Stochastic thermodynamics of chemical reactions coupled to finite reservoirs

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(Dated: 5 March 2020)

Biomolecular processes are typically modeled using chemical reaction networks coupled to infinitely large chemical reservoirs. A difference in chemical potential between these reservoirs can drive the system into a non-equilibrium steady state (NESS). In reality, cells are finite systems containing a finite number of molecules. In such systems, a NESS can be reached with the help of an externally driven pump for which we introduce a simple model. Crucial parameters are the pumping rate and the finite size of the chemical reservoir. We apply this model to a simple biochemical oscillator, the Brusselator, and quantify the performance using the number of coherent oscillations. As a surprising result, we find that higher precision can be achieved with finite-size reservoirs even though the corresponding current fluctuations are larger than in the ideal infinite case.

I. INTRODUCTION

Biological systems require a constant supply of energy to perform their tasks. There are numerous examples from molecular motors1–4 such as kinesin or myosin to biological switches and oscillators such as the circadian clock5,6, the MinDE system7–11 or the interlinked GTPase cascade12–15. All of these systems reach a non-equilibrium steady state (NESS) by extracting energy from nucleotide phosphates such as adenosine or guanosine triphosphate (ATP or GTP)16,17. Chemical energy is released through a hydrolysis reaction which breaks one of the phosphate bonds (dephosphorylation) and converts a nucleotide triphosphate (ATP) into a nucleotide diphosphate (ADP, GDP) and an inorganic phosphate (P_i).

How do cells maintain an excess of ATP to remain in a NESS? At equilibrium conditions, ADP and P_i are predominant over ATP due to a large difference in free energy. Living systems rely on cellular respiration, a metabolic process that recycles ADP into ATP18,19. It starts with glycolysis which converts glucose into pyruvates, then a series of oxidative phosphorylation result in the pumping of protons across the cell membrane creating an electrochemical gradient.

The final recycling step is performed by a rotary molecular motor, namely the ATP synthase or F0F1-ATPase in bacteria20,21. The main purpose of this molecular motor is to maintain the cell in a NESS. The F0-part is embedded in the membrane and couples to the proton gradient to rotate a central shaft. The F1-motor uses ATP hydrolysis to rotate in the opposite direction. By coupling the two parts with a strong enough proton gradient, the F1-motor rotates in reverse and thereby synthesizes ATP from ADP and P_i. Experimental techniques have enabled the observations of individual trajectories at the single molecule level22–24. From such trajectories, efficiencies for the motor could be computed25–27.

Thermodynamics generally relies on infinitely large reservoirs for which the temperature or the concentration of external chemical species are assumed to be constant. In reality, cells are finite system with a finite number of molecules. As a consequence, real biological oscillators do not have infinitely big chemistats at their disposal. In this paper we take this into consideration by introducing finite chemical reservoirs. Reactions in which a molecule leaves or enters the chemistat will change its concentration depending on the bath size. We quantify this effect with a parameter $A$ which describes how large the bath is compared to the rest of the system. The change in concentration is inversly proportional to the bath size, so in the limit $A \to \infty$ the change vanishes and we recover the ideal reservoir. The role of F0F1-ATPase is modeled by a simple unimolecular driven reaction with reaction speed $\gamma$. This upholds the chemical free energy difference between the reservoirs. In a different context, a finite-size temperature bath has been considered in28,29 where it was modeled as a set of independent linear oscillators.

A natural question is how finite chemical reservoirs affect the performance of biological systems. Naively, one may expect that finite reservoirs would introduce additional noise into the system and lead to a decrease of its quality. We show that a simple biochemical oscillator with finite reservoirs can achieve higher precision than its counterpart with ideal reservoirs despite the increase in fluctuations. The relation between the precision of biochemical oscillations and the energy required to sustain them has received much attention recently for ideal reservoirs30–39.

This paper is organized as follows. In Section II, we introduce the Brusselator model and its modified version with a pumping mechanism. In Section III, we show that higher precision can be achieved with finite reservoirs despite showing larger fluctuations. We find that there is an optimal reservoir size and pumping speed which outperforms the ideal reservoir case. We conclude in Section IV.

