Entropy production of a steady-growth cell with catalytic reactions

Yusuke Himeoka and Kunihiko Kaneko
Department of Basic Science, University of Tokyo, Komaba, Meguro-ku, Tokyo 153-8902, Japan
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Cells generally convert external nutrient resources to support metabolism and growth. Understanding the thermodynamic efficiency of this conversion is essential to determine the general characteristics of cellular growth. Using a simple protocell model with catalytic reaction dynamics to synthesize the necessary enzyme and membrane components from nutrients, the entropy production per unit-cell-volume growth is calculated analytically and numerically based on the rate equation for chemical kinetics and linear nonequilibrium thermodynamics. The minimal entropy production per unit-cell growth is found to be achieved at a nonzero nutrient uptake rate rather than at a quasistatic limit as in the standard Carnot engine. This difference appears because the equilibration mediated by the enzyme exists only within cells that grow through enzyme and membrane synthesis. Optimal nutrient uptake is also confirmed by protocell models with many chemical components synthesized through a catalytic reaction network. The possible relevance of the identified optimal uptake to optimal yield for cellular growth is also discussed.

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I. INTRODUCTION

A cell is a system that transforms nutrients into substrates for growth and division. By assuming that the nutrient flow from the outside of a cell is an energy and material source, the cell can be regarded as a system to transform energy and matter into cellular reproduction. It is important to thermodynamically study the efficiency of this transformation [1–5]. Regarding material transformation, the yield is defined as the molar concentration of nutrients (carbon sources) needed to synthesize a molar unit of biomass (cell content) and has been measured in several microbes [6–10]. As the conversion of nutrients to cell content is not perfect and material loss to the outside of a cell occurs as waste, the yield is generally lower than unity. The yield also changes with nutrient conditions and measurements in several microbes show that the yield is maximized at a certain finite nutrient flow rate. The basic logic underlying the optimization of yield at a finite nutrient flow rate rather than at a quasistatic limit is not fully understood.

A cell can also be regarded as a type of thermodynamic engine to transform nutrient energy into cell contents. It is necessary to study the thermodynamic efficiency or entropy production during the process of cell reproduction. The thermodynamic efficiency of metabolism has been measured in several microbes under several nutrient conditions [9,11–15] and Westerhoff and co-workers computed it by applying the phenomenological flow-force relationship of the linear thermodynamics to catabolism and anabolism [4,16] to show that the efficiency is optimal at a finite nutrient flow. Although such a phenomenological approach is important for technological application, a physiochemical approach is also necessary to highlight the difference between cellular machinery and the Carnot engine by characterizing the basic thermodynamic properties in a simple protocell model. Indeed, when viewed as a thermodynamic engine, a cell has remarkable differences from the standard Carnot-cycle engine.

The cell sits in a single reservoir, without a need to switch contacts between different baths. The cell grows autonomously to reproduce. To consider the nature of such a system, it is necessary to establish the following three points distinguishing the cell from the standard Carnot engine [17].

First, cells contain catalysts (enzymes). The enzyme exists only within a compartmentalized cell encapsulated by a membrane and thus enables reactions to convert resources to intracellular components to occur within a reasonable time scale within a cell but not outside the cell. Without the catalyst, extensive time is required for the reaction. Thus, the reaction is regarded to occur only in the presence of the catalyst. This leads to an intriguing nonequilibrium situation: Let us consider the reaction $R + C \leftrightarrow P + C$ with R the resource, P the product, and C the catalyst. Then, under the existence of C, the system approaches an equilibrium concentration ratio with $[R]/[P] = \exp[-\beta(\mu_R - \mu_P)]$ and μ_R and μ_P the standard chemical potentials of the resource and product, respectively, and β the inverse temperature. In contrast, outside the cell, R and P are disconnected by reactions within the normal time scale; [18] therefore, their concentration ratio can take on any value. In this sense, a cell can be regarded as a machine that has the ability to equilibrate the extracellular environment.

Second, while considering the dynamical process, it is important to note that the catalysts are synthesized within the cell as a result of catalytic reactions. The time scale to approach equilibrium can depend on the abundance of the catalyst, which depends on the reaction dynamics themselves. Based on the first and second points mentioned above, the approach to equilibrium in the intracellular environment depends on catalyst abundance, which also depends on the flow rate of nutrients from outside the cell. Hence, the thermodynamic efficiency could show a nontrivial dependence upon the nutrient flow.

Third, cell-volume growth results from membrane synthesis from nutrient components, facilitated by the catalyst, whereas the concentrations of the catalyst and nutrient are diluted by cell growth, which results in a nonstandard factor for thermodynamic characteristics.

These three issues, which are fundamental to cell reproduction, are mutually connected and thus inherent to a self-reproducing, or autopoietic, system. In contrast to dynamical system studies for self-reproduction in catalytic reaction networks [20–23], however, the thermodynamic characteristics for such systems have not been fully explored.

