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Thermodynamic dissipation does not bound replicator growth and decay rates

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ABSTRACT

In a well-known paper, Jeremy England derived a bound on the free energy dissipated by a self-replicating system [J. L. England, "Statistical physics of self-replication," J. Chem. Phys. **139**, 121923 (2013)]. This bound is usually interpreted as a universal relationship that connects thermodynamic dissipation to replicator per-capita decay and growth rates. We argue from basic thermodynamic principles against this interpretation. In fact, we suggest that such a relationship cannot exist in principle, because it is impossible for a thermodynamically consistent replicator to undergo both per-capita growth and per-capita decay back into reactants. Instead, replicator may decay into separate waste products, but in that case, replication and decay are two independent physical processes, and there is no universal relationship that connects their thermodynamic and dynamical properties.

I. INTRODUCTION

Research in thermodynamics has shown that there are universal relationships between the thermodynamic and dynamic properties of nonequilibrium processes. The most famous relationship, termed *local detailed balance* (LDB), says that the statistical irreversibility of a microscopic process is directly related to the thermodynamic dissipation, i.e., the entropy production in the system and the environment during that process.[2] The generality of LDB hints at the possibility of universal bounds on the thermodynamic properties of living systems.

This idea inspired a 2013 paper by England on the thermodynamics of self-replicating systems.[1] Consider a population of replicators with per-capita replication rate g and per-capita decay rate δ, where decay is defined as the "reversion of the replicator back into the exact set of reactants in its environment out of which it was made."[1] A system with fixed per-capita rates of replication g and decay δ may be said to exhibit *first-order growth* and *first-order decay*. The stochastic dynamics of first-order growth and decay may be described by a Markovian birth–death master equation,

$$\dot{p}_n(t) = (n-1)gp_{n-1}(t) + (n+1)\delta p_{n+1}(t) - n(g+\delta)p_n(t),$$

where $p_n(t)$ is the probability that the population contains n replicators at time t. For large population sizes n, this master equation may be approximated as[3]

$$\dot{p}_n(t) \approx ng(p_{n-1}(t) - p_n(t)) - \delta n(p_n(t) - p_{n+1}(t)), \quad (1)$$

which appears as Eq. (9) in Ref. 1. Finally, neglecting fluctuations for large n, the expected population size at time t will grow exponentially as

$$\langle n \rangle_{p(t)} \approx \langle n \rangle_{p(0)} e^{(g-\delta)t}. \quad (2)$$

Equation (2) relates per-capita replication and decay rates in the master equation to long-term population dynamics.

The main result of England's paper[1] [Eq. (10)] is a thermodynamic bound on the ratio of growth to decay rates,

$$\Delta s_{\text{tot}} \geq \ln \frac{g}{\delta}, \quad (3)$$

where Δs_{tot} is the entropy production incurred when a single replicator makes a copy of itself. The quantity Δs_{tot} is proportional to the nonequilibrium free energy dissipated during replication.[4] England illustrates the bound using two real-world systems of interest: an

RNA-based molecular replicator constructed by Lincoln and Joyce[5] and an *E. coli* bacterium.

Bound (3) appears to bridge two different worlds: the physical world of thermodynamic dissipation and the biological world of replicator dynamics. From an intellectual perspective, we find England's proposal stimulating and elegant. However, by studying the thermodynamics of simple molecular replicators,[6] we have come to find that bound (3) must be interpreted with great care.

In this paper, we argue that—contrary to standard interpretations of England's result—inequality (3) does not provide a thermodynamic bound on the growth and decay rates of replicators. First, in Sec. III, we derive a kind of "impossibility theorem." It shows that no bound like (3) can apply to self-replicating systems, because a replicator cannot undergo both first-order growth and first-order decay back into reactants without violating the laws of thermodynamics. Rather, as we discuss in Sec. IV, two options present themselves. First, a replicator may decay via the reverse process of autocatalysis, in which case decay will not be first-order. Alternatively, a replicator may undergo first-order decay into a different set of waste products, in which case there is no universal relationship between the physical properties of the two independent processes of replication and decay.

We emphasize that our analysis employs the same setup and theoretical framework (stochastic thermodynamics) as does England's paper. Thus, our work is not meant as a critique of the general approach of stochastic thermodynamics, but rather of a particular application to replicating systems.

Before proceeding to our analysis, we first review the derivation of England's result, in the process filling in a few subtle details.

II. BACKGROUND

We begin by reviewing the setup and derivation of England's bound (3) in Ref. 1. We proceed in several steps. In Sec. II A, we derive a "weak" version of LDB that applies at the level of coarse-grained macrostates. This is a general result that relates dissipation and statistical irreversibility for arbitrary choices of macrostates and systems, whether replicating or not. In Sec. II B, we derive England's bound by applying the weak version of LDB to the special case of self-replicating systems. In Sec. II C, we derive a generalized version of England's bound, which will be useful for our analysis below.

A. Local detailed balance and coarse-graining

Consider a system coupled to a heat bath at temperature T, which undergoes an undriven (time-independent) process over time interval $[t, t+\tau]$. The system's microscopic dynamics are described by the conditional probability $P_\tau(x \to y)$ that the system ends in microstate y at time $t+\tau$, given that it started in microstate x at time t. We generally focus on chemical or biological systems in solution that are overdamped, meaning that their momentum degrees-of-freedom equilibrate quickly and can be ignored at the microscopic level of description. Each microstate x might specify the position of each particle in the system. In other cases, the microstates may represent coarse-grained "mesostates," e.g., they may specify only the positions of the solute particles and the counts of different particle types in a well-mixed system. In all cases, we require that each microstate x is internally in equilibrium. Another requirement is that the microscopic dynamics are Markovian over timescale τ, meaning that the probability of microstate at time $t+\tau$ depends only on the microstate at time t.

