Non-equilibrium dynamics of stochastic gene regulation

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Abstract The process of gene regulation is comprised of intrinsically random events resulting in large cell-to-cell variability in mRNA and protein numbers. With gene expression being the central dogma of molecular biology, it is essential to understand the origin and role of these fluctuations. An intriguing observation is that the number of mRNA present in a cell are not only random and small but also that they are produced in bursts. The gene switches between an active and an inactive state, and the active gene transcribes mRNA in bursts. Transcriptional noise being bursty, so are the number of proteins and the subsequent gene expression levels. It is natural to ask the question: what is the reason for the bursty mRNA dynamics? And can the bursty dynamics be shown to be entropically favorable by studying the reaction kinetics underlying the gene regulation mechanism? The dynamics being an out-of-equilibrium process, the fluctuation theorem for entropy production in the reversible reaction channel is discussed. We compute the entropy production rate for varying degrees of burstiness. We find that the reaction parameters that maximize the burstiness simultaneously maximize the entropy production rate.

Keywords Transcriptional bursts · Fluctuation theorem

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The mechanism of gene regulation is intrinsically a stochastic process involving a cascade of random events. The intermediary steps involving regulatory mechanisms, transcription and translation are all probabilistic events contributing to the randomness. Moreover, active genes, mRNAs and proteins involved in each of these steps are few in number; hence, the fluctuations reflecting the stochastic gene expression noise are significant and cannot be ignored [1–4]. The typical assumptions in studying these fluctuations in mRNA and protein numbers had been that they follow a Poisson distribution that can be explained by a simple birth-death process [5, 6]. However, the advent of advanced experimental techniques, namely single-molecule fluorescence in situ hybridization with single transcript resolution, revealed that the distributions are not Poissonian [7–9]. mRNAs are produced in bursts separated by long quiescent periods. Bursty dynamics can also be explained by simple models where a gene is considered to be either in an OFF or an ON state [10]. When the gene is ON, then only it can transcribe, and

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suitable tuning of rate constants produces burstiness. While models can match the experimental findings, it is also natural to ask why a cell chooses bursty dynamics. In a recent work, it was shown that the information representation in a cell is optimized by kinetic parameters corresponding to bursty dynamics [11]. The mRNA dynamics should efficiently encode the information contained in the levels of input stimuli and resort to bursty dynamics to maximize the information transfer. While the past study had been information-theoretic, the present approach in this work is to explore the bursty dynamics in gene regulation in terms of thermodynamic quantities. Can the choice of reaction kinetic parameters be entropically explained? The problem in this approach is that the gene regulation involves reactions that are out of equilibrium and notions of thermodynamic quantities, like entropy, are no longer applicable. However, non-equilibrium systems obey the remarkable fluctuation-dissipation theorem. In the context of non-equilibrium chemical reactions, it has been shown that fluctuation-dissipation theorem relates to the entropy production rate [12, 13]. We can simulate the transcriptional time series and estimate the entropy production rate from the reaction kinetics. We find that, for stochastic gene regulation, the choice of the kinetic parameters that results in the bursty dynamics also maximizes the entropy production rate.

The process of mRNA transcription can be described by the following set of reactions:

The gene can be either in an OFF state or an ON state and switches between these two states with rate k_{on} and k_{off} . When the gene is in the ON state, transcription can take place, giving an mRNA (M) with a rate k_{tx} . Finally, the mRNA has a finite lifetime and can degrade with rate k_d . The model was introduced by Peccoud and Ycart [14] and can be considered as a Markov process, which can be described by a master equation. Let $P_{0,n}(t)$ [$P_{1,n}(t)$] be the probability that at time t the gene is inactive [active] and n molecules of mRNA (M) are present. The master equations describing the dynamics of the probabilities are:

$$\begin{aligned} P'_{0,n}(t) &= -(k_{on} + nk_d)P_{0,n} + (n+1)k_dP_{1,n+1} + k_{off}P_{1,n} \\ P'_{1,n}(t) &= -(k_{off} + k_{tx} + nk_d)P_{1,n} + (n+1)k_dP_{1,n+1} + k_{tx}P_{1,n-1} + k_{on}P_{0,n} \end{aligned} \quad (2)$$