On the other hand, there are extensive studies on thermodynamic efficiency for a system that operates at a nonequilibrium condition with a finite velocity, as well as the optimality on the power efficiency [24–27], with some applications to molecular motors [28,29]. However, the above three issues that are essential to reproducing cells have not been discussed in the traditional thermodynamic context so far. In particular, with the encapsulated catalysts that exist only within a cell, reactions that do not exist on the outside of a cell can progress within a cell within the normal time scale we are concerned. In the standard time scale, the equilibration is possible only within a cell whose speed is facilitated by the enzymes that are produced as a result of the intracellular reactions. How this autonomous regulation of the time scale together with the cell-volume growth influences the thermodynamic efficiency is the main concern of the present paper.

In the present study we determine these characteristics using simple reaction dynamics consisting of the nutrient, catalyst, and membrane. In Sec. II we consider a simple protocell model consisting of a membrane precursor and catalyst under a given nutrient flow. The entropy production by chemical production per unit-cell-volume growth is shown to be minimized at a certain finite nutrient flow. The mechanism underlying this optimization is discussed in relation to the above-mentioned three characteristics of a cell. The entropy production by material flow is discussed in Sec. II A and basically does not change the conclusion described above. A protocell model consisting of a variety of catalysts that form a network, together with nutrients and membrane precursors, has been investigated to confirm that the conclusion described above is not altered. The biological relevance of our results is discussed in Sec. III.

II. ENTROPY PRODUCTION OF AN AUTOPOIETIC CELL

A. Two-component model

We study the entropy production rate σ resulting from the intracellular reaction for the minimal protocell model consisting only of the synthesis of the enzyme and membrane precursor from the nutrient, which then leads to cellular growth [8,30–32] (see Fig. 1 for a schematic representation).

The model consists of the nutrient, membrane precursor, and enzyme, where the enzyme and membrane precursor are synthesized from the nutrient under catalysis by the enzyme. Moreover, by assuming that the diffusion constant of the nutrient is sufficiently large, the internal nutrient concentration is regarded as being equal to the external nutrient concentration. Based on the rate equation for chemical kinetics, our model is given by the two-component ordinary differential equations

$$\frac{dx}{dt} = \kappa_x x(kr - x) - x\lambda,$$
$$\frac{dy}{dt} = \kappa_y x(lr - y) - \phi y - y\lambda. \quad (1)$$

where the variables x and y denote the concentrations of the enzyme and membrane precursor, respectively, and $\lambda \equiv \frac{1}{V}\frac{dV}{dt}$ denotes the cell-volume growth rate to be determined. Here the first terms with κ in both equations represent the change

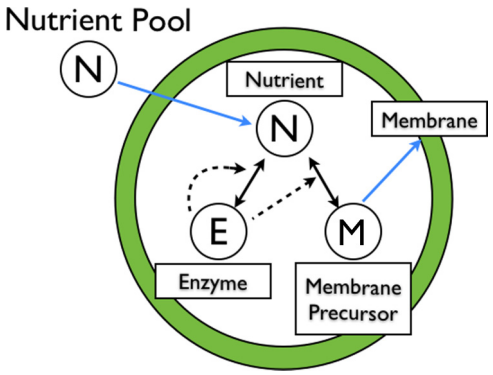

FIG. 1. (Color online) Schematic representation of our three-component protocell model. Here N, M, and E denote nutrient, membrane precursor, and enzyme, respectively. The nutrient is taken up from the extracellular nutrient pool by diffusion, indicated by a blue arrow. All chemical reactions, indicated by black solid arrows, are reversible and catalyzed by the enzyme, as indicated by dashed arrows. Membrane precursors are transformed to the membrane as indicated by the green ring with some leaks. The membrane growth results in an increase in cell volume.

in the concentrations by the reactions $N \leftrightarrow E$ and $N \leftrightarrow M$, respectively, the term ϕy is due to the consumption of the membrane precursor molecules to produce the membrane ($M \rightarrow$ membrane), and the last terms represent the dilution of the concentrations of all chemical species due to the volume expansion with the rate λ. The notation of the parameters is defined as follows: r is the nutrient (i.e., resource) concentration; $k = e^{-\beta(\mu_x - \mu_r)}$ and $l = e^{-\beta(\mu_y - \mu_r)}$ are the rate constants of each chemical reaction, with μ_r, μ_x, and μ_y the standard chemical potentials of the nutrient, x, and y, respectively; κ_i is the catalytic capacity of the enzyme for the component i ($i = x, y$) [33]; and ϕ is the consumption rate of the membrane precursor to produce the membrane such that the volume growth rate λ is given by $\lambda = \gamma\phi y$, where γ is the conversion rate from membrane molecules to the cell volume.

