

Thermodynamic Uncertainty Relation and Thermodynamic Speed Limit in Deterministic Chemical Reaction Networks

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We generalize the thermodynamic uncertainty relation (TUR) and thermodynamic speed limit (TSL) for deterministic chemical reaction networks (CRNs). The scaled diffusion coefficient derived by considering the connection between macro- and mesoscopic CRNs plays an essential role in our results. The TUR shows that the product of the entropy production rate and the ratio of the scaled diffusion coefficient to the square of the rate of concentration change is bounded below by two. The TSL states a trade-off relation between speed and thermodynamic quantities, the entropy production, and the time-averaged scaled diffusion coefficient. The results are proved under the general setting of open and nonideal CRNs.

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Introduction.—It has been a fundamental question whether there are universal laws in nonequilibrium systems or processes like equilibrium thermodynamics. In the last two decades, our understanding of the thermodynamic structure of nonequilibrium mesoscopic systems has been substantially gained with the aid of stochastic thermodynamics [1,2].

The following are two examples of discoveries made by stochastic thermodynamics. One is thermodynamic uncertainty relation (TUR) [3,4]. A TUR states a trade-off relation between a relative fluctuation and dissipation. The former is typically evaluated by the diffusion constant D and a current J as $2D/J^2$, while the latter is given by the entropy production rate σ . The original TUR shows the trade-off relation by an inequality $\mathcal{Q} := (2D/J^2)\sigma \geq 2$ [3]. Subsequently, various variants in mesoscopic systems [5–19] and an extension to quantum systems [20] have been developed. The other example is a thermodynamic speed limit (TSL) [21–24]. A TSL gives a lower bound to the time it takes for a system to change using thermodynamic quantities such as the entropy production. TSLs typically indicate a universal trade-off between speed and dissipation. Speed limits (SLs) were originally developed for microscopic systems described by quantum mechanics [25,26]. To date, many SLs have been found by using mathematically elaborated methods [27–37].

However, the universal thermodynamic principles, TUR and TSL, have been restricted to meso- or microscopic

systems described by stochastic thermodynamics or quantum mechanics. Whether such principles hold in other nonequilibrium systems, like deterministic chemical reaction networks (CRNs), is nontrivial. Chemical thermodynamics has been an essential thermodynamic theory of nonequilibrium systems since before the birth of stochastic thermodynamics [38–40]. Remarkably, the original derivation of TUR is obtained in a stochastic model of enzymatic reaction [3]. Mesoscopic theory of chemical reactions can be described by stochastic thermodynamics [41,42], while macroscopic theory, e.g., thermodynamic theory of biochemical reaction networks, is not [40,43]. Because of their deep connection [44,45], wisdom of stochastic thermodynamics is still useful for macroscopic chemical thermodynamics [35,46–51]. However, the latest knowledge of stochastic thermodynamics, such as TUR and TSL, has not been sufficiently considered in chemical thermodynamics.

In this Letter, we obtain a TUR and a TSL in deterministic CRNs by focusing on a relationship between the meso- and macroscopic theory of chemical reactions. In both the TUR and TSL, the intrinsic fluctuations of CRNs play an important role. The fluctuations in chemical reactions get smaller when the size of the system increases, as shown in Fig. 1. However, they can be considered in macroscopic CRNs by scaling by the volume (the scaled diffusion coefficient \tilde{D} in Fig. 1). We obtain a TUR between this measure of fluctuations \tilde{D} , the rate of concentration change, and the entropy production rate. This measure of fluctuations is also important in the TSL, which shows a relation between speed and thermodynamic quantities, the scaled diffusion coefficient, and the entropy production. These results are proved under highly general settings used in recent studies [47,51]. We illustrate the TUR and TSL in concrete models of CRNs.

