Entropy production constrains information throughput in gene regulation

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Biological signal processing typically requires energy, leading us to hypothesize that a cell's information processing capacity is constrained by its energy dissipation. Signals and their processing mechanisms are often modeled using Markovian chemical reaction networks (CRNs). To enable rigorous analysis, we review and reformulate stochastic thermodynamics for open CRNs, utilizing Kurtz's process-based formulation. In particular, we revisit the identification of the energy dissipation rate with the entropy production rate (EPR) at the non-equilibrium steady state (NESS). We also highlight potential inconsistencies in traditional formulations for generic Markov processes when applied to open CRNs, which may lead to erroneous conclusions about equilibrium, reversibility, and the EPR. Additionally, we review the concepts of mutual information (MI) and directed information (DI) between continuous-time trajectories of CRNs, which capture the transmission of spatiotemporal patterns. We generalize existing expressions for the MI, originally accounting for transmission between two species, to now include transmission between arbitrary subnetworks. A rigorous derivation of the DI between subnetworks is presented. Based on channel coding theorems for continuous-time channels with feedback, we argue that directed information is the appropriate metric for quantifying information throughput in cellular signal processing. To support our initial hypothesis within the context of gene regulation, we present two case studies involving small promoter models: a two-state nonequilibrium promoter and a three-state promoter featuring two activation levels. We provide analytical expressions of the directed information rate (DIR) and maximize them subject to an upper bound on the EPR. The maximum is shown to increase with the EPR.

I. INTRODUCTION

Energy consumption is essential for gene regulatory mechanisms and intracellular signal transduction in both prokaryotes and eukaryotes. For example, in eukaryotes, chromatin remodeling complexes use ATP to maintain gene expression profiles[1,2]. In prokaryotes, e.g., the conversion of ATP to cAMP provides a cofactor for regulatory transcription factors like the catabolite-activating protein (CAP)[3]. Gene regulatory networks are an essential part of signal processing in cells[4], motivating an information-theoretic analysis of the network and its single regulatory elements like promoter architectures.

There is increasing evidence that cells represent information in the spatiotemporal variation of signaling molecules when processing internal or external stimuli[5–7]. The benefit of stochastic chemical reaction networks (CRNs) is that these models account for the discrete nature of reactions and molecule counts. Any static or dynamical representation of information is thus accurately captured in the trajectories of a CRN. In complement, accurate thermodynamic characterization is also possible with CRNs.

We hypothesize that the information throughput in gene regulatory networks is limited by the amount of energy required. Such trade-offs between energy dissipation and precision in cellular decision making and adaptation have been described as an emerging general design principle of biological systems[8]. Therefore, in this paper, we propose the directed information[9] (DI) between continuous-time stochastic processes to quantify the directed information throughput in a CRN. We then use stochastic thermodynamics for CRNs (sTD) to quantify the energy dissipation rate and at the non-equilibrium steady state (NESS) and identify it with the entropy production rate (EPR). Finally, we conduct information-theoretic case studies on minimal models to support our hypothesis. We envision that further developments in this area will help in the design of new information processing genetic circuits that optimally handle the trade-offs.

A. Previous related work

A powerful formalization of the description of Markovian chemical reaction networks was provided by Kurtz and Anderson[10]. They demonstrated how counting processes relevant to these networks can be represented using Poisson processes, leading to a random time-change representation. From that, they obtain a stochastic equation for continuous-time Markov jump processes, i.e., their trajectory-level description. Our introduction to CRNs largely follows their work, supplemented by some thermodynamically relevant concepts.

Information theory was pioneered by Shannon and laid the foundation for the digital age. One of his landmark contributions was the channel coding theorem[11], which determines the maximum rate at which information can be reliably transmitted despite noise corrupting the received signal. A key aspect of Shannon's work was his abstraction of noise corruption through the concept of a transmission channel, characterized by the conditional distribution of the output given the input. He introduced mutual information, a functional of the joint distribution of input and output, to quantify their stochastic dependency and thereby the information exchange between them. The channel coding theorem identifies the supremum of the mutual information for a given transmission channel as the maximum transmission rate at which the error prob-