In the stationary state, λ takes a positive constant value of $y > 0$ for $r > 0$ [34]. Thus, the protocell volume increases exponentially in time. We define the entropy production rate per unit volume at this steady-growth state as σ. In computing σ, spatial inhomogeneity is not considered through the assumption of local homogeneous equilibrium. Thus, the entropy produced during the doubling in the cell volume is given by

$$S = \int_0^T \int_{V(t)} \sigma \, dV dt = \int_0^T V_0 e^{\lambda t} \sigma \, dt = \frac{\sigma}{\lambda} V_0, \quad (2)$$

where V_0 is the initial cell volume and T is doubling time of the cell [35].

We denote by $\eta \equiv \sigma/\lambda$ the entropy production per unit-cell-volume growth. Generally, if η is smaller, the thermodynamic efficiency for a cell growth is higher. For larger η, more energetic loss occurs in the reaction process. Hereafter, we study the dependence of η on the nutrient condition and the growth rate λ.

In this section we consider only the entropy production by the chemical reaction; the entropy production by the

flow of chemicals from the outside of the cell will be considered in the next section. The calculation of the entropy production rate among different components is performed by virtually introducing chemical baths for different components that are mutually in disequilibrium and then applying linear nonequilibrium thermodynamics for calculation. This may result in stringent requisites; however, this step is adopted to address the thermodynamic efficiency of a cell with growth, as general steady-state thermodynamics are not established currently.

Then the entropy production rate by the reactions is given by $\sigma = \sum_i J_i \frac{A_i}{T}$, where J_i is the chemical flow and A_i is the affinity for each reaction. Here we set $T = 1$ without loss of generality.

For the calculation we assume that κ_x and κ_y are identical for simplicity, denoted by κ. Then, by rescaling the variables as

$$\tilde{x} = x\gamma, \quad \tilde{y} = y\gamma, \quad \tilde{r} = lr\gamma, \quad \tau = t\phi, \tag{3}$$

Eq. (1) is written as

$$\begin{aligned} \frac{d\tilde{x}}{d\tau} &= \tilde{\kappa}\tilde{x}(\tilde{k}\tilde{r} - \tilde{x}) - \tilde{x}\tilde{y}, \\ \frac{d\tilde{y}}{d\tau} &= \tilde{\kappa}\tilde{x}(\tilde{r} - \tilde{y}) - \tilde{y} - \tilde{y}^2, \end{aligned} \tag{4}$$

where $\tilde{\kappa} = \frac{\kappa}{\phi\gamma}$ and $\tilde{k} = k/l$. The stationary solution of the equation for $\tilde{\kappa} = 1$ is given by

$$\tilde{x} = \frac{\tilde{k}\tilde{r}(1 + \tilde{k}\tilde{r})}{1 + \tilde{r} + \tilde{k}\tilde{r}}, \quad \tilde{y} = \frac{\tilde{k}\tilde{r}^2}{1 + \tilde{r} + \tilde{k}\tilde{r}}.$$

Following this assumption, the entropy production rate by the chemical reaction σ at the stationary state is calculated as $\sigma = \sigma_x + \sigma_y$ with $\sigma_i = J_i \frac{A_i}{T}$ for the enzymatic reaction $i = x$ and the membrane reaction $i = y$. The flows are given by $\tilde{J}_x = \tilde{\kappa}\tilde{x}(\tilde{k}\tilde{r} - \tilde{x})$ and $\tilde{J}_y = \tilde{\kappa}\tilde{x}(\tilde{r} - \tilde{y})$, whereas the affinities are given by $A_x = T\ln(\tilde{k}\tilde{r}/\tilde{x})$ and $A_y = T\ln(\tilde{r}/\tilde{y})$. We omit the tilde for affinities because the affinities are not affected by the scale transformation. Therefore, we obtain

$$\tilde{\sigma} = \tilde{\kappa}\tilde{x}(\tilde{k}\tilde{r} - \tilde{x})\ln(\tilde{k}\tilde{r}/\tilde{x}) + \tilde{\kappa}\tilde{x}(\tilde{r} - \tilde{y})\ln(\tilde{r}/\tilde{y}).$$

The dependence of $\tilde{\eta} \equiv \tilde{\sigma}/\tilde{y} = \gamma\eta$ upon $\tilde{k}$ and $\tilde{r}$ thus obtained is plotted in Fig. 2 for $\tilde{\kappa} = 1$. As shown, the entropy production per unit growth shows a nonmonotonic dependence on the nutrient concentration and is minimized at a nonzero nutrient concentration. Because the nutrient uptake rate is a monotonic function of the nutrient concentration, this result means that the entropy production per unit growth η is minimal at a finite nutrient uptake rate. This result is in strong contrast with the thermal engine, where the entropy production is minimal at a quasistatic limit.

