研究論文

A Generalized Entropy-Production Consistent with Perturbation Response in Biological Regulatory Systems†

Katsumi Sakata [1,2], Isseki Yu [1,*], Ramesh Katam [3] and Toshiyuki Saito [2]

Generalized entropy-production (GEP) is a measure of increased disorderliness in natural systems. In this article, a novel GEP is proposed, which is formulated as a quadratic form based on Jacobian matrix derived from the ordinary differential equations for the target systems. The proposed GEP has an advantage associated with eigenvalues of the Jacobian matrix, which characterizes the perturbation response of the target system. The results showed that, in numerical experiments for four biological regulatory systems the proposed GEP was consistent with perturbation response such that with the decrease in an average of the proposed GEP, the deviation from the steady state by impulsive perturbation has converged fast. The proposed GEP makes the property, a system often transitions to a new state with lower entropy, found by Kondepudi and Prigogine in chemical systems is applicable to the four biological regulatory systems.

Key words : Generalized Entropy, Biological Regulatory System

1. Introduction

Schrödinger suggested that life systems take orderliness from its environment and sustain itself at a fairly high level of orderliness, or at a fairly low level of thermodynamic entropy [1]. Sakata et al. focused on a genetic regulatory model and revealed the orderliness of a genetic regulatory system measured by Shannon entropy is influenced by a level of environmental stimulus on the system elements such as reactants and products of reactions [2]. By the suggestion, Schrödinger inspired a new line of inquiry that broadly centers around the evolutionary systems theory [3]. Recent studies on simulations for evolving networks have shown that a hierarchical neural structure enhances evolvability by adapting faster to new environments than non-hierarchical structures [4].

Similar to Schrödinger's studies, thermodynamic entropy is used as a measure of disorderliness in natural systems [5]. However, in most biological systems, the magnitude of the thermal fluctuations in system variables is much smaller than the magnitude of the system variable itself. Thus, alteration in the thermodynamic entropy in the biological systems is difficult to measure by using the thermodynamic valuables of the biological systems [6]. As an alternative of thermodynamic entropy, generalized entropy was developed and applied in investigating pathways [7] and risk management in financial economics [8]. Mielke et al. [9] developed a generalized entropy-production (GEP) which is independent of thermodynamic valuables of the target system. The GEP has been formulated as a positive-definite quadratic form for a linear approximation matrix of non-linear dynamics of the target system. In their formulation, the linear approximation matrix is substantially identical to a negative Jacobian-matrix, wherein, Jacobian matrix is a linear approximation matrix derived from ordinary differential equations of a regulatory system [10]. Prigogine and Kondepudi suggested a relationship between entropy and perturbation response in regulatory systems [11], while GEP has not been associated with dynamics parameters of the target system which characterize response (e.g. perturbation response) of the target system.

In this study, a Jacobian matrix is diagonalized using a regular matrix whose elements are composed of the eigenvectors of the Jacobian matrix. Then, the proposed GEP is formulated as a quadratic form of the inverse of the diagonal matrix. Numerical experiments were conducted to validate the relationship between the proposed GEP and response to impulsive perturbation in four biological regulatory systems. The details of the

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1 Department of Life Science and Informatics, Maebashi Institute of Technology, 2 Department of Radiation Effects Research, National Institute of Radiological Sciences, 3 Department of Biological Sciences, Florida A&M University
* Correspondence: yu@maebashi-it.ac.jp

study are given below under Section 2: mathematical formulation, Section 3: numerical experiments and Section 4: method for the experiments. Finally, in Section 5: discussion on the property of biological regulatory systems in application of the proposed GEP, and conclusion with final remarks and future works.

2. Mathematical formulation

2.1. Conventional GEP

Ordinary differential equations for a regulatory system are described as [10]:

$$\begin{cases} \dfrac{d}{dt}x_1 = F_1(x_1,\cdots,x_n) \\ \quad\vdots \\ \dfrac{d}{dt}x_n = F_n(x_1,\cdots,x_n) \end{cases} \tag{1}$$

where, $\boldsymbol{x}=(x_1,\ldots,x_n)^{\mathrm{T}}$ and F_i (i=1,…,n) are state vector of the regulatory system and i-th ordinary differential equation of the regulatory system, respectively. We define a fixed point: (x_1,…,x_n) with dx_i/dt=0 for all i=1,…,n. In case of n=2, a fixed point is an intersection of two nullclines (dx/dt=0 and dy/dt=0) as examples shown in right panels in Fig. 1(a-d).