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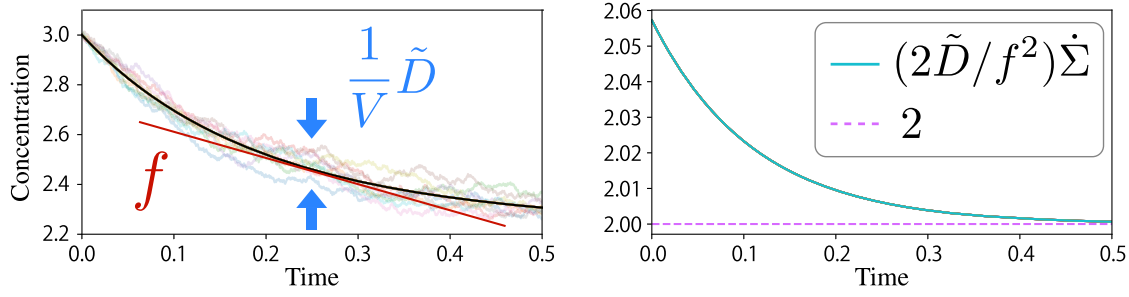
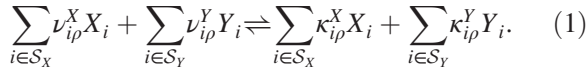


FIG. 1. Schematic diagram of thermodynamic uncertainty relation in chemical thermodynamics [Eq. (11)]. The left graph shows the concentrations of A in a reaction $2A \rightleftharpoons B$ calculated by the chemical Langevin equation corresponding to the Fokker–Planck equation (10). The dark curve is obtained with the volume V set 10^7 times as great as that for the light curves. Although the same number of curves are plotted for each V , the curves concentrate on the single curve when V is large. By taking the thermodynamic limit in such a way, we have a rigorous inequality between the changing rate of the concentration f , the scaled diffusion coefficient \tilde{D} , and the entropy production rate $\dot{\Sigma}$, namely, the thermodynamic uncertainty relation, as shown in the right figure.

Setup.—We examine open CRNs that consist of $N + N'$ chemical species. Within them, we assume that the concentrations of N' species are controlled externally. We denote the N kinds of internal species by $X_i (i \in \mathcal{S}_X := \{1, \dots, N\})$, and denote the other chemostatted species by $Y_i (i \in \mathcal{S}_Y := \{N + 1, \dots, N + N'\})$. Here, we define \mathcal{S}_X and \mathcal{S}_Y as the index sets of the two kinds of species. We may use α to collectively represent X and Y . That is, α_i means X_i if $i \in \mathcal{S}_X$, and vice versa. Chemical reaction networks have M reversible reactions labeled by $\rho \in \mathcal{R} := \{1, \dots, M\}$. Each reaction has two directions of reaction since it is reversible. We call one of the two the forward reaction and the other the backward reaction. We denote the number of α_i involved in the ρ th forward reaction by $\nu_{i\rho}^\alpha$ and that involved in the backward reaction by $\kappa_{i\rho}^\alpha$. Then, the ρ th reaction can be written as follows:



For both the internal species and the chemostatted species, we define the respective stoichiometric coefficient matrix \mathbf{S}^α by $\mathbf{S}_{i\rho}^\alpha := \kappa_{i\rho}^\alpha - \nu_{i\rho}^\alpha$. Each element $\mathbf{S}_{i\rho}^\alpha$ gives the net increase (respectively, decrease) in α_i molecule in the ρ th forward (respectively, backward) reaction. Combining them, we can obtain the total stoichiometric coefficient matrix $\mathbf{S} = [(\mathbf{S}^X)^\top (\mathbf{S}^Y)^\top]^\top$, where the superscript \top represents the transposition.