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II. MODELS

A. The Brusselator model

The Brusselator is arguably the simplest set of chemical reactions that can exhibit oscillations as sketched in Fig. 1 (a). It consists of two chemical species X and Y in a volume Ω. X and Y molecules can be produced from chemiostats containing A and B molecules, respectively. The set of chemical reactions is

\[
\begin{align*}
A & \xrightarrow{k_1} X, \\
B & \xrightarrow{k_2} Y, \\
2X + Y & \xrightarrow{k_3} 3X,
\end{align*}
\]

where the \(k_1, k_{-1}, k_2, k_{-2}\) and \(k_3\) are transition rates. Through a chemical free energy difference \(\Delta \mu\) between the chemiostats the system is driven out of equilibrium into a NESS. Thermodynamic consistency requires the rates \(k_i\) and \(\Delta \mu \equiv \mu_B - \mu_A\) to be related via the local detailed balance condition, which in this case reads

\[
e^{\Delta \mu} = \frac{[B]k_2k_{-1}}{[A]k_{-2}k_1},
\]

where we set \(\beta = 1\) throughout this paper\(^{40}\). The thermodynamic force \(\Delta \mu\) must be above a certain critical threshold \(\Delta \mu_c\) for biochemical oscillations to set in\(^{31,33}\).

B. The Brusselator with finite reservoirs

In the original Brusselator, the concentrations \([A]\) and \([B]\) remain constant, i.e., are chemiostatted. For finite reservoirs this is no longer the case. The number of A and B molecules will now be part of the system and changes according to the set of chemical reactions. We introduce a parameter, \(\Lambda\), which characterizes the size of the reservoirs compared with the system size \(\Omega\). The initial number of molecules in the bath is given by (1)

\[
\begin{align*}
n_A &= [A] \Lambda \Omega, \\
n_B &= [B] \Lambda \Omega,
\end{align*}
\]

where \([A]\) and \([B]\) are the chemiostatted concentrations from the original model. The total number of molecules \(N_{\text{tot}} = n_X + n_Y + n_A + n_B\) becomes a conserved quantity.

In such a system, the NESS can be maintained by an externally driven pump, which sustains a chemical gradient between A and B. The simplest possible reaction scheme achieving this feature is

\[
A \xrightarrow{\gamma_+} B,
\]

where \(\gamma_{\pm}\) are transition rates, see Fig. 1 (b). With this additional reaction, the local detailed balance condition reads

\[
e^{\Delta \mu} = \frac{\gamma_+k_2k_{-1}}{\gamma_-k_{-2}k_1}.
\]

We assume that the rates \(k_i\) are fixed, thus Eq. (5) relates the ratio of \(\gamma_+\) and \(\gamma_-\) to a given \(\Delta \mu\). As a free parameter, we choose \(\gamma \equiv \gamma_+\), which is the characteristic timescale of the pump. Our modified model is then described by three parameters: the size ratio \(\Lambda\), the speed of the pump \(\gamma\) and the chemical free energy difference \(\Delta \mu\) between the finite reservoirs.

C. Chemical master equation and deterministic equations

The evolution of the probability to find the system in a state \(n \equiv (n_X, n_Y, n_A, n_B)\) at time \(t\) is described by the chemical master equation (CME)\(^{41}\)
\[ \partial_t P(n, t) = \left\{ k_1 \left[ (n_A + 1) \epsilon_X^+ \epsilon_X^- - n_A \right] + k_2 \left[ (n_B + 1) \epsilon_Y^+ \epsilon_Y^- - n_B \right] \\
+ k_{-1} \left[ (n_X + 1) \epsilon_X^+ \epsilon_X - n_X \right] + k_{-2} \left[ (n_Y + 1) \epsilon_Y^+ \epsilon_Y - n_Y \right] \\
+ \frac{k_3}{\Omega^2} \left[ (n_X - 1)(n_X - 2)(n_Y + 1) \epsilon_X^+ \epsilon_Y + (n_X + 1)n_X(n_X - 1)\epsilon_X^+ \epsilon_Y^- \\
- n_X(n_X - 1)n_Y - n_X(n_X - 1)(n_X - 2) \right] \\
+ \gamma^+ \left[ (n_A + 1) \epsilon_A^+ \epsilon_B^- - n_A \right] + \gamma^- \left[ (n_B + 1) \epsilon_B^+ \epsilon_A^- - n_B \right] \right\} P(n, t), \]

where we define the step operators as
\[ \epsilon_X^\pm P(n, t) \equiv P(n_X \pm 1, n_Y, n_A, n_B), \]
\[ \epsilon_Y^\pm P(n, t) \equiv P(n_X, n_Y \pm 1, n_A, n_B), \]
\[ \epsilon_A^\pm P(n, t) \equiv P(n_X, n_Y, n_A \pm 1, n_B), \]
\[ \epsilon_B^\pm P(n, t) \equiv P(n_X, n_Y, n_A, n_B \pm 1, t). \] (7)

