

# Deriving the Fluctuation Theorem for Information-Transmission Systems Using a Cyclic Chain-Reaction Sequence

Tatsuaki Tsuruyama<sup>1,2</sup>

<sup>1</sup>Clinical Bioresource Center, Kyoto University Hospital, Kyoto 606-8507, Japan

<sup>2</sup>Tazuke Kofukai Medical Research Institute, 2-4-20 Ogimachi, Kita-ku, Osaka 530-8480, Japan

ORCID 0000-0002-3118-2826 T.T.

§ Corresponding author: Tatsuaki Tsuruyama, MD, PhD; Department of Drug and Discovery Medicine, Kyoto University, Graduate School of Medicine, Kyoto, Japan; Center for Anatomical, Pathology, and Forensic Medical Research, Kyoto University Graduate School of Medicine, Sakyo-ku-yohidakonoecho, Kyoto city, 606-8501, Japan

Tel.: +81 75 753 4427; Fax: +81 75 753 4493

E-mail address: [tsuruyam@kuhp.kyoto-u.ac.jp](mailto:tsuruyam@kuhp.kyoto-u.ac.jp); [tatsuakitsuruyama@gmail.com](mailto:tatsuakitsuruyama@gmail.com)

## **ABSTRACT**

Chemical chain-reactions are pathways that can transmit information, as demonstrated by signal-transduction reactions in cell biology. In this study, we defined entropy as the logarithm of the concentration ratio of chemical species and considered the channel capacity for information transmission by maximizing the entropy. We hypothesized that the reaction chain has an orientation in which the reaction time for the reverse reaction is sufficiently long. According to this model, the logarithm of the forward and reverse transitional probability ratio was found to indicate the entropy-time average per unit reaction time, corresponding to the fluctuation theorem for thermodynamics regarding entropy production rate. This conclusion illuminates the process of signal transduction in cells and other biochemical systems and may provide insights into the relation between thermodynamic and information entropy.

## Introduction

This paper presents a generalized fluctuation theorem (FT) for chemical chain-reactions and investigates the rate of information transmissible using a chemical pathway to develop a unified understanding of thermodynamic and information entropy. The FT and the Jarzynski equality are considered significant achievements of non-equilibrium thermodynamics.<sup>1,2</sup> Gaspard et al. have demonstrated that Onsager's reciprocity relations can be derived from the FT for a chain-reaction system.<sup>3</sup> The FT relates to the probability distribution of the time-averaged entropy production. Herein, we aim to prove the FT theoretically by redefining the chain-reaction from the viewpoint of information transmission. Consequently, we aim to demonstrate that the average rate of entropy production is critical to the information transmission channel capacity of the chain-reaction.

Let us consider a continuous chain-reaction consisting of  $n$  species,  $X_j (j = 1, 2, \dots, n)$ . Such a system would be isothermal in contact with the chemostat at the boundary, and out of equilibrium. The flux of the chemical species from the chemostat continuously generates entropy in the course of the chain-reaction. The temporal evolution of such a chain-reaction can be regarded as a Markov stochastic process described by the master equation governing the probability distribution of the random variables for the intermediate species participating in the chain. If the system is described by a probability distribution that is a steady-state solution of the master equation, it is considered to have reached a non-equilibrium steady state.

Reaction systems transmit information on the concentration change of  $X_1$  as the concentration change of  $X_n$  through code strings.<sup>4</sup> For example, in a biological cell, an environmental change triggers the conformation change of the receptor protein on the cell membrane. The adaptor molecule of the receptor promotes the chemical reaction in the cytoplasm. Consequently, the cytoplasmic protein that possesses the DNA-binding ability alters the structure of the DNA and promotes the transduction of the genetic information to the protein translation to express the genetic information.

In this study, we defined the amount of information entropy transmitted by the concentration ratio of the chemical species. Subsequently, the transmission capacity, that is, the channel capacity of the path, was defined as the logarithm of the number of chemical reactions occurring per unit time during information transmission.

## Methods

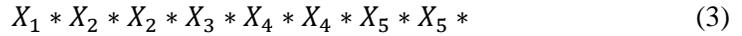
### Model chain-reaction that transmits information

Consider a chemical chain-reaction path consisting of  $n$  chemical species  $X_j (j = 1, 2, \dots, n)$  :



This conversion forms a cycle that is linked to a path in which  $X_{j-1}^*$  converts  $X_j$  into  $X_j^*$  and  $X_j^*$  converts  $X_{j+1}$  into  $X_{j+1}^*$ .  $X_j$  is converted spontaneously into  $X_j^*$  following the reaction. For a continuous reaction, the chemostat is necessary and the reaction system is essentially a non-equilibrium system. In (1) and (2), the substrate (S) for this conversion is supplied by the chemostat attached to the reaction system. S is transformed into the product P in the course of the conversion  $X_j$  into  $X_j^*$  system.