We also consider the kinetics of CRNs. Let $[\alpha]_t = ([\alpha_i]_t)_{i \in \mathcal{S}_\alpha}$ denote the concentrations of α_i 's at time t . Throughout this Letter, we only consider homogeneous CRNs where the concentrations do not depend on the position. Let the rate of the ρ th reaction be $J_\rho = J_\rho^+ - J_\rho^-$, where J_ρ^+ (respectively, J_ρ^-) is the reaction rate of the forward (respectively, backward) reaction. They are functions of the concentrations. Then, the kinetics of the concentrations are given by the rate equation

$$\frac{d[\mathbf{X}]_t}{dt} = \mathbf{S}^X \mathbf{J}, \quad \frac{d[\mathbf{Y}]_t}{dt} = \mathbf{S}^Y \mathbf{J} + \mathcal{J}^Y, \quad (2)$$

where $\mathbf{J} = (J_\rho)_{\rho \in \mathcal{R}}$ is the vector of reaction rates and $\mathcal{J}^Y = (\mathcal{J}_i^Y)_{i \in \mathcal{S}_Y}$ is the vector of external flows to control the concentrations of the chemostatted species.

We introduce thermodynamic structure to CRNs. To this end, we adopt the local detailed balance condition introduced in Ref. [51],

$$-(\boldsymbol{\mu}^\top \mathbf{S})_\rho = RT \ln \frac{J_\rho^+}{J_\rho^-}, \quad (3)$$

where $\boldsymbol{\mu} = (\mu_i)_{i \in \mathcal{S}_X \cup \mathcal{S}_Y}$ is the chemical potential, $(\cdot)_\rho$ is the ρ th element of the vector, R is the gas constant, and T is the temperature. This is a core assumption when extending the framework of chemical thermodynamics to nonideal systems [51]. Because of the local detailed balance condition, the entropy production rate of chemical reactions is given as follows [47,51,52]:

$$\dot{\Sigma} = R \sum_{\rho \in \mathcal{R}} J_\rho \ln \frac{J_\rho^+}{J_\rho^-} \geq 0, \quad (4)$$

where the inequality is obtained since the signs of $J_\rho = J_\rho^+ - J_\rho^-$ and $\ln(J_\rho^+/J_\rho^-)$ are the same, and it expresses the second law of thermodynamics. The total entropy production during a time interval $[0, \tau]$ is given by integrating the entropy production rate as $\Sigma := \int_0^\tau dt \dot{\Sigma}$. Hereafter, we set $R = 1$.

In addition to the entropy production that involves all the reactions, we formally introduce partial entropy productions for specific chemical species. To define partial entropy productions, we define a subset of \mathcal{R} for each subset of species $\mathcal{S} \subset \mathcal{S}_X \cup \mathcal{S}_Y$ by $\mathcal{R}_\mathcal{S} := \{\rho \in \mathcal{R} | \exists i \in \mathcal{S}, \mathbf{S}_{i\rho} \neq 0\}$. Next, we define the partial entropy production rate for a subset of chemical species \mathcal{S} by

$$\dot{\Sigma}_S := \sum_{\rho \in \mathcal{R}_S} J_\rho \ln \frac{J_\rho^+}{J_\rho^-}. \quad (5)$$

The partial entropy production is given by integrating the partial entropy production rate $\Sigma_S := \int_0^\tau dt \dot{\Sigma}_S$. If \mathcal{S} is a subset of \mathcal{S}' , \mathcal{R}_S is also a subset of $\mathcal{R}_{S'}$. Thus, if $\mathcal{S} \subset \mathcal{S}'$, $\dot{\Sigma}_S \leq \dot{\Sigma}_{S'}$ and $\Sigma_S \leq \Sigma_{S'}$ hold. When \mathcal{S} has only one element α_i , we may substitute i for \mathcal{S} like $\dot{\Sigma}_i$ or \mathcal{R}_i .