In the deterministic limit \((\Omega \to \infty)\), we obtain from Eq. (6) the rate equations for the concentrations,
\[ I \equiv \sum_n n_1 P(n, t) / \Omega \quad I \in \{X, Y, A, B\}. \] (8)
as
\[ \dot{X} = k_1 A - k_{-1} X + k_3 (X^2 Y - X^3), \]
\[ \dot{Y} = k_2 B - k_{-2} Y + k_3 (X^3 - X^2 Y), \]
\[ \dot{A} = -k_1 A - k_{-1} X - \gamma_A^+ A + \gamma_A^- B, \]
\[ \dot{B} = -k_2 B + k_{-2} Y + \gamma_A^+ A - \gamma_B^- B. \] (9)

D. Stochastic simulations

We have performed continuous time Monte Carlo simulations of Eq. (6) using Gillespie’s algorithm\(^{32}\). For all simulations we set the parameters to \(\Omega = 1000, k_1 = 0.1/\Lambda, k_{-1} = 0.1, k_2 = 0.1/\Lambda, k_{-2} = 0.003, k_3 = 0.001\) and \(N_{\text{tot}} = 7.5 \cdot \Omega \cdot \Lambda\). The rates \(k_1\) and \(k_2\) are scaled with \(1/\Lambda\) in order to make the reaction propensities \(k_1 n_A\) and \(k_2 n_B\) independent of \(\Lambda\). This ensures that we recover the ideal reservoirs dynamics in the limit \(\Lambda \to \infty\). We choose \(\Delta \mu, \gamma\) and \(\Lambda\) as control parameters.

E. Precision of oscillations and diffusion coefficient

In Fig. 2(a), we plot an example of an oscillating trajectory for species X and B. Such oscillations occur in systems with a finite number of molecules that display large fluctuations. To quantify the precision of oscillations, we compute the correlation function for species X which is defined as
\[ C_X(t) \equiv \frac{\langle (n_X(t) - \langle n_X \rangle)(n_X(0) - \langle n_X \rangle) \rangle}{\langle n_X^2 \rangle - \langle n_X \rangle^2} = \exp(-t/\tau_c) \cos(2\pi T), \] (10)
where the bracket denote an average over stochastic trajectories, \(\tau_c\) is the correlation time and \(T\) the period length. In Fig. 2(b), we show a typical correlation function in the oscillating regime. The number of coherent oscillations is defined as the correlation time divided by the period length, i.e.,
\[ \mathcal{N} \equiv \frac{\tau_c}{T}. \] (11)

It measures how long different realizations of the oscillator stay coherent with each other. Thus \(\mathcal{N}\) is a natural choice to quantify the precision of biochemical oscillations\(^{30,32}\).

As a measure for fluctuations, we consider the current conjugated to the thermodynamic force \(\Delta \mu\), which is related to the entropy production. In the original Bruselator, this current is given by the rate of consumption of B. In our modified model, the thermodynamic flux is related to the pumping scheme (4). We can analyse its fluctuations by considering the stochastic time-integrated current \(Z\). In a stochastic trajectory, this random variable increases by one if a B is converted to an A molecule, which happens if the transition with rate \(\gamma_+\) takes place. Likewise \(Z\) decreases by one if an A is converted to a B molecule, which happens if the transition with rate \(\gamma_-\) takes place, i.e.,
\[ B \xrightarrow{\gamma_+} A \quad Z \to Z + 1, \]
\[ A \xrightarrow{\gamma_-} B \quad Z \to Z - 1. \] (12)
The average thermodynamic flux is then defined as
\[ J \equiv \lim_{T \to \infty} \frac{\langle Z \rangle}{T \Omega}, \] (13)
where \(T\) is the sampling time interval. Note that we choose our system parameters such that \(J\) does not depend on the reservoir size \(\Lambda\), see Section II D for further explanations. In the steady-state, the rate of entropy production is simply given by \(\sigma \equiv J \Delta \mu\). The fluctuations can be quantified by the diffusion coefficient, which is defined as
\[ D \equiv \lim_{T \to \infty} \frac{\langle Z^2 \rangle - \langle Z \rangle^2}{2\Omega T}, \] (14)
At the onset of oscillations, this quantity diverges as a power-law with the system size\(^{35}\). Interestingly, \(D\) has
a universal lower bound that depends only on the thermodynamic force $\Delta \mu$, which follows from the thermodynamic uncertainty relation\textsuperscript{43–45}. We choose $D$ as a quantifier for the fluctuations of the system.

