The channel capacity and information density of biochemical signaling cascades based on Tsallis q-statistics

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Abstract

Theory of chemical reaction network recent developed and application of the framework for informatics has been aimed. Here, we hypothesized chemical reaction network that obeys Tsallis q-statistics. We applied the Crooks fluctuation theorem for analysis of an idealized coding way on a simple chemical reaction cascade from perspectives of information conveyed along the signaling pathways. As a result, the information could be quantitatively calculated using Tsallis q-statistics. This mathematically formulating provides a general quantitative viewpoint of biological cellular signaling suitable to evaluate redundancies in actual signaling cascades.
Biological signaling is an open, non-equilibrium system owing to the outside supply of metabolites and its use of non-linear chemical reaction steps. Intracellular signaling is a reaction cascade in which the proteins carrying signals is serially modified in the former step. There are very few studies on the work fluctuation theorem relating the biological non-equilibrium forward and reversed trajectories taken from other statistical distributions.

Non-equilibrium statistical mechanics have recently established a method to calculate the free energy differences between two equilibrium states from the perspective measurements of a non-equilibrium work. These methods are based on the Jarzynski equality (1-5) and the Crooks’ work fluctuation theorem (1-4, 6, 7). Consider a system initially in equilibrium at temperature $\beta = 1/k_B T$ ($k_B$ is the Boltzmann constant), which is externally driven by the outside supply of metabolites such as ATP from its initial equilibrium state $I$ to the final equilibrium state $F$ by a non-equilibrium process. Let $p_j[\zeta]$ be equal to the probability of the phase space trajectory $\zeta$, for the system driven between the two states in forward direction. This satisfies the Crooks’ work fluctuation theorem,

$$\frac{p_F(\zeta^F)}{p_I(\zeta^I)} = \exp\left[ \beta(W - \Delta F) \right] \quad [1]$$

where we regard $W$ as the chemical work performed on the driven system, and $\Delta F$ as the Helmholtz free energy difference between the two equilibrium states of the biological system that is under isothermal and isobaric process state. There are very few studies on the work fluctuation theorem relating the non-equilibrium forward and reversed trajectories taken from other statistical distributions. No generalized connection has been established between Tsallis statistics and non-equilibrium work relations at a single temperature. Ponmurugan previously reported the $q$-statistic’s generalization of the Crooks work fluctuation theorem (8, 9). The theory of Tsallis
statistics based on a generalized form of entropy, $S_q (q \in \mathbb{R})$, when $Q = 1$ recovers the formula of Boltzmann and Gibbs. No generalized connection has been established between Tsallis statistics and non-equilibrium work relations at a single temperature.

The generalized Tsallis entropy is given by the expression:

$$S_q = k_B \frac{1 - c_{+q}}{q - 1}$$

[2]

Here, $w$ is the total number of microstates of the system, and $p_j$ is the probability of the system at microstate $j$. Let us consider that, when conveying cascade signal:

$$A_i + A_j + M \leftrightarrow A_i + S_1$$
$$S_1 + A_2 + M \leftrightarrow S_1 + S_2$$
$$\ldots$$
$$S_j + A_{j+1} + M \leftrightarrow S_j + S_{j+1}$$
$$\ldots$$
$$S_{n-1} + A_n + M \leftrightarrow S_{n-1} + S_n$$
$$S_n + DNA \to S_n - DNA + RNA \, (*)$$

[3]

In scheme $(*)$, we consider an open homogeneous reactor in contact with chemiostats of a signal mediator $M$, which drive the BSC out of equilibrium. Each activated signaling molecule $S_j$ potentially activates $A_j$. Signaling finally terminates when $S_n$ translocates into the nucleus, binds to genomic DNA, and promotes subsequent transcription of RNA (Fig. 1). Here, $S_j$ is the $j$-th form of the signaling molecule. In this cascade, the signaling molecule reversibly conveys information in the orientation from $S_j$ to $S_n$.