Main results.—We first state and prove the most important inequality for the derivation of our results

$$|f_i| \leq \sqrt{\tilde{D}_{ii} \dot{\Sigma}_i}, \quad (6)$$

where $f_i := \sum_{\rho \in \mathcal{R}} \mathbf{S}_{i\rho} J_\rho$ and $\tilde{D}_{ii} := (1/2) \sum_{\rho \in \mathcal{R}} \mathbf{S}_{i\rho}^2 \times (J_\rho^+ + J_\rho^-)$. We note that the range of summation in the definition of f_i and \tilde{D}_{ii} can be replaced by the subset \mathcal{R}_i , namely, $f_i = \sum_{\rho \in \mathcal{R}_i} \mathbf{S}_{i\rho} J_\rho$ and $\tilde{D}_{ii} = (1/2) \sum_{\rho \in \mathcal{R}_i} \mathbf{S}_{i\rho}^2 \times (J_\rho^+ + J_\rho^-)$, because $\mathbf{S}_{i\rho} = 0$ if $\rho \notin \mathcal{R}_i$. This inequality is shown as follows. From the Cauchy–Schwarz inequality, we find

$$\left| \sum_{\rho \in \mathcal{R}_i} \mathbf{S}_{i\rho} J_\rho \right| = \left| \sum_{\rho \in \mathcal{R}_i} \mathbf{S}_{i\rho} \sqrt{J_\rho^+ + J_\rho^-} \frac{J_\rho}{\sqrt{J_\rho^+ + J_\rho^-}} \right| \quad (7)$$

$$\leq \sqrt{\sum_{\rho \in \mathcal{R}_i} \mathbf{S}_{i\rho}^2 (J_\rho^+ + J_\rho^-)} \sqrt{\sum_{\rho \in \mathcal{R}_i} \frac{J_\rho^2}{J_\rho^+ + J_\rho^-}}. \quad (8)$$

By using an inequality $2(a-b)^2/(a+b) \leq (a-b) \ln(a/b)$ that holds for any nonnegative real numbers a, b , we have

$$\sum_{\rho \in \mathcal{R}_i} \frac{J_\rho^2}{J_\rho^+ + J_\rho^-} \leq \frac{1}{2} \sum_{\rho \in \mathcal{R}_i} J_\rho \ln \frac{J_\rho^+}{J_\rho^-} = \frac{1}{2} \dot{\Sigma}_i. \quad (9)$$

By combining these inequalities, we can obtain Eq. (6).

We next show how this inequality readily leads to a TUR. Our results are completely described by macroscopic quantities such as reaction rates, but the quantities appearing in Eq. (6), f_i and \tilde{D}_{ii} , should be understood from the mesoscopic point of view. Here, we assume $d[\mathbf{Y}]_t/dt = \mathbf{0}$, but this assumption does not lose the generality of our discussion. When the stochasticity of reactions is strong, chemical reactions are described as Markov jump processes [53]. By taking the thermodynamic limit, we can remove all the effects of the noise to recover the rate equation [44,45]. If we leave the lowest-order noise, we have the chemical Fokker–Planck equation [54]

$$\frac{\partial p(t, \mathbf{x})}{\partial t} = - \sum_{i \in \mathcal{S}_X} \frac{\partial}{\partial x_i} [f_i p(t, \mathbf{x})] + \frac{1}{V} \sum_{i, j \in \mathcal{S}_X} \frac{\partial^2}{\partial x_i \partial x_j} [\tilde{D}_{ij} p(t, \mathbf{x})], \quad (10)$$

where \mathbf{x} is the random variable that corresponds to the concentration, and V is the volume as an expanding parameter. This chemical Fokker–Planck equation has f_i as the deterministic drift, and $V^{-1} \tilde{D}_{ij} = (2V)^{-1} \sum_{\rho \in \mathcal{R}} \mathbf{S}_{i\rho} \mathbf{S}_{j\rho} \times (J_\rho^+ + J_\rho^-)$ as the diffusion coefficient matrix (for derivation, see Supplemental Material [55]). Thus, f_i and \tilde{D}_{ii} can be seen as the measures of drifts and fluctuations that the CRN intrinsically has. We call this scaled diffusion coefficient \tilde{D}_{ij} simply the diffusion coefficient. As well as the ratio of the diffusion constant to the square of a current $2D/J^2$ that appears in the conventional TUR, the ratio of the diffusion coefficient to the square of the drift $2\tilde{D}_{ii}/f_i^2$ represents a relative fluctuation of the CRN. Therefore, the following relation can be seen as a thermodynamic uncertainty relation in chemical reactions:

$$\left(\min_{i \in \mathcal{S}_X \cup \mathcal{S}_Y} \frac{2\tilde{D}_{ii}}{f_i^2} \right) \dot{\Sigma} \geq 2, \quad (11)$$

where chemostatted species are reintroduced because the inequality in Eq. (6) holds for all $i \in \mathcal{S}_X \cup \mathcal{S}_Y$. This inequality is our first result. It is obtained from Eq. (6) and the fact that $\dot{\Sigma}_i \leq \dot{\Sigma}$. It shows the trade-off relation between the entropy production rate $\dot{\Sigma}$ and the minimum of the relative fluctuation of chemical reactions $\min_{i \in \mathcal{S}_X \cup \mathcal{S}_Y} 2\tilde{D}_{ii}/f_i^2$. As long as the local detailed balance condition (3) is satisfied, it holds in any homogeneous CRNs, even if they are open, nonideal, and nonstationary; thus, it is a universal law of chemical reactions.

By integrating the inequality in Eq. (6), we obtain a TSL of CRNs similar to the ones that have already been known in stochastic thermodynamics [21,23]. The following inequality is our second main result:

$$\tau \geq \frac{L_S([\mathbf{X}]_0, [\mathbf{X}]_\tau)^2}{\langle \tilde{D}_S \rangle_\tau \Sigma_S} =: \tau_S, \quad (12)$$

where \mathcal{S} is a subset of \mathcal{S}_X that has $|\mathcal{S}|$ elements, $L_S([\mathbf{X}]_t, [\mathbf{X}]_{t'}) := |\mathcal{S}|^{-1} \sum_{i \in \mathcal{S}} |[X_i]_t - [X_i]_{t'}|$, \tilde{D}_S is the average of the diagonal elements of the diffusion coefficient matrix with respect to \mathcal{S} given by $\tilde{D}_S := |\mathcal{S}|^{-1} \sum_{i \in \mathcal{S}} \tilde{D}_{ii}$, and the bracket represents the time average $\langle \tilde{D}_S \rangle_\tau := \tau^{-1} \int_0^\tau dt \tilde{D}_S$. This inequality indicates a trade-off relation between speed and other physical quantities, the diffusion coefficient, and the entropy production. It gives a lower bound to the time needed for a concentration distribution to change into another one. It shows that the time average of the diffusion coefficient or the entropy production must be increased when one tries making the time shorter by controlling external parameters. In particular, if the diffusion coefficient does not depend on parameters so much, the entropy production will be the complementary quantity to the changing speed. We will demonstrate this trade-off relation by a numerical calculation.

We prove the TSL. Because of the rate equation $d[X_i]_t/dt = f_i$, we have $|[X_i]_0 - [X_i]_\tau| = |\int_0^\tau dt f_i|$. From the triangle inequality and the inequality in Eq. (6), we find

$$\left| \int_0^\tau dt f_i \right| \leq \int_0^\tau dt |f_i| \leq \int_0^\tau dt \sqrt{\tilde{D}_{ii} \dot{\Sigma}_i}. \quad (13)$$

By using the Cauchy–Schwarz inequality, we see that it is bounded as

$$\left| \int_0^\tau dt \sqrt{\tilde{D}_{ii} \dot{\Sigma}_i} \right| \leq \sqrt{\int_0^\tau dt \tilde{D}_{ii}} \sqrt{\int_0^\tau dt \dot{\Sigma}_i} = \sqrt{\tau \langle \tilde{D}_{ii} \rangle_\tau \Sigma_i}. \quad (14)$$

