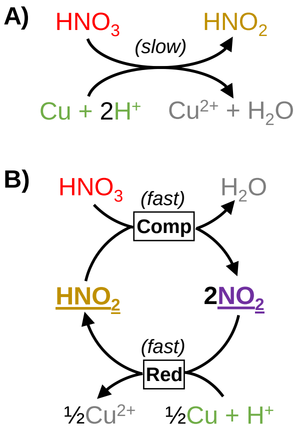

Fig. 3. Autocatalytic dissolution of copper in nitric acid and kinetic separation between food species. (A) Direct reaction between HNO_3, Cu, and H^+ is slow, which "kinetically separates" the food species HNO_3, Cu, and H^+. **(B)** Autocatalytic dissolution of copper consists of two fast reactions: the comproportionation between HNO_3 and HNO_2, which yields NO_2, and the reduction of NO_2 by Cu and H^+, which produces HNO_2.

The dissolution of copper in nitric acid (Evans, 1944; Ostwald, 1901) shows an example of **kinetic separation** in an autocatalytic system (Fig. 3). Upon addition of a piece of copper metal to a nitric acid solution, the dissolution of copper is slow at the beginning, which is a consequence of the fact that the rate of heterogeneous reaction between Cu and HNO_3 is low (Fig. 3A). As the dissolution reaction continues, nitrous acid (HNO_2) is slowly formed by the reaction between HNO_3, H^+ and electrons from Cu. Once HNO_2 is formed, it activates a new reaction pathway that is much faster than the direct reaction between the Cu metal and nitric acid (Fig. 3B):

$$\mathbf{HNO_2} + HNO_3 \rightarrow \mathbf{2NO_2} + H_2O$$

$$\mathbf{2NO_2} + Cu + 2H^+ \rightarrow \mathbf{2HNO_2} + Cu^{2+}$$

Here, HNO_2 and NO_2 catalyze the formation of themselves through these two fast reactions, and this pathway is thus autocatalytic. Now consider another metal Z in the mixture that directly and quickly reacts with nitric acid; even if Z can be dissolved through the autocatalysis of NO_2 and HNO_2, the autocatalytic dynamics may be obscured. In this case, slowing the reaction between the oxidative food, HNO_3, and the reductive food, metal and H^+, is important for observing autocatalytic dynamics; the food species are kinetically separated as a consequence of the dramatic differences between the rate constants involved. Another classic example of kinetic separation is the formose reaction, because the direct dimerization between formaldehydes is dramatically slower (perhaps not even possible except through a radical mechanism) than the autocatalytic pathway formed by ketose-aldose isomerizations, aldol reactions, and retro-aldol reactions (Breslow, 1959).

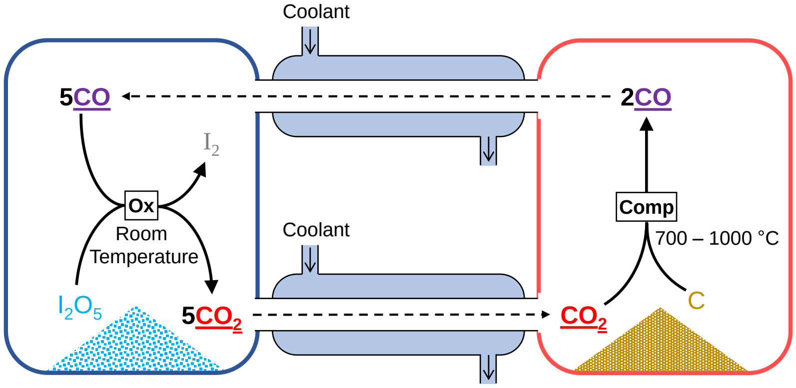

Fig. 4. Autocatalytic amplification of CO and CO_2 based on spatial separation between food species. Two reactors are connected by tunnels with cooling jackets; the right reactor is heated up to 700 – 1000 °C (Лидин et al., 2007, p. 79), while the left reactor is at room temperature (Лидин et al., 2007, p. 216). In the right reactor, CO_2 is heated and comproportionates with C to produce more CO; then the hot CO moves to the left reactor while being cooled down to room temperature. In the left reactor, CO is oxidized to CO_2 by reacting with I_2O_5, then this room-temperature CO_2 moves to the right reactor. To initiate the autocatalytic cycle, at least a small amount of CO_2 or CO molecules need to be added as a "seed."