III. RESULTS

A. Deterministic equations

We first consider the deterministic Eq. (9) and study its non-equilibrium steady state solutions for which the left-hand side vanishes. These equations are solved numerically. By computing the power spectrum of the trajectories we can classify whether the system oscillates or not. We obtain the phase diagrams shown in Fig. 3. The grey area marks the set of parameters for which the system oscillates. In all three cross sections there is an interplay between the parameters. For example, in Fig. 3 (a), if the finite reservoir size ratio $\Lambda$ is too large for a fixed $\Delta \mu$ the oscillations may vanish. A too large thermodynamic force $\Delta \mu$ for a fixed $\Lambda$ can also make the oscillations vanish. We observe the same effect in Fig. 3 (b) for $\gamma$, namely, a range of possible timescales for the pump that leads to oscillations. In Fig. 3 (c) the interplay is most crucial: increasing both $\Delta \mu$ and $\gamma$ too far makes oscillations vanish as well.

B. CME

We now consider oscillations in a system with a finite number of molecules that can display large fluctuations. We choose the diffusion coefficient $D$, Eq. (14), to quantify the fluctuations of the system and the number of coherent oscillations $N$, Eq. (11), to quantify the precision of oscillations. In Fig. 4, we plot the diffusion coefficient $D$ and the number of coherent oscillations $N$ along the
arrows shown in Fig. 3. At the phase transition, the diffusion coefficient has a local maximum\(^{33}\). Surprisingly, we observe that both \(\mathcal{N}\) and \(D\) increase simultaneously, in other words, higher precision can be achieved with higher fluctuations. This is in contrast to the Brusselator model\(^{33}\) and unicyclic models\(^{46,47}\). The same feature, however, is shared by other models, such as the activator-inhibitor model\(^{33}\). In this sense, \(\mathcal{N}\) and \(D\) are not always strongly correlated in biochemical oscillators.

Why do oscillations to vanish? First, \(\Delta \mu\) must be above a critical value \(\Delta \mu_c\) for oscillations to occur, which is also the case for the standard Brusselator. In our modified model, the threshold \(\Delta \mu_c\) depends on the parameters \(\Lambda\) and \(\gamma\). Moreover, \(\gamma\) and \(\Lambda\) must be above certain thresholds for oscillations to set in; their specific critical values depend on the system parameters. In Fig. 4 (a) and (b), we observe a decrease in the precision of oscillations for increasing \(\Lambda\). As \(\Lambda\) increases, so does \(\Delta \mu_c\), which causes \(\mathcal{N}\) to decrease and, in Fig. 4 (b), even to vanish. Most remarkably, we find that \(\mathcal{N}(\Lambda)\) approaches \(\mathcal{N}(\Lambda \to \infty)\), which corresponds to the infinite reservoir from above. This result implies that the oscillations driven by finite reservoirs can show higher precision than ones with ideal reservoirs despite having larger fluctuations. In this sense, the finite reservoirs outperform the infinite ones.

Second, for finite reservoirs, oscillations can vanish when \(\Delta \mu\) and \(\gamma\) are too large, see Fig. 3 (c). As shown in Fig. 4 (c) and (d), \(\mathcal{N}\) reaches a maximum and vanishes for large \(\Delta \mu\) and \(\gamma\). For an explanation of this suprising effect, we plot the phase portrait of the deterministic system in Fig. 5. In the steady-state, the deterministic system will remain on a limit cycle as shown in Fig. 5 (a). This is no longer the case for the stochastic system which can explore larger cycles due to fluctuations. We illustrate this by perturbing a deterministic trajectory located on the limit cycle as indicated by the red arrow. Where streamlines are dense, such a perturbation can lead to a large change in the trajectory. The system goes through a large cycle before converging back to the limit cycle.

