Thermodynamic dissipation does not bound replicator growth and decay rates

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In a well-known paper, Jeremy England derived a bound on the free energy dissipated by a self-replicating system [England, "Statistical physics of self-replication", *The Journal of Chemical Physics*, 2013]. This bound is usually interpreted as a universal relationship that links thermodynamic dissipation to the replicator's per-capita decay and growth rates. Contrary to this interpretation, we argue from thermodynamic principles that such a relationship cannot exist. In particular, we show that it is impossible for a system to undergo both replication and per-capita decay back into reactants. While it is possible for a system to undergo replication and decay into separate waste products, in that case replication and decay are two independent physical processes, and there is no universal relationship between 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 temporal irreversibility of a stochastic physical process is related to the amount of entropy produced in the system and the environment during that process [2]. The generality of LDB suggests that it may imply 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]. In this paper, England considered a population of replicators that evolves according to a stochastic master equation [Eq. (9) in Ref. [1]],

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

where $p_n(t)$ is the probability of n replicators, g is the per-capita replication rate, and δ is the per-capita decay rate, defined as the "reversion of the replicator back into the exact set of reactants in its environment out of which it was made". For large population sizes, fluctuations can be neglected and $n(t)$, the population at time t, will grow exponentially as

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

This shows how the per-capita replication and decay rates in the master equation are related to long-term population dynamics. We will refer to replication and decay with per-capita rates g and δ as *first-order replication* and *first-order decay*.

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

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

where Δs_{tot} is the entropy production incurred when a single replicator makes a copy of itself. As we explain below, the quantity Δs_{tot} is proportional to the free energy dissipated during replication. England illustrates the bound using two real-world systems of interest: an RNA-based molecular replicator constructed by Lincoln and Joyce [3] and an *E. coli* bacterium.

The 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 [4], we have come to find that the bound (3) must be interpreted with great care.

In this paper, we argue that, contrary to standard interpretations of this result, inequality (3) does not provide a thermodynamic bound on the growth and decay rates of replicators. In fact, we argue that there cannot be a bound of this type. We begin by proving a general "impossibility theorem" that shows that it is thermodynamically infeasible for a first-order replicator to undergo first-order decay back into reactants. Instead, a replicator can decay either by undergoing the reverse process of autocatalysis, in which case decay is not first-order, or by decaying into a different set of waste products, in which case there cannot be a universal relationship between properties of the two independent processes of replication and decay.

Nonetheless, we emphasize that the bound (3) is valid as long as Δs_{tot}, g and δ are appropriately interpreted. Specifically, the bound applies to the forward and reverse transitions between two fixed macrostates of an arbitrary physical system, which may or may not be a replicator. However, as we show below, considering transitions between two fixed macrostates is not enough to capture the kinetics and thermodynamics of replication.

II. BACKGROUND

We begin with a high-level summary of the derivation of England's bound (3). For details, we refer the reader to Ref. [1].

England considers an undriven system coupled to a heat bath at temperature T. The system is associated with two arbitrary macrostates **I** and **II**, i.e., two subsets of microstates. Macrostate **I** is associated with a probability distribution over microstates, $p_{\mathbf{I}}(i)$, whose support is restricted to **I**. Macrostate **II** is also associated with a probability distribution $p_{\mathbf{II}}(i)$ with

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support restricted to $\mathbf{II}$, defined by propagating the distribution $p_{\mathbf{I}}$ under the microscopic stochastic dynamics over time dt and then conditioning on membership in macrostate $\mathbf{II}$.