Spatial separation can also limit the interaction between oxidative food and reductive food. For example, consider the comproportionation direction of the Boudouard reaction, possible under high temperatures (Лидин et al., 2007, p. 79; 马 et al., 2003, p. 135):

$$CO_2(g) + C(s) \rightarrow 2CO(g)$$

This reaction has the potential to couple with the oxidation of CO by I_2O_5 under room temperature (Лидин et al., 2007, p. 216) to form a CompAC:

$$\mathbf{CO_2}(g) + C(s) \rightarrow \mathbf{2CO}(g)$$

$$\mathbf{5CO}(g) + I_2O_5(s) \rightarrow \mathbf{5CO_2}(g) + I_2(s/g)$$

where the autocatalysts CO_2 and CO consume C and I_2O_5 as food, generating I_2 as waste. This CompAC could be difficult to observe, however, in the case where one simply mixes the food species C and I_2O_5 together in a heated reactor. This is because I_2O_5 will directly decompose to I_2 and O_2 (马 et al., 2003, p. 323) and/or react with C (Wu et al., 2018) at temperatures much lower than the desired temperature of $CO_2 + C \rightarrow 2CO$; thus, the autocatalytic dynamics may be obscured.

One way to facilitate the observation of this CompAC is to place I_2O_5 and C, which are solids, in two reactors connected by two tunnels only allowing the diffusion of gaseous molecules; the temperature of the reactor with I_2O_5 is low while that of the reactor with C is high, with the tunnels surrounded by cooling jackets (Fig. 4). Carried out in this way, the I_2O_5 and C will be spatially separated and cannot directly react with each other (Blokhuis et al., 2020) while each resides in a reactor with appropriate reaction conditions. To initiate the conversion of I_2O_5 and C into CO_2 and CO, a small amount of CO_2 or CO gas needs to be introduced to a reactor or tunnel as a "seed." With CO_2 as the seed, C will first react with CO_2 to produce more CO by $CO_2 + C \rightarrow 2CO$ in the hot reactor. The hot CO gas will then move mainly through the upper tunnel and be cooled down, eventually making contact with I_2O_5 in the other reactor and reacting to regenerate CO_2 by $5CO + I_2O_5 \rightarrow 5CO_2 + I_2$. Then the low-temperature CO_2 will move mainly through the lower tunnel to enter the hot reactor. As this process continues, more and more CO_2 and CO will be synthesized within the connected reactors by autocatalysis.

Compared to kinetic separation, spatial separation is able to not only inhibit direct and rapid reactions between food species, but also organize reactions that require very different conditions into an autocatalytic cycle. In abiotic environments, spatial separation may occur in multiple forms (Benner et al., 2012; Kitadai and Maruyama, 2018; Sasselov et al., 2020; Stüeken et al., 2013). For example, if an autocatalytic cycle needs food from hydrothermal vents and the atmosphere, the food species can be separated by the body of water above the vents; if the food species are from different minerals, they can be separated by geographical barriers, such as mountains and rivers, or by simple spacing between different rocks or ores.

If the physicochemical conditions are insufficient to afford effective kinetic or spatial separation, then **temporal separation** between food species may also be factored. For example, consider the CompAC:

$$2H_2S + \mathbf{SO_2} \rightarrow \mathbf{3S} + 2H_2O$$

$$\mathbf{S} + O_2 \rightarrow \mathbf{SO_2}$$

where the autocatalysts SO_2 and S consume H_2S and O_2, generating H_2O as a waste product. Given that the reaction volume is seeded by a small amount of liquid SO_2 blanketed by an inert gas (e.g., N_2) and the volume periodically receives and releases gaseous molecules in the following pattern (Fig. 5), autocatalysis can be achieved:

(i) H_2S is received at a temperature between the boiling points of H_2S and SO_2;

(ii) the reaction volume is closed at a temperature high enough to allow for $2H_2S + SO_2 \rightarrow 3S + 2H_2O$;

(iii) gases are released at a temperature between the boiling points of H_2O and S;

(iv) O_2 is received at a temperature between the boiling points of O_2 and S;

(v) the reaction volume is closed at a temperature high enough to allow for $S + O_2 \rightarrow SO_2$;

(vi) gases are released at a temperature between the boiling points of O_2 and SO_2, and then starting over at step (i).