Linearization of Eq. (1) at a fixed point gives:

$$\frac{d}{dt}\begin{pmatrix}\Delta x_1\\ \vdots \\ \Delta x_n\end{pmatrix} = \begin{pmatrix}\dfrac{\partial F_1}{\partial x_1} & \cdots & \dfrac{\partial F_1}{\partial x_n}\\ \vdots & & \vdots \\ \dfrac{\partial F_n}{\partial x_1} & \cdots & \dfrac{\partial F_n}{\partial x_n}\end{pmatrix}\begin{pmatrix}\Delta x_1\\ \vdots \\ \Delta x_n\end{pmatrix} \tag{2}$$

Using vector notation, Eq. (2) is described as:

$$\Delta\dot{\mathbf{x}} = \frac{d}{dt}\Delta\mathbf{x} = \mathbf{J}\,\Delta\mathbf{x} \tag{3}$$

where, $\Delta\mathbf{x}$ and $\mathbf{J}$ are deviation from the fixed point and Jacobian matrix, respectively [10]. A GEP has been derived by Mielke et al. using a positive-definite matrix $\mathbf{M}$ which is referred as mobility matrix [9]:

$$\frac{d}{dt}S(\Delta\mathbf{x}) = \Delta\dot{\mathbf{x}}^{\mathrm{T}}\mathbf{M}^{-1}\Delta\dot{\mathbf{x}} \tag{4}$$

where, $\mathbf{M}$ is defined as multiplication between negative Jacobian matrix ($-\mathbf{J}$) and $n\times n$ covariance matrix ($\mathbf{G}$):

$$\mathbf{M}=-\mathbf{J}\mathbf{G} \tag{5}$$

Mielke et al. have assumed positive-definiteness for the mobility matrix $\mathbf{M}$. It ensures invertibility of $\mathbf{M}$ and forces the generalized entropy $S(\Delta\mathbf{x})$ in Eq. (4) to increase as $\frac{d}{dt}S(\Delta\mathbf{x})\geq 0$ [9].

2.2. Proposed GEP

Generally, a square matrix is diagonalized using a regular matrix whose elements are eigenvectors of the square matrix, the diagonal elements of the outcome diagonal matrix are eigenvalues of the square matrix [12]. We have set a $n\times n$ regular matrix $\mathbf{P}$ by lining up eigenvectors of the Jacobian matrix ($\mathbf{J}$) as: $\mathbf{P}=\left(\text{Eigen vector}_i \text{ of } \mathbf{J}\right)$, where i=1,…,n. When diagonalize a negative Jacobian matrix using matrix $\mathbf{P}$, the proposed mobility matrix ($\mathbf{M}_{\mathrm{P}}$) is defined as:

$$\mathbf{M}_{\mathrm{P}} = \mathbf{P}^{-1}(-\mathbf{J})\mathbf{P} \tag{6}$$

After the diagonalization, the diagonal elements of $\mathbf{M}_{\mathrm{P}}$ are sign-inversed eigenvalues of the Jacobian matrix ($\mathbf{J}$):

$$\mathbf{M}_{\mathrm{P}} = \begin{pmatrix}-\lambda_1 & & 0\\ & \ddots & \\ 0 & & -\lambda_n\end{pmatrix} \tag{7}$$

where λ_i is i-th eigenvalue of $\mathbf{J}$. For a non-periodic stable fixed point, all eigenvalues of $\mathbf{J}$ are negative real numbers $\lambda_i<0$ (i=1,…,n) [10], and $\mathbf{M}_{\mathrm{P}}$ automatically forced to be positive-definite, which ensures invertibility of $\mathbf{M}_{\mathrm{P}}$. The proposed GEP is:

$$\frac{d}{dt}S_{\mathrm{P}}(\Delta\mathbf{x}) = \Delta\dot{\mathbf{x}}^{\mathrm{T}}\mathbf{M}_{\mathrm{P}}{}^{-1}\Delta\dot{\mathbf{x}} \tag{8}$$

It forced to be $\frac{d}{dt}S_{\mathrm{P}}(\Delta\mathbf{x})\geq 0$ as Mielke et al.'s GEP by the positive-definiteness of $\mathbf{M}_{\mathrm{P}}$.