Peccoud and Ycart [14] obtained the steady-state solution of the master equation by the method of generating functions and here we will give a brief outline. Let the generating functions for the asymptotic distribution of mRNA be:

$$G_m(z) = \sum_{n=0}^{\infty} z^n P_{m,n} \quad m = 0, 1. \quad (3)$$

Using which the Eq. (2) in steady-state yields:

$$\begin{aligned} k_d(z-1)G'_0(z) &= -k_{on}G_0(z) + k_{off}G_1(z) \\ k_d(z-1)G'_1(z) &= k_{on}G_0(z) - k_{off}G_1(z) - k_{tx}(1-z)G_1(z). \end{aligned}$$

Now we can cast the above as a second-order differential equation in G_0 :

$$-k_d^2(1-z)G_0'' + k_d[k_{on} + k_{off} + k_d + k_{tx}(1-z)]G_0' - k_{on}k_{tx}G_0 = 0$$

giving the solution in terms of hypergeometric functions ${}_1F_1$ [15]:

$$G_0(z) = \frac{k_{off}}{k_{on} + k_{off}} {}_1F_1\left(\frac{k_{on}}{k_d}, \frac{k_{on} + k_{off} + k_d}{k_d}, \frac{k_{tx}}{k_d}(z-1)\right)$$

using which it is easy to compute $G_1(z)$. Let the generating function for mRNA distribution be $G(z) = G_0(z) + G_1(z)$ and it is possible to obtain the steady-state mRNA distribution, which is not shown here for brevity. We are rather interested in the first two moments of the distribution. The k -moment values of the distribution are given by $e_k = G^{(k)}(z=1)$. The mean and variance of the distribution are:

$$\bar{n} = \frac{k_{on}}{k_{on} + k_{off}} \frac{k_{tx}}{k_d}$$

$$\sigma^2 = \frac{k_{on}}{k_{on} + k_{off}} \frac{k_{tx}}{k_d} + \frac{k_{on}k_{off}}{(k_{on} + k_{off})^2} \frac{k_{tx}^2}{k_d(k_{on} + k_{off} + k_d)}.$$

The burstiness of the stochastic dynamics can be quantified by the Fano factor:

$$F = \frac{\sigma^2}{\bar{n}} = 1 + \frac{k_{tx}/k_{on}}{\left(1 + \frac{k_{off}}{k_{on}}\right)} \frac{k_{off}/k_{on}}{\left(1 + \frac{k_{off}}{k_{on}} + \frac{k_d}{k_{on}}\right)}. \quad (4)$$

The changes in the mean level of mRNA produced are mediated by changes in the kinetic parameters $\{k_{on}, k_{off}, k_{tx}, k_d\}$ and it is easy to see that $F > 1$ for any positive reaction rates. If the gene is always ON, i.e., in the limit $k_{off} = 0$, then the Fano factor $F = 1$, and the distribution of mRNA numbers is Poissonian, as expected. The gene off rate, $k_{off} \neq 0$, determines the burst duration. However, the competition between the rate constants is such that the dependence of the burstiness on k_{off} is non-monotonic. It is easy to see that in the limit $k_{off} \gg 1$, the Fano factor, $F \rightarrow 1$. Thus, k_{off} in particular plays a key role in mRNA dynamics and in recent studies it has also been experimentally observed that burstiness and mRNA expression level can be matched by modulating the gene off rate (k_{off}) [11]. In the present study, we consider k_{off} to be a tuning parameter to produce various levels of burstiness. In Fig. 1 we plot the Fano factor as a function of k_{off} . There is a critical value k_{off}^{max} for which the burstiness (F) is maximized. The k_{off}^{max} can be easily computed from Eq. (4) and turns out to be $k_{off}^{max} = k_{on} \sqrt{1 + k_d/k_{on}}$. In Fig. 1 we plot the Fano factor for different k_d values. In the instance when $k_d < k_{on}$, $k_{off}^{max} \approx k_{on} = 3.0 \text{ min}^{-1}$ and when $k_d \approx k_{on}$, $k_{off}^{max} \approx \sqrt{2}k_{on} = 4.2 \text{ min}^{-1}$. The key observation is that k_{off}^{max} is independent of k_{tx} .

