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On the exclusion of exponential autocatalysts by sub-exponential autocatalysts

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ABSTRACT

Selection among autocatalytic species fundamentally depends on their growth law: exponential species, whose number of copies grows exponentially, are mutually exclusive, while sub-exponential ones, whose number of copies grows polynomially, can coexist. Here we consider competitions between autocatalytic species with different growth laws and make the simple yet counterintuitive observation that sub-exponential species can exclude exponential ones while the reverse is, in principle, impossible. This observation has implications for scenarios pertaining to the emergence of natural selection.

1. Introduction

Autocatalysts are molecules that catalyze their own formation, leading to an auto-amplification process: the presence of more autocatalysts of a species leads to a decrease in the time required to produce additional autocatalysts of the same species (Hanopolskyi et al., 2020). This auto-amplification can cause the number of autocatalysts of a species to grow at a rate proportional to their concentration, a relationship mathematically described by $dA/dt = kA$, where A denotes the concentration of the autocatalytic species and k its replication rate. This model results in an exponential growth dynamics, $A(t) \sim e^{kt}$. This is not, however, the only dynamics that autocatalysts may follow. In fact, most non-enzymatic autocatalysts studied to date show a different behavior where their growth rate is sub-linear in their concentration and better described by $dA/dt = kA^n$ with $n < 1$ (Hanopolskyi et al., 2020; von Kiedrowski, 1986; Sievers and Von Kiedrowski, 1998; Wang and Sutherland, 1997; Szathmáry and Gladkih, 1989). This corresponds to a slower, polynomial dynamics, of the form $A(t) \sim t^{1/(1-n)}$. The value $n \approx 1/2$ has most often been observed, leading to $A(t) \sim t^2$, also known as parabolic growth (von Kiedrowski, 1993). In autocatalysis through template replication, this value is understood as arising from product inhibition, the common rebinding of a product to a template (von Kiedrowski, 1993). As far as growth and selection are concerned, however, the underlying mechanisms are not essential.

Instead, past works have stressed that the value of n captures the most fundamental distinction, setting apart exponential ($n = 1$) from sub-exponential ($n < 1$) autocatalytic species (Szathmáry and Gladkih, 1989; Wills et al., 1998; Szathmáry, 1991). While exponential species with different k are mutually exclusive, sub-exponential ones generally coexist, with exclusion taking place only in particular limiting cases (Wills et al., 1998; Lifson and Lifson, 1999; von Kiedrowski and Szathmáry, 2001; Scheuring and Szathmáry, 2001). As a consequence of this result, the field of experimental abiogenesis and the broader community engaged in developing non-enzymatic autocatalysts have concentrated their efforts on creating autocatalysts that can achieve exponential growth (von Kiedrowski, 1993; Hanopolskyi et al., 2020; Robertson et al., 2000; Issac and Chmielewski, 2002; Juritz et al., 2022; Colomb-Delsuc et al., 2015; Virgo et al., 2012; Zeravcic and Brenner, 2014; Dempster et al., 2015; Zhuo et al., 2019). However, the theoretical studies on which this conclusion is based have only considered autocatalytic species with different growth parameters k and the same exponent n, without exploring the possibility for n to differ between competitors. Yet, n is well-recognized to be, as much as k, an effective parameter that can vary between autocatalytic species and can therefore be subject to selection. Here, we extend previous analyses to study the selection of competing autocatalytic species with different exponents n, in addition to different parameters k. As we show, the results are counterintuitive and challenge the view that only exponential autocatalytic species can be excluding: sub-exponential autocatalytic species can exclude exponential ones, but not vice versa.

2. Models

The simplest setting to study autocatalysis under resource limitation is that of a continuous stirred-tank reactor, or chemostat (Novick and Szilard, 1950), where the resource needed for reproduction is introduced and removed at a constant rate, such that its concentration R is

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coupled to the concentration A of the autocatalytic species by

$$\frac{dA}{dt} = kRA^n - DA,\qquad \frac{dR}{dt} = D(R_0 - R) - kRA^n. \tag{1}$$

In these equations, k denotes the species replication rate constant, n signifies its reaction order, and D serves a dual purpose: it represents both a common dilution or decay rate for the autocatalytic species and the resource, as well as the rate at which the resource is replenished from a reservoir with concentration R_0. In what follows, we introduce $\tau = Dt$ and $\kappa = k/D$ to have effectively $D = 1$,

$$\frac{dA}{d\tau} = \kappa RA^n - A,\qquad \frac{dR}{d\tau} = R_0 - R - \kappa RA^n. \tag{2}$$