Let us investigate properties of the proposed GEP. The inverse matrix of $\mathbf{M}_{\mathrm{P}}$ is:

$$\mathbf{M}_{\mathrm{P}}{}^{-1} = \begin{pmatrix}-1/\lambda_1 & & 0\\ & \ddots & \\ 0 & & -1/\lambda_n\end{pmatrix} \tag{9}$$

thus, Eq. (8) is rewritten as:

$$\frac{d}{dt}S_{\mathrm{P}}(\Delta\mathbf{x}) = \sum_{i=1}^{n}\frac{\Delta\dot{x}_i^2}{-\lambda_i} \tag{10}$$

Eq. (10) indicates the proposed GEP is square of a weighted distance from the origin of coordinate to $\Delta\dot{\mathbf{x}}\,(\Delta\dot{x}_1,\cdots,\Delta\dot{x}_n)$, where the weight coefficients are $1/(-\lambda_i)$ (i=1,…,n). For an identical $\Delta\dot{\mathbf{x}}$, different sets of

weight coefficients $1/(-\lambda_i)$ (i=1,…,n) give different weighted distances.

Meanwhile, an initial perturbation for a regulatory system is described as:

$$\Delta \mathbf{x}_0 = c_1 \mathbf{v}_1 + \cdots + c_n \mathbf{v}_n \quad (11)$$

where $\mathbf{v}_i$ and c_i are i-th eigenvector and coefficient, respectively [10]. The perturbation at time t is [10]:

$$\begin{aligned} \Delta \mathbf{x}(t) &= \exp(\mathbf{J}t)\Delta \mathbf{x}_0 \\ &= \exp(\mathbf{J}t)(c_1 \mathbf{v}_1 + \cdots + c_n \mathbf{v}_n) \\ &= c_1 \exp(\lambda_1 t)\mathbf{v}_1 + \cdots + c_n \exp(\lambda_n t)\mathbf{v}_n \end{aligned} \quad (12)$$

For a negative eigenvalue λ_i, the magnitude of the i-th term $|c_i \exp(\lambda_i t)\mathbf{v}_i|$ in right side of Eq. (12) decreases at a decay rate λ_i. As $|\lambda_i|$ increases, the magnitude of decay rate increases, and decay occurs at a faster rate. These findings suggest that, the decay rate is dependent on the eigenvalues of **J** involved in the proposed GEP. Thus, the proposed GEP is associated with the dynamic parameter of the target system, which is eigenvalues of the Jacobian matrix **J** of the target system, and the eigenvalues are related to the decay rate which characterizes response of the target system.

3. Numerical experiments

For the four biological regulatory systems (Fig. 1(a-d)), alterations in the proposed GEP around original fixed points were investigated in the condition, that flows of the components in the biological regulatory systems were sustained. The investigated biological regulatory systems were Griffith's genetic regulatory system [13], the genetic regulatory system by Gardner et al. [14], neural system [15], and intraguild predation system [16]. All of the four biological regulatory systems have two components (n=2). The original fixed points are fixed point (FP) -1, -2, -3, -4 and -5 in Fig. 1(a-d) which are intersections of two nullclines (dx/dt=0 and dy/dt=0) in the condition that flow_x=flow_y=0 in the biological regulatory systems.

Let us define GEP_{ave} for n=2 systems as an average of GEP for the points $\Delta\dot{\mathbf{x}}(\Delta\dot{x}_1, \Delta\dot{x}_2)$ whose Euclidean distance from the origin of the coordinate is one:

$$\begin{aligned} \text{GEP}_{\text{ave}} &= \frac{1}{2\pi}\int_0^{2\pi}\left(\frac{\cos^2\theta}{-\lambda_1} + \frac{\sin^2\theta}{-\lambda_2}\right)d\theta \\ &= \frac{1}{2\pi}\left(\frac{1}{-\lambda_1} + \frac{1}{-\lambda_2}\right) \end{aligned} \quad (13)$$

GEP_{ave} and response to impulsive perturbation were calculated for the four biological regulatory systems (Fig. 2). The method for calculating GEP_{ave} and response to impulsive perturbation is given in Section 4.