For the stochastic system, fluctuations are constantly perturbing the trajectory, which stochastically leads to the appearance of large cycles. Their appearance results in a decrease of the number of coherent oscillations as these large cycles are no longer coherent with the oscillations in the limit cycle. As \(\Delta \mu\) and \(\gamma\) are increased and \(\Lambda\) decreased, transitions from the inner limit cycle onto a larger cycle are much more likely to happen. Finally, an additional fixed-point appears as shown in Fig. 5 (b). As the new fixed-point is stable (Fig. 5 (c)), the system becomes bistable and trajectories that leave the limit cycle to this fixed-point return on a much larger timescale, thus, explaining why \(\mathcal{N}\) vanishes.

For the parameter range plotted in Fig. 4 as indicated in Fig. 3, the oscillations of \(n_X(t)\) and \(n_Y(t)\) are stabilized by oscillations in the number of \(A\) and \(B\) molecules in the reservoirs as shown in Fig. 2 (a). Oscillations

FIG. 4. Comparison between the diffusion coefficient (blue squares) the number of coherent oscillations (red circles) as a function of the reservoir size \(\Lambda\) for (a) and (b), pumping timescale \(\gamma\) for (c) and thermodynamic force \(\Delta \mu\) for (d).
can occur because the pumping mechanism Eq. (4) does not attempt to keep the reservoir concentrations fixed. Rather, it restores the ratio of the bath concentrations to a fixed value given by $\Delta \mu$, since $[A]/[B]$ is proportional to $e^{-\Delta \mu}$ according to the local detailed balance condition Eq. (5). At small bath scales $\Lambda$, from the systems perspective bath oscillations become noticeable and could qualitatively explain the improved precision of finite reservoirs in Fig. 4(a).

IV. CONCLUSION

We have introduced a simple model for the role of finite reservoirs in chemical reaction networks. To uphold a NESS, we have introduced a pumping mechanism that better reflects the real conditions in biological systems than the usual assumption of infinite reservoirs. We have considered the simplest possible mechanism, a first-order chemical reaction converting species between reservoirs. This class of reservoirs is characterised by two parameters: the bath scale $\Lambda$, which relates the reservoir size to the rest of the system and the timescale of the pumping mechanism $\gamma$. The ideal reservoirs are recovered in the limit $\Lambda \to \infty$ (independently of $\gamma$).

As a case study, we have investigated a biochemical oscillator, the Brusselator, with our simple pumping mechanism. We quantify the precision of oscillations by measuring the number of coherent oscillations and the diffusion coefficient associated with the pump. We find that the highest precision of oscillations occurs at finite parameters $\Delta \mu$, $\gamma$ and $\Lambda$. This is in contrast to the Brusselator model\textsuperscript{33} and other unicyclic models\textsuperscript{46,47} considered in the previous literature, where the precision of oscillations monotonically increases with the control parameter $\Delta \mu$. As a main result, we find that a system with finite reservoirs can outperform one with ideal reservoirs despite having larger fluctuations.

Our framework could be extended by considering more sophisticated pumping mechanisms. It would be interesting to consider the ATP synthase, for which thermodynamically consistent models exist\textsuperscript{27}. Specifically, it would be interesting to study the relation between the efficiency of the motor and the precision of oscillations. Another interesting case is the coupling of biochemical clocks which can be optimized to maximize the precision of oscillations\textsuperscript{37}. Moreover, it has been shown recently that periodically driven oscillator can achieve better coherence than under NESS conditions\textsuperscript{48}. It would be interesting to investigate how fluctuations in the periodic protocol affect the precision of oscillations. Finally, we expect that considering finite reservoirs may show further surprises for biochemical systems beyond the enhanced precision of oscillations discovered here.

FIG. 5. Phase portrait in the X-Y plane. (a) Emergence of additional larger cycles. We perturb the deterministic system along the red arrow. The system then goes through a larger cycle and converges back to the limit cycle. For the stochastic system, such events are more likely as $\Delta \mu$ and $\gamma$ increase. (b) Appearance of an additional fixed-point in the red square as $\Lambda$ decreases. (c) Locally stable fixed-point. The timescale for transitions between the fixed-point and the limit cycle is much larger than a period of oscillations.
DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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