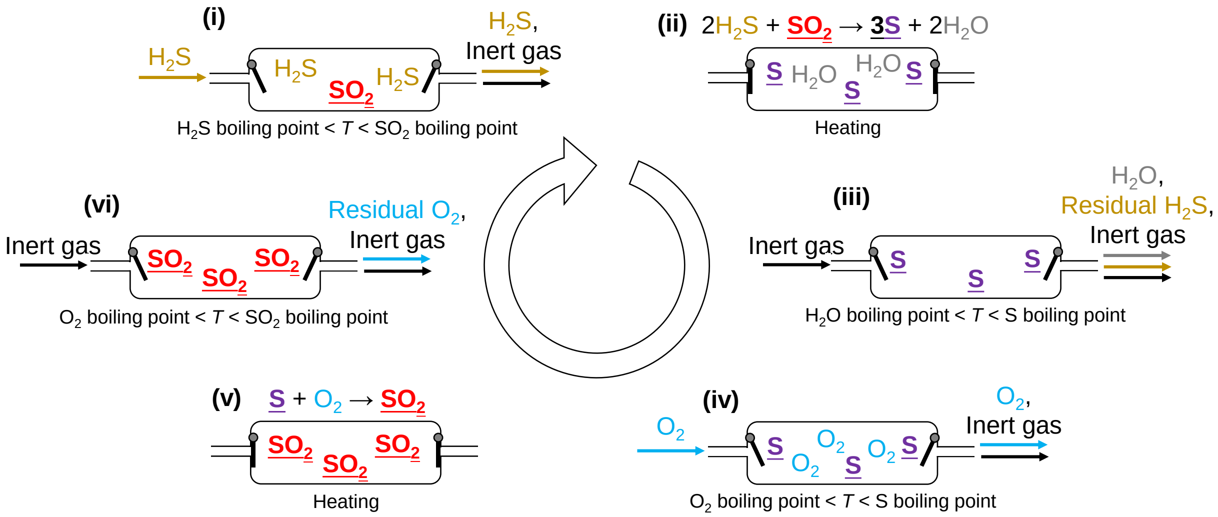

Fig. 5. Autocatalytic amplification of SO_2 and S based on temporal separation between food species. In a periodically open-closed reactor with some liquid SO_2 present at the beginning, the input of food species H_2S and O_2 are temporally separated such that the direct reaction between them is impossible but the autocatalytic amplification of SO_2 and S is still afforded. **(i)** The reactor is open, receiving H_2S at a temperature between the boiling points of H_2S and SO_2. **(ii)** The reactor is closed; the comproportionation between H_2S and SO_2 produces S and H_2O. **(iii)** The reactor is open, releasing H_2O and residual H_2S at a temperature between the boiling points of H_2O and S. **(iv)** The reactor is open, receiving O_2 at a temperature between the boiling points of O_2 and S. **(v)** The reactor is closed; S is oxidized to SO_2 by O_2, completing the autocatalytic cycle. **(vi)** The reactor is open, releasing residual O_2 at a temperature between the boiling points of O_2 and SO_2. Boiling points: $O_2 < H_2S < SO_2 < H_2O < S$.

Under these periodically changing environmental conditions, wherein the food species H_2S and O_2 are provided at different, non-overlapping time intervals (i.e., temporally separated), the observation of autocatalytic amplification of SO_2 and S is expected. In a natural environment, temporal separation may appear in multiple forms, such as intermittent raining, tidal cycles, geyser eruptions, a diurnal cycle, or secondary weathering or runoff patterns that lead to chemical oscillations.