The system possesses an equilibrium Boltzmann distribution,

$$P_{\mathrm{eq}}(x) = \frac{1}{Z} e^{-E(x)/k_B T}, \tag{4}$$

where $E(x)$ is the energy of microstate x. According to the principle of "detailed balance," the forward and backward probability fluxes across each microscopic transition $x \to y$ balance in equilibrium,

$$P_{\mathrm{eq}}(x) P_\tau(x \to y) = P_{\mathrm{eq}}(y) P_\tau(y \to x). \tag{5}$$

The ratio of the forward to backward transition probabilities can be written as

$$\frac{P_\tau(x \to y)}{P_\tau(y \to x)} = \frac{P_{\mathrm{eq}}(y)}{P_{\mathrm{eq}}(x)} = e^{[E(x)-E(y)]/k_B T}. \tag{6}$$

By the first law of thermodynamics, the energy lost by the system during the transition $x \to y$ is equal to the heat transferred to the bath, $Q(x \to y) = E(x) - E(y)$, and therefore,

$$\frac{P_\tau(x \to y)}{P_\tau(y \to x)} = e^{Q(x \to y)/k_B T}. \tag{7}$$

Observe that $Q(x \to y)/k_B T$ is the increase in the thermodynamic entropy of the heat bath during the transition $x \to y$. Equation (7) is a special case of the general principle of "local detailed balance" (LDB), which says that the statistical irreversibility of microscopic transitions is related to the increase in the thermodynamic entropy of the environment.

Suppose that the system is associated with two macrostates **I** and **II**, i.e., two subsets of microstates, which, in principle, may be chosen arbitrarily. Macrostate **I** is described by a probability distribution $P_{\mathbf{I}}(x)$ over microstates with support restricted to **I**. Macrostate **II** is also described by a probability distribution over microstates $P_{\mathbf{II}}(y)$. This distribution is defined by propagating the distribution $P_{\mathbf{I}}$ under the microscopic dynamics and then conditioning on membership in macrostate **II**,

$$P_{\mathbf{II}}(y) = \frac{\mathbb{1}_{\mathbf{II}}(y) \int_{\mathbf{I}} P_{\mathbf{I}}(x) P_\tau(x \to y)\, dx}{\int_{\mathbf{II}} \int_{\mathbf{I}} P_{\mathbf{I}}(x) P_\tau(x \to y')\, dx\, dy'},$$

where $\mathbb{1}$ is the indicator function. In principle, the distributions **I** and **II** may be arbitrarily far from internal equilibrium.

Entropy production refers to the increase in the entropy of the system and its environment during a process. In stochastic thermodynamics, the entropy production incurred when going from macrostate **I** to macrostate **II** is defined as[4,7]

$$\Delta s_{\mathrm{tot}}(\mathbf{I} \to \mathbf{II}) = [S(P_{\mathbf{II}}) - S(P_{\mathbf{I}})] + \langle Q \rangle_{\mathbf{I} \to \mathbf{II}} / k_B T, \tag{8}$$

where $S(P_{\mathbf{II}}) - S(P_{\mathbf{I}})$ is the increase in the system's Shannon entropy and $\langle Q \rangle_{\mathbf{I} \to \mathbf{II}}$ is the average heat generated. Here, we use the notation

$$\langle \cdots \rangle_{\mathbf{I} \to \mathbf{II}} = \frac{\int_{\mathbf{II}} \int_{\mathbf{I}} P_{\mathbf{I}}(x) P_\tau(x \to y) \cdots dx\, dy}{\int_{\mathbf{II}} \int_{\mathbf{I}} P_{\mathbf{I}}(x) P_\tau(x \to y)\, dx\, dy} \tag{9}$$

to indicate the expectation of a trajectory-level quantity conditioned on initial macrostate **I** and final macrostate **II**.

To derive a bound on the entropy production, consider the conditional probability $\pi(\mathbf{I} \to \mathbf{II})$ that the final microstate belongs to macrostate **II**, given that the initial microstate is drawn from $P_{\mathbf{I}}$. Consider also the conditional probability $\pi(\mathbf{II} \to \mathbf{I})$ that the final microstate belongs to macrostate **I**, given that the initial microstate is drawn from $P_{\mathbf{II}}$. As shown in Ref. 1, $\Delta s_{\mathrm{tot}}(\mathbf{I} \to \mathbf{II})$ is bounded by the logarithmic ratio of these two transition probabilities,

$$\Delta s_{\mathrm{tot}}(\mathbf{I} \to \mathbf{II}) \geq \ln \frac{\pi(\mathbf{I} \to \mathbf{II})}{\pi(\mathbf{II} \to \mathbf{I})}. \tag{10}$$

Bound (10) can be derived from the microscopic principle of LDB (7). To do so, let us write the macrostate transition probabilities as

$$\pi(\mathbf{I} \to \mathbf{II}) = \int_{\mathbf{I}} \int_{\mathbf{II}} P_{\mathbf{I}}(x) P_\tau(x \to y)\, dx\, dy, \tag{11}$$

$$\pi(\mathbf{II} \to \mathbf{I}) = \int_{\mathbf{II}} \int_{\mathbf{I}} P_{\mathbf{II}}(y) P_\tau(y \to x)\, dy\, dx. \tag{12}$$

The ratio of these transition probabilities can be written as

$$\frac{\pi(\mathbf{II} \to \mathbf{I})}{\pi(\mathbf{I} \to \mathbf{II})} = \frac{\int_{\mathbf{II}} \int_{\mathbf{I}} P_{\mathbf{I}}(x) P_\tau(x \to y) e^{\ln \frac{P_{\mathbf{II}}(y)}{P_{\mathbf{I}}(x)} - \ln \frac{P_\tau(x \to y)}{P_\tau(y \to x)}}\, dy\, dx}{\int_{\mathbf{I}} \int_{\mathbf{II}} P_{\mathbf{I}}(x) P_\tau(x \to y)\, dx\, dy}.$$

Using the expression of LDB (7) and notation (9) gives

$$\begin{aligned} \frac{\pi(\mathbf{II} \to \mathbf{I})}{\pi(\mathbf{I} \to \mathbf{II})} &= \left\langle e^{-\left[\ln \frac{P_{\mathbf{I}}(x)}{P_{\mathbf{II}}(y)} + Q(x \to y)/k_B T\right]} \right\rangle_{\mathbf{I} \to \mathbf{II}} \\ &\geq e^{-\left\langle \ln \frac{P_{\mathbf{I}}(x)}{P_{\mathbf{II}}(y)} + Q(x \to y)/k_B T \right\rangle_{\mathbf{I} \to \mathbf{II}}} = e^{-\Delta s_{\mathrm{tot}}(\mathbf{I} \to \mathbf{II})}, \end{aligned}$$

where the second line uses Jensen's inequality and then Eq. (8) [note that $\left\langle \ln \frac{P_{\mathbf{I}}(x)}{P_{\mathbf{II}}(y)} \right\rangle_{\mathbf{I} \to \mathbf{II}} = S(P_{\mathbf{II}}) - S(P_{\mathbf{I}})$]. Bound (10) follows by taking logarithms and rearranging.