Figures 3(a) and 3(b) shows the entropy production per unit growth $\tilde{\sigma}_x/\tilde{\lambda}$ and $\tilde{\sigma}_y/\tilde{\lambda}$ for each reaction that produces components x and y, respectively. This shows that the nonmonotonic dependence on the nutrient in Fig. 2 is attributable to $\tilde{\sigma}_y/\tilde{\lambda}$. As mentioned above, an important characteristic of cells is that intracellular reactions are facilitated by enzymes that are autonomously synthesized. Thus, the equilibrium distribution of chemicals in the presence of enzymes is different from the external chemical distribution. The decrease in η under low

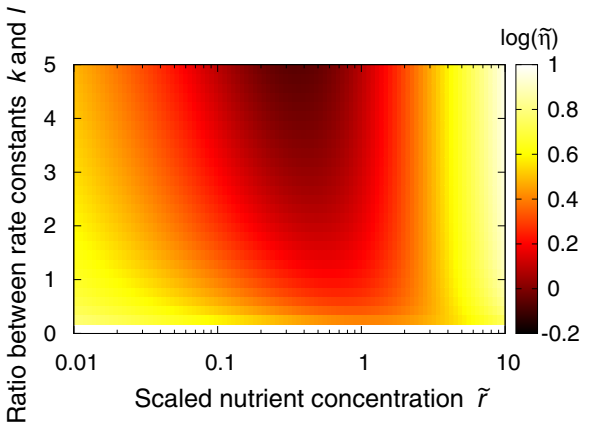

FIG. 2. (Color online) Logarithm of $\tilde{\eta}$ plotted as a function of scaled nutrient concentration $\tilde{r}$ and $\tilde{k} = k/l$, the ratio between two rate constants, with the color code given in the side bar. It is calculated from the solutions of Eq. (4). The parameter $\tilde{\kappa}$ is chosen to be 1.0. For given $\tilde{k}$, there is an optimal nutrient concentration that gives the minimum $\tilde{\eta}$.

nutrient concentrations is explained accordingly: The extracellular concentrations of the nutrient and of the membrane precursor are far from equilibrium in the presence of catalysts. Therefore, their intracellular concentrations under conditions

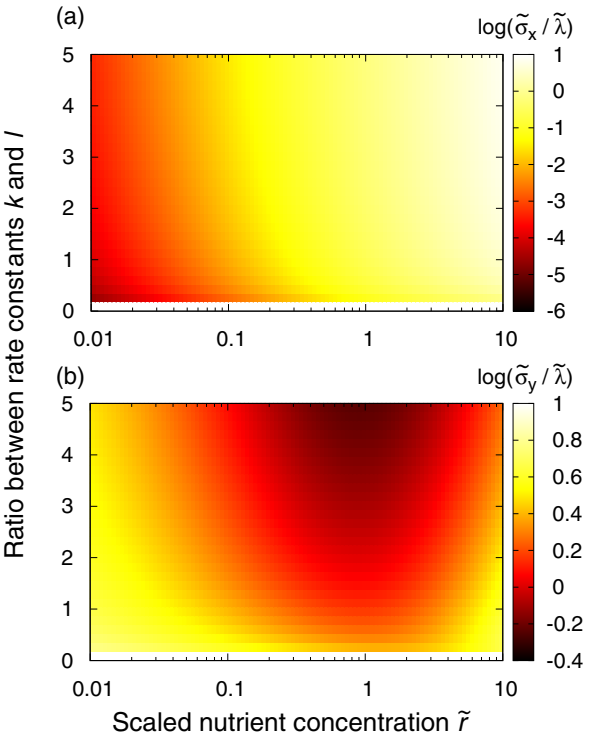

FIG. 3. (Color online) Logarithm of the rescaled entropy production rate per unit rescaled growth rate $\tilde{\sigma}_x/\tilde{\lambda}$ and $\tilde{\sigma}_y/\tilde{\lambda}$ for the enzyme and membrane precursor synthesis reactions, respectively, plotted as a function of the rescaled nutrient concentration $\tilde{r}$ and the ratio between rate constants $\tilde{k}$, computed by Eq. (4): (a) $\tilde{\sigma}_x/\tilde{\lambda}$ for the enzyme producing reaction and (b) $\tilde{\sigma}_y/\tilde{\lambda}$ for the membrane precursor producing reaction.

of low nutrient uptake remain far from equilibrium and still similar to the external concentrations because of insufficiency of the enzyme. However, when the amount of nutrient uptake increases, the amount of enzyme increases and the system approaches intracellular equilibrium; therefore, the entropy production per unit growth decreases.

In contrast, with further increases in nutrient uptake, the entropy production rate increases as a result of the increase in cellular growth; the entropy production rate $\sigma = \sum_i J_i \frac{A_i}{T}$ of the reaction increases linearly with the reaction speed J_i. In the steady state, the reaction speed J_i is roughly estimated by λp_i, with p_i the concentration of the product of the ith reaction, because the dilution due to the cell-volume expansion and the production of the chemical reaction should be balanced. For example, the dynamics of the enzyme concentration are given by $\frac{dx}{dt} = x(kr - x) - \lambda x$. At steady state, the enzyme production rate $x(kr - x)$ is balanced with λx according to Eq. (1). Thus, σ_x increases with λx. In summary, for a cell with a high growth rate, increased enzyme abundance is needed, which, however, leads to a higher entropy production rate [36,37].