ability asymptotically approaches zero. This limiting rate is known as the channel capacity. Marko developed a theory of bidirectional communication, highlighting that communication, unlike mere transmission, is intrinsically bidirectional[12]. Building on his ideas, Massey established a consistent theory of information transmission that incorporates the use of feedback by emphasizing the distinction between statistical and causal dependence[13]. Feedback is not an inherent feature of the channel itself; rather, it is integrated into the encoding of the signals transmitted through the channel. In particular, Massey introduced the concept of directed information and demonstrated that, when used in place of mutual information, it accurately extends the channel coding theorem to transmission with the use of feedback. For channels that are used without feedback, directed information reduces to mutual information. Weissman *et al.* further generalized the traditional notion of directed information between finite-length discrete-time sequences to a notion between continuous-time trajectories[9]. They also proved a channel coding theorem for a broad class of continuous-time channels, used with feedback, and derived the channel capacity via the directed information. Although it is not immediately clear whether the channel between trajectories of subnetworks within a CRN falls into this class, the inherent multidirectionality of causal dependencies in CRNs, coupled with their continuous-time description, suggests that directed information between continuous-time trajectories is the appropriate information-theoretic measure for quantifying directional information throughput in CRNs.

The use of information theory in systems biology is a relatively recent research field[14]. The initial applications focused on analyzing gene regulatory networks by characterizing the mutual information of the joint distribution of network elements at steady-state[15] or at individual time points[16]. Hansen and O'Shea first accounted for dynamic information transduction by considering particular dynamic features as amplitude and frequency[17]. Tostevin and ten Wolde first considered the mutual information between trajectories, recognizing that relevant information may be contained in the temporal dynamics of the input signal[18]. They provide the mutual information rate, i.e., the asymptotic differential information gain, under a linear-noise Gaussian approximation. Lestas *et al.* used the mutual information between trajectories as a tool to lower bound the cost of suppressing molecular fluctuations of the input species via feedback under a Langevin approximation of the input[19]. Nakahira *et al.* extended their work on biomolecular control and identified the directed information as the appropriate information measure[20].

A measure-theoretic account for the mutual information between the trajectories of two species of a class of biochemical reaction networks was first given by Duso and Zechner[21] and later generalized by Moor and Zechner[22]. To compute the mutual information they proposed several methods: a combination of stochastic simulation (SSA)[23] and moment closure approximation, a quasi-exact approach combining SSA and numerical integration and an analytical approximation. Moor and Zechner further showed that the trajectory mutual information decomposes into a pair of transfer entropies. These transfer entropies are in fact identical to to DI from input to output and vice versa. In this paper, we further generalize the expression for the mutual information in[22] to encompass the information flow between subnetworks. Sinzger *et al.* and Gehri *et al.* advanced techniques for analytically and numerically computing the mutual information of the Poisson channel, which can be regarded as a minimal module of a CRN[24–26]. In the traditional definition of the Poisson channel[27], the mutual information equals directed information[9,26]. Finally, Reinhardt *et al.* developed an exact Monte Carlo method called path weight sampling to compute the mutual information between trajectories[28], which currently represents the state-of-the-art approach for calculating mutual information in large networks.

Schnakenberg first formulated steady-state thermodynamics for Markov jump processes, defined via their infinitesimal generator, and derived a cycle decomposition for the entropy production rate[29]. A first formulation of stochastic thermodynamics for CRNs beyond steady state was done by Schmiedl and Seifert[30]. Rao and Esposito reformulated sTD for CRNs with emphasis on topological properties and conservation laws[31]. By leveraging the CRNs topology, they proposed a new Gibbs potential for the CRN, leading to a more informative thermodynamic description. Our review of sTD mainly follows Schmiedl and Rao, without explicitly considering conservation laws or fluctuation theorems. In particular, we leverage the benefits of representing trajectory-wise thermodynamic quantities via formal counting process integrals.

B. Outline

The paper is organized as follows. In Sec. II we introduce the process-based description of microscopically reversible Markovian CRNs as developed by Kurtz and Anderson[10].

The concepts of mutual information and directed information between continuous-time processes are both introduced in a general measure-theoretic way in Sec. III. We then use a classical expression[32] that links the mutual information between jump processes to the characterization of the counting processes of the distinct reactions. To obtain the MI between arbitrary subnetworks of the CRN, we introduce a notion of indistinguishability of different reactions from the perspective of the subnetworks. We also novelly and rigorously derive the directed information between subnetworks. All presented expressions allow for simultaneous jumps in the input and output species.