Bound (10) is a general inequality that applies to various choices of macrostates and systems, whether replicating or not. It may be interpreted as a "weak" version of LDB that applies to transitions between coarse-grained macrostates. It is weak in the sense that it relates statistical irreversibility and thermodynamic dissipation via an inequality, in contrast to the stronger version of LDB (7) that holds as an equality at the microscopic level.

The weak version of LDB (10) is derived using Jensen's inequality, and it turns into equality when Jensen's inequality is tight. In turn, Jensen's inequality is tight when the quantity $\ln \frac{P_{\mathbf{I}}(x)}{P_{\mathbf{II}}(y)} + Q(x \to y)/k_B T$ (the fluctuating dissipation incurred by microscopic trajectory $x \to y$) is the same for every trajectory that connects macrostate **I** to macrostate **II**. There are two ways this can happen.

The first is that the macrostates are in internal equilibrium, meaning that the macrostate distribution has a restricted Boltzmann form,

$$P_{\mathbf{I}}(x) = \frac{1}{Z_{\mathbf{I}}} \mathbb{1}_{\mathbf{I}}(x) e^{-E(x)/k_B T}, \qquad Z_{\mathbf{I}} = \int_{\mathbf{I}} e^{-E(x)/k_B T}\, dx,$$

and similarly for $P_{\mathbf{II}}$ and $Z_{\mathbf{II}}$. With a bit of rearranging, we find that the fluctuating dissipation is then given by

$$\ln \frac{P_{\mathbf{I}}(x)}{P_{\mathbf{II}}(y)} + Q(x \to y)/k_B T = \ln Z_{\mathbf{II}} - \ln Z_{\mathbf{I}}.$$

The quantity $\ln Z_{\mathbf{II}} - \ln Z_{\mathbf{I}}$ is proportional to the loss of equilibrium free energy in going from macrostate **I** to macrostate **II**, and it does not depend on x or y. In this case, there are no fluctuations in the fluctuating dissipation, and the weak version of LDB becomes an equality, $\Delta s_{\mathrm{tot}}(\mathbf{I} \to \mathbf{II}) = \ln \frac{\pi(\mathbf{I} \to \mathbf{II})}{\pi(\mathbf{II} \to \mathbf{I})} = \ln Z_{\mathbf{II}} - \ln Z_{\mathbf{I}}$.

The second way that the weak version of LDB can be tight is when all the trajectories that connect macrostates **I** and **II** incur the same dissipation, even though the two macrostates may not be in internal equilibrium. For instance, this may occur because there is a single chemical reaction, or a single sequence of chemical reactions, that transforms the system between macrostates **I** and **II**.

Conversely, when there are large fluctuations in the dissipation incurred by different trajectories $x \to y$, Jensen's inequality may be very loose, therefore also the weak version of LDB may be very loose. Such fluctuations can occur when the macrostates are not in internal equilibrium, and there exist multiple alternative pathways that go between macrostates **I** and **II**. It is a well-known limitation of stochastic thermodynamics that the exact relationship between statistical irreversibility and thermodynamic dissipation only holds at the microscopic level.[2] It is also known that statistical irreversibility at the coarse-grained level often underestimates the true amount of dissipation by many orders of magnitude (for example, see Ref. 8). We return to this issue in Sec. IV below, when we discuss thermodynamics bounds for replicating systems with multiple degradation pathways.

B. Application to replicating systems

Following England,[1] we now apply the weak version of LDB (10) to the special case of replicating systems. To do so, we define macrostate **I** as the set of microstates that contain a single replicator, along with any reactants needed for successful replication. Macrostate **II** is defined as the set of microstates that contain two replicators: the parent replicator found in macrostate **I** and its new offspring, as well as any side products that result from replication. Importantly, although the overall system is not driven, macrostate **I** may contain highly energetic reactants that drive replication forward.

The transition probability $\pi(\mathbf{I} \to \mathbf{II})$ over time τ is approximated using the per-capita replication rate as $\pi(\mathbf{I} \to \mathbf{II}) \approx g\tau$. The transition probability $\pi(\mathbf{II} \to \mathbf{I})$, corresponding to the reversion of the new offspring back into "the exact set of reactants in its environment out of which it was made," is approximated using the per-capita decay rate as $\pi(\mathbf{II} \to \mathbf{I}) \approx \delta\tau$. This is not $2\delta\tau$ because, in England's analysis, the parent and offspring replicators are distinguished under **II**, and $\pi(\mathbf{II} \to \mathbf{I})$ refers only to the decay of the new offspring [see also discussion below (14)]. Plugging these two approximations into (10) and simplifying recovers England bound (3).

We note that England's bound involves the same per-capita growth g and decay rates δ that appear in the birth–death mas-

ter equation (1) that describes population-level dynamics. This birth–death equation specifies a continuous-time Markov chain, in which the statistics of future replication and decay events depend only on the current number of replicators, not on prior history. The assumption of Markovian population dynamics is standard in population biology[9] and chemistry,[10,11] and it is a reasonable starting point for relating dissipation to population dynamics. In principle, it may be justified under a separation-of-timescales, where the timescales of division and internal relaxation are shorter than waiting times between replication events.

C. Generalization of England's bound

Observe that the term $\Delta s_{\rm tot} \equiv \Delta s_{\rm tot}(\mathbf{I} \to \mathbf{II})$ in England's bound (3) refers specifically to the entropy produced when the system goes from a macrostate with one replicator to a macrostate with two replicators. Without additional assumptions, this does not necessarily equal the entropy produced when the system goes from two to three replicators, three to four replicators, etc. However, to study the thermodynamics of self-replicating systems, we need a general expression for the entropy production that holds at all population sizes.

