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# Non-equilibrium thermodynamics of biological signal transduction predicts conservation of entropy production rate

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## ABSTRACT

Studies have reported that bio-cellular signal transduction can be investigated based on thermodynamics. This short article aims to consider signal transduction carried out by signaling molecules from the perspective of *non-equilibrium* thermodynamics. Under conditions in which total entropy production rate was minimized, the entropy production rate per signaling molecule was conserved independently of the steps during signal transduction. Accordingly, the conserved production rate can be defined as the channel capacity of the given signal transduction cascade. Non-equilibrium thermodynamics provides a theoretical framework for cell signal transduction.

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## 1. Introduction

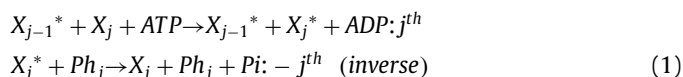
Biological systems exist in a non-equilibrium state known as homeostasis (Crofts, 2007). The intracellular signal transduction system perceives changes in the external environment via receptors and converts these signals into a chain reaction (Hollenberg, 2002; Wang et al., 2002; Xin et al., 2011). For example the extracellular signal-regulated kinase, calcium, and nuclear factor kappa-B pathways have been extensively studied from a biophysical perspective (Selimkhanov et al., 2014).

Recent studies have shown that signal transduction can be quantitatively described by mutual entropy and other parameters from the viewpoint of information science (McGrath et al., 2017; Uda and Kuroda, 2016; Uda et al., 2013). Information thermodynamics has provided a theoretical framework in which signaling systems utilize fluctuations (Sagawa et al., 2014). Fluctuations in the concentrations of signaling molecules may cause transduction of information related to the external environment to alter gene expression. Understanding how fluctuations can be conveyed through a signaling transduction system will enable quantification of signal levels. Our earlier studies showed that the entropy production rate at each step of signal transduction is conserved based on the entropy coding theory (Tsuruyama, 2018a, 2018b; Tsuruyama, 2018d).

In the current study, we evaluated which thermodynamic parameters are conserved based on non-equilibrium linear ther-

modynamics. To date, a model of the mitogen-activated protein kinase (MAPK) cascade has been considered (Blossey et al., 2012; Purutçuoğlu and Wit, 2012; Qiao et al., 2007; Wang et al., 2002; Yoon and Deisboeck, 2009; Zumsande and Gross, 2010). The sequential activation of epidermal growth factor receptor (EGFR), Ras, c-Raf, MAPK-extracellular signal-regulated kinase (MEK), and kinase-extracellular signal-regulated kinase (ERK) occurs following stimulation with epidermal growth factor (EGF) on the EGFR. This MAPK cascade allows for cell growth and proliferation. Mutations in EGFR promote the upregulation of this cascade in lung and other cancers (Yoshizawa et al., 2013).

Below, a simple MAPK signal transduction model is assumed, which is the same as the previously reported model (Tsuruyama, 2018b; Tsuruyama, 2018d). In this model,  $R (= X_1)$ , denoting the receptor protein, binds to the receptor protein on the cell membrane surface and is activated by an extracellular ligand protein ( $L$ ). In turn, the receptor-ligand complex  $X_1 - L^*$  activates  $X_2$ , and the active form  $X_2^*$  further activates the next signaling molecule  $X_3$ . In this manner, the activated signaling molecule species  $X_{j-1}^*$  can activate  $X_j$  ( $1 \leq j \leq n$ ).



This activation results in by phosphorylation of amino acid residues, such as tyrosine, by inorganic phosphate ( $Pi$ ) donated from the metabolite adenosine triphosphate (ATP). In the cascade,  $X_j^*$  is the active form that can transmit the biological information and  $X_j$  is the inactive form. Finally, the  $X_n$  active form  $X_n^*$  migrates

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to the nucleus and binds to DNA, where RNA (ribonucleotide)<sub>N</sub> is synthesized (transcribed) from N ribonucleotides through the catalytic action by RNA polymerase. In the inverse orientation of signal transduction, inactivation of X<sub>j</sub><sup>\*</sup> is catalyzed by the phosphatase Ph<sub>j</sub> (1 ≤ j ≤ n - 1) and Pi is released. The number of steps is shown to the right of Eq. (1).