As a basis for comparison, each of these three types of separation is utilized in essential ways by living organisms. For example, CO_2 and H_2O are kinetically separated during photosynthesis; otherwise, CO_2 and H_2O will spontaneously react to produce monosaccharides under sunlight. Intracellular compartments (e.g., the nucleus or the mitochondria in eukaryotes) or macromolecular centralization of multifaceted processes (e.g., ribosomal subunit interactions) can provide a microscopic structural basis of spatial separation (Cuevas-Zuviría et al., 2023; Hartwell et al., 1999). Temporal separation can be mediated by vegetative growth and reproductive growth. One underexplored implication for prebiotic chemistry is that a stoichiometric capability for abiotic autocatalysis may be relatively common across elements, but circumstances facilitating effective separation of key food species and reactions may be a more substantial bottleneck to actualizing autocatalytic dynamics under most cosmochemical and geochemical conditions.

Implications for biosignature interpretation

One of the most challenging aspects of assessing the existence of life beyond Earth is the possibility that chemical conditions on remotely sensed bodies may generate complex variations that resemble biotic influence (Neveu et al., 2018). Autocatalytic cycles in general, and key reactions that compose CompACs in particular, may present significant challenges to biosignature characterization under conditions of pressure, temperature and energy input that exoplanets can facilitate. The collated list of CompACs can serve as a useful compendium for alternative chemical systems to be compared to remote sensing data in the event that anomalous compositions or redox disequilibria are detected (Meadows et al., 2022).

Another question relevant to both biosignature characterization and evolutionary biology is the extent to which bioessential inorganic cofactors are utilized as a result of selection among many possible options, or whether they are more likely to be imprinted upon biology through a broader planetary or physicochemical context (Kacar et al., 2021). Recent studies of reconstructed ancestral metal cofactor binding sites have provided reasonable cause for scrutinizing facile assumptions that link biological utilization to general environmental abundance (Garcia et al., 2020). Responsive chemical dynamics afforded by autocatalysis are potentially impactful to biochemistry whether incorporated within the cell or mediated through external interactions. One intriguing possibility is that the same basic properties of the redox-active class of metal cofactors (e.g. iron, copper, manganese, molybdenum, etc.) (Andreini et al., 2008) that can support complex comproportionation-driven chemical dynamics are, in parallel, coincident with their propensity for biological utilization. In this view, organic chemistry may open novel possibilities for chemical separation (kinetic, temporal, or spatial) that lack geochemical counterparts. To better assess which chemical species played more critical roles during the origins or early evolution of life, theoretical analyses based on principles of chemistry and empirical data obtained by geochemical studies can be leveraged. For example, one may test whether an element with more oxidation states and a Frost diagram where the curve is generally more concave up (Weller et al., 2018, pp. 200–204) is more likely to underlie complex dynamics based on CompACs, and then to test these attributes against the probability of biological uptake.

4. Conclusions

Life utilizes examples of three different separation mechanisms (kinetic, spatial, and temporal) to modulate aspects of cellular homeostasis while at the same time facilitating contingent responses to stimuli. Examples provided by a small number of well-studied autocatalytic systems such as the formose reaction or the Belousov-Zhabotinsky reaction show how only under conditions of effective separation can chemical disequilibria be leveraged to generate suitably “life-like” compositional variations. Based on an analysis of presence of comproportionation reactions observed across elemental groups reported in the literature, we demonstrate that abiotic autocatalytic reaction systems underpinned by comproportionation are more frequent than previously thought and their presence is not restricted to a specific part of the periodic table. CompACs with the potential to interact are probably a general phenomenon rather than a collection of special cases.

The collated CompAC reaction sets establish a starting point for a more systematic assessment of the conditions under which complicated dynamics afforded by autocatalysis can occur in geochemical or cosmochemical settings relevant to the search for life in the universe. Such a systematic assessment may be necessary for pushing forward our understanding of abiogenesis, for disentangling false positive chemical disequilibria from *bona fide* biosignatures, and for circumscribing conditions suitable for the organization of complex chemical systems in general.

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Conflict of interests

The authors declare no conflict of interests.

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