Here, we introduce this general expression for the entropy production, and we then use it to derive a generalized form of England's bound. In particular, we consider the entropy production when a system is transformed from a macrostate with n replicators to a macrostate with n' replicators. As we show in the Appendix, this entropy production is given by

$$\Delta s_{\rm tot}(n \to n') \approx (n' - n)\sigma_{\rm rep} + \ln \frac{n!}{n'!}. \tag{13}$$

The first term $(n' - n)\sigma_{\rm rep}$ is the contribution that is extensive in the number of additional replicators. The term $\sigma_{\rm rep}$ is the entropy produced during the synthesis of a single replicator (and side products) from reactants, and its value will depend on the specific physical properties of the replicator [see Eq. (A9) in the Appendix]. The second term, $\ln(n!/n'!)$, reflects the entropy increase due to the change of the concentration of replicators in solution. Equation (13) holds even when $n' < n$ and even when the right hand side of Eq. (13) is negative (in which case the transformation $n \to n'$ is thermodynamically disfavored).

To derive Eq. (13) in the Appendix, we introduce several standard assumptions: (1) replicators and other chemical species are found in dilute, well-mixed solution, (2) different replicators are statistically indistinguishable from each other, as are the other chemical species, and (3) macrostates corresponding to $1, 2, 3, \ldots$ replicators differ only in terms of the counts of replicators, reactants, and side products involved in replication. Importantly, we do not assume that the replicators are in internal equilibrium, so the result also applies to far-from-equilibrium systems such as living cells.

We now derive a generalized version of England's bound (3). For two macrostates containing n and $n+1$ replicators, Eq. (13) gives $\Delta s_{\rm tot}(n \to n+1) \approx \sigma_{\rm rep} - \ln(n+1)$. Assuming first-order growth and decay, the transition probabilities between these two macrostates may be approximated as $\pi(n \to n+1) \approx ng\tau$ and $\pi(n+1 \to n) \approx (n+1)\delta\tau$. The weak form of LDB (10) gives $\Delta s_{\rm tot}(n \to n+1) \geq \ln \frac{ng}{(n+1)\delta}$. Combining and simplifying leads to our generalized bound,

$$\sigma_{\rm rep} \geq \ln \frac{g}{\delta} + \ln n, \tag{14}$$

which relates the per-capita dissipation $\sigma_{\rm rep}$, per-capita growth g, per-capita decay δ, and the population size n.

Note that in England's analysis, macrostate **II** (with two replicators) is defined so that the parent and offspring replicators are distinguished, and the transition probability $\pi(\mathbf{II} \to \mathbf{I}) \approx \delta\tau$ refers only to the decay of the offspring. In our derivation of Eq. (13), the replicators are treated as statistically indistinguishable, and the transition $n+1 \to n$ represents the decay of any of the $n+1$ replicators, occurring with probability $\approx (n+1)\delta\tau$. The difference is mostly one of convention, not physical content. For the $1 \to 2$ transition $(n = 1)$, two bounds (3) and (14) are essentially equivalent.

Careful readers may have noticed a thermodynamic inconsistency in the generalized version of England's bound (14). This inconsistency is considered in depth in Sec. III.

III. IMPOSSIBILITY THEOREM

England's bound is usually interpreted as a universal relationship that relates thermodynamic dissipation to replicator per-capita growth and decay rates. However, we now argue against the validity of this interpretation, even in principle. Our critique is based on an "impossibility theorem," which shows that a thermodynamically consistent replicator cannot undergo both first-order growth and first-order decay back into reactants.

There are several equivalent ways to demonstrate our impossibility result. We do it via two general theoretical arguments, plus a concrete model of a simple autocatalytic chemical system.

The first (and perhaps simplest) way to demonstrate our impossibility result is to consider England's bound, in the generalized form (14) that applies to arbitrary population sizes. A thermodynamically consistent replicator has a finite per-capita dissipation $\sigma_{\rm rep}$. However, bound (14) holds for all $n \geq 0$, which can only be true if $\sigma_{\rm rep} = \infty$. In fact, considering the derivation of this bound, it is only possible to have a finite $\sigma_{\rm rep}$ and fixed per-capita growth rate $0 < g < \infty$ if the decay probability scales in a non-first-order manner, as $\pi(n+1 \to n) \propto n^2$ or faster. Conversely, it is only possible to have a finite $\sigma_{\rm rep}$ and fixed per-capita decay rate $0 < \delta < \infty$ if the replication probability does not scale with population size.

A second way to demonstrate our impossibility result is to consider two macrostates: macrostate **1** contains a single replicator (same as **I** above), while macrostate **0** contains no replicators, only the reactants needed for replication. Assuming first-order decay, the transition probability $\pi(\mathbf{1} \to \mathbf{0}) \approx \delta\tau$ reflects the decay of the single replicator into reactants. The transition probability $\pi(\mathbf{0} \to \mathbf{1}) \approx \gamma\tau$ captures the spontaneous (uncatalyzed) formation of replicator from reactants, where we introduced the rate constant γ of uncatalyzed formation. Combining Eq. (13) and the weak form of LDB (10) gives a bound on the entropy produced during the decay process $\mathbf{1} \to \mathbf{0}$,

$$\Delta s_{\rm tot}(\mathbf{1} \to \mathbf{0}) \approx -\sigma_{\rm rep} \geq \ln \frac{\delta}{\gamma}. \tag{15}$$

Meanwhile, the generalized England's bound (14) for $n = 1$ implies that $\ln(g/\delta) \leq \sigma_{\text{rep}}$. Combining gives the inequality

$$\ln \frac{g}{\delta} \leq \ln \frac{\gamma}{\delta}, \tag{16}$$

which implies $g \leq \gamma$. However, the defining property of self-replication is *autocatalysis*, meaning that the formation of a new replicator in the presence of an existing replicator should be much faster than spontaneous formation directly from reactants,

$$\gamma \ll g. \tag{17}$$

In fact, perfect first-order growth would require that $\gamma = 0$. More generally, if inequality (17) did not hold, one could not interpret macrostate transitions like $n \to n + 1$ as replication events, since the new replicator could instead form spontaneously from reactants. It is clear that inequalities (16) and (17) are in contradiction with each other.