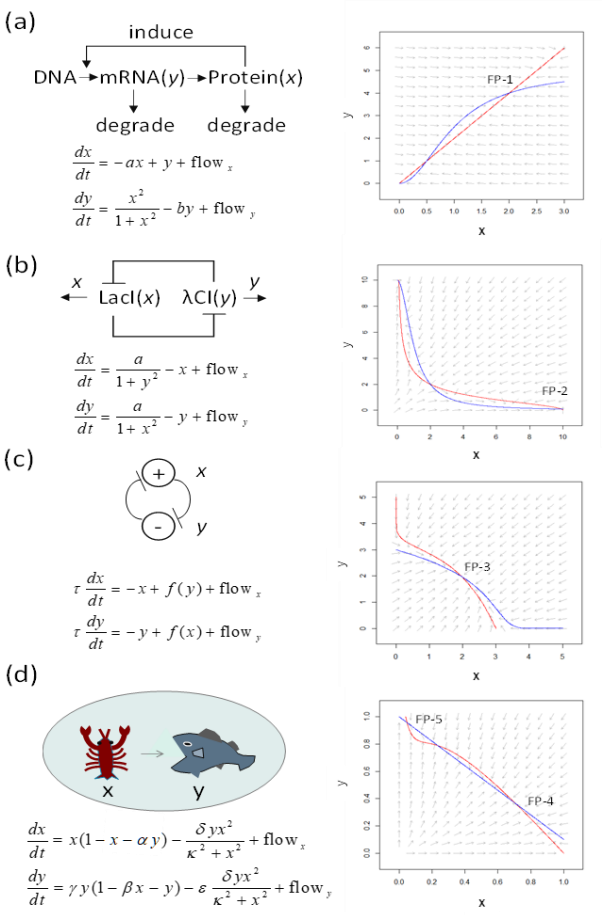

Figure 1. Biological regulatory system models. (**a**) Griffith's genetic regulatory system [13]. A translated protein induces transcription of the gene which codes itself. Protein and mRNA amounts are denoted as x and y, respectively (upper left panel). Parameter values used in numerical experiments: a=2 and b=0.2. (**b**) the genetic regulatory system by Gardner et al. [14]. The regulatory system is known as a toggle switch in the genetic network of *Escherichia coli*. LacI and λCI repressors suppress each other. LacI and λCI amounts are denoted as x and y, respectively (upper left panel). Parameter value used in numerical experiments: a=10. (**c**) Neural system [15]. Each node (marked as "+" or "−") representing a population of neurons ("plus" or "minus" neurons) inhibits mutually. Total synaptic outputs of the two nodes are denoted as x and y (upper left panel). The function f (·) (lower left panel) corresponds to the synaptic input / output function of the neurons (see Figure S1). Parameter value used in numerical experiments: τ=1. (**d**) Intraguild predation system [15]. For a closed lake ecosystem, crayfish and bass densities are denoted as x and y, respectively (upper left panel).

Parameter values used in numerical experiments: α=0.7, β=0.9, γ=1.5, δ=0.075, ε=0.01 and κ=0.1. In panels (a-d), a schematic diagram (upper left panels), differential equations for the system model (lower left panels), and vector-field and nullclines (right panels) are shown. In the nullclines, red and blue lines mean dx/dt=0 and dy/dt=0, respectively. FP-n means the n-th non-periodic stable fixed point corresponding to the intersection of the red (dx/dt=0) and blue (dy/dt=0) lines.