The concepts of stochastic thermodynamics for closed and open chemical reaction networks are pedagogically introduced in Sec. IV. In particular, we express thermodynamic characteristics of random trajectories using counting process integrals, a common technique for CRNs. Then, in Sec. IV C, we review the common identification of the EPR of the NESS, as derived from the kinetic model, with the energy dissipation rate. In Sec. IV E we formulate time-reversed reaction counting processes to express the KL-divergence of the CRNs dynamics from its time-reversal. This divergence is commonly used to quantify the degree of thermodynamic irreversibility. Using these formal tools, we review the relation of ir-

reversibility and entropy production in the context of CRNs. The discussion concludes with a listing of the four equivalent conditions for thermodynamic equilibrium in CRNs. Throughout, we highlights differences and inconsistencies in the traditional formulation of sTD for generic Markov processes, defined via their infinitesimal generator, in the context of CRNs.

Finally, in Sec. V, we showcase the combination of the tools provided throughout the paper and explore how energy dissipation constrains the maximum information throughput in gene regulation, using two minimal promoter models as case studies. The first is a nonequilibrium two-state promoter model with parallel reaction channels, and the second is a three-state promoter model. Both models describe the switching between a single transcriptionally active state and an inactive state. We derive analytical expressions for the directed information (DI) between the promoter's switching activity and the RNA copy number, and we optimize the directed information rate (DIR) under an upper bound on the promoter's entropy production rate.

In the following let $(\Omega, \mathscr{F}, \mathbb{P})$ be a probability space with complete filtration $\mathscr{F} = \{\mathscr{F}_t\}_{t\geq 0}$. In the information-theoretic context we refer to X and Y as the channel input and output, respectively.

II. MARKOVIAN STOCHASTIC CHEMICAL REACTION NETWORKS

A stochastic chemical reaction network (CRN) consists of $N \in \mathbb{N}$ chemical species $\mathsf{Z} = (\mathsf{Z}_1, \ldots, \mathsf{Z}_N)$ and $M \in \mathbb{N}$ reaction channels $\mathscr{R}_1, \ldots, \mathscr{R}_M$ with stoichiometric balance equations

$$\mathscr{R}_m: \quad \sum_{n=1}^{N} a_n^{(m)} \mathsf{Z}_n \quad \underset{\lambda_m^-}{\overset{\lambda_m^+}{\rightleftharpoons}} \quad \sum_{n=1}^{N} b_n^{(m)} \mathsf{Z}_n,$$

wherein $a^{(m)}, b^{(m)} \in \mathbb{N}^N$ represent the number of reacting molecules of each species and the number of product molecules, respectively, for the forward reaction, and vice versa for the backward reaction. The difference of product and reactant species of $\mathscr{R}_m$ forms the stoichiometric change vector $\nu_m = b^{(m)} - a^{(m)}$ of the forward reaction. For each reaction channel, the backward reaction microscopically reverses the forward reaction. We assume that all reactions are elementary[33], i.e., there are no reaction intermediates and each reaction has only a single transition state in the reaction coordinate diagram as illustrated in Fig. 1 (a).

Let $\{Z(t) \in \mathbb{Z}_{\geq 0}^N\}_{t\geq 0}$ be the continuous-time Markov chain of the copy number vector of the chemical species Z. We assume the rates of the reactions, commonly referred to as propensity functions, to obey stochastic mass action kinetics[10,31]

$$\lambda_m^+(z) = k_m^+ \prod_{n=1}^{N} \binom{z_n}{a_n^{(m)}}, \; \lambda_m^-(z) = k_m^- \prod_{n=1}^{N} \binom{z_n}{b_n^{(m)}} \tag{1}$$

with $z \in \mathbb{Z}_{\geq 0}^N$ and stochastic rate constants $k_m^+ > 0$ and $k_m^- \geq 0$. A conversion of the discrete molecule numbers to concentrations in a finite solvent volume V gives rise to another pair of

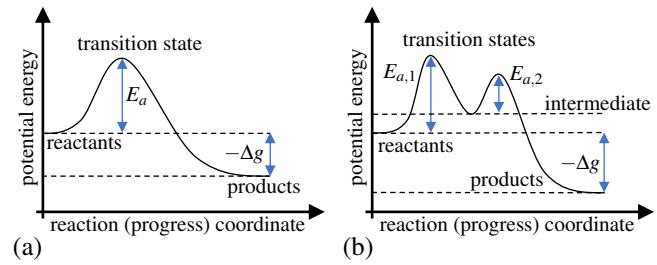


FIG. 1: Exemplary reaction coordinate diagrams for (a) elementary reactions and (b) a non-elementary reaction with a single intermediate. E_a denotes the activation energy of the reaction, while $-\Delta g$ is amount of energy released by the reaction.