## 2. Result

### 2.1. Nonequilibrium thermodynamics of intracellular signaling

Signal transduction can occur because of the entropy difference between the (j-1)-th and next (j+1)-th signal step with respect to the difference in the proportion of X<sub>j</sub><sup>\*</sup> and X<sub>j</sub> (1 ≤ j ≤ n) (Fig. 1). Here, we defined the occurrence probability, p<sub>j</sub> and, p<sub>j</sub><sup>\*</sup>, which represents the selection probability of 1 ≤ j ≤ X<sub>j</sub> or X<sub>j</sub><sup>\*</sup>, respectively: p<sub>j</sub> = X<sub>j</sub>/X and p<sub>j</sub><sup>\*</sup> = X<sub>j</sub><sup>\*</sup>/X. Here, X represents the total concentration of signaling molecules. Because signaling molecules are macromolecules, they are localized and the individual steps are hypothesized to be compartmentalized in the cytoplasm.

We considered the entropy current from the j-th to (j+1)-th step consisting of X<sub>j</sub><sup>\*</sup>. The entropy S<sub>j</sub> of the j-th compartment with a minimal concentration difference in X<sub>j</sub><sup>\*</sup>, dp<sub>j</sub><sup>\*</sup>, and in X<sub>j</sub>, dp<sub>j</sub> (= -dp<sub>j</sub><sup>\*</sup>), is described as follows:

$$S_j \equiv k_B [S_j^0(T) - (p_j + dp_j) \log(p_j + dp_j) - (p_j^* + dp_j^*) \log(p_j^* + dp_j^*)] \quad (2)$$

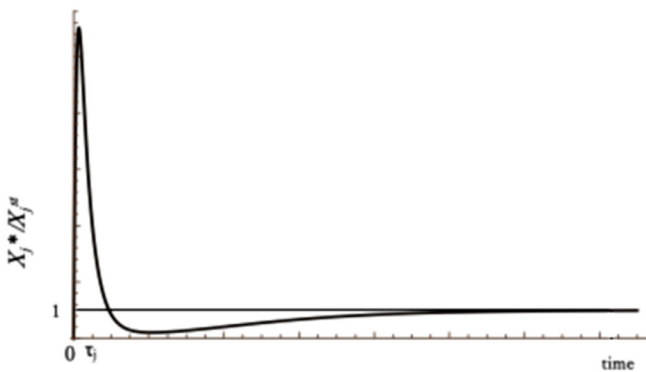
k<sub>B</sub> denotes the Boltzmann coefficient. T denotes reaction temperature. Because the increase and decrease are not observed in the (j+1)-th step in the initial phase of signal transduction from the j-th to (j+1)-th steps, the entropy S<sub>j+1</sub> of the j+1 compartment is described as follows:

$$S_{j+1} \equiv k_B [S_{j+1}^0(T) - p_j \log p_j - p_j^* \log p_j^*] \quad (3)$$

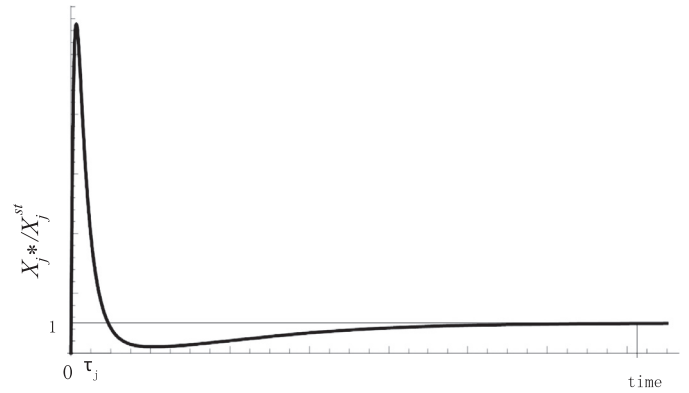
Here, T denotes the reaction temperature in the cell and S<sub>j+1</sub><sup>0</sup> = S<sub>j+1</sub><sup>0</sup>, because other components of signaling molecules did not differ in the j-th step in the signal transduction. The entropy signal current J<sub>j</sub> arises from the gradient of entropy difference S<sub>j</sub> - S<sub>j+1</sub> (see Appendix A):