We would now like to observe the temporal evolution of mRNA molecules. Let us consider that the reactive process is a succession of random jumps. The dynamics is such that the system randomly visits different time-ordered accessible states, $\{X_i\}$, which defines a path or a trajectory. A typical trajectory can be generated by Gillespie's algorithm [16], where the reactants for the r th reaction are updated as $X_k = X_{k-1} + c_r$, where c_r are the stoichiometric coefficient. The r th reaction occurs at times $t_k = t_{k-1} + \tau_k$ where τ_k 's are chosen from an

Fig. 1 Fano factor $F = \frac{\sigma^2}{n}$ is shown as a function of k_{off} for different k_d . The rate constants are: $k_{on}=3 \text{ min}^{-1}$, $k_{rx}=20 \text{ min}^{-1}$. The Fano factor is maximum at $k_{off}^{\max} \approx \{3.1, 4.2, 5.2\} \text{ min}^{-1}$ for $k_d = \{0.3, 3.0, 6.0\} \text{ min}^{-1}$, respectively

exponential distribution. The successive number of molecules obtained at time $0 < t_1 < t_2 < \dots < t_n < t$ define a forward path

$$x(t) = X_0 \xrightarrow{r_1} X_1 \xrightarrow{r_2} X_2 \xrightarrow{r_3} \dots \xrightarrow{r_n} X_n \quad (5)$$

and similarly a time-reversed path

$$x^R(t) = X_n \xrightarrow{-r_n} \dots \xrightarrow{-r_3} X_2 \xrightarrow{-r_2} X_1 \xrightarrow{-r_1} X_0. \quad (6)$$

The disparity in the probability of the forward path and the reverse path will characterize the underlying non-equilibrium process [12, 13, 17]. Let W_{r_i} be the transition rate for r th reaction involving reactants X_i and X_{i+1} (W_{r_i} is that of the reverse reaction). A function $Z(t)$ quantifying the ratio of the product of forward transition events to the reversed transition events is defined as:

$$\begin{aligned} Z(t) &= \ln \frac{W_{r_1}(X_0|X_1)W_{r_2}(X_1|X_2)\dots W_{r_n}(X_{n-1}|X_n)}{W_{-r_1}(X_1|X_0)W_{-r_2}(X_2|X_1)\dots W_{-r_n}(X_n|X_{n-1})} \\ &= \sum_k \ln \left[\frac{W_{r_k}(X_{k-1}|X_k)}{W_{-r_k}(X_k|X_{k-1})} \right]. \end{aligned} \quad (7)$$

Since the events are time-ordered, the above ratio can be approximated to be the ratio of the stationary probability distributions of the forward and the reversed paths, $P_{st}[x(t)]$ and $P_{st}[x^R(t)]$, respectively, and we write Eq. (7) as

$$Z(t) \approx \ln \frac{P_{st}[x(t)]}{P_{st}[x^R(t)]}. \quad (8)$$

The above quantity is like a Lebowitz-Spohn like-functional [18], in terms of which the fluctuation-dissipation theorem can now be established for non-equilibrium reactions and reads as

$$< \exp[-Z(t)] > = 1. \quad (9)$$

Note that for equilibrium situations $P_{st}[x(t)] = P_{st}[x^R(t)]$ and fluctuation theorem is trivially true.

We will now compute the change of entropy in the system. Let us consider r th reaction involving species X such that $W_r(X - c_r | X)$ be the transition rate from $X - c_r$ state to X . The evolution of the probability distribution $P(X, t)$ is given by the master equation:

$$\begin{aligned} \frac{dP}{dt} &= \sum_r [W_r(X - c_r | X)P(X - c_r, t) - W_{-r}(X | X - c_r)P(X, t)] \\ &= \sum_r J_r(X, t) \rightarrow \text{reaction rates} \end{aligned} \quad (10)$$

From the definition of entropy for a Markov process $S(t) = -\sum_X P(X, t) \ln P(X, t)$ and using the conservation law of probabilities and symmetries of the transition rates, Eq. (10) yields the total entropy variation

$$\frac{dS}{dt} = \frac{1}{2} \sum_{r, X} J_r(X, t) \ln \frac{P(X - c_r, t)}{P(X, t)}. \quad (11)$$

The rate of change of entropy can be considered to have contributions from a flux term and a production term [17]

$$\frac{dS}{dt} = \left(\frac{dS}{dt} \right)_p + \left(\frac{dS}{dt} \right)_f. \quad (12)$$