The entropy produced when going from macrostate $\mathbf{I}$ to macrostate $\mathbf{II}$ is

$$\Delta s_{\text{tot}}(\mathbf{I} \to \mathbf{II}) = \langle Q \rangle / k_B T + \Delta s_{\text{int}} \,. \tag{4}$$

Here, $\langle Q \rangle$ is the expected amount of heat released to the bath during the transition $\mathbf{I} \to \mathbf{II}$, k_B is Boltzmann constant, and

$$\Delta s_{\text{int}} = S(p_{\mathbf{II}}) - S(p_{\mathbf{I}})$$

is the increase of the internal Shannon entropy in going from macrostate $\mathbf{I}$ to $\mathbf{II}$. We may also write the entropy production in terms of the dissipated free energy,

$$\Delta s_{\text{tot}}(\mathbf{I} \to \mathbf{II}) = (\mathcal{F}_{\mathbf{I}} - \mathcal{F}_{\mathbf{II}})/k_B T, \tag{5}$$

where $\mathcal{F}_{\mathbf{I}} = \langle E \rangle_{p_{\mathbf{I}}} - k_B T\, S(p_{\mathbf{I}})$ is the free energy of macrostate $\mathbf{I}$ given energy function E, and similarly for $\mathcal{F}_{\mathbf{II}}$. Eqs. (4) and (5) are equivalent since $\langle Q \rangle = \langle E \rangle_{p_{\mathbf{I}}} - \langle E \rangle_{p_{\mathbf{II}}}$ by the first law of thermodynamics.

To derive a bound on the entropy production, England calculates the (conditional) transition probability $\pi(\mathbf{I} \to \mathbf{II})$ that the final microstate belongs to macrostate $\mathbf{II}$, given that the initial microstate is drawn from $p_{\mathbf{I}}$. He also calculates the transition probability $\pi(\mathbf{II} \to \mathbf{I})$ that the final microstate belongs to macrostate $\mathbf{I}$, given that the initial microstate is drawn from $p_{\mathbf{II}}$. England shows that the entropy production involved in going from $\mathbf{I}$ to $\mathbf{II}$ is bounded by the log ratio of these two transition probabilities,

$$\Delta s_{\text{tot}}(\mathbf{I} \to \mathbf{II}) \geq \ln \frac{\pi(\mathbf{I} \to \mathbf{II})}{\pi(\mathbf{II} \to \mathbf{I})}. \tag{6}$$

This result is derived by assuming overdamped dynamics and invoking the principle of LDB, along with some mathematical manipulation. It is a useful and general inequality that applies to many types of physical processes.

To make the connection to self-replication, England defines macrostate $\mathbf{I}$ as the set of microstates that contain a single replicator, plus reactants needed for successful replication. Macrostate $\mathbf{II}$ is defined as the set of microstates that contain two replicators: the parent replicator found in microstate $\mathbf{I}$ and its new offspring. We emphasize that although the overall system is undriven, macrostate $\mathbf{I}$ may nonetheless contain high-energy reactants that drive the replication transition $\mathbf{I} \to \mathbf{II}$ forward. The transition probability $\pi(\mathbf{I} \to \mathbf{II})$ of replication is approximated using a first-order replication rate g as $\pi(\mathbf{I} \to \mathbf{II}) \approx g\, dt$. The transition probability $\pi(\mathbf{II} \to \mathbf{I})$, which corresponds to the reversion of the offspring replicator back into "the exact set of reactants in its environment out of which it was made", is approximated using a first-order decay rate δ as $\pi(\mathbf{II} \to \mathbf{I}) \approx \delta\, dt$ (see also [5]).

III. IMPOSSIBILITY THEOREM

We now point out an issue with the above analysis which arises from the fact that it is not possible for a system to undergo both first-order replication and first-order decay back into reactants.

To introduce our argument, we consider another macrostate $\mathbf{0}$ whose microstates do not contain any replicator but only the reactants needed for replication. The transition probability $\pi(\mathbf{I} \to \mathbf{0})$ refers to the reversion of the single replicator in $\mathbf{I}$ back into reactants, while the transition probability $\pi(\mathbf{0} \to \mathbf{I})$ refers to the spontaneous (uncatalyzed) formation of replicator from reactants. Applying the inequality (6) to these macrostates yields a bound on the entropy produced during the transition $\mathbf{I} \to \mathbf{0}$:

$$\Delta s_{\text{tot}}(\mathbf{I} \to \mathbf{0}) = (\mathcal{F}_{\mathbf{I}} - \mathcal{F}_{\mathbf{0}})/k_B T \geq \ln \frac{\pi(\mathbf{I} \to \mathbf{0})}{\pi(\mathbf{0} \to \mathbf{I})}, \tag{7}$$

where $\mathcal{F}_{\mathbf{0}}$ is the free energy of macrostate $\mathbf{0}$.