The minimal concentration of resource that allows an autocatalytic species to grow ($dA/d\tau > 0$) is $R = A^{1-n}/\kappa$. When growth is sub-exponential ($n < 1$), A therefore grows whenever it is small enough. More specifically, a stability analysis indicates that the boundary equilibrium $A = 0$ is always unstable when $n < 1$ ($\lim_{A\to 0} d^2A/d\tau^2 = +\infty$): this implies that sub-exponential autocatalytic species can never become extinct. When, instead, growth is exponential ($n = 1$), survival solely depends on the concentration of resource and is possible only if $R > 1/\kappa$; correspondingly, the boundary equilibrium $A = 0$ is unstable only if $R > 1/\kappa$ in this case. This fundamental difference is the key to understanding why sub-exponential autocatalytic species can coexist while exponential ones exclude each others but also, as we show below, why sub-exponential autocatalytic species can exclude exponential ones but not conversely.

To study exclusion and coexistence of species subject to a common limiting resource, we extend the model to include two species dependent on the same resource,

$$\frac{dA_1}{d\tau} = \kappa_1 RA_1^{n_1} - A_1,\qquad \frac{dA_2}{d\tau} = \kappa_2 RA_2^{n_2} - A_2,\qquad \frac{dR}{d\tau} = R_0 - R - \sum_{i=1}^{2} \kappa_i RA_i^{n_i}. \tag{3}$$

Here, we view the concentration R_0 of resource in the reservoir as an extrinsic or "environmental" parameter, but the parameters κ_i and n_i as parameters intrinsic to each autocatalytic species i and therefore potentially subject to selection. Our point is to identify the intrinsic and extrinsic conditions that lead to the exclusion of one species by another. To this end, we consider that a first, resident species has reached a steady state and analyze whether a second, invading species, can grow when introduced in infinitesimal quantity in the background of the resident one (Szathmáry, 1991; Lifson and Lifson, 1997; Scheuring and Szathmáry, 2001).

3. Results

When the two autocatalytic species are exponential ($n_1 = n_2 = 1$), the invading species faces a concentration of resource $\bar{R}_1$ set by the resident autocatalysts with $\bar{R}_1 = 1/\kappa_1$ if $\kappa_1 > 1/R_0$ and $\bar{R}_1 = R_0$ otherwise, in which case the resident autocatalysts do not survive by themselves. If $\kappa_2 < \kappa_1$, the invading species cannot grow, while if $\kappa_2 > \kappa_1$ and $\kappa_2 > 1/R_0$ it grows to eventually exclude the resident species. This is the essence of the exclusion principle (Szathmáry and Gladkih, 1989): two exponential autocatalytic species cannot coexist if they depend on the same resource and have different replication rate constants.

If the resident species is exponential ($n_1 = 1$) but the invading one is sub-exponential ($n_2 < 1$), however, the situation is different since the sub-exponential species can always grow provided its concentration is low enough, i.e., provided $A_2 < (R/\kappa_2)^{1/(1-n_2)}$. There is therefore no way for the resident exponential autocatalytic species to exclude an invading sub-exponential species. If, on the other hand, the resident species is sub-exponential and the invading species is exponential, two scenarios are possible. If $\kappa_1 > 1/\bar{R}_2$, where $\bar{R}_2$ is the steady state concentration of resource in presence of the sub-exponential species alone, the exponential species can invade and come to coexist with the sub-exponential one. If, however, $\kappa_1 < 1/\bar{R}_2$, the exponential species cannot invade and is therefore excluded.

Beyond this invasion analysis, the condition for exclusion of a exponential ($n_1 = 1$) autocatalytic species by a sub-exponential ($n_2 < 1$) one is

$$R_0 < 1/\kappa_1 + (\kappa_2/\kappa_1)^{\frac{1}{1-n_2}}. \tag{4}$$

This includes, in particular, levels of resource R_0 where the exponential species would survive by itself but is excluded by the sub-exponential species, when $1/\kappa_1 < R_0 < 1/\kappa_1 + (\kappa_2/\kappa_1)^{\frac{1}{1-n_2}}$. This is illustrated in Fig. 1A with the case of an exponentially growing autocatalytic species ($n_1 = 1$) competing with a parabolically growing species ($n_2 = 1/2$).

Finally, when two sub-exponential species ($n_1 < 1$ and $n_2 < 1$) compete, they necessarily coexist. In the particular case where they have same exponent ($n_1 = n_2 = n$), their relative concentration at steady state only depends on their intrinsic parameters, $\bar{A}_1/\bar{A}_2 = (\kappa_1/\kappa_2)^{1/(1-n)}$. More generally, however, their relative concentration is controlled by the amount of resource R_0. In this case again, when R_0 is low, the most abundant one can be, somewhat counterintuitively, the one with lowest exponent n (Fig. 1B).