Finally, we illustrate our impossibility result using a simple but concrete model. Consider an autocatalytic chemical reaction such as

$$X + A \underset{\kappa_1^-}{\overset{\kappa_1}{\rightleftharpoons}} 2X, \tag{18}$$

where X is a replicating molecule and A is a reactant necessary for replication. For simplicity, we assume that the reaction is elementary with mass-action kinetics. We also assume that molecular counts are sufficiently large such that the system can be described in terms of deterministic number concentrations, $n = [X]$ and $a = [A]$. Reaction (18) exhibits forward flux $\kappa_1 na$ with forward rate constant κ_1 and reverse flux $\kappa_1^- n^2$ with backward rate constant κ_1^-. We note that the reverse flux is second-order in n. For convenience, we will sometimes use the term *uncopying* to refer to the reverse direction of autocatalysis, i.e., the catalyzed reversion of the replicator back into reactants ($2X \to X + A$).

Suppose that X can also decay back into reactant in an uncatalyzed fashion,

$$X \underset{\kappa_2^-}{\overset{\kappa_2}{\rightleftharpoons}} A. \tag{19}$$

This decay reaction has forward flux $\kappa_2 n$ and reverse flux $\kappa_2^- a$. Reactions (18) and (19) have opposite stoichiometry and therefore opposite free energy of reaction $-\Delta G$. In the setting of chemical thermodynamics, local detailed balance implies that $-\Delta G$ (in units of J per reaction) is equal to the logarithmic ratio of the forward to backward fluxes,[12]

$$-\Delta G = k_B T \ln \frac{\kappa_1 na}{\kappa_1^- n^2} = k_B T \ln \frac{\kappa_2^- a}{\kappa_2 n}. \tag{20}$$

In order for the system to exhibit first-order growth rather than uncatalyzed formation, it must be that $\kappa_1 na \gg \kappa_2^- a$ so that the creation of replicators is dominated by autocatalysis, not the reverse of the decay reaction. In order for the system to undergo first-order decay, rather than second-order uncopying, it must be that $\kappa_2 n \gg \kappa_1^- n^2$. However, these two inequalities are incompatible with Eq. (20), highlighting the thermodynamic inconsistency. The underlying reason is that replication ($X + A \to 2X$) is thermodynamically favored over uncopying ($2X \to X + A$) to the same extent that uncatalyzed formation ($A \to X$) is favored over first-order decay ($X \to A$). Thus, if first-order decay is the dominant pathway for destruction, uncatalyzed formation must be the dominant pathway for formation.

Of course, if the first-order decay reaction (19) occurs at negligible rates, then the system would exhibit first-order growth via the forward direction of (18). In addition, decay back into reactants would occur due to uncopying, the reverse direction of the catalyzed reaction (18). However, in this case, decay will not be first-order [e.g., the elementary autocatalytic reaction (18) leads to second-order decay, $\kappa_1^- n^2$], so it will be inconsistent with the master equation (1). It will also be inconsistent with the exponential growth equation (2), which only holds for first-order growth and first-order decay.

Above, we showed that a thermodynamically consistent replicator cannot simultaneously exhibit first-order growth and first-order decay back into reactants. Of course, many replicators do exhibit both first-order growth and first-order decay. As we discuss in Sec. IV, they do so by decaying into different waste products, instead of reverting back into their original reactants.

IV. ALTERNATIVE DEGRADATION PATHWAYS

Until now, we followed England's analysis in assuming that the decay transition involves "reversion of the replicator back into the exact set of reactants in its environment out of which it was made." However, in most replicators of interest, the actual decay process that is observed is not reversion back into reactants, but rather a separate degradation process into different waste products. Such replicators can exhibit both first-order growth and first-order decay. However, as we argue here, if there is no general relationship between the processes of replication and decay, then there cannot be a universal thermodynamic bound that constrains their replication and decay rates. A related point was raised in an insightful paper by Saakian and Qian.[3]

As a concrete example, consider again the autocatalytic replicator (18) discussed above. Imagine that the dominant decay process is neither uncopying, the reverse of reaction (18), nor uncatalyzed reversion back to reactants, reaction (19). Rather, decay involves a separate reaction,

$$X \underset{\kappa_3^-}{\overset{\kappa_3}{\rightleftharpoons}} W, \tag{21}$$

where W is a waste product different from the reactant A.

As an example, let us consider the RNA replicator by Lincoln and Joyce[5] discussed in England's paper.[1] Here, replication consumes a reactant RNA molecule with a triphosphate group and releases an inorganic pyrophosphate as a side product. [The reaction scheme of the RNA replicator is slightly more complex than elementary scheme (18), but this does not change the general point of our argument.] Decay can proceed along one of two paths. The first is the reverse of replication, known as "pyrophosphorolysis,"[13–15] in which a pyrophosphate is consumed and a triphosphate-charged RNA molecule is produced. The second is spontaneous "hydrolysis"

of the RNA phosphodiester bond. Hydrolysis is a separate reaction that does not involve pyrophosphate, and it produces a "waste" RNA molecule, with the triphosphate group replaced by a monophosphate group.

We use the term *degradation* to refer to the decay of the replicator into different waste products, as opposed to reversion into the initial reactants. Because replication and degradation are independent processes, not reverse directions of the same process, in general, they have independent thermodynamic properties. In such cases, the derivation of Eq. (13) in the Appendix does not apply, nor does the impossibility result derived from it in Sec. III. Moreover, both replication and degradation may be thermodynamically favored in the forward direction, allowing simultaneous first-order growth and first-order degradation. For instance, for an autocatalytic replicator with reactions (18) and (21), the per-capita replication rate may be taken as $g = \kappa_1 a$ (over timescales where the reactant concentration a is approximately constant) and the per-capita degradation rate may be taken as $\delta = \kappa_3$.

Notably, when considering actual examples,[1] England calculates the decay rate as the rate of degradation into waste products, rather than the rate of reversion back into reactants. For example, for the RNA replicator, his estimate is based on the rate of RNA hydrolysis, not pyrophosphorolysis. For the *E. coli*, his estimate is based on the time required for all peptide bonds in a single cell to undergo hydrolysis. This differs from the rate of reversion back into reactants, which would involve the reverse reaction of protein bond formation, de-respiration of released carbon dioxide into glucose and oxygen, etc.