To the above Eq. (11) we add and subtract a term $\ln \frac{W_r(X - c_r | X)}{W_{-r}(X | X + c_r)}$ and get

$$\frac{dS}{dt} = \frac{1}{2} \sum_{r, X} J_r(X, t) \left[\underbrace{\ln \frac{P(X - c_r, t)}{P(X, t)} + \ln \frac{W_r(X - c_r | X)}{W_{-r}(X | X + c_r)}}_{\text{production term}} - \ln \frac{W_r(X - c_r | X)}{W_{-r}(X | X + c_r)} \right] \quad (13)$$

$$= \frac{1}{2} \sum_{r, X} J_r(X, t) \left[\ln \frac{W_r(X - c_r | X)P(X - c_r, t)}{W_{-r}(X | X - c_r)P(X, t)} - \frac{1}{2} \sum_{r, X} J_r(X, t) \ln \frac{W_r(X - c_r | X)}{W_{-r}(X | X + c_r)} \right] \quad (14)$$

and we identify the entropy flux term as

$$\left(\frac{dS}{dt} \right)_f = -\frac{1}{2} \sum_{X, r} \ln \frac{W_r(X - c_r | X)}{W_{-r}(X | X + c_r)} J_r(X, t) \quad (15)$$

and the entropy production term as

$$\left(\frac{dS}{dt} \right)_p = \frac{1}{2} \sum_{X, r} J_r(X, t) A_r(X, t) \quad (16)$$

where

$$A_r = \ln \frac{W_r(X-c_r|X)P(X-c_r, t)}{W_{-r}(X|X-c_r)P(X, t)}$$

$$J_r = W_r(X-c_r|X)P(X-c_r, t) - W_{-r}(X|X-c_r)P(X, t).$$

Following the inequality $(A+B)\ln(A/B) \geq 0$, the entropy production rate $\left(\frac{dS}{dt}\right)_p \geq 0$. Again, note that this is in agreement with the second law of thermodynamics.

Let us now calculate the average of Z , using the expression in Eq. (7), and the statistical average is weighted by time integrals of the reaction rates $J_r(X, t)$,

$$\begin{aligned} \langle Z(t) \rangle &= \int_0^t \frac{1}{2} \sum_{X,r} J_r(X, \tau) \ln \left[\frac{W_r(X-c_r|X)}{W_{-r}(X|X+c_r)} \right] d\tau \\ &= - \lim_{t \rightarrow \infty} \frac{1}{t} \int_0^t \left(\frac{dS}{d\tau} \right)_f d\tau \\ &= - \left(\frac{dS}{dt} \right)_f, \end{aligned} \quad (17)$$

The second step follows from the definition in Eq. (15). The average of Z has now been related to the flux term in entropy production. Since, total entropy variation vanishes on averaging

$$\overline{\frac{dS}{dt}} = \overline{\left(\frac{dS}{dt} \right)_p} + \overline{\left(\frac{dS}{dt} \right)_f} = 0. \quad (18)$$

Eqs. (17) and (18) give

$$\langle Z(t) \rangle = \overline{\left(\frac{dS}{dt} \right)_p} \quad (19)$$

Thus, the entropy production rate is the average of the quantity $Z(t)$ and can be easily computed from the first derivative of the corresponding moment generating function, defined as

$$Q(n) = \lim_{t \rightarrow \infty} -\frac{1}{t} \ln[\langle \exp[\eta Z(t)] \rangle]. \quad (20)$$

The statistical average can be explicitly written as

$$\langle \exp[-\eta Z(t)] \rangle = \sum_{x(t)} P_{st}[x(t)] \exp[-\eta Z(t)] \quad (21)$$

$$\approx \sum_{x(t)} P_{st}[x(t)] \left[\frac{P_{st}[x^R(t)]}{P_{st}[x(t)]} \right]^\eta \quad (22)$$

$$= \sum_{x(t)} P_{st}[x^R(t)] \left[\frac{P_{st}[x(t)]}{P_{st}[x^R(t)]} \right]^{1-\eta} \quad (23)$$

$$= \sum_{x^R(t)} P_{st}[x(t)] \left[\frac{P_{st}[x^R(t)]}{P_{st}[x(t)]} \right]^{1-\eta} \quad (24)$$

$$= \langle \exp[-(1-\eta)Z(t)] \rangle \quad (25)$$

Finally, using the definition in Eq. (20), the integrated fluctuation theorem, Eq. (9), can be expressed very simply in terms of the moment generating function as

$$Q(\eta) = Q(1-\eta). \quad (26)$$

In our subsequent numerical analysis we will confirm that the above symmetry exists and hence the fluctuation theorem is valid in the context of stochastic gene regulation. Moreover, the derivative of the moment-generating function yields the mean of $Z(t)$, which is the entropy production rate

$$\langle Z(t) \rangle = \left(\frac{dQ(\eta)}{d\eta} \right)_{\eta=0} = - \left(\frac{dQ(\eta)}{d\eta} \right)_{\eta=1}. \quad (27)$$

We now verify the fluctuation theorem for stochastic gene regulation. It is to be borne in mind that all the reactions involved in the process (Eq. 1) are not reversible. The above formalism is valid for reversible reactions for which we can define a forward and the time-reversed path. Since we are interested in the maximal bursty phase, which as shown above is independent of transcription k_{tx} , we study the reversible reaction channel. A similar approach was taken for studying the chemical reaction for non-equilibrium systems and the fluctuation theorem was verified [19].