In contrast, if the enzyme concentration is fixed externally, the entropy production per unit growth η is minimized at the zero limit of the nutrient concentration. In this case, the reaction dynamics (1) are reduced to

$$\frac{dy}{dt} = c(lr - y) - \phi y - \phi y^2, \tag{5}$$

where c is a constant representing the concentration of the enzyme. In this case, the stationary solution is given by $y = \frac{1}{2}\{-(1 + c/\phi) + \sqrt{[1 + (c\phi)^2] + 4clr/\phi}\}$ and, accordingly, $\eta^{-1} = (1 + y)\ln(lr/y)$. There is no optimal nutrient concentration in this expression because $\frac{\partial \eta^{-1}}{\partial r}$ is always positive for any $r,l > 0$. This is consistent with the explanation mentioned above for Eq. (4). If the enzyme abundance is fixed to be independent of the nutrient uptake, the speed of approaching equilibrium is not altered by the nutrient condition; therefore, the entropy production just increases monotonically because of the cell-volume growth.

B. Additional entropy production by material flow

Thus far, we have considered only entropy production by chemical reactions. In addition, the material flow also contributes to entropy production, which is taken into account now.

To discuss the flow of nutrients, the dynamics of the nutrient concentration cannot be neglected. By including the temporal evolution of the nutrient concentration, the dynamics of the cellular state are given by

$$\begin{aligned} \frac{dr}{dt} &= -\kappa_x x(kr - x) - \kappa_y x(lr - y) - r\lambda + D(r_{\rm ext} - r), \\ \frac{dx}{dt} &= \kappa_x x(kr - x) - x\lambda, \\ \frac{dy}{dt} &= \kappa_y x(lr - y) - \phi y - y\lambda. \end{aligned} \tag{6}$$

where x, y, and r are the enzyme, membrane precursor, and nutrient concentration, respectively, and $\lambda = \frac{1}{V}\frac{dV}{dt} = \gamma\phi y$. The rate constants k and l are determined by the standard chemical potential of each chemical. Additionally, the nutrient is taken up with rate D from the extracellular environment with a concentration $r_{\rm ext}$.

The entropy production by chemical flow is derived from nutrient uptake and membrane consumption, which (again by assuming linear nonequilibrium thermodynamics) are given by $\vec{J}_r \cdot \vec{\nabla}(-\mu_r/T)$ and $\vec{J}_y \cdot \vec{\nabla}(-\mu_y/T)$, respectively, where $\vec{J}_i$ is the material flow of component i and μ is the chemical potential. Integration of the terms with the spatial gradient over a space results in $D(r_{\rm ext} - r)\frac{r_{\rm ext} - r}{r}/T$ and $\phi y/T$ [38,39]. We neglect the entropy production of the solvent with the assumption that the intra- and extracellular solvent concentrations are identical [40]. The contribution of dilution of the nutrient resulting from cellular growth is approximated as $\sigma_{d,r} \approx r\lambda$ by using the formula of entropy change resulting from the isothermal expansion of an ideal solution [41]; for other species, we use the same formula.

We set κ_x, κ_y, D, γ, and ϕ equal to unity and $l = k$, for the sake of simplicity. Indeed, the characteristic behavior of η is independent of this choice. Then, the fixed-point solutions of Eq. (6) are obtained against two parameters k and $r_{\rm ext}$. From the solution, the entropy production per unit growth is computed, as shown in Fig. 4(a). We note that here again the minimal η is achieved for a finite nutrient uptake, i.e., under nonequilibrium chemical flow. In Fig. 4(b) we plotted $(\sigma_{\rm mf} + \sigma_d)/\lambda$, the entropy production excluding that derived from the

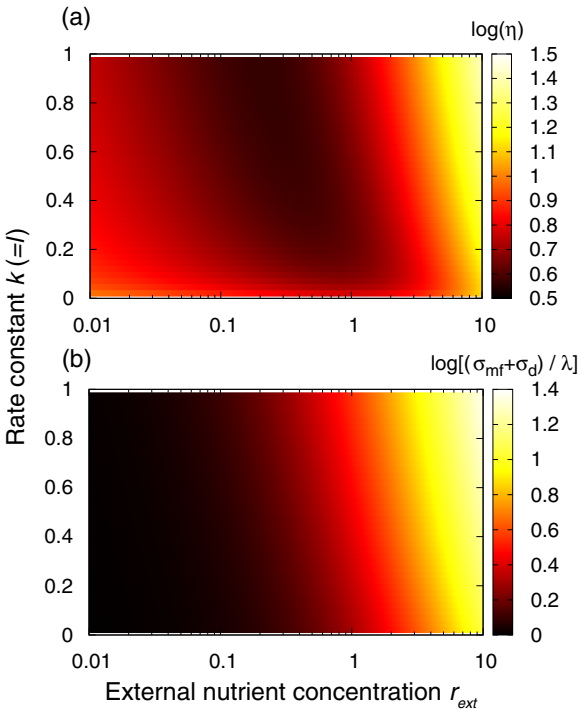

FIG. 4. (Color online) Entropy production plotted as a function of the external nutrient concentration $r_{\rm ext}$ and the rate constant k (=l), calculated from the fixed-point solution of Eq. (6): (a) the logarithm of total entropy production per unit-cell growth η and (b) the logarithm of the entropy production per unit growth by material flow $\sigma_{\rm mf}/\lambda$ and dilution σ_d/λ only. The parameters are chosen to be $\kappa_x = 1.0$, $\kappa_y = 1.0$, $D = 1.0$, $\phi = 1.0$, $\gamma = 1.0$, and $l = k$.