Nonetheless, in England's original bound, δ refers to the rate of reversion back into original reactants, rather than degradation into other waste products. To make the connection to degradation, England assumes that reversion is slower than degradation,

$$\delta \leq \delta', \tag{22}$$

where δ' is the degradation rate. Bound (3) then holds in the weaker form with the reversion rate δ replaced by the degradation rate δ', as in $\Delta s_{\mathrm{tot}} \geq \ln(g/\delta')$. However, there are some problems with this approach.

For one, the bound may be violated, because there is no *a priori* reason that reversion must be slower than degradation. For example, for the RNA replicator, England assumes that hydrolysis (degradation) is faster than pyrophosphorolysis (reversion), but, in fact, there is no universal relationship between the rates of two processes. Moreover, the rate of pyrophosphorolysis depends on the concentration of pyrophosphate,[13–15] while that of hydrolysis does not. At increased pyrophosphate concentrations, reversion by pyrophosphorolysis has been observed to proceed as fast as a minute per nucleotide,[14] orders of magnitude faster than degradation by hydrolysis (estimated at ~4 years per nucleotide[1]).

Even for an entire *E. coli* bacterium, it may be debated whether degradation is always faster than reversion of an offspring cell into starting reactants. There are various scenarios that can be imagined that accelerate reversion; for instance, the parent cell might run its Krebs cycle in reverse. Of course, there is no doubt that such a reversion is hyper-astronomically unlikely, but one may still wonder whether it is undeniably *more unlikely* than the hydrolysis of all peptide bonds, whose probability England estimates at $e^{-6.7\times10^{10}}$ (!) given a 20-min generation time.[1] In any case, common-sense intuitions about such astronomically unlikely events should be treated with caution.

The best way to demonstrate that degradation is faster than reversion is to observe how a replicator actually decays. In many cases, degradation will be the dominant decay process. However, even in such cases, there is usually no meaningful thermodynamic constraint on growth and degradation rates, because the two sides of (22) refer to two independent physical processes and their difference is completely uncontrolled.

Consider again *E. coli* bacteria. They are never observed to undergo hydrolysis of all peptide bonds, instead they simply die at the rate of $\approx 5 \times 10^{-4}$ per generation.[16] This death rate can be related to England's estimate of the entropy produced during *E. coli* replication, $\approx 3.3 \times 10^{11}$.[1] Plugging these numbers into bound (3) gives

$$\Delta s_{\mathrm{tot}}(\mathbf{I} \to \mathbf{II}) = 3.3 \times 10^{11} \geq 7.6 \approx -\ln\left(5 \times 10^{-4}\right). \tag{23}$$

This inequality is not biologically or physically meaningful because the two sides differ by a factor of about 50×10^9. To put things in perspective, the inequality tells us that no less than $7.6\ k_B T$ of free energy must be dissipated in order to replicate a bacterium. This is a tiny amount, less than the dissipation produced by the hydrolysis of a single ATP molecule ($\approx 20\ k_B T$).

Above, we argued that the inequality between reversion and degradation (22) may be violated, or it may hold but be so weak that it is irrelevant. Nonetheless, one may wonder whether the reverse transition probability $\pi(\mathbf{II} \to \mathbf{I})$, as appears in inequality (10), may be defined to account for both reversion and degradation so that no further weakening of the bound is necessary. In fact, whether $\pi(\mathbf{II} \to \mathbf{I})$ accounts for degradation or not depends in a subtle way on the definition of macrostates **I** and **II**. As an example, consider a replicator that undergoes degradation into waste species W. Now imagine two different ways of defining these macrostates. Under the first definition, the microstates in **I** and **II** all contain the same fixed number of waste molecules W. Since degradation increases the number of waste molecules, the transition $\mathbf{II} \to \mathbf{I}$ will not include degradation and the transition probability $\pi(\mathbf{II} \to \mathbf{I})$ will only account for reversion back to reactants. Under the second (arguably more realistic) definition, the precise number of waste molecules varies among different microstates in **I** and/or **II**. Then, the transition probability $\pi(\mathbf{II} \to \mathbf{I})$ will account for both pathways, reversion and degradation.

Nonetheless, under either definition, we end up with the same very weak thermodynamic bound (23). Imagine that degradation is many orders of magnitude more likely than reversion, as in the *E. coli* that undergoes degradation by death at the rate of $\delta' = 5 \times 10^{-4}$ per generation. Under the first definition of the macrostates, $\pi(\mathbf{II} \to \mathbf{I})$ will account only for reversion and therefore be tiny compared to $\delta'\tau$, so inequalities (22) and (23) will be incredibly weak. Under the second definition of the macrostates, $\pi(\mathbf{II} \to \mathbf{I})$ will account for both reversion and decay, and inequality (22) may be nearly tight. However, the entropy production $\Delta s_{\mathrm{tot}}(\mathbf{I} \to \mathbf{II})$ and transition probability $\pi(\mathbf{I} \to \mathbf{II})$ that characterize replication do not depend significantly on whether the degradation waste products are allowed to fluctuate or not, since these waste molecules are not involved in replication. Therefore, to the extent

that $\pi(\mathbf{II} \to \mathbf{I})$ becomes much larger and (22) tighter, the weak LDB bound (10) will become looser. This reflects the fact, discussed above in Sec. II A, that the weak version of LDB may become very loose when macrostates are internally out of equilibrium and multiple alternative pathways are present.

V. CONCLUSION

In this paper, we considered England's bound (3) that relates thermodynamic dissipation $\Delta s_{\mathrm{tot}}(\mathbf{I} \to \mathbf{II})$ to per-capita decay δ and growth g rates. This bound has physical meaning if decay is the reverse process of replication, meaning that the offspring replicator reverts back to its original reactants. However, as we showed in our impossibility theorem, for a thermodynamically consistent replicator, this reverse process cannot be first-order; hence, δ cannot be interpreted as a per-capita decay rate.

Alternatively, the decay rate may be defined as the per-capita rate of degradation into different waste products δ', rather than original reactants. In this case, there is no universal relationship between the degradation rate δ' and physical properties of replication, such as the growth rate g and the entropy production $\Delta s_{\mathrm{tot}}(\mathbf{I} \to \mathbf{II})$. Therefore, the resulting bound (3) is not physically meaningful, and it can even be violated.