At the same time, 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. Thus, we may say that a system is self-replicating only if

$$\pi(\mathbf{0} \to \mathbf{I}) \ll \pi(\mathbf{I} \to \mathbf{II}). \tag{8}$$

If this condition did not hold, we should not interpret the transition $\mathbf{I} \to \mathbf{II}$ as "replication", since the new offspring can arise due to spontaneous formation from reactants. Also, we could not describe replication with a first-order rate constant g as in the master equation (1), since the growth term would not be linear in population size.

Suppose that each replicator undergoes first-order decay with rate δ, as in the master equation (1). Then, the transition probability of ending in macrostate $\mathbf{0}$ after starting in macrostate $\mathbf{I}$ should be approximately $\delta\, dt$, the same as the transition probability of ending in $\mathbf{I}$ after starting in $\mathbf{II}$:

$$\pi(\mathbf{I} \to \mathbf{0}) \approx \delta\, dt \approx \pi(\mathbf{II} \to \mathbf{I}). \tag{9}$$

Observe also that $\mathcal{F}_{\mathbf{I}} - \mathcal{F}_{\mathbf{0}}$, the decrease of free energy when a replicator undergoes reversion back into reactants, should be the opposite of $\mathcal{F}_{\mathbf{I}} - \mathcal{F}_{\mathbf{II}}$, the decrease of free energy when reactants are converted into a new replicator during a replication event. This implies that the entropy production for the two transitions should be related as

$$\Delta s_{\text{tot}}(\mathbf{I} \to \mathbf{0}) \approx -\Delta s_{\text{tot}}(\mathbf{I} \to \mathbf{II}) \tag{10}$$

Plugging (9) and (10) into (7) gives

$$\Delta s_{\text{tot}}(\mathbf{I} \to \mathbf{II}) \leq \ln \frac{\pi(\mathbf{0} \to \mathbf{I})}{\pi(\mathbf{II} \to \mathbf{I})}.$$

This can be combined with (6) and simplified to give

$$\pi(\mathbf{0} \to \mathbf{I}) \geq \pi(\mathbf{I} \to \mathbf{II}). \tag{11}$$

However, we have arrived at a contradiction with the necessary condition for self-replication (8).

The idea behind this argument can also be illustrated using a simple but concrete model. Consider an autocatalytic chemical reaction such as

$$X + A \underset{\kappa_1^-}{\overset{\kappa_1}{\rightleftharpoons}} 2X \,, \tag{12}$$

where X is a replicator molecule and A is a substrate reactant. For simplicity, we assume that the reaction is elementary with mass-action kinetics, and that the molecular counts are sufficiently large such that the system can be described in terms of deterministic number concentrations, $n = [X]$ and $a = [A]$. Reaction (12) 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, that is the catalyzed reversion of the replicator back into substrate ($2X \to X + A$).

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

$$X \underset{\kappa_2^-}{\overset{\kappa_2}{\rightleftharpoons}} A\,. \tag{13}$$

This decay reaction will have forward flux $\kappa_2 n$ and reverse flux $\kappa_2^- a$. The two reactions (12) and (13) have opposite stoichiometry and therefore opposite free energy of reaction $-\Delta G$. The principle of LDB states that $-\Delta G$ (in units of J per reaction) can be expressed as the log ratio of forward and backward fluxes [6],

$$-\Delta G/k_B T = \ln \frac{\kappa_1 na}{\kappa_1^- n^2} = \ln \frac{\kappa_2^- a}{\kappa_2 n}. \tag{14}$$

Now, in order for the system to exhibit first-order replication rather than uncatalyzed formation, it must be that $\kappa_1 na \gg \kappa_2^- a$, such 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 $\kappa_2 n \gg \kappa_1^- n^2$. It can be seen that these two inequalities are incompatible with Eq. (14), highlighting the thermodynamic inconsistency.