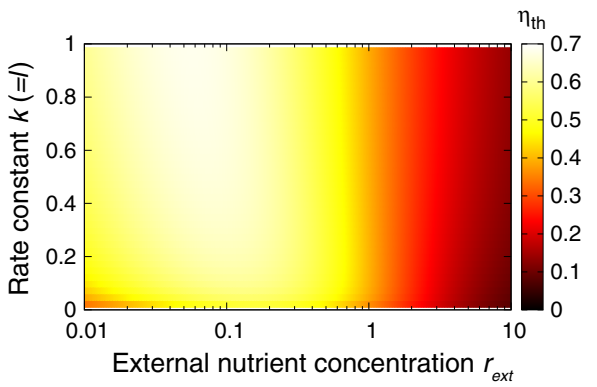

FIG. 5. (Color online) Thermodynamic efficiency for the model (6) plotted as a function of the external nutrient concentration $r_{\rm ext}$ and the rate constant k ($=l$). The parameters are set as $\mu_r = 0.0$, $D = 1.0$, $\phi = 1.0$, $\gamma = 1.0$, and $\kappa_x = \kappa_y = 1.0$. The standard concentrations are chosen to be 10^{-8}.

chemical reaction. It increases monotonically with the external nutrient concentration. Entropy production is primarily derived from chemical reactions; therefore, the conclusion of Sec. II A is unchanged.

Note that the so-called thermodynamic efficiency is defined as $\eta_{\rm th} = -\frac{J_a \Delta G_a}{J_c \Delta G_c}$, where J_c and J_a are the rates of catabolism and anabolism and ΔG_c and ΔG_a are the affinities of catabolism and anabolism [4,11]. Here the optimality with regard to entropy production η also leads to the optimal thermodynamic efficiency, which, in the present case, is computed by $\eta_{\rm th} = \frac{J_y \mu_y}{J_r \mu_r}$, where $J_r = D(r_{\rm ext} - r)$ and $J_y = \phi y$ are the absolute values of the uptake (and consumption) flow of chemical species r (and y) and μ_i is the chemical potential of the ith chemical species. It is computed by using the chemical potential of the nutrient $\mu_r = \mu_r^0 + T \ln(r/r_0)$, with μ_r^0 the standard chemical potential for the nutrient and r_0 its standard concentration (the chemical potentials for x and y are computed in the same way). This thermodynamic efficiency also takes a local maximum value at a nonzero nutrient uptake rate (see Fig. 5).

III. EXTENSION TO A MULTICOMPONENT MODEL

It is worthwhile to check the generality of our result for a system with a large number of chemical species as in the present cell. For this purpose, we introduce a model given by

$$\begin{aligned}
\frac{dx_1}{dt} &= \sum_{j=1}^{N} \sum_{k=2}^{N-1} [C(1,j;k) k_{1j} x_j - C(j,1;k) k_{j1} x_1] x_k \\
&\quad + (X_1 - x_1) - x_1 \lambda, \\
\frac{dx_i}{dt} &= \sum_{j=1}^{N} \sum_{k=2}^{N-1} [C(i,j;k) k_{ij} x_j - C(j,i;k) k_{ji} x_i] x_k \\
&\quad - x_i \lambda \quad (1 < i < N-1), \\
\frac{dx_N}{dt} &= \sum_{j=1}^{N} \sum_{k=2}^{N-1} [C(N,j;k) k_{Nj} x_j - C(j,N;k) k_{jN} x_N] x_k \\
&\quad - \phi x_N - x_N \lambda, \quad \lambda = x_N,
\end{aligned} \tag{7}$$

where the variables x_1, x_N, and x_i $(1 < i < N)$ denote the concentrations of the nutrient, membrane precursor, and enzymes, respectively, and X_1 is the external concentration of the nutrient. Each element of the reaction tensor $C(i,j;k)$ is unity if the reaction of j to i catalyzed by k exists; otherwise, it is set to zero. Here the nutrient and the membrane precursor cannot catalyze any reaction, whereas the other components $i = 2, \ldots, N-1$ form a catalytic reaction network [21,42–44]. All chemical reactions are reversible in our model; therefore $C(i,j;k)$ is equal to unity if and only if $C(j,i;k)$ equals unity. For the sake of simplicity, we assume that the catalytic capacity, nutrient uptake rate, membrane precursor consumption rate, and conversion rate from the membrane molecule to the cell volume are unity. The standard chemical potential μ_i for each chemical species is assigned by uniform random numbers within $[0,1]$, whereas k_{ij} is given by $\min\{1, \exp[-\beta(\mu_i - \mu_j)]\}$ accordingly [43].