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AUTHOR DECLARATIONS

Conflict of Interest

The author has no conflicts to disclose.

Author Contributions

Artemy Kolchinsky: Conceptualization (equal); Formal analysis (equal); Funding acquisition (equal); Writing – original draft (equal); Writing – review & editing (equal).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

APPENDIX: DERIVATION OF EQ. (13)

Here, we derive expression (13) for the entropy produced when transforming a system from a macrostate with n replicators to a macrostate with n' replicators. We note that similar results can be found in the literature on chemical thermodynamics.[17]

We consider a system containing some replicators, which may be chemical or biological in nature. The system may also contain $K-1$ other chemical species that serve as additional reactants or side products of replication. We label the different species using $\alpha \in \{1, \dots, K\}$, with $\alpha = 1$ indicating the replicator and $\alpha \in \{2, \dots, K\}$ indicating reactants and side products.

Each microstate x is written as $x = (\vec{c}, \vec{y}, \vec{s})$, where $\vec{c} = (c_1, \dots, c_K)$ indicates the vector of population counts of species $\alpha \in \{1, \dots, K\}$, $\vec{y}$ encodes the state of all particles of all species, and $\vec{s}$ encodes the state of all solvent particles, plus any other subsystems (catalytic surfaces, etc.) that are not directly involved in replication as a reactant or a side product. The vector $\vec{y} = (\vec{y}^{(1)}, \dots, \vec{y}^{(K)})$ is further decomposed into vectors $\vec{y}^{(\alpha)}$ representing particles of each species, and each $\vec{y}^{(\alpha)}$ is further decomposed as $\vec{y}^{(\alpha)} = (\vec{y}^{(\alpha,1)}, \dots, \vec{y}^{(\alpha,c_\alpha)})$, where $\vec{y}^{(\alpha,i)}$ encodes the state of particle i of species α. In particular, $\vec{y}^{(\alpha,i)}$ encodes the position of the particle within the reactor volume, plus internal degrees of freedom (e.g., configurational, rotational, and vibrational modes, internal structure in the case of complex particles, etc.). The order of the indices i of the particles of each species is arbitrary, so any $\vec{y}^{(\alpha)}$ and $\vec{y}^{(\alpha)\prime}$ that differ only in the ordering of particles are equivalent.

The macrostate containing n replicators is represented by $P_n(x) \equiv P_n(\vec{c}, \vec{y}, \vec{s})$, a distribution over microstates with support restricted to microstates with $c_1 = n$.

We introduce several standard assumptions. First, the macrostates P_n differ only in the number of replicators and reactant/product species, while other statistical properties are the same. In particular, the statistical properties of the solvent are the same, $P_n(\vec{s}) \equiv P(\vec{s})$, and so are the conditional probabilities of population counts, up to differences due to consumption/creation of species by replicator synthesis,

$$P_n(\vec{c}|\vec{s}) = P_0(\vec{c} - n\vec{\Delta}|\vec{s}). \tag{A1}$$

The vector $\vec{\Delta}$ specifies the stoichiometry of replicator synthesis, where $\Delta_\alpha > 0$ is the number of α created as side products and $\Delta_\alpha < 0$ is the number of α consumed as reactants. By definition, $\Delta_1 = 1$ (the synthesis of a replicator creates one replicator).

In addition, we assume that the particles of species $\alpha \in \{1, \dots, K\}$ are in dilute, well-mixed solution without long-range interactions. Then, the energy of a typical microstate $x = (\vec{c}, \vec{y}, \vec{s})$ is approximately additive,

$$E(\vec{c}, \vec{y}, \vec{s}) \approx E_\emptyset(\vec{s}) + \sum_{\alpha=1}^{K} \sum_{i=1}^{c_\alpha} E_\alpha(\vec{y}^{(\alpha,i)}, \vec{s}). \tag{A2}$$

Here, $E_\emptyset(\vec{s})$ is the solvent energy and $E_\alpha(\,\cdot\,, \vec{s})$ is the single-particle energy for species α, which may account for particle–solvent interactions. Assumptions of well-mixedness imply that correlations between particles are negligible, once conditioned on the state of the solvent $\vec{s}$. Thus, the probability of any microstate $x = (\vec{c}, \vec{y}, \vec{s})$ factors in the following manner:

$$P_n(\vec{c}, \vec{y}, \vec{s}) \approx P(\vec{s}) P_n(\vec{c}|\vec{s}) \prod_{\alpha=1}^{K} \prod_{i=1}^{c_\alpha} P_{n,\alpha,i}(\vec{y}^{(\alpha,i)}|\vec{s}), \tag{A3}$$

where $P_{n,\alpha,i}$ is the conditional probability distribution of particle i of species α in a system with n replicators.

Finally, we assume that particles in each species have indistinguishable statistical properties,

$$P_{n,\alpha,i}(\,\cdot\,|\vec{s}, \vec{c}) = \omega_\alpha(\,\cdot\,|\vec{s}). \tag{A4}$$

The conditional distribution ω_α encodes the statistical properties of a single particle of species α, and it does not depend on particle label i, replicator count n, nor the counts of other species. Importantly, we do not assume that the distribution ω_α has a Boltzmann form. Thus, the internal state of the replicators and other species may be arbitrarily far-from-equilibrium. For instance, when studying biological replicators, ω_1 might represent the highly nonequilibrium steady-state distribution of a living bacterium.

We now evaluate the entropy produced when the system is transformed from macrostate P_n to macrostate $P_{n'}$. As in Eq. (8), the entropy production is given by

$$\Delta s_{\text{tot}}(n \to n') = [S(P_{n'}) - S(P_n)] + \langle Q \rangle_{n \to n'}/k_B T, \tag{A5}$$

where the heat is equal to the change of loss of expected energy, $\langle Q \rangle_{n \to n'} = \langle E \rangle_{P_n} - \langle E \rangle_{P_{n'}}$.