Let us consider all the possible distinct messages. These messages will correspond to all the possible combinations of symbols $S_{mj}$ whose total duration is $T_x$. Here we consider $A_{mj}$, the total number of such distinct messages and the reverse messages, which will differ in the order of the symbols uses, and in the selection of symbols. The negative suffix $-j$ implies inverse signal transmission against the assumed polarity of the cascade. We assume absolutely no restriction, no constraint, no correlation in the use of the different symbols. All of the $M$ messages of total duration $T_x$ are to be considered as equally probable a priori. Then when we select one of these messages, we obtain information that is derived from above serial alphabetic sentences consisting of $S_{mj}$,

$$I_x = KlnT_x \, \, \, [4]$$
We formulated the BSC as a system in which the concentration of modified proteins minimally fluctuates around the value at the steady state in the absence of a specific signal event. The amplified modification fluctuation steps are assigned a positive step number \( j \) (\( 1 \leq j \leq n \)) in which \( S_j \) molecules participate in the \( j \)-th \( (1 \leq j \leq n) \) step of the BSC,

\[
S_j : S_j = S_j^e \to S_j^e + dS_j \quad [5]
\]

In above step, we set the entropy production rate as \( \sigma_j \). The de-modification steps are assigned a negative step number \( j \) \( (-n \leq j \leq -1) \) in which \( S_j \) molecules participate in the \( j \)-th \( (1 \leq j \leq -n) \) step of the BSC.

\[
S_{-j} : S_j = S_j^e + dS_j \to S_j^e \quad [5']
\]

In above step, we set the entropy production rate as \( \sigma_j \). \( e \) signifies concentration of \( S_j \) at the initial state. Our cell signaling formulation begins by assuming a total continuous duration,

\[
T_x \stackrel{\Delta}{=} \sum_{j=1}^{n} S_j f_{\pm j} \equiv \sum_{j=1}^{n} S_j t_{\pm j} \quad [6]
\]

We computed the total number of messages or different combinations of such symbols when the numbers \( S_1, S_2, \ldots, S_j, \ldots, S_n \) of the different symbols used in the messages were given in advance. We set

We introduced the total number of signaling molecules \( \Lambda_\pm \):

\[
\Lambda_\pm = \sum_{j=1}^{n} S_{\pm j} \quad [7]
\]

to the total number of signaling molecules in the signaling event, and \( S_j \) is the number of \( j \)-th signaling molecules in the cascade. \( p_j \) is the occurrence probability of the \( j \)-th code, and \( t_j \) signifies the duration of the code. In the following summations over \( j \), \( j = 0 \) is excluded, and hence

\[
p_{\pm j} \triangleq \frac{S_{\pm j}}{\Lambda_\pm}, \quad \sum_{j=1}^{n} p_{+ j} = 1 \quad \text{and} \quad \sum_{j=1}^{n} p_{- j} = 1 \quad [8]
\]

represents the relative density of the \( j \)-th step of the total cascade. And

\[
c_{\pm q} = \sum_{j=1}^{n} p_{\pm j}^q \quad [9],
\]
which satisfies Q-statistics. We can rewrite [6] using [7] and [8] in the main text so that

\[ T_z = \Lambda_z \sum p_z f_{zj} \]  \[10\]

Here, we introduce the formula as follows:

\[ T_{xq} = \Lambda_x \sum p^q_j t_{xj} \]  \[11\]

Our aim is to optimize the ideal coding way, which is equivalent to maximizing the information per signaling pathway (10). We can maximize Tsallis entropy as follows collecting [8], [9], and [11]:

\[ dS_{xq} - \alpha d \sum p_{zj} - \beta d \sum p^q_{zj} - \gamma dT_{xq} = 0 \]  \[12\]

The above is an application of Lagrange’s non-determined coefficient determination method. The variables are \( N , p_1 , p_2 , \ldots , p_n \). Differentiating [12] we obtain:

\[ dS_{xq} = -d\Lambda_x k_b \frac{1-\sum p^q_{zj}}{q_z - 1} - \Lambda_x dp_{zj} \frac{1-\sum p^q_{zj}}{q_z - 1} \]
\[ -\Lambda_x dq_z \left( \frac{1-\sum p^q_{zj} \log q_z (q_z - 1) \sum p^q_{zj}}{(q_z - 1)^2} \right) \]  \[13\]

Substituting [13] into [12], since \( dN \) and \( dp_{zj} \) are independent variables, we can write:

\[ \beta_z p^q_{zj} \log q_z + \gamma \Lambda_t z_{zj} p^q_{zj} \log q_z - \Lambda_z \left( p_{zj} - p^q_{zj} + p_{zj} (q_z - 1) \log p_{zj} \right) \frac{1-\sum p^q_{zj}}{(q_z - 1)^2} \]  \[14\]

\[ \alpha_z + q_z p_{zj}^q - \beta \gamma q_z p_{zj}^q - \Lambda_z \frac{q_z p_{zj}^q - 1}{q_z - 1} = 0 \]  \[15\]

\[ \gamma_z t_{zj} p^q_{zj} - \frac{p^q_{zj} - p_{zj}}{q_z - 1} = 0 \]  \[16\]