Numerical simulations reveal that there again exists an optimal point of η for each randomly generated reaction network of $N = 100$. The dependence of η on the nutrient concentration is plotted in Fig. 6(a), overlaid for different networks. Although the nutrient concentration to give the optimal value is network dependent, it always exists at a finite nutrient concentration; therefore, the entropy production is

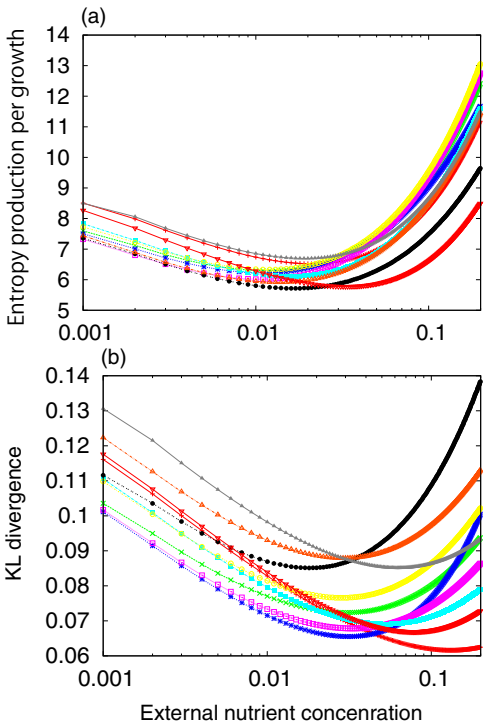

FIG. 6. (Color online) Entropy production and deviation from equilibrium calculated from the steady-state solution of the multicomponent model (7) plotted as a function of the external nutrient concentration: (a) entropy production rate per growth rate η and (b) Kullback-Leibler divergence of the steady-state distribution from the Boltzmann distribution defined in Eq. (8). The results of ten randomly generated networks are overlaid. The number of chemical species is set as 100, whereas the parameter ϕ is chosen to be unity, and the ratio of the average number of reactions to the number of chemical species is set to 3.

minimized at a nonzero nutrient concentration. To determine a possible relationship with the optimality of η and equilibrium in the presence of a catalyst we also compute the Kullback-Leibler (KL) divergence of the steady-state distribution from the equilibrium Boltzmann distribution [17] as a function of the external nutrient concentration, expressed as

$$D_{\mathrm{KL}}(\mathbf{p}||\mathbf{q}) = \sum_{i=1}^{N} p_i \ln \frac{p_i}{q_i}, \tag{8}$$

where p_i and q_i are $p_i = e^{-\mu_i}/\sum_j e^{-\mu_j}$ and $q_i = {x^{\mathrm{st}}}_i/\sum_j x_j^{\mathrm{st}}$, respectively ($x_i^{\mathrm{st}}$ is the concentration of the ith chemical species in the steady state) [45]. The KL divergence for each network shows nonmonotonic behavior, as shown in Fig. 6(b). Although the optimal nutrient concentration does not agree with the optimum for η, each KL divergence decreases in the region where η is reduced. In this sense, it is suggested that the reduction of η in our model (7) is related to the equilibration process of abundant enzymes synthesized as a result of a relatively high rate of nutrient uptake as discussed for Eqs. (1) and (6).

IV. SUMMARY AND DISCUSSION

To discuss the thermodynamic nature of a reproducing cell, we have studied simple protocell models in which nutrients are diffused from the extracellular environment and necessary enzymes for the intracellular reactions are synthesized to facilitate chemical reactions, including the synthesis of membrane components, which leads to the growth of the cell volume. In the models, cell growth is achieved through nutrient consumption by the reactions described above. We computed η, which is the entropy production per unit-cell-volume growth and found that the value was minimized at a certain nutrient uptake rate. This optimization stems from the constraint that cells have to synthesize enzymes to facilitate chemical reactions, i.e., the autopoietic nature of cells. In general, the concentrations of nutrients and membrane components in extracellular environments are different from those in equilibrium achieved in the presence of enzymes and the intracellular state moves towards equilibrium by synthesizing enzymes to increase the speed of chemical reactions. The equilibration reduces the entropy per unit chemical reaction. However, faster cell-volume growth leads to a higher dilution of chemicals; therefore, faster chemical reactions are required to maintain the steady-state concentration of chemicals. Because the entropy production rate of the reaction increases (roughly linearly) with the frequency of net chemical reactions, η then increases for a higher growth range. Thus, the existence of an optimal nutrient content is explained by the requirement for reproduction mentioned in the Introduction, i.e., equilibration of nonequilibrium environmental conditions facilitated by the enzyme, autocatalytic processes to synthesize the enzyme, and cell-volume increase resulting from membrane synthesis.