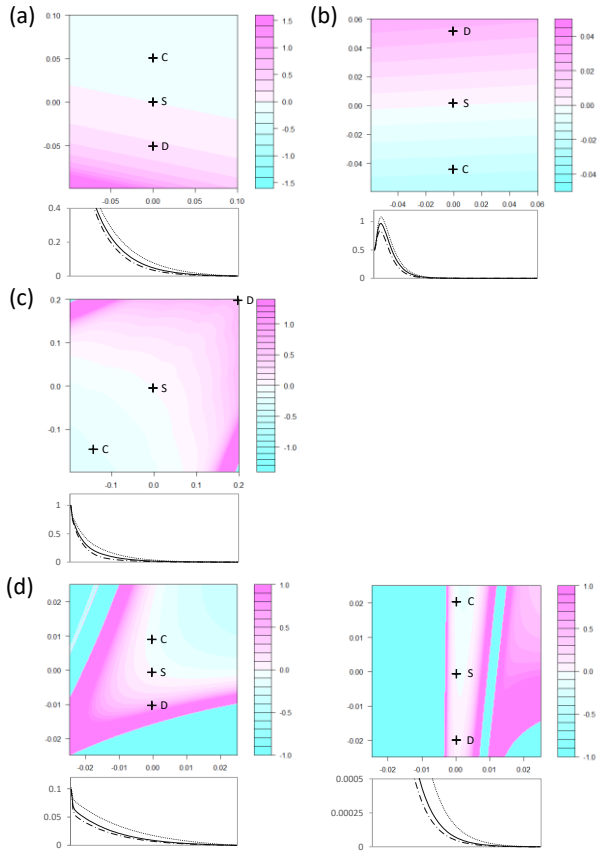

Figure 2. Alterations in proposed Generalized Entropy-Production (GEP) and perturbation responses in the four biological regulatory systems. (**a**) Around FP-1 in Griffith's genetic regulatory system [13]. (**b**) Around FP-2 in the genetic regulatory system by Gardner et al. [14]. (**c**) Around FP-3 in neural system [15]. (**d**) Around FP-4 (left panels) and -5 (right panels) in intraguild predation system [16]. In panels (a-d), upper panels show normalized GEP_{ave} alteration as a function of $flow_x$ (horizontal axis) and $flow_y$ (vertical axis) in each differential equation shown in Fig.1 (a-d).

The normalized GEP_{ave} alteration was calculated as {(GEP_{ave} at the corresponding value of $flow_x$ and $flow_y$) − (GEP_{ave} at $flow_x$=0 and $flow_y$=0)} / (GEP_{ave} at $flow_x$=0 and $flow_y$=0). The lower panels show temporal profiles of response to impulsive perturbation. The horizontal and vertical axes mean the number of iterations in numerical calculation (the full scale is 100) and the deviation from steady state, respectively. The deviation from steady state was calculated as: $\sqrt{(x-x_S)^2+(y-y_S)^2}$, where x_S and y_S mean the coordinate of steady state (at the number of iterations=100). The solid, doted and chain lines correspond to the result in the condition for the values of the flows at the plus mark tagged "S", "D" and "C" in the upper panels, respectively. Where, the plus mark tagged "S" corresponds to normalized GEP_{ave} alteration without the flows ($flow_x$=0 and $flow_y$=0), and in the case, the normalized GEP_{ave} alteration becomes 0 mathematically.

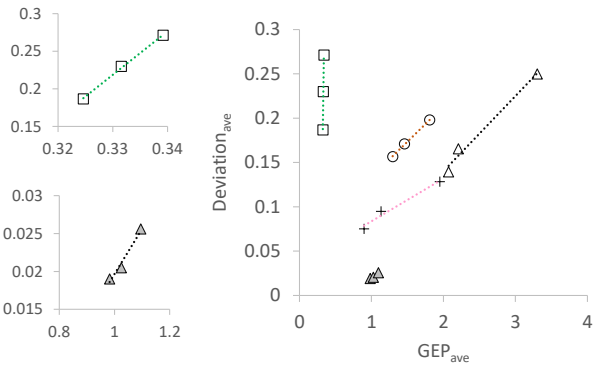

Figure 3. Relation between the average of proposed GEP and deviation. Horizontal and vertical axes indicate the average of proposed GEP and the time average of the deviation from the steady state caused by the impulsive perturbation. The time average was calculated over the number of iterations (100) in a numerical calculation. Circle, rectangle, plus-mark, open-triangle, and filled-triangle indicate the result for FP-1 in Griffith's genetic regulatory system [13], FP-2 in the genetic regulatory system by Gardner et al. [14], FP-3 in Neural system [15], FP-4 and FP-5 in intraguild predation system [16], respectively. Left panels show enlarged diagrams for FP-2 and FP-5. A dotted line indicates linear approximation of the data for each fixed point.