To calculate the expected energy and entropy, it will be useful to consider the energy and entropy contribution from a single particle of species α as

$$\mathcal{E}_\alpha := \int P(\vec{s}) \omega_\alpha(\vec{z}|\vec{s}) E_\alpha(\vec{z}, \vec{s})\, d\vec{z},$$
$$\mathcal{S}_\alpha := -\int P(\vec{s}) \omega_\alpha(\vec{z}|\vec{s}) \ln\, \omega_\alpha(\vec{z}|\vec{s})\, d\vec{z}.$$

Using the above definitions and assumptions, we may write the expected energy under P_n as

$$\begin{aligned}
\langle E \rangle_{P_n} &\approx \langle E_\emptyset(\vec{s}) \rangle_P + \int d\vec{s} \sum_{\alpha=1}^{K} \sum_{c_\alpha=1} P_n(c_\alpha, \vec{s}) c_\alpha \langle E_\alpha \rangle_{\omega_\alpha(\cdot|\vec{s})} \\
&= \langle E_\emptyset(\vec{s}) \rangle_P + \int d\vec{s} \sum_{\alpha} \sum_{c_\alpha=1} P_0(c_\alpha, \vec{s})(c_\alpha + n\Delta_\alpha) \langle E_\alpha \rangle_{\omega_\alpha(\cdot|\vec{s})} \\
&= \langle E \rangle_{P_0} + n \sum_{\alpha=1}^{K} \Delta_\alpha \mathcal{E}_\alpha \\
&= \langle E \rangle_{P_0} + n \left[\mathcal{E}_1 + \sum_{\alpha=2}^{K} \Delta_\alpha \mathcal{E}_\alpha \right].
\end{aligned} \tag{A6}$$

In the second line, we performed the change of variables $c_\alpha \mapsto c_\alpha + n\Delta_\alpha$ and then used Eq. (A1).

To compute the Shannon entropy, we write

$$\begin{aligned}
S(P_n) &= S[P(\vec{s})] + S[P_n(\vec{c}|\vec{s})] + S[P_n(\vec{y}|\vec{c}, \vec{s})] \\
&\approx S[P(\vec{s})] + S[P_0(\vec{c}|\vec{s})] + \sum_{\alpha=1}^{K} S[P_n(\vec{y}^{(\alpha)}|\vec{c}, \vec{s})],
\end{aligned} \tag{A7}$$

where we first used the chain rule for Shannon entropy, $S[P_n(\vec{c}|\vec{s})] = S[P_0(\vec{c} - n\vec{\Delta}|\vec{s})] = S[P_0(\vec{c}|\vec{s})]$, and Eq. (A3). For each species α, we have

$$S[P_n(\vec{y}^{(\alpha)}|\vec{c}, \vec{s})] = \int d\vec{s} \sum_{c_\alpha=1} P_n(c_\alpha, \vec{s}) \left[c_\alpha \langle -\ln\, \omega_\alpha(\vec{z}|\vec{s}) \rangle_{\omega_\alpha(\cdot|\vec{s})} - \ln\, c_\alpha! \right],$$

where $-\ln c_\alpha!$ accounts for the fact that the indexing order of the particles does not matter. We further rewrite the right side as

$$\begin{aligned}
&\int d\vec{s} \sum_{c_\alpha=1} P_0(c_\alpha, \vec{s}) \left[(c_\alpha + n\Delta_\alpha) \langle -\ln\, \omega_\alpha(\vec{z}|\vec{s}) \rangle_{\omega_\alpha(\cdot|\vec{s})} - \ln (c_\alpha + n\Delta_\alpha)! \right] \\
&\quad = S[P_0(\vec{y}^{(\alpha)}|\vec{c}, \vec{s})] + n\Delta_\alpha \mathcal{S}_\alpha + \left\langle \ln \frac{c_\alpha!}{(c_\alpha + n\Delta_\alpha)!} \right\rangle_{P_0},
\end{aligned}$$

where we again performed the change of variables $c_\alpha \mapsto c_\alpha + n\Delta_\alpha$. Combining with Eq. (A7) gives

$$S(P_n) = S(P_0) + n\Delta_\alpha \mathcal{S}_\alpha + \left\langle \ln \frac{c_\alpha!}{(c_\alpha + n\Delta_\alpha)!} \right\rangle_{P_0}. \tag{A8}$$

We simplify the factorial terms in Eq. (A8) in the following manner. For the replicator species $\alpha = 1$, we write

$$\left\langle \ln \frac{c_1!}{(c_1 + n\Delta_1)!} \right\rangle_{P_0} = -\ln\, n!,$$

which follows from $\Delta_1 = 1$ and $c_1 = 0$ for all microstates with support under P_0. For non-replicator species $\alpha > 1$, we assume that their counts are very large, relative to the number consumed or produced by replicator synthesis. We then apply Stirling's approximation $\ln x! \approx x \ln x - x$ and simplify

$$\begin{aligned}
\ln \frac{c_\alpha!}{(c_\alpha + n\Delta_\alpha)!} &\approx n\Delta_\alpha - c_\alpha \ln \frac{c_\alpha + n\Delta_\alpha}{c_\alpha} - n\Delta_\alpha \ln (c_\alpha + n\Delta_\alpha) \\
&\approx -n\Delta_\alpha \ln (c_\alpha + n\Delta_\alpha) \\
&\approx -n\Delta_\alpha \ln\, c_\alpha.
\end{aligned}$$

These approximations are valid when $c_\alpha \gg |n\Delta_\alpha|$.

Finally, combining with Eq. (A8) gives

$$S(P_n) \approx S(P_0) + n \left[\mathcal{S}_1 + \sum_{\alpha=2}^{K} \Delta_\alpha (\mathcal{S}_\alpha - \langle \ln\, c_\alpha \rangle_{P_0}) \right] - \ln\, n!.$$

Plugging this and Eq. (A6) into Eq. (A5) gives expression (13) in the main text, with per-capita entropy production,

$$\sigma_{\text{rep}} \approx \mathcal{S}_1 - \frac{\mathcal{E}_1}{k_B T} + \sum_{\alpha=2}^{K} \Delta_\alpha \left(\mathcal{S}_\alpha - \langle \ln\, c_\alpha \rangle_{P_0} - \frac{\mathcal{E}_\alpha}{k_B T} \right). \tag{A9}$$

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