In the present model, all chemical components thus synthesized are not decomposed; they are only diluted. However, each component generally has a specific decomposition time or deactivation time as a catalyst. We can include these decomposition rates, which can also be regarded as diffusion to the extracellular environment with a null concentration. Then the equilibration effect is clearer, although the results regarding optimal nutrient uptake are unchanged.

Note that in the present cell model, there is only a single stationary state, given the external condition. In a complex reaction system, as in the present cell, there can be multiple stationary states with different growth rates and the selection process among them is also important [46,47]. A comparison of thermodynamic efficiency among different states will also be important [48].

In the present study we focused on the case with a single entropy production that corresponds to dissipated energy per unit growth. In microbial biology, however, material loss is discussed as biological yield, as mentioned in the Introduction, and it is thus reported that the optimal yield is achieved at a certain finite nutrient flow. Material loss is not directly included in the present model; therefore, we cannot discuss the yield derived directly from entropy production. However, it may be possible to assume that energy dissipation is correlated with material dissipation.

For example, the stoichiometry of metabolism is suggested to depend on dissipated energy [49]. Here metabolism consists of two distinct parts: catabolism and anabolism. For catabolism, the energy is transported through energy currency molecules such as ATP, NADPH, and GTP, which are synthesized from the nutrient molecule. In this process, molecular decomposition also occurs, leading to the loss of nutrient molecules. In addition, the abundance of energy-currency molecules and the utilized energy are correlated. Hence, for both catabolism and anabolism, the energy dissipation and material loss are expected to be correlated. Indeed, a linear relationship between the yield and the inverse of thermodynamic loss (i.e., a quantity similar to $1/\eta$ here) is suggested from microbial experiments [49,50].

Considering the correlation between energy and matter, the minimal entropy production at a finite nutrient flow that we have shown here may provide an explanation for the finding of optimal yield at a finite nutrient flow. Future studies should examine the relationship between minimal entropy production and optimal yield by choosing an appropriate model that includes ATP synthesis and waste products in a cell. Currently, although our models are too simple to capture such complex biochemistry in a cell, they should initiate discussion regarding the thermodynamics of cellular growth.

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[33] In other words, the forward and backward reaction rates are given by $\kappa_x k$ and κ_x, $\kappa_y \ell$, κ_y, respectively. We used the present parametrization, to separate the timescales of chemical reactions as represented as κ_i, $(i = x, y)$, from the ratios of forward to backward reactions that are given by the exponential of the free energy difference.

[34] In our model, another stationary solution $(x, y) = (0,0)$ exists. However this solution is an unstable fixed point of the differential equation for $X > 0$.

[35] This is nothing but the relationship between the total entropy production through cell reproduction and the entropy production per time and volume. Specific contribution of material flow, cell volume growth, and reactions to the entropy roduction rate σ will be analyzed below.

[36] For membrane production in Eq.(1), $(\phi + \lambda)y$ balances with the synthesis of the membrane precursor, but the tendency does not change.

[37] The increase of entropy production rate with λ mentioned above does not mean that the factor λ would totally be canceled with the factor σ in Eq. (2). The intra-cellular state concentrations of chemicals depend on λ, so that σ/λ has further dependence on λ.

[38] The entropy production rate of material flow under a one-dimensional gradient of chemical concentration $u_i(x)$ (of the species i at the position x) is estimated as $\int_a^b J_i(x)\frac{d}{dx}[-\mu_i(x)/T]dx \approx \int_a^b D_i[u_i(b) - u_i(a)](\frac{u_i(b)-u_i(a)}{(b-a)u_i(a)})\frac{dx}{T} = \frac{D_i}{T}\frac{[u_i(b)-u_i(a)]^2}{u_i(a)}$ by assuming that $b - a$ is small.

[39] To neglect possible correction by the spatial inhomogeneity on the entropy production by reaction, it might be necessary to assume that the spatial gradient is restricted at round the membrane, and not extends through the cells, while this correction would be smaller.

[40] The extracellular membrane concentration is assumed to be zero in our model; Eq.(1), we adopted entropy production rate of membrane consumption as a diffusion process.

[41] Entropy production during isothermal expansion of an ideal solution from the initial volume V_i to a terminal volume V_t is $\Delta S = \ln(V_t/V_i)$ per unit mole. Because λ is the volume expansion rate in this context and $V_t = V_i + \lambda\Delta t$, the change in entropy density is written as $\Delta s_v = \ln(1 + \lambda\Delta t)$ per unit mole. The approximated formula is obtained by expanding $\ln(1 + \lambda\Delta t)$ into the Taylor series and taking the limit of Δt to zero. Of course, $\frac{\Delta s_v}{\Delta t}$, the entropy change per unit time of the system, is generally different from the entropy production rates because there is an increase in the entropy due to the heat flow from the environment, so the entropy production by the expansion can be smaller. At any rate, the above Δs_v is smaller than the other entropy production terms and the estimate here is not essential to our result.

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