In essence, 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 (13) occurs at negligible rates, then the system would exhibit first-order replication via the forward direction of (12). In addition, decay back into reactants would occur due to uncopying, the reverse direction of the catalyzed reaction (12). In terms of the transition probabilities between macrostates, $\pi(\mathbf{II} \to \mathbf{I})$ would be non-zero due to uncopying, while $\pi(\mathbf{I} \to \mathbf{0})$ would be negligible since decay would only occur if two or more replicators are present. Equality would no longer hold in (9), thereby avoiding the undesirable conclusion that replicators must form spontaneously from reactants.

However, in the case of uncopying (catalyzed decay), the decay rate of any particular replicator will depend on how many other replicators it encounters, and so decay cannot be first-order (e.g., the elementary autocatalytic reaction (12) leads to second-order decay, $\kappa_1^- n^2$). This kind of decay is inconsistent with the master equation (1), which has the first-order term δn, as well as the exponential growth equation (2), which only holds for first-order replication and first-order decay.

To summarize, a thermodynamically consistent replicator cannot simultaneously exhibit first-order replication and first-order decay back into reactants. Of course, many replicators do exhibit both first-order replication and first-order decay. As we discuss in the next section, they do so by decaying into different waste products, not reverting back into their original reactants.

IV. ALTERNATIVE DEGRADATION PATHWAYS

Until now, we followed England in assuming that the decay transition $\mathbf{II} \to \mathbf{I}$ 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 decay process that is actually observed is not reversion back into reactants, but rather degradation into different waste products. Such a system can exhibit both first-order replication and 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 relationship between thermodynamics of replication and decay rates. We note that some related issues were raised in an insightful paper by Saakian and Qian [7].

As a concrete example, consider again the autocatalytic replicator discussed in the previous section. Imagine that the dominant decay process is neither uncatalyzed reversion back to reactants, as in reaction (13), nor uncopying, as in the reverse of reaction (12). Rather, decay involves a separate reaction

$$X \underset{\kappa_3^-}{\overset{\kappa_3}{\rightleftharpoons}} W, \tag{15}$$

where W is a waste product different from the substrate reactant A. Let us consider the RNA replicator [3][8] discussed in England's paper [1]. In this system, the replication reaction consumes a reactant RNA molecule with a triphosphate group and releases an inorganic pyrophosphate as a side product. Decay can proceed in one of two ways. The first is the reverse of replication, known as *pyrophosphorolysis* in the literature [9–11], 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. For this reason, Eq. (10) does not apply, and both replication and degradation may be thermodynamically favored in the forward direction, allowing simultaneous first-order replication and first-order degradation. For instance, for an autocatalytic replicator with reactions (12) and (15),

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, it is estimated as the rate of RNA hydrolysis, not pyrophosphorolysis. For the *E. coli,* it is estimated in terms of 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.

In the original LDB-type bound (6), the reverse transition probability $\pi(\mathbf{II} \to \mathbf{I})$ refers to reversion back into original reactants, not degradation into other waste products. In order to connect this bound to degradation, England assumes that reversion is slower than degradation, so

$$\pi(\mathbf{II} \to \mathbf{I}) \leq \delta' \, dt. \tag{16}$$

where δ' is the degradation rate. The result (3) then follows from (6), with δ taken to be the degradation rate δ'. However, there are some problems with this approach.

For one, 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 this is questionable since there is no universal relationship between these the rates of two processes. Moreover, the rate of pyrophosphorolysis depends on the concentration of pyrophosphate [9–11], while that of hydrolysis does not. At increased pyrophosphate concentrations, pyrophosphorolysis can proceed as fast as a minute per nucleotide, at least in the context of the bacterial polymerase system where it has been studied [10]. This can be order of magnitude faster than hydrolysis, which is on the order of 4 years per nucleotide [1].