rate constants $\kappa_m^+ > 0$, $\kappa_m^- \geq 0$, such that

$$k_m^+ = \kappa_m^+ \frac{V \prod_{n=1}^{N} a_n^{(m)}!}{\prod_{n=1}^{N} V^{a_n^{(m)}}}, \qquad k_m^- = \kappa_m^- \frac{V \prod_{n=1}^{N} b_n^{(m)}!}{\prod_{n=1}^{N} V^{b_n^{(m)}}},$$

due to consistency of physical units in both the deterministic ODE model (of the concentrations) and the probability evolution equation of the stochastic model[34]. κ_m^+ and κ_m^- can be identified with the rate constants of the deterministic law of mass action by taking the macroscopic limit. A reaction is called microscopically reversible if $k_m^- > 0$. A CRN is called microscopically reversible if all reactions are microscopically reversible. In the following, a CRN is assumed to be microscopically reversible unless otherwise noted.

For each reactions of channel $\mathscr{R}_m$ we denote the counting processes of reactions in the forward and reverse direction as $\{R_m^+(t) \in \mathbb{Z}_{\geq 0}\}_{t\geq 0}$ with $R_m^+(0) = 0$ and $\{R_m^-(t) \in \mathbb{Z}_{\geq 0}\}_{t\geq 0}$ with $R_m^-(0) = 0$, respectively. These can be represented via random time changes

$$R_m^\rho(t) = N_m^\rho \left(\int_0^t \lambda_m^\rho(Z(s))\, \mathrm{d}s \right)$$

of $2M$ independent unit-rate Poisson processes $\{N_m^\rho(t) \in \mathbb{Z}_{\geq 0}\}_{t\geq 0}$ with $N_m^\rho(0) = 0$ for $m \in \{1, \ldots, M\}$ and $\rho \in \{+, -\}$[10]. Then the random state $Z(t)$ of the CRN with random initial value $Z(0)$ obeys

$$Z(t) = Z(0) + \sum_{m=1}^{M} \nu_m (R_m^+(t) - R_m^-(t)).$$

The probability mass function $p(z,t) = \mathbb{P}(Z(t) = z)$ follows the chemical master equation[30,31,35]

$$\begin{aligned} \partial_t p(z,t) = \sum_{m=1}^{M} & \lambda_m^+(z - \nu_m) p(z - \nu_m, t) \\ & + \lambda_m^-(z + \nu_m) p(z + \nu_m, t) \\ & - (\lambda_m^+(z) + \lambda_m^-(z)) p(z,t) \end{aligned} \tag{2}$$

Before proceeding, we recapitulate the model assumptions made so far, as they are fundamental for stochastic thermodynamics of CRNs. Assuming a Markov process description

means that the future dynamics of the mesoscopic system is sufficiently described by the current state and does not depend on the past. In particular, the future dynamics do also not depend on the particular microstate, the system is in, but just on the current mesostate z.

The above assumptions about the species Z have implications for the environment in which the reaction network is embedded. Since the propensity functions are independent of time and space, the embedding environment must be seen as thermally equilibrated and spatially homogeneous from the perspective of the chemical species[36]. That is, the surrounding of each molecule of Z homogenizes spatially on a much faster time scale than the reactions occur. In addition, the temperature, pressure, and volume of the solvent are constant over time and space. Similarly, the molecular composition of the solvent, which can affect the rate constants (e.g., its acidity), remains constant over time.

According to Gillespie, in the light of collision theory the elementary reaction assumption is plausible up to bimolecular reactions and the dynamics is rigorously shown to follow stochastic mass action kinetics under the above assumptions on the environment[36]. In other cases, in particular when the chemical species represent different conformations of polymers as is common in gene expression models, a more careful justification of the elementary reaction assumption and the Markov assumption may be required. The relevance of the elementary reaction assumption for stochastic thermodynamics of CRNs is discussed at the end of Sec. IV A.