The analysis can be extended to investigate the conditions under which a sub-exponential autocatalytic species ($n < 1$) can exclude a super-exponential one ($n > 1$). The minimal concentration of resource that allows super-exponential species to grow ($dA/d\tau > 0$) increases as their concentration decreases, $R = 1/(A^{n-1}\kappa)$. Therefore, in a situation where the resident species is sub-exponential, an autocatalytic species introduced in infinitesimal quantity is less advantaged when it is super-exponential than when it is exponential. However, a resident species requires a smaller concentration of resource when it is super-exponential than when it is exponential, and it is therefore more difficult to displace. The results of the competition of a super-exponential species with another species therefore depends strongly on the initial conditions. This has been referred to as the "survival of the first" in previous studies (Plasson et al., 2011). Autocatalytic species growing super-exponentially have, however, not been demonstrated experimentally so far, even though theoretical models that include hypercycles could result in it (Eigen, 1971; Eigen and Schuster, 1977; Eigen, 2013; Szathmáry, 2013).

4. Discussion

The primary aim of this paper is to highlight that a sub-exponential autocatalytic species can exclude an exponential autocatalytic species and, more generally, that a sub-exponential species can dominate one of higher replication order, i.e., following a growth law $dA/dt = kA^n$ with a larger exponent n. This selection for autocatalytic species of lower order occurs because autocatalytic dynamics depends not only on the growth order n, but also on the replication rate constant k: a species with a lower reaction order can outcompete another with a higher reaction order if it has a greater replication rate constant.

Our results rely on the phenomenological equation $dA/dt = kA^n$, which is widely employed to model the competitive dynamics of autocatalysts dependent on a common limiting resource (Szathmáry and Gladkih, 1989; Szathmáry, 1991; Lifson and Lifson, 1999; von Kiedrowski and Szathmáry, 2001; Scheuring and Szathmáry, 2001; Hanopolskyi et al., 2020). In practice, the parameters k and n may be either inferred from experimental data (von Kiedrowski, 1986; Sievers and Von Kiedrowski, 1998; Issac and Chmielewski, 2002; Colomb-Delsuc et al., 2015; Zhang et al., 2007), or derived from mechanistic

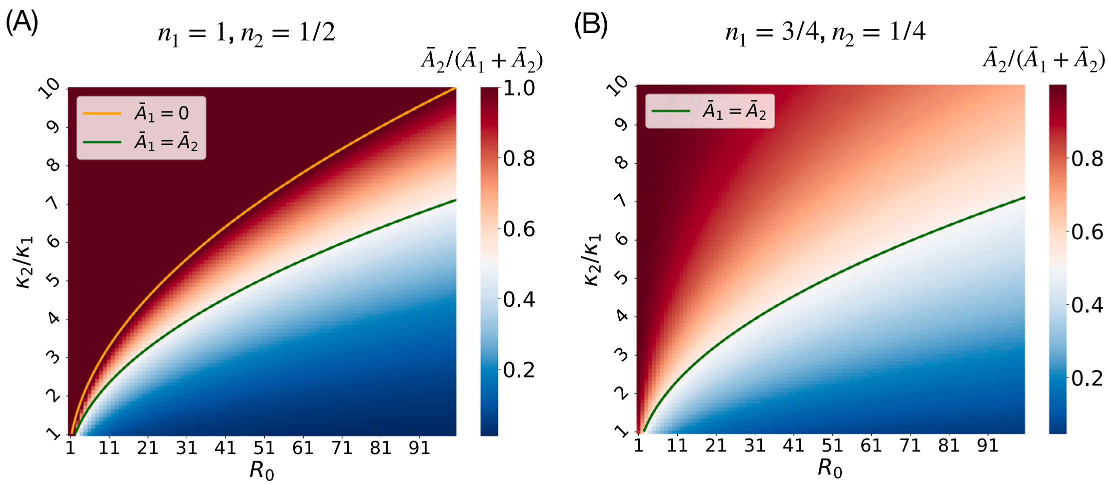

Fig. 1. Exclusion and coexistence in competitions of autocatalytic species with different growth laws, i.e., different exponents n. **A.** Mixture of a exponential and a sub-exponential autocatalytic species: $n_1 = 1$ and $n_2 = 1/2$. **B.** Mixture of two sub-exponential species: $n_1 = 3/4$ and $n_2 = 1/4$. The graphs show the relative concentration at steady state of one of two species, $\bar{A}_2/(\bar{A}_2 + \bar{A}_1)$, as a function of the total concentration of resource R_0 and of the ratio κ_2/κ_1, when $\kappa_1 = 1$. The steady-state concentrations are obtained by numerical integration of the kinetic equations, Eq. (3). In A, the orange line indicates the total concentration of resource R_0 below which the exponential autocatalytic species is excluded ($\bar{A}_1 = 0$). The green lines indicate the total concentration R_0 for which the two species are in same proportion, $\bar{A}_1 = \bar{A}_2$.