Herein, we allocated the chemical species that transmitted positive information in the forward direction the code  $X_j^*$ , and those that transmitted negative information in the reverse direction the code  $X_j$ . This code sequence is a time-series of chemical species arranged in the order in which the chemical reactions occur. For example, an increase in  $X_1^*$  can be transmitted as an increase in the final species  $X_n^*$  through a chain-reaction path. The code sequence for the forward chain-reaction can therefore be written as<sup>4</sup>



The redundant appearance of the species coding was intentionally permitted. The code sequence for the reverse chain-reaction can therefore be written as



An increase in  $X_5$  can be transmitted as an increase in the initial species  $X_1$  through the chain-reaction path. It is possible for  $X_j$  and  $X_j^*$  to appear in a mixed order as follows:



We computed the total number of messages or different combinations of such symbols possible when the numbers  $X_1, X_2, \dots, X_j, \dots, X_n$  of the different species used in the sequences were provided in advance. In this study, we considered a message of total duration  $\tau_j$ , corresponding to the reaction time of the  $j^{\text{th}}$ -step. The total duration of the message is given by

$$\tau = \sum X_j \tau_j = X \sum_{j=1}^n p_{\pm j} \tau_{\pm j} = X \left( \sum_{j=1}^n p_j \tau_j - \sum_{j=1}^n p_{-j} \tau_{-j} \right) \quad (6)$$

where  $\tau_j$  signifies the duration of conversion of  $X_j$  to  $X_j^*$ , and  $\tau_{-j}$  signifies the duration of conversion of  $X_j^*$  to  $X_j$ . The difference between this model and traditional thermodynamics lies in the introduction of the

reaction time, which corresponds to the length of the code in the code. Here, we give  $\tau_j$  a positive value and  $\tau_{-j}$  a negative value. This sign-convention is used to distinguish the direction of the reaction path. We define the total number of symbols  $X$  and the relative proportions  $p_j$  and  $p_j^*$  as

$$p_j = X_j/X \quad (7)$$

$$p_j^* = X_j^*/X \quad (8)$$

where

$$\sum_{j=1}^n (p_j + p_j^*) = 1 \quad (9)$$

Here,  $X$  represents the total concentration of the signaling molecules.

$$X = \sum_{j=1}^n X_j + X_j^* \quad (10)$$

Subsequently, the total number of signal events,  $\Psi$ , is defined for the entire path, as follows:

$$\Psi = \frac{X_j!}{\prod_{j=1}^n X_j! \prod_{j=1}^n X_j^*!} \quad (11)$$

Shannon's entropy  $S$ , which is the logarithm of  $\Psi$ , is given by Starling's formula, as follows:

$$S = \log \Psi \simeq X \left( \sum_{j=1}^n p_j \log p_j + \sum_{j=1}^n p_j^* \log p_j^* \right) \quad (12)$$

Shannon defined the channel capacity as follows:

$$C = \lim_{t \rightarrow \infty} K \frac{\log \Psi_{max}}{\tau} = \max \lim_{t \rightarrow \infty} K \frac{S_{max}}{\tau} \quad (13)$$

Here, if we use entropy units, we take  $K = k_B$ , Boltzmann's constant. In contrast, in information science,  $K$  is equivalent to  $\log_2 e$ . To obtain the maximum value of  $KS_{max}/\tau$  using the non-determined parameters  $a$  and  $b$ , we define a function  $G$ , and apply Lagrange's method to maximize  $G$  under the constraints (5), (6), (7), and (10).

$$\begin{aligned} G(p_1, p_2, \dots, p_n; p_1^*, p_2^*, \dots, p_n^*) &= S - a \sum_{j=1}^n (p_j + p_j^*) - b\tau \\ &= S - a \sum_{j=1}^n (p_j + p_j^*) - bX \sum_{j=1}^n (p_j \tau_j - p_{-j} \tau_{-j}) \end{aligned} \quad (14)$$

Therefore, we have

$$\frac{\partial G}{\partial p_j} = -X(\log p_j - b\tau_j) - a - X \quad (15)$$

$$\frac{\partial G}{\partial p_j^*} = -X(\log p_j^* + b\tau_{-j}) - a - X \quad (16)$$

$$\frac{\partial G}{\partial X} = -\left(\sum_{j=1}^n p_j \log p_j + \sum_{j=1}^n p_j^* \log p_j^*\right) - b\left(\sum_{j=1}^n \tau_j p_j - \sum_{j=1}^n \tau_{-j} p_{-j}\right) \quad (17)$$