In Fig. 2 we show the moment-generating function for varying k_{off} . When k_{off} is small or large (i.e., when the burstiness is less) the process is near equilibrium. In this regime, the symmetry of $Q(\eta)$ indicates that the fluctuation theorem is satisfied. In intermediate values of k_{off} , burstiness is maximum, and the system is driven out of equilibrium. The important finding of this work is that if we compute the entropy production rate, it not only shows the non-monotonic dependence on k_{off} as was seen in the exact calculation of the Fano factor F

Fig. 2 Moment-generating function $Q(\eta)$ shown for varying k_{off} . The rate constants are: $k_{on}=3\text{ min}^{-1}$, $k_{tx}=20\text{ min}^{-1}$, $k_d=0.3\text{ min}^{-1}$. The ensemble averages are computed over 10^6 realizations

Fig. 3 Entropy production rate shown as a function of k_{off} for $k_d = 0.3 \text{ min}^{-1} \ll k_{on}$ and $k_d = 3 \text{ min}^{-1} = k_{on}$. The transcriptional rate constant: $k_{tx} = 20 \text{ min}^{-1}$. The ensemble averages are computed over 10^6 realizations

Fig. 4 Entropy production rate shown for varying k_{on} . The rate constants are: $k_{off} = 3 \text{ min}^{-1}$, $k_{tx} = 20 \text{ min}^{-1}$, $k_d = 0.3 \text{ min}^{-1}$. The ensemble averages are computed over 10^6 realizations. *Inset* shows the variation of the Fano factor as a function of k_{on} for identical parameters

(quantifying the burstiness), but that it is also maximum for the k_{off} value, for which the burstiness is also maximized. The entropy production rate is shown in Fig. 3, and is maximum for $k_{off} \approx 3.0 \text{ min}^{-1}$, for $k_{on} = 3.0 \text{ min}^{-1}$, and $k_{on} \gg k_d = 0.3 \text{ min}^{-1}$. This value can be compared with the exact calculation of $k_{off}^{max} \approx 3.1$ in Fig. 1, for which the burstiness (Fano factor) is also maximum under similar conditions. It is also important to check the generality of the formalism in different parameter regimes. We check for the case when $k_d \approx k_{on} = 3.0 \text{ min}^{-1}$, we again find that the $k_{off}^{max} \approx 4$ obtained from the maximum entropy production is in good agreement with the exact calculation of $k_{off}^{max} \approx 4.2$ in Fig. 1 for which the burstiness (Fano factor) is maximized. Next, we check for the dependence on k_{on} . Note that the Fano factor, $F \approx 1/k_{on}^2$, i.e., the maximum burstiness, is expected as $k_{on} \rightarrow 0$ assuming all other parameters are held constant. The maximum entropy production exactly captures this feature as shown in Fig. 4. Finally, the dependence of the Fano factor on the transcription rate is k_{tx} is linear and will be maximized for a choice of $k_{tx} \rightarrow \infty$ and can also be easily verified numerically.

In summary, we have analyzed a model of stochastic gene regulation that exhibits transcriptional burstiness in mRNA dynamics. As the system is being driven out of equilibrium, we use the tools of non-equilibrium statistical mechanics to estimate the entropy production rate. The observation of burstiness and entropy production rate being simultaneously maximized is an indicator that bursty dynamics is entropically driven. We have verified the estimation of the entropy production rate for different reaction parameters and find that k_{off} s that maximize burstiness and entropy production are always in good agreement. The generality of the formalism for different parameter regimes has also been tested. It is very enticing to conclude that the bursty dynamics is favored due to the principle of maximum entropy production [20]. However, the exact thermodynamic principles underlying the entropy production are still unsettled. The principle of maximum entropy production can be countered by the principle of minimum entropy production [21, 22] or the existence of any such principle that extremizes entropy [23]. We would like to point out that incorporating notions of non-equilibrium dynamics can be key in our understanding of transcriptional fluctuations. It will be interesting to establish the fluctuation theorem for different network motifs of gene regulatory networks. Moreover, it has been observed that gene expression can exhibit sub-Poissonian or anti-bursting dynamics (i.e., Fano factors < 1) [24]. Modeling anti-bursting dynamics is beyond the scope of the ON-OFF model presented here and future studies need to be undertaken in that direction.