models (von Kiedrowski, 1993). Derivations from mechanistic models bring an important nuance by showing that sub-exponential growth typically arises as an approximation of a more general relationship $dA/dt = f(A)$, where $f(A) \sim A^n$ with $n < 1$ for sufficiently high concentrations of A (von Kiedrowski, 1993; Scheuring and Szathmáry, 2001; Wills et al., 1998). At low concentration, however, this sub-exponential growth typically turns into an exponential growth, since $dA/dt \approx f'(0)A$ for small values of A. The presence of these two regimes is well understood when sub-exponential growth stems from product inhibition (von Kiedrowski, 1993; Sievers and Von Kiedrowski, 1998), which is necessarily negligible at low autocatalyst concentration. This dependence of the growth rate on the concentration of autocatalyst is generic and, in the absence of mechanistic details, autocatalytic growth can typically be captured through logistic or similarly shaped functions, for which the growth of an autocatalyst is exponential at low concentration and decreases at higher concentration (Schuster, 2019; Bentea et al., 2017). In any case, this implies that a sub-exponential autocatalytic species following a growth law with these two regimes becomes extinct below a certain concentration, which opens the possibility for an exponential one to exclude it. This does not affect, however, the possibility for the same sub-exponential species to exclude an exponential species, as we have noted.

Current research on autocatalysis is geared towards the experimental design of exponential autocatalytic species, motivated by the desire to observe exclusion, which is viewed as a key step towards achieving evolution by natural selection (Szathmáry and Smith, 1997; Lifson, 2001; Wills et al., 1998; Colomb-Delsuc et al., 2015). The exclusion principle, first formulated by Gause in an ecological context (Gause, 1934), states that among two exponential species, the one with the higher replication rate will outcompete the other, irrespective of the magnitude of the difference between the rates (Szathmáry and Gladkih, 1989). Yet, our findings indicate that sub-exponential autocatalytic species can outperform their exponential and even super-exponential counterparts, and can therefore also cause selection by exclusion. As such, sub-exponential autocatalytic species set constraints on the evolutionary emergence of the first exponential ones. The issue takes on particular importance when we recognize the interrelated nature of the parameters k and n arising from mechanistic models. These parameters are indeed influenced by shared physical factors like reaction volume and autocatalyst-substrate interaction strength, resulting in a trade-off between them. Given that we have shown that k can be the primary determinant of autocatalyst dominance, this type of physical correlation further calls into question an exclusive emphasis on exponential autocatalysts.

CRediT authorship contribution statement

Yann Sakref: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Olivier Rivoire:** Conceptualization, Formal analysis, Funding acquisition, Investigation, 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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References

Bentea, Lucian, Watzky, Murielle A., Finke, Richard G., 2017. Sigmoidal nucleation and growth curves across nature fit by the finke-watzky model of slow continuous nucleation and autocatalytic growth: Explicit formulas for the lag and growth times plus other key insights. J. Phys. Chem. C 121 (9), 5302–5312.
Colomb-Delsuc, Mathieu, Mattia, Elio, Sadownik, Jan W., Otto, Sijbren, 2015. Exponential self-replication enabled through a fibre elongation/breakage mechanism. Nat. Commun. 6 (7427).
Dempster, Joshua M., Zhang, Rui, Cruz, Monica Olvera De La, 2015. Self-replication with magnetic dipolar colloids. Phys. Rev. E 92 (4), 042305.
Eigen, Manfred, 1971. Selforganization of matter and the evolution of biological macromolecules. Naturwissenschaften volume 58, 465–523.
Eigen, Manfred, 2013. From Strange Simplicity to Complex Familiarity. Oxford University Press.
Eigen, Manfred, Schuster, Peter, 1977. A principle of natural self-organization. Naturwissenschaften 64 (11), 541–565.
Gause, J.F., 1934. The Struggle for Existence. The Williams & Wilkins Company.
Hanopolskyi, Anton I., Smaliak, Viktoryia A., Novichkov, Alexander I., Semenov, Sergey N., 2020. Autocatalysis: Kinetics, mechanisms and design. ChemSystemsChem 3 (1), e2000026.
Issac, Roy, Chmielewski, Jean, 2002. Approaching exponential growth with a self-replicating peptide. J. Am. Chem. Soc. 124 (24), 6808–6809.