Setting the left-hand sides of Eqs. (15), (16), and (17) as equal to zero, we have

$$a = -X \quad (18)$$

$$-\log p_j = b\tau_j \quad (19)$$

$$-\log p_{-j} = -b\tau_{-j} \quad (20)$$

From Eqs. (19) and (20), we find that  $b$  is the average entropy produced per unit reaction time, and can be considered to be the average “entropy production rate.” Furthermore, substituting Eqs. (19) and (20) into the right-hand side of Eq.(12), we have

$$S_{max} \simeq -X\left(\sum_{j=1}^n p_j b\tau_j - \sum_{j=1}^n p_j^* b\tau_{-j}\right) = -b\tau \quad (21)$$

Hence, the channel capacity of the path is given by

$$C = -b \quad (22)$$

Therefore, the negative of the rate of entropy production is equal to the channel capacity of the reaction path. In non-equilibrium information thermodynamics, the average entropy production rate may be a critical parameter rather than the entropy describing the non-equilibrium system.

### Fluctuation theorem of the cyclic reaction path

Thereafter, the probability function of step  $j + 1$ , given step  $j$ , is defined as  $P(j+1|j)$  and the probability function of step  $j$ , given step  $j+1$ , is defined as  $P(j|j+1)$ , when the transitional probability function is given as follows:

$$P(j+1|j) = \frac{X p_j \tau_j}{X \sum_{j=1}^n p_j \tau_j} = \frac{p_j \tau_j}{\sum_{j=1}^n p_j \tau_j} \quad (23)$$

$$P(j|j+1) = \frac{X p_{-j} \tau_{-j}}{X \sum_{j=1}^n p_{-j} \tau_{-j}} = \frac{p_{-j} \tau_{-j}}{\sum_{j=1}^n p_{-j} \tau_{-j}} \quad (24)$$

The function  $Z_j(t)$  of the  $j^{\text{th}}$  reaction is given as

$$Z_j(t) = \log \frac{P(j|j+1)}{P(j+1|j)} \quad (25)$$

Substituting Eqs.(23), and (24) into (25) gives

$$Z_j(t) = \log \frac{p_j \tau_j / \sum_{j=\pm 1}^{\pm n} p_j \tau_j}{p_{-j} \tau_{-j} / \sum_{j=\pm 1}^{\pm n} p_j \tau_j} = \log \frac{e^{-b \tau_j \tau_j}}{-e^{b \tau_{-j} \tau_{-j}}} \quad (26)$$

We then take the logarithm of the average  $\langle Z_j(t) \rangle$  for the reaction time  $\tau_j - \tau_{-j}$ .

$$\langle Z_j(t) \rangle = \frac{1}{\tau_j - \tau_{-j}} Z_j(t) = -b + \frac{1}{\tau_j - \tau_{-j}} \log \frac{\tau_j}{\tau_{-j}} \quad (27)$$

When the absolute value of the duration  $\tau_j - \tau_{-j}$  is sufficiently longer, we have

$$\lim_{\tau_j - \tau_{-j} \rightarrow \infty} \frac{1}{\tau_j - \tau_{-j}} \langle Z_j(t) \rangle = -b \quad (28)$$

Here, the right-hand side has a negative value, indicating that the transmitted information possesses a “negative” entropy rate. Thus, the FT for the reaction path can be obtained.

## Conclusions

The FT was discovered through numerical simulations by Evans et al.<sup>5</sup> The proof was given using a system having a heat bath as an instance of a non-equilibrium system. The FT indicates that reversible time-evolution is derived from reversible dynamical systems. Additionally, there are reports that the Green-Kubo formula<sup>6</sup> for linear response remain valid when using the FT. However, the FT assumes a detailed balance, which significantly limits the applicability of the theorem. In the proof of the FT, the  $(q, p)$  phase-space volume that relates to the entropy is not conserved in a general dynamic system in contact with a conventional heat bath but is considered a reversible system. Previously, a detailed balance was hypothesized in which the Jacobian of the time evolution operator that transforms  $(q, p)$  to  $(q, -p)$  in phase-space is 1. This operator is a critical requirement in the derivation of the FT. Therefore, to expand the applicability of this theorem, the proof of the FT should be provided without assuming a detailed balance.