Taking summation for $i \in \mathcal{S}$ leads to

$$\sum_{i \in \mathcal{S}} |[X_i]_0 - [X_i]_\tau| \leq \sqrt{\tau} \sum_{i \in \mathcal{S}} \sqrt{\langle \tilde{D}_{ii} \rangle_\tau \Sigma_i} \quad (15)$$

$$\leq \sqrt{\tau \Sigma_{\mathcal{S}}} \sum_{i \in \mathcal{S}} \sqrt{\langle \tilde{D}_{ii} \rangle_\tau}, \quad (16)$$

where we use the fact that $\{i\} \subset \mathcal{S}$, so $\Sigma_i \leq \Sigma_{\mathcal{S}}$. The Cauchy–Schwarz inequality finally yields the following inequality:

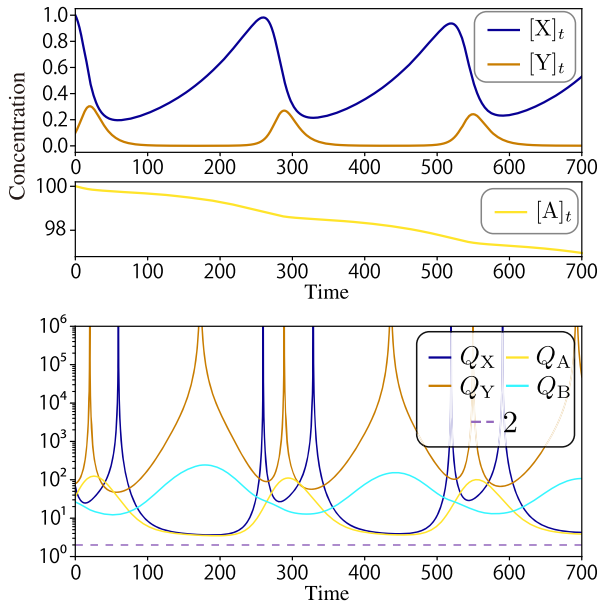
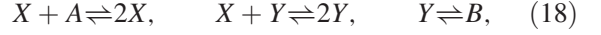


FIG. 2. Upper: concentration changes of X , Y , and A in the damped Lotka–Volterra model [Eq. (18)] are shown. The former two oscillate, while that of A monotonically decreases. Lower: confirmation of the TUR (11). Q_i 's are always bounded below by two. Those of oscillating species X , Y are larger than that of the monotonically changing species A on average.

$$\sum_{i \in \mathcal{S}} |[X_i]_0 - [X_i]_\tau| \leq \sqrt{\tau \Sigma_{\mathcal{S}}} \sqrt{|\mathcal{S}| \langle \tilde{D}_{ii} \rangle_\tau}. \quad (17)$$

This inequality is readily turned into the form of Eq. (12).

Example of the TUR.—We illustrate the TUR through a model of an open oscillatory CRN. We consider the following damped Lotka–Volterra chemical reaction model [57]:



where we set the concentration of B constant, so it is a model of an open CRN. We numerically solve the rate equation, assuming that the reaction rates are given by the mass-action law (for details, see Supplemental Material [55]). As shown in the upper two panels in Fig. 2, the concentrations of X and Y oscillate, while that of A monotonically decreases.

In the lower panel of Fig. 2, we exhibit $Q_i := (2\tilde{D}_{ii}/f_i^2)\dot{\Sigma}$ for $i \in \{X, Y, A, B\}$. They are bounded below by two,