Solving above equations, we have:

\[ \alpha_z = -\Lambda_z \left[ (p_{zj} - p^q_{zj}) q_z + p^q_{zj} (q_z - 1) q_z \log p_{zj} + (q_z - 1) (p_{zj} - p^q_{zj}) q_z \log q_z \right] \]  \[17\]

\[ \beta_z = \Lambda \frac{p_{zj}^q \left( p_{zj} (q_z - 1) \log p_{zj} - (p^q_{zj} - p_{zj}) (1 + (q_z - 1) \log q_z) \right)}{(q_z - 1)^2 \log q_z} \]  \[18\]

\[ \gamma_z = \frac{1 - p_{zj}^q}{(q_z - 1) t_{zj}} \]  \[19\]
Rewriting [19] using Tsallis entropy [2], we have:

\[- \log_q p_{\pm j} = \gamma_{\pm} t_{\pm j} \]  \[20\]

As shown in [20], \( \gamma_z \) is a constant equal to the extended entropy production rate of the whole cascade (i.e., is independent of the \( j \)-numbering of the cascade), since we have optimized the signaling in the cellular system or organized a single signaling event per cascade reaction.

### C. Mathematical formulation of the idealized signaling pathway

The probability distribution functions \( p_j \) and \( p_{-j} \) can be expressed in terms of the transition rates.

Here, we introduce the function \( \Omega_{q_{\pm j}} \) of the \( j \)-th step in the cascade:

\[ \Omega_{q_{\pm j}} = \log_q \frac{p_{-j}}{p_{+j}} \]  \[21\]

According to [20] and [21], we obtain:

\[ \Omega_{q_{\pm j}} = -\gamma_j + \gamma_{-j} \]  \[22\]

In the actual cascade, the reverse reaction that was accompanied with dephosphorylation takes sufficiently long time,

\[ \tau_j \gg \tau_{-j} \]  \[23\]

Therefore, after the passage of a sufficient period of time \( \tau_{j} \) and \( \tau_{-j} \), the fluctuation theorem for Tsallis distribution yields using Ponmurugan’s study (8, 9):

\[ \lim_{t_{-j} \to 0} \frac{1}{t_{-j}} \Omega_{q_{\pm j}} = \lim_{t_{-j} \to 0} \frac{-\gamma_j + \gamma_{-j}}{t_{-j}} = \left\langle \sigma_{-j} / c_{\pm} \right\rangle = \left\langle \sigma_{q_{\pm}} \right\rangle \]  \[24\]

Therefore, \( \gamma_z \) in [20] is given using

\[ \gamma_{-j} = \left\langle \sigma_{q_{-j}} \right\rangle \]  \[25\]

Therefore, we obtain the following simple formulation using [20]:

\[- \log_q p_{-j} = \sigma_{q_{-j}} t_{-j} \]  \[26\]

Therefore, the information density \( i_z \) and channel capacity \( C_{-j} \) of the reverse cascade are given by:
\[ i_\pm \triangleq -\sum p_{\pm}^q \log_q p_{\pm} = \sigma_q \sum p_{\pm}^q t_{\pm} = \sigma_q \frac{T^q}{\Lambda} \quad \text{[27]} \]
\[ C_\pm = i\Lambda_\pm / T^q_\pm = \sigma_q \quad \text{[28]} \]

**DISCUSSION**

We have demonstrated a more general form of idealized coding in a reaction cascade, based on the fluctuation theorem due to system relaxation in the framework of Tsallis statistics. Many biological phenomena such as protein phosphorylation signaling may obey the power law and be described from the perspective of generalized Tsallis statistics. For instance, the phosphorylation ratio may be localized around the mean value more than the normal distribution, when the signaling system has the ability to reduce the phosphorylation fluctuation around the ratio at the steady state. To date, there have been few studies based on the idealized coding for formulation of biological signaling systems. In the current study, we obtained the idealized coding form that was a near replacement for the entropy production rate by the extended Tsallis entropy production rate. In particular, Eqs. [26]-[28] are the fundamental formulae describing the relation of Tsallis entropy with appearance probability of the individual steps.
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