Juritz, Jordan, Poulton, Jenny M., Ouldridge, Thomas E., 2022. Minimal mechanism for cyclic templating of length-controlled copolymers under isothermal conditions. J. Chem. Phys. 156 (7).
Lifson, Shneior, 2001. On the crucial stages in the origin of animate matter. J. Theoret. Biol. 44 (1), 1–8.
Lifson, Shneior, Lifson, Hanna, 1997. Coexistence and darwinian selection among replicators: Response to the preceding paper by scheuring and szathmary. J. Mol. Evol. 212 (1), 107–109.
Lifson, Shneior, Lifson, Hanna, 1999. A model of prebiotic replication: Survival of the fittest versus extinction of the unfittest. J. Theoret. Biol. 199 (4), 425–433.
Novick, Aaron, Szilard, Leo, 1950. Description of the chemostat. Science 112 (2920), 715–716.
Plasson, Raphael, Brandenburg, Axel, Jullien, Ludovic, Bersini, Hugues, 2011. Autocatalysis: At the root of self-replication. Artif. Life 17 (3), 219–236.
Robertson, Andrew, Sinclair, Andrew J., Philp, Douglas, 2000. Minimal self-replicating systems. Chem. Soc. Rev. 29 (2), 141–152, Publisher: Royal Society of Chemistry.
Scheuring, Istvan, Szathmáry, Eörs, 2001. Survival of replicators with parabolic growth tendency and exponential decay. J. Theoret. Biol. 212 (1), 99–105.
Schuster, Peter, 2019. What is special about autocatalysis? Monatsh Chem. 150, 763–775.
Sievers, Dirk, Von Kiedrowski, Günter, 1998. Self-Replication of Hexadeoxynucleotide Analogues: Autocatalysis versus Cross-Catalysis. Chem. Eur. J. 4 (4), 629–641.
Szathmáry, Eörs, 1991. Simple growth laws and selection consequences. Trends Ecol. Evol. 6 (11), 366–370.
Szathmáry, Eörs, 2013. On the propagation of a conceptual error concerning hypercycles and cooperation. J. Syst. Chem. 4 (1), 1.
Szathmáry, Eörs, Gladkih, Irina, 1989. Sub-exponential growth and coexistence of non-enzymatically replicating templates. J. Theoret. Biol. 138 (1), 55–58.
Szathmáry, Eörs, Smith, John Maynard, 1997. From replicators to reproducers: The first major transitions leading to life. J. Theoret. Biol. 187 (4), 555–571.
Virgo, Nathaniel, Fernando, Chrisantha, Bigge, Bill, Husbands, Phil, 2012. Evolvable physical self-replicators. Artif. Life 18 (2), 129–142.
von Kiedrowski, Günter, 1986. A self-replicating hexadeoxynucleotide. Angew. Chem., Int. Ed. Engl. 25 (10), 932–935.
von Kiedrowski, Gunter, 1993. Minimal replicator theory I: Parabolic versus exponential growth. In: Bioorganic Chemistry Frontiers, Vol. 3. Spring.
von Kiedrowski, G., Szathmáry, Eörs, 2001. Selection versus coexistence of parabolic replicators spreading on surfaces. Selection 1 (3), 173–180.
Wang, Bing, Sutherland, Ian O., 1997. Self-replication in a Diels–Alder reaction. Chem. Commun. 16, 1495–1496.
Wills, Peter R., Kauffman, Stuart A., Stadler, Barbel M.R., Stadler, Peter F., 1998. Selection dynamics in autocatalytic systems: Templates replicating through binary ligation. Bull. Math. Biol. 118 (60), 1073–1098.
Zeravcic, Zorana, Brenner, Michael P., 2014. Self-replicating colloidal clusters. Proc. Natl. Acad. Sci. 111 (5), 1748–1753.
Zhang, David Yu, Turberfield, Andrew J., Yurke, Bernard, Winfree, Erik, 2007. Engineering Entropy-Driven Reactions and Networks Catalyzed by DNA, Vol. 318.
Zhuo, Rebecca, Zhou, Feng, He, Xiaojin, Sha, Ruojie, Seeman, Nadrian C., Chaikin, Paul M., 2019. Litters of self-replicating origami cross-tiles. Proc. Natl. Acad. Sci. 116 (6), 1952–1957.