References

- Balazsi, G., van Oudenaarden, A., Collins, J.J.: Cellular decision making and biological noise: from microbes to mammals. *Cell* **144**(6), 910–925 (2011)
- Elowitz, M.B., Levine, A.J., Siggia, E.D., Swain, P.S.: Stochastic gene expression in a single cell. *Science* **297**(5584), 1183–1186 (2002)
- McAdams, H.H., Arkin, A.: Stochastic mechanisms in gene expression. *Proc. Natl. Acad. Sci. U.S.A.* **94**(3), 814–819 (1997)
- Thattai, M., van Oudenaarden, A.: Intrinsic noise in gene regulatory networks. *Proc. Natl. Acad. Sci. U.S.A.* **98**(15), 8614–8619 (2001)
- Van Kampen, N. G.: *Stochastic Processes in Physics and Chemistry* (Vol. 1). Access Online via Elsevier (1992)
- Paulsson, J.: Models of stochastic gene expression. *Phys. Life. Rev.* **2**(2), 157–175 (2005)
- Golding, I., Paulsson, J., Zawilski, S.M., Cox, E.C.: Real-time kinetics of gene activity in individual bacteria. *Cell* **123**(6), 1025–1036 (2005)
- Raj, A., Peskin, C.S., Tranchina, D., Vargas, D.Y., Tyagi, S.: Stochastic mRNA synthesis in mammalian cells. *PLoS Biol.* **4**(10), e309 (2006)
- Raj, A., van Oudenaarden, A.: Single-molecule approaches to stochastic gene expression. *Annu. Rev. Biophys.* **38**, 255–270 (2009)

10. Shahrezaei, V., Swain, P.S.: Analytical distributions for stochastic gene expression. *Proc. Natl. Acad. Sci. U.S.A.* **105**(45), 17256–17261 (2008)
11. So, L.H., Ghosh, A., Zong, C., Seplveda, L.A., Segev, R., Golding, I.: General properties of transcriptional time series in *Escherichia coli*. *Nat. Genet.* **43**(6), 554–560 (2011)
12. Seifert, U.: Fluctuation theorem for birth-death or chemical master equations with time-dependent rates. *J. Phys. A Math. Gen.* **37**(42), L517–L521 (2004)
13. Gaspard, P.: Fluctuation theorem for nonequilibrium reactions. *J. Chem. Phys.* **120**, 8898 (2004)
14. Peccoud, J., Ycart, B.: Markovian modeling of gene-product synthesis. *Theor. Popul. Biol.* **48**(2), 222–234 (1995)
15. Gradshteyn, I. S., Ryzhik, I. M.: *Table of Integrals, Series, and Products* (Academic Press, New York) (1980)
16. Gillespie, D.T.: Exact stochastic simulation of coupled chemical reactions. *J. Phys. Chem.* **81**(25), 2340–2361 (1977)
17. Jiu-Li, L., Van den Broeck, C., Nicolis, G.: Stability criteria and fluctuations around nonequilibrium states. *Zeitschrift für Physik B Condensed Matter* **56**(2), 165–170 (1984)
18. Lebowitz, J.L., Spohn, H.: A Gallavotti Cohen-type symmetry in the large deviation functional for stochastic dynamics. *J. Stat. Phys.* **95**(1–2), 333–365 (1999)
19. Xiao, T., Hou, Z.: Fluctuation theorem for entropy production in a chemical reaction channel. *Sci. China Chem.* **53**(2), 396–401 (2010)
20. Martyushev, L.M., Seleznev, V.D.: Maximum entropy production principle in physics, chemistry and biology. *Phys. Rep.* **426**(1), 1–45 (2006)
21. Klein, M.J., Meijer, P.H.: Principle of minimum entropy production. *Phys. Rev.* **96**(2), 250 (1954)
22. Jaynes, E.T.: The minimum entropy production principle. *Annu. Rev. Phys. Chem.* **31**(1), 579–601 (1980)
23. Ross, J., Corlan, A.D., Muller, S.C.: Proposed principles of maximum local entropy production. *J. Phys. Chem. B* **116**(27), 7858–7865 (2012)
24. Sanchez, A., Golding, I.: Genetic determinants and cellular constraints in noisy gene expression. *Science* **342**(6163), 1188–1193 (2013)