$$J_j = D_j X \nabla (S_j - S_{j+1}) \simeq D_j \log \frac{p_j}{p_j^*} \nabla X_{j^*} \sim D_j \frac{X_{j^*}(j) - X_{j^*}(j+1)}{l_j} \quad (4)$$

Above entropy signal current is described using the diffusion coefficient of X<sub>j</sub><sup>\*</sup>, D<sub>j</sub>. Here, l<sub>j</sub> is equal to the mean free path of



**Fig. 1.** Signaling molecules X<sub>j</sub> and X<sub>j</sub><sup>\*</sup> are included in j-th compartment. l<sub>j</sub> (1 ≤ j ≤ n) denotes the free path of X<sub>j</sub><sup>\*</sup> and distance between the hypothetical j-th and (j+1)-th compartment. The driving force of the signaling molecule is the gradient of the entropy between the hypothetical j-th and (j+1)-th compartment that is produced by the difference in the proportion of X<sub>j</sub> and X<sub>j</sub><sup>\*</sup>.



**Fig. 2.** Common time course of the j-th step. The vertical axis denotes the ratio X<sub>j</sub><sup>\*</sup>/X<sub>j</sub><sup>st</sup>. The horizontal axis denotes the duration (min) of the j-th step. τ<sub>j</sub> represents the duration of the j-th step signaling corresponding to the period in which X<sub>j</sub><sup>\*</sup> and X<sub>j</sub><sup>\*</sup>/X<sub>j</sub><sup>st</sup> increase to the maximum value.

X<sub>j</sub><sup>\*</sup> between the j-th and (j+1)-th step-compartments during the diffusion duration τ<sub>j</sub>, which represents the duration corresponding to the period in which X<sub>j</sub><sup>\*</sup> increases to the maximum value in the concentration (Fig. 2). X<sub>j</sub>(j)<sup>\*</sup> = X<sub>j</sub><sup>\*</sup> and X<sub>j</sub>(j+1)<sup>\*</sup> represent the concentrations of signaling molecules in the j-th and (j+1)-th step compartments (Fig. 1). In the j+1 compartment, X<sub>j</sub>(j+1)<sup>\*</sup> is equal to the concentration during the steady state, X<sub>j</sub><sup>st</sup>, because the signal has not reached the (j+1)-th step compartment.

Accordingly, the rate of entropy production from the diffusion process dS<sub>j</sub><sup>D</sup> in the j-th step is simply given by the following equation:

$$\frac{dS_j^D}{dt} = J_j \cdot \nabla (S_j - S_{j+1}) = D_j \frac{1}{X_{j^*}^{st}} \left( \frac{X_{j^*} - X_{j^*}^{st}}{l_j} \right)^2 = D_j \frac{1}{X_{j^*}^{st}} \left( \frac{\Delta X_{j^*}}{l_j} \right)^2 \quad (5)$$

with

$$\Delta X_{j^*} \equiv X_{j^*} - X_{j^*}^{st} \quad (6)$$

Above, substitution of D<sub>j</sub> = l<sub>j</sub><sup>2</sup>/τ<sub>j</sub> into Eq. (5) gives the rate of dS<sub>j</sub><sup>D</sup> in the j-th step:

$$\frac{dS_j^D}{dt} = \Delta X_{j^*}^2 / \tau_j = X_{j^*}^{*2} N_j \quad (7)$$

In above, 1/τ<sub>j</sub> is equal to the signal event number N<sub>j</sub> per unit time.