Recently, it has been suggested that the FT remains valid without assuming a detailed balance, which is the premise of the proof, and its wide application is expected.<sup>6</sup>

Considering the aforementioned theoretical requirements for the application of FT, the current study considered a chain-reaction as a code sequence to model signal transduction in biophysical systems<sup>7</sup>. We made two simple premises for deriving the FT using this model: (i) maximization of Shannon entropy<sup>8</sup>, and (ii) the reverse chemical-reaction time is sufficiently longer than the forward chemical-reaction time. The irreversibility of time is represented by the reaction time with a negative sign of  $\tau_j$ . This is also an important feature of this model. Although the reaction time does not explicitly indicate the passage of time, it is essential to specify the rate of reaction, assuming that the reverse reaction is considerably slower than the forward chemical reaction ( $|\tau_j| \gg \tau_j$ ). Thus, detailed balance and equilibrium states are not explicitly assumed. Instead, we assumed that the Shannon entropy maximization principle remains valid even in a steady or non-equilibrium state. Thereafter, we could derive the FT for the chemical chain-reaction; however, the adaptation of the theorem needed further refinement. In other words, it is necessary to examine in greater detail how far the entropy-maximizing principle can be applied in a non-equilibrium system.<sup>9</sup>

In this study, equations (18) and (19) were derived from the viewpoint of source-coding in information engineering. The amount of information transmissible through the chemical-reaction chain, i.e, channel capacity was represented by this entropy-time average,  $KS_{max}/\tau$ . Therefore, we can recognize that this channel capacity is an essential quantity in information transmission. Considering that the entropy-time average obtained from the logarithm of the function  $Z_j(t)$  is the expression of the new FT,<sup>7,10</sup> the information transmitted by the chemical reaction provides a unified understanding of thermodynamic and information entropy.

The models and analyses presented here remain preliminary and are based on a simplified approach; however, a more detailed analysis based on stochastic thermodynamics is required for cyclic reactions.<sup>11,12</sup> The introduction of encoding theory may provide novel insights into information thermodynamics. This study also provides important implications for the natural computing of binary coding by two chemical species,  $X_j$  and  $X_j^*$ . Entropy-coding of a chemical reaction may also provide insights into natural computing applications. In future, it will be possible to measure the amount of information transmitted in specific chemical reactions. We will report it elsewhere.

## **Acknowledgments**

This research was funded by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (Synergy of Fluctuation and Structure: Quest for Universal Laws in Non-Equilibrium Systems, P2013-201 Grant-in-Aid for Scientific Research on Innovative Areas, MEXT, Japan)

---

## **Author Contributions**

T.T. prepared the manuscript.

## **Competing Financial Interests Statement**

The authors have read the journal's policy and declare that there are no competing interests. Furthermore, no conflict of interest exists with respect to employment, consultancy, products in development, or modified products. The funding agencies had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## References and Notes

- 1 Crooks, G. E. Entropy production fluctuation theorem and the nonequilibrium work relation for free energy differences. *Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics* **60**, 2721-2726 (1999).
- 2 Collin, D. *et al.* Verification of the Crooks fluctuation theorem and recovery of RNA folding free energies. *Nature* **437**, 231-234, doi:10.1038/nature04061 (2005).
- 3 Andrieux, D. & Gaspard, P. Fluctuation theorem and Onsager reciprocity relations. *J Chem Phys* **121**, 6167-6174, doi:10.1063/1.1782391 (2004).
- 4 Brillouin, L. Science and Information Theory. *Dover Publication Inc.* **2nd ed.**, 42 (2013).
- 5 Evans, D. J., Searles, D. J. & Mittag, E. Fluctuation theorem for Hamiltonian systems: Le Chatelier's principle. *Phys Rev E Stat Nonlin Soft Matter Phys* **63**, 051105 (2001).
- 6 Chong, S. H., Otsuki, M. & Hayakawa, H. Generalized Green-Kubo relation and integral fluctuation theorem for driven dissipative systems without microscopic time reversibility. *Phys Rev E Stat Nonlin Soft Matter Phys* **81**, 041130 (2010).
- 7 Andrieux, D. & Gaspard, P. Temporal disorder and fluctuation theorem in chemical reactions. *Phys Rev E Stat Nonlin Soft Matter Phys* **77**, 031137 (2008).
- 8 Shannon, C. E. A mathematical theory of communication. *Bell Syst. Tech. J.* **27**, 379-423 (1948).
- 9 Tsuruyama, T. Non-equilibrium thermodynamics of biological signal transduction predicts conservation of entropy production rate. *J Theor Biol* **472**, 84-87, doi:10.1016/j.jtbi.2019.04.008 (2019).
- 10 Gaspard, P. Fluctuation theorem for nonequilibrium reactions. *J Chem Phys* **120**, 8898-8905, doi:10.1063/1.1688758 (2004).
- 11 Seifert, U. Entropy production along a stochastic trajectory and an integral fluctuation theorem. *Phys Rev Lett* **95**, 040602 (2005).
- 12 Seifert, U. *Entropy Production along a Stochastic Trajectory and an Integral Fluctuation Theorem*. Vol. 95 (Physical review letters, 2005).