III. INFORMATION EXCHANGE BETWEEN SUBNETWORKS

The MI between two $\mathscr{F}$-adapted stochastic processes on a finite interval $[0,t)$, $t>0$ is defined via the Radon-Nikodym derivative between the joint probability measure $\mathbb{P}^{XY}_{[0,t)}$ of input and output trajectories $(X_{[0,t)},Y_{[0,t)}) = \{X(s),Y(s)\}_{s\in[0,t)}$ and the product of the respective marginal measures $\mathbb{P}^{X}_{[0,t)}$, $\mathbb{P}^{Y}_{[0,t)}$ of $X_{[0,t]} = \{X(s)\}_{s\in[0,t]}$, $Y_{[0,t]} = \{Y(s)\}_{s\in[0,t]}$:

$$\mathbb{I}(X_{[0,t)};Y_{[0,t)}) := \mathbb{E}\left[\ln \frac{\mathrm{d}\mathbb{P}^{XY}_{[0,t)}}{\mathrm{d}(\mathbb{P}^{X}_{[0,t)}\otimes\mathbb{P}^{Y}_{[0,t)})}\right]$$

The mutual information rate (MIR) is defined as its asymptotic slope

$$\bar{\mathbb{I}}(X;Y) := \lim_{t\to\infty}\frac{1}{t}\mathbb{I}(X_{[0,t)};Y_{[0,t)}),$$

with $(X,Y) = \{X(t),Y(t)\}_{t\geq 0}$. In turn, the DI is defined as[9]

$$\mathbb{I}(X_{[0,t)}\to Y_{[0,t)}) := \inf_{\boldsymbol{t}\in\mathscr{T}([0,t))}\sum_{i=1}^{n(\boldsymbol{t})}\mathbb{I}(Y_{[t_{i-1},t_i)};X_{[0,t_i)}\mid Y_{[0,t_{i-1})}), \tag{3}$$

where $\mathscr{T}([0,t)) = \{\boldsymbol{t} = (t_i)_{i\in\{1,\dots,n\}} : 0<t_1<\cdots<t_n<t, n\in\mathbb{N}\}$ is the set of all finite sequences partitioning the interval $[0,t)$ and $n(\boldsymbol{t})$ denotes the length of the sequence $\boldsymbol{t}$. Consequently, the directed information rate (DIR) is

$$\mathbb{I}(X_{[0,t)}\to Y_{[0,t)}) := \lim_{t\to\infty}\frac{1}{t}\mathbb{I}(X_{[0,t)}\to Y_{[0,t)}).$$

It has been shown that[9]

$$\mathbb{I}(X_{[0,t)}\to Y_{[0,t)}) = \int_0^t \lim_{h\searrow 0}\frac{1}{h}\mathbb{I}(Y_{[s,s+h)};X_{[0,s+h)}\mid Y_{[0,s)})\,\mathrm{d}s, \tag{4}$$

which is easier to evaluate than the original definition in Equation (3). Mutual and directed information are related by the information conservation law[9]

$$\mathbb{I}(X_{[0,t)}\to Y_{[0,t)}) + \mathbb{I}(Y_{[0,t)}\to X_{[0,t)}) = \mathbb{I}(X_{[0,t)};Y_{[0,t)}).$$

The structural symmetry of this conservation law suggests that $\mathbb{I}(X_{[0,t)}\to Y_{[0,t)})$ and $\mathbb{I}(Y_{[0,t)}\to X_{[0,t)})$ are given by structurally equivalent expressions, although generally $\mathbb{I}(X_{[0,t)}\to Y_{[0,t)}) \neq \mathbb{I}(Y_{[0,t)}\to X_{[0,t)})$.

Let $\mathscr{F}^{XY} = \{\mathscr{F}^{XY}_t\}_{t\geq 0}$ and $\mathscr{F}^{Y} = \{\mathscr{F}^{Y}_t\}_{t\geq 0}$ be the internal filtrations of (X,Y), respectively, Y, where $\mathscr{F}^{XY}_t = \sigma((X(s),Y(s)),0\leq s\leq t)$ and $\mathscr{F}^{Y}_t = \sigma(Y(s),0\leq s\leq t)$. $\mathscr{F}^{X}$ be analogous. The evaluation of the MI between jump-like processes has long been linked to a filtering problem[32,37,38]. In the following, we adapt the expression for the MI between priecewise-constant jump processes on continuous state spaces by Boel *et al.* to suit our specific needs. We then argue, first by the structural symmetry and then by Equation (4) how the MI is decomposed into the two directed information expressions.