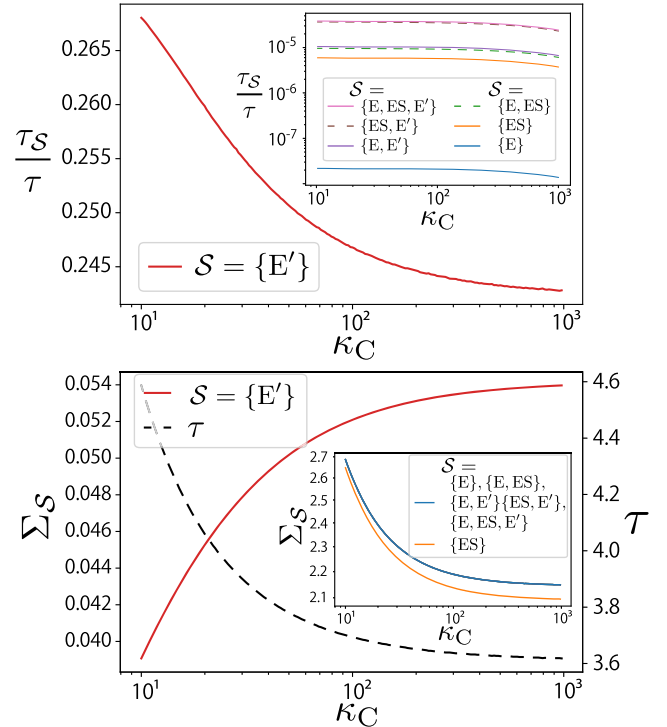


FIG. 3. For the model of CRN (19), we can see that the TSL holds in the shown range of parameter κ_C for all subsets (upper). As expected from the relatively tight inequality $\tau_{\{E'\}}/\tau \sim 0.25 < 1$, there is a trade-off between speed τ and the partial dissipation $\Sigma_{E'}$ (lower). On the other hand, for subsets other than $\{E'\}$, the TSL is not a good estimation (upper inset). Therefore, the trade-off between partial dissipation and speed does not hold for them (lower inset). We note that we observed only a few percent of changes in the averaged diffusion coefficient and the distance between the initial and final distribution when changing the parameter κ_C .

shown by the purple dashed line. On average, Q_i 's of the oscillating species are bigger than Q_A . That is because f_i 's of oscillating species oscillate around zero and are smaller on average than f_A , while \tilde{D}_{ii} 's take nonzero values that are the same order as the diffusion coefficient of A . From a mesoscopic point of view, \tilde{D}_{ii}/f_i^2 is simply seen as a measure of fluctuations, so this may imply connections between macroscopic oscillation and mesoscopic fluctuations.

Example of the TSL.—We numerically examine the TSL and the expected trade-off relation. To this end, we consider a model of enzymatic reaction with a coenzyme



We assume $[S]$ and $[P]$ are kept at constant value, and the system is first in a steady state with a certain value of $[C]_0$. Next, the CRN comes in contact with a particle reservoir of C , where the concentration of C is $[C]^{\text{ext}} \neq [C]_0$. The system starts to evolve with an external flow $\mathcal{J}_C^Y = -\kappa_C([C] - [C]^{\text{ext}})$, where κ_C is a constant [58] (for details, see Supplemental Material [55]). We define τ as the time it takes for the system to reach another steady state. By increasing the speed κ_C of exchanging C , we can decrease τ .

From the upper panel in Fig. 3, we can confirm the TSL. The TSL for $\{E'\}$ gives a nice bound $\tau_{E'}/\tau \sim 0.25$, but the other TSLs, shown in the inset, do not bound τ very well. As a result, while there is a clear trade-off relation between speed τ and the partial entropy production $\Sigma_{E'}$, as we see in the lower panel in Fig. 3, the other partial entropy productions do not increase, as shown in the inset. Our TSL is characterized by the fact that it is possible to find a tight bound and acquire some trade-off relation by appropriately choosing a subset of chemical species.

Conclusion.—We have shown a TUR between the fluctuation defined by the scaled diffusion coefficient and the changing rate of concentration and dissipation, namely, the entropy production rate, in deterministic CRNs. We have also obtained a TSL. The lower bound on the time it takes when an initial concentration distribution goes to another final distribution is given by combining the entropy production and intrinsic fluctuation. These results are proved under quite general settings, so they reinforce the universality of TURs and TSLs.

In addition to the TSL we have derived, there exist speed limits and trade-offs in CRNs. One example is the information geometric speed limit [35], and its relationship with the TSL is summarized in Supplemental Material [55]. Additionally, many trade-off relations have been found for various biochemical processes [59–63]. The relationship between these individual trade-offs and our general result of the TSL is still not well understood, and future research is needed. We expect the general result to give a new and unified perspective to our understanding of biochemical processes.

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