Subsequently, the rate of the j-th step in (1), v<sub>j</sub>, which is equal to the phosphorylation rate of forward signal transduction, is given using the kinetic coefficient k<sub>j</sub> for the j-th step:

$$v_j = k_j [ATP] X_j X_{j-1}^* \quad (8)$$

The rate of the -j-th step, v<sub>-j</sub>, is equal to dephosphorylation rate of the backward signal transduction, and is determined using the kinetic coefficient k<sub>-j</sub>:

$$v_{-j} = k_{-j} Ph_j X_j^* \quad (9)$$

Let us consider the signal transduction system that remains in a precise balance around the steady state. Accordingly, from Eqs. (8) and (9):

$$v_j^{st} = v_{-j}^{st}. \quad (10)$$

In an actual signal transduction process, the chemical entropy production rate per unit volume is determined using chemical affinity of the j-th step reaction A<sub>j</sub>, the extent of reaction ξ<sub>j</sub>, and the rate of dS<sub>j</sub><sup>C</sup> in the j-th step from the chemical reaction of j-th

step is given by according to the second law of thermodynamics:

$$\frac{dS_j^C}{dt} = \frac{A_j}{T} \xi_j \geq 0 \quad (11)$$

with

$$\frac{A_j}{T} = \log \frac{v_j}{v_{-j}} \quad (12)$$

Here, we identified that the concentration fluctuation is transmitted by the signal transduction (Tsuruyama, 2018a; Tsuruyama, 2018c). Then the rate of the extent of reaction  $\xi_j$  is given by:

$$\begin{aligned} \dot{\xi}_j &= v_j - v_{-j} = k_j[ATP]X_{j-1}^*X_j - k_{-j}X_j^*Ph_j \\ &= k_j[ATP]X_{j-1}^*(X_j^{st} + \Delta X_j) - k_{-j}(X_j^{st*} + \Delta X_j^*)Ph_j \\ &= -(k_j[ATP]X_{j-1}^* + k_{-j}Ph_j)\Delta X_j^* = -\alpha_j\Delta X_j^* \end{aligned} \quad (13)$$

with

$$\alpha_j \equiv k_j[ATP] + k_{-j}Ph_j \quad (14)$$

In above, we used Eq. (6),  $X_j = X_j^{st} + \Delta X_j$  and  $\Delta X_j = -\Delta X_j^*$ . From Eqs. (6) and (12), the affinity is given by (Appendix B):

$$\begin{aligned} \frac{A_j}{T} &= k_B \log \frac{k_j[ATP]X_{j-1}^*(X_j^{st} + \Delta X_j)}{k_{-j}(X_j^{st*} + \Delta X_j^*)Ph_j} \\ &= k_B \log \frac{(1 + \Delta X_j/X_j^{st})}{(1 + \Delta X_j^*/X_j^{st*})} = -\frac{X_j^0}{X_j^{st}X_j^{st*}} \Delta X_j^* \end{aligned} \quad (15)$$

The rate of entropy production in the  $j$ -th step is described as:

$$\frac{dS_j^C}{dt} = \frac{\alpha_j X_j^0}{X_j^{st}X_j^{st*}} (\Delta X_j^*)^2 = \beta_j (\Delta X_j^*)^2, \quad (16)$$

and

$$\frac{\alpha_j X_j^0}{X_j^{st}X_j^{st*}} \equiv \beta_j \quad (17)$$

Thus, the entropy production rate is described by the square of the fluctuation. By adding Eqs. (16) and (7), the total entropy production rate  $P$  is given by:

$$P \equiv \frac{dS}{dt} = \sum_{j=1}^n \left( \frac{dS_j^D}{dt} + \frac{dS_j^C}{dt} \right) = \sum_{j=1}^n (\beta_j + N_j) (\Delta X_j^*)^2 \quad (18)$$

Here, we used  $dS_j = dS_j^D + dS_j^C$ . The above Eq. (18) indicates that the signal transduction system is carried out with the chemical reaction and diffusion of the signaling molecules.