The flows of components ($flow_x \neq 0$ and/or $flow_y \neq 0$) were given to the ordinary differential equations in Fig. 1 (a-d), and the ordinary differential equations were solved numerically (see Section 4). The fixed points were shifted from their original positions (FP-1, -2, -3, -4 and -5 in Fig.

1(a-d)), and GEP_{ave}s were altered (Fig. 2 (a-d)). For the different values of flows ($flow_x$ and/or $flow_y$) in the regulatory systems (Fig. 1 (a-d)), perturbation responses were also altered (Fig. 2 (a-d)). We found a common tendency across all of the five non-periodic stable fixed points investigated in the four biological regulatory systems: as GEP_{ave} decreased, the deviation from the steady state by the impulsive perturbation converged fast (Fig. 2 (a-e)). This tendency was confirmed in the diagrams in Fig. 3: as GEP_{ave} (horizontal axis in the diagrams) decreases, the time average of the deviation from the steady state by the impulsive perturbation (indicated as "$Deviation_{ave}$" in the vertical axis) decreases.

4. Numerical Calculation Method

The ordinary differential equations in lower left panels in Fig. 1(a-d) were used for the four biological regulatory systems. For the calculation of GEP_{ave}, eigenvalues were calculated using the Jacobian matrix derived from the corresponding ordinary differential equations in Fig. 1(a-d) and the coordinate (x, y) of transferred fixed point by the flows of components ($flow_x \neq 0$ and/or $flow_y \neq 0$) from their original fixed point. Then, the eigenvalues were substituted in Eq. (13), and GEP_{ave} was calculated. For the calculation of response to impulsive perturbation, the initial value of y in the ordinary differential equations in lower left panels in Fig. 1(a-d) was shifted from its steady state value, and the ordinary differential equations were numerically solved using package deSolve provided by the open source data analysis system R [17]. The source codes in R (version 3.4.0) for calculating GEP_{ave} and response to impulsive perturbation are available in Supplementary Information: Computer codes 1-8.

5. Discussion and concluding remarks

Kondepudi and Prigogine found a property in chemical systems that is driven by instability, a chemical system often transitions to a new state with lower entropy [11]. In Numerical experiments, a stable fixed point in the four biological regulatory systems was shifted from its original position to a new stable point by the flows of components ($flow_x \neq 0$ and/or $flow_y \neq 0$), and GEP_{ave} was altered from its original value to a new value (Fig. 2 (a-d)). In each of the numerical experiment result (upper panels in Fig. 2(a-d)), a continuum region next to the original fixed point (the plus mark tagged "S" in upper panels in Fig. 2(a-d)) was observed, where the normalized GEP_{ave} {(GEP_{ave} at the corresponding value of $flow_x$ and $flow_y$) − (GEP_{ave} at $flow_x$=0 and $flow_y$=0)} / (GEP_{ave} at $flow_x$=0 and $flow_y$=0) was negative (upper panels in Fig. 2 (a-d)). The continuum region corresponds to a set of new stable states with lower GEP_{ave} than the GEP_{ave} at the original stable fixed point. Based on interpretations that (i) the $flow_x \neq 0$ and/or $flow_y \neq 0$ are provided from environment, and (ii) GEP_{ave} is a measure of disorderliness as thermodynamic entropy [5], the Schrödinger's suggestion "A life system takes orderliness from its environment and sustains itself at a fairly high level of orderliness" is consistent with the numerical experiment results, in some cases in which the normalized GEP_{ave} was negative. In the cases, where the GEP_{ave} decreased (as shown in upper panels in Fig. 2 (a-d)), the decrease corresponds to the increase of orderliness of the biological regulatory system.

The proposed GEP was consistent with perturbation response, as the average of the proposed GEP decreased, the deviation from the steady state by the impulsive perturbation converged at faster rate. The proposed GEP makes the property, a system often transitions to a new state with lower entropy, as found by Kondepudi and Prigogine in chemical systems applicable to the biological regulatory systems. Further studies on GEP for periodic stable and non-stable fixed points are needed to evaluate the hypothesis under stable and non-stable conditions.

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