Even for the *E. coli* bacterium, it seems debatable 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, reversion is a hyper-astronomically unlikely, but one may ask whether it is necessarily more unlikely than hydrolysis of all peptide bonds, whose probability England estimates at $e^{-6.7\times10^{10}}$ per 20 minute generation time (in decimal notation, this number has billions of zeros after the decimal point) [1]. Common-sense intuitions about the relative likelihood of 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 and (16) is mathematically valid. However, even in such cases, there is no meaningful thermodynamic relationship between dissipation and growth and degradation rates, because the two sides of (16) refer to two independent physical processes and their difference is completely uncontrolled. Consider again the *E. coli*. Bacteria are never observed to undergo hydrolysis of all peptide bonds, but are instead observed to die at the rate of $\approx 5 \times 10^{-4}$ per generation [12]. This death rate can be related to England's estimate of the entropy produced during replication, $\Delta s_{\text{tot}}(\mathbf{I} \to \mathbf{II}) \approx 3.3 \times 10^{11}$ [1]. Plugging these numbers into (3) gives

$$\Delta s_{\text{tot}}(\mathbf{I} \to \mathbf{II}) = 3.3 \times 10^{11} \geq 7.6 \approx -\ln(5 \times 10^{-4}). \tag{17}$$

This inequality is not biologically or physically meaningful because the two sides differ by a factor of about 50 billion. To put things in perspective, the inequality predicts 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 (16) between the probability of reversion $\pi(\mathbf{II} \to \mathbf{I})$ and degradation $\delta' \, dt$ may be violated, or it may hold but be so weak that it is irrelevant. One may wonder if the transition probability $\pi(\mathbf{II} \to \mathbf{I})$ may be defined to also account for degradation, such that (16) approaches equality. In fact, whether $\pi(\mathbf{II} \to \mathbf{I})$ does or does not account for degradation depends in a subtle way on the definition of macrostates $\mathbf{I}$ and $\mathbf{II}$. Consider a replicator that undergoes degradation into waste species W, and imagine two different ways of defining these macrostates. Under the first definition, the microstates in $\mathbf{I}$ and $\mathbf{II}$ all contain the same fixed number of waste molecules. Since degradation increases the number of waste molecules, the transition $\mathbf{II} \to \mathbf{I}$ will not include degradation and, as assumed by England, the transition probability $\pi(\mathbf{II} \to \mathbf{I})$ will only account for reversion back to reactants. Under the second, and arguably more realistic, definition, the precise number of waste molecules fluctuates among different microstates in $\mathbf{I}$ and/or $\mathbf{II}$. Then, the transition probability $\pi(\mathbf{II} \to \mathbf{I})$ will account for both reversion and degradation.

Now suppose that degradation is many orders of magnitude more likely than reversion, as in the *E. coli* that undergoes 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 be tiny compared to $\delta' \, dt$, so the inequalities (16) and (17) will be incredibly weak. This is the case considered above. Under the second definition of the macrostates, $\pi(\mathbf{II} \to \mathbf{I})$ will be much larger, and the inequality (16) may be nearly tight. However, the entropy production $\Delta s_{\text{tot}}(\mathbf{I} \to \mathbf{II})$ and transition probability $\pi(\mathbf{I} \to \mathbf{II})$ associated with replication do not depend much on whether the waste products are allowed to fluctuate or not, since they are not involved in replication. Therefore, to the extent that $\pi(\mathbf{II} \to \mathbf{I})$ becomes much larger and (16) tighter, LDB-type bound (6) must become much looser. At the end of the day, we end up with the same very weak thermodynamic bound (17). Thus, our general conclusions are not affected by the particular way that macrostates are defined.

V. CONCLUSION

In this paper, we considered England's proposed bound on the thermodynamics of replication, $\Delta s_{\text{tot}} \geq \ln(g/\delta)$. As we showed, this bound has physical meaning if the decay rate δ

refers to the reverse of replication, in which the offspring replicator reverts back to its original reactants due to interactions with the parent replicator. However, this reverse process cannot be first-order, hence δ cannot be interpreted as a per-capita decay rate. In fact, in general, a thermodynamically consistent replicator cannot exhibit both first-order replication and first-order replication back to reactants.

Alternatively, the decay rate may be defined in terms of the per-capita rate of degradation into waste products δ'. In this case, however, there is no universal physical relationship between the degradation rate δ' and properties of replication, such as g and $\Delta s_{\text{tot}}(\mathbf{I} \to \mathbf{II})$. Therefore, the resulting bound (3) is not physically meaningful and can be violated.

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