## 2.2. Conservation of entropy production rate in signal transduction

Here, we considered the principle of minimal total entropy production rate for its application to (18), which is a partial derivative of  $P$  with respect to the concentration fluctuation of the signaling molecule  $\Delta X_j^*$  and change in the rate:

$$\frac{\partial P}{\partial \Delta X_j^*} = 2(\beta_j + N_j)\Delta X_j^* - 2(\beta_n + N_n)\Delta X_n^* \quad (19)$$

Setting the right side of Eq. (19) equal to zero, at all  $j$  ( $1 \leq j \leq n$ ) from the rearrangement gives

$$(\beta_j + N_j)\Delta X_j^* = C(n)(1 \leq j \leq n) \quad (20)$$

$C(n) = (\beta_n + N_n)\Delta X_n^*$  on the right side of Eq. (20) is independent of the step number  $j$ , but only depends on the  $n$  step and a conserved quantity in cell signal transduction. Substitution of Eq. (20) into Eq. (18) gives

$$P(n) = C(n) \sum_{j=1}^n \Delta X_j^* = \sum_{j=1}^n P_j \quad (21)$$

$$P_j \equiv C(n)\Delta X_j^* \quad (22)$$

In above,  $\sum_{j=1}^n \Delta X_j^* = \Delta X^*$ . The entropy production rate per signaling molecule  $P_j / \Delta X_j^* = \sigma$  is found to be conserved,  $C(n)$ , during the signal cascade.

$$\sigma = \beta_j + N_j = C(n) \quad (23)$$

## 3. Conclusions

Considering the locality of the second law of thermodynamics, entropy can be divided into entropy derived from a chemical reaction and entropy produced by the diffusion of signaling molecules (Glansdorff et al., 1974; Yoshikawa, 1992). The increase in entropy occurs primarily because of the hydrolysis of ATP, which is abundantly present in the chemical baths. In fact, the entropy production rate  $\sigma$  shown in Eq. (20) or Eq. (23) is given by the amount of phosphorylated signaling molecule  $\beta_j$  and signaling number  $N_j$  per unit time. In conclusion, the conserved production rate can be defined as the channel capacity of the given signal transduction cascade.

To apply the linear law for chemical affinity, in general, the formula  $A_j / k_B T \ll 1$  is required (Jou et al., 2010). Therefore, from Eq. [15], we can obtain:

$$\begin{aligned} \dot{\xi}_j &= k_j[ATP]X_{j-1}^*X_j \left( 1 - \frac{k_{-j}X_j^*Ph_j}{k_j[ATP]X_{j-1}^*X_j} \right) \\ &= k_j[ATP]X_{j-1}^*X_j (1 - \exp(-A_j/k_B T)) \\ &\simeq k_j[ATP]X_{j-1}^*X_j (A_j/k_B T) \end{aligned} \quad (24)$$

This shows that the linear-law can be applied only when the signal reaction proceeds near the equilibrium or to the reaction with sufficiently low activation energy. Further, from Eqs. (15) and (24),

$$\dot{\xi}_j = -\frac{k_j}{k_B} [ATP]X_{j-1}^*X_j \frac{X_j^0}{X_j^{st}X_j^{st*}} \Delta X_j^* \quad (25)$$

The high-order items of the fluctuation, the right side can be approximated when  $X_j^*$  is sufficiently smaller than  $X_j$  as

$$\dot{\xi}_j \simeq -\frac{k_j}{k_B} [ATP] \left( \frac{X_{j-1}^{st*}}{X_j^{st*}} \right) X_j^0 \Delta X_j^* \quad (26)$$

Therefore, the extent of reaction is proportional to the fluctuation of signaling molecule and concentration of ATP. Thus, from Eqs. (13) and (26), we can simply rewrite  $\alpha_j$  instead of Eq. (14) without  $Ph_j$ :

$$\alpha_j \simeq \frac{k_j}{k_B} [ATP] \left( \frac{X_{j-1}^{st*}}{X_j^{st*}} \right) X_j^0 \quad (27)$$

Substitute of Eq. (27) into Eq. (17) gives

$$\beta_j \simeq \frac{k_j}{k_B} [ATP] \left( \frac{X_{j-1}^{st}}{X_j^{st}} \right) \left( \frac{X_j^0}{X_j^{st*}} \right)^2 \quad (28)$$

The principle of entropy maximization implies that the first derivative of entropy with respect to time is always positive according to the second law of thermodynamics for the equilibrium state. In the current analysis, the system settles into a non-equilibrium steady state and that the second derivative of entropy with respect to time approaches zero with the passage of time (the first derivative is always positive according to the second law of thermodynamics in the non-equilibrium steady state) and we applied the minimization method of the entropy production rate (Glansdorff et al., 1974; Damiret et al., 2018; Kondepudi et al., 1998).

In previous studies, we considered forming the code sequence in the order of activation of signaling molecules, such as  $X_1X_2X_3X_4$ . Suppose that this sequence corresponds to an event of signal transduction, then the probability that the signaling molecule  $X_j$  is activated in the signaling molecule can be given by  $p_j$ . A simple entropy-coding expression of  $-\log p_j = \zeta \tau_j$  is given from information theory (Brillouin, 2013; Tsuruyama, 2018b; Tsuruyama, 2018c; Tsuruyama, 2018d). Because  $-\log p_j$  gives the entropy in the information theory,  $\zeta$  gives the average entropy production rate during  $\tau_j$  and  $\zeta$  does not depend on the subscript  $j$  of the signal transduction step. This encoding method is a well-known method of giving a shorter code length for frequent codes and longer code length for less frequent codes and  $\zeta$  is referred as the channel capacity of the signal cascade (Brillouin, 2013). The relationship between the conservation of  $\zeta$  and  $\sigma$  in the Eq. (23) is still not yet clear in the information science viewpoints. The conservation of  $\zeta$  is an information theoretic requirement to minimize redundancy, while the conservation of  $\sigma$  is a request from linear non-equilibrium thermodynamics and may relate to the problem of information channel coding to minimize errors. In the future, we need a discussion based on theoretical investigation between information science and non-equilibrium thermodynamics. In addition, the spatial derivative of the entropy should be based on the channel coding. However, the current study can at least point out this orientation of theoretical investigation.

In conclusion, this study provides support for quantifying signal transduction and a promising framework for detecting active pathways among response networks.

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## Author contributions

TT described manuscript and analyzed the model.

## Appendix A

The detailed calculation in Eq. (4) is as follows:

$$\begin{aligned} J_j &= D_j X_j^* \nabla (S_j - S_{j+1}) \simeq D_j X_j^* \nabla \log \frac{X_j}{X_j^*} \\ &= D_j X_j^* \left( \frac{1}{X_j} \nabla X_j - \frac{1}{X_j^*} \nabla X_j^* \right) \sim -D_j X_j^* \frac{1}{X_j^*} \nabla X_j^* \\ &\sim D_j \frac{X_j^*(j) - X_j^*(j+1)}{l_j} \end{aligned}$$

Here, we approximated  $\nabla X_j^*$  as  $(X_j^*(j) - X_j^*(j+1))/l_j$  and neglected  $\nabla X_j$  because the concentration of inactive signaling molecules is nearly kept constant. In above, the spatial gradient of the inactive signaling molecule  $X_j$  is neglected.  $r$  denotes the spatial coordinate.

## Appendix B

The detailed calculation in Eq. (15) is as follows:

$$\begin{aligned} \frac{A_j}{T} &= \log \frac{k_j [ATP] X_j (X_{j+1}^{st} + \Delta X_{j+1})}{k_{-j} (X_{j+1}^{*st} + \Delta X_{j+1}^*) Ph_{j+1}} \\ &= \log \frac{(1 + \Delta X_{j+1}/X_{j+1}^{st})}{(1 + \Delta X_{j+1}^*/X_{j+1}^{*st})} \end{aligned}$$

$$\begin{aligned} &\simeq \Delta X_{j+1}/X_{j+1}^{st} - \Delta X_{j+1}^*/X_{j+1}^{*st} \\ &= -\frac{X_{j+1}^0}{X_{j+1}^{st} X_{j+1}^{*st}} \Delta X_{j+1}^* \end{aligned}$$

The approximation,  $\log(1+x) \sim x$  when  $x \ll 1$ , was used.

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