A. Trajectory Information between Subnetworks

To simplify notation, we redefine the set of bidirectional reactions $\{1,\dots,M\}\cup\{-m\colon k^-_m>0\}$, which has cardinality M', as unidirectional reaction channels $\mathscr{R}'_1,\dots,\mathscr{R}'_{M'}$ with stoichiometric balanced equations

$$\mathscr{R}'_{m'}:\quad \sum_{n=1}^{N}\tilde{a}^{(m')}_n \mathsf{Z}_n \quad\xrightarrow{\lambda'_{m'}}\quad \sum_{n=1}^{N}\tilde{b}^{(m')}_n \mathsf{Z}_n$$

and change vectors $\nu'_{m'} = \tilde{b}^{(m')} - \tilde{a}^{(m')}$. For clarity, we will omit the prime notation in the remainder of this section.

Let $\mathscr{S}^X,\mathscr{S}^Y\subset\{1,\dots,N\}$ be arbitrary sets in the index set of chemical species of the core system. They represent the subsets of species between which we want to characterize information exchange. Hence, we have $X = \{Z_n(s)\colon n\in\mathscr{S}^X\}_{s\geq 0}$ and $Y = \{Z_n(s)\colon n\in\mathscr{S}^Y\}_{s\geq 0}$. Let

$$\mathscr{V} := \{\nu_m\in\mathbb{Z}^N\colon 1\leq m\leq M\}\setminus\{0\}$$

be the set of non-zero change vectors and

$$\pi_X:\mathscr{V}\to\mathbb{Z}^{|\mathscr{S}^X|},\ \nu\mapsto\nu_X = (\tilde{b}^{(m)}_n - \tilde{a}^{(m)}_n\colon n\in\mathscr{S}_X)$$
$$\mathscr{V}_X := \{\pi_X(\nu)\mid\nu\in\mathscr{V}\}\setminus\{0\}$$

be the reduction to the coordinates of the subnetwork of X and the corresponding set of non-zero change vectors. For Y we analogously define π_Y and $\mathscr{V}_Y$.

Definition 1. *The reactions $\mathscr{R}_m$ and $\mathscr{R}_{\tilde{m}}$ are called X-indistinguishable if*

$$\pi_X(\nu_m) = \pi_X(\nu_{\tilde{m}})$$

and analogously for Y.

As an example, consider the set of species X, Y, A and the X-indistinguishable reactions $\emptyset \to \mathsf{X}$, $\mathsf{X} \to 2\mathsf{X}$, $\mathsf{Y}+\mathsf{A} \to \mathsf{Y}+\mathsf{X}$, which all increase the amount of X by one. Definition 1 allow us to account for the indistinguishability of changes in the marginal subnetwork compared to the entire network. This is important for the definition of the reaction counting processes associated with the joint and marginal probability measure $\mathbb{P}^{XY}_{[0,t)}$, $\mathbb{P}^{X}_{[0,t)}$ and $\mathbb{P}^{Y}_{[0,t)}$.

Let $V\colon \{1,\dots,M\} \to \mathscr{V} \cup \{0\}$, $m \mapsto \nu_m$ bet the mapping from reaction index to change vector. We now distinguish between reaction counters of changes in X or Y. Set

$$\begin{aligned} R^X_t(\nu_X) &:= \sum_{\nu \in \pi_X^{-1}(\nu_X)} R_{V^{-1}(\nu)}(t), \\ R^Y_t(\nu_Y) &:= \sum_{\nu \in \pi_Y^{-1}(\nu_Y)} R_{V^{-1}(\nu)}(t) \end{aligned}$$

for all $\nu_X \in \mathscr{V}_X$ and $\nu_Y \in \mathscr{V}_Y$. In this notation the time dependence is shifted to the lower index and the functional arguments are the respective marginal change vectors. The corresponding propensity functions of subsystem changes are

$$\begin{aligned} \lambda^X(\nu_X, z) &:= \sum_{\nu \in \pi_X^{-1}(\nu_X)} \lambda_{V^{-1}(\nu)}(z), \\ \lambda^Y(\nu_Y, z) &:= \sum_{\nu \in \pi_Y^{-1}(\nu_Y)} \lambda_{V^{-1}(\nu)}(z) \end{aligned}$$

With this notation, we obtain the process equations

$$\begin{aligned} X(t) =& X(0) + \sum_{\nu_X \in \mathscr{V}_X} \nu_X \, R^X_t(\nu_X), \\ Y(t) =& Y(0) + \sum_{\nu_Y \in \mathscr{V}_Y} \nu_Y \, R^Y_t(\nu_Y). \end{aligned}$$

To compute the MI, we must represent the evolution of X and Y relative to the histories of the marginalized and joint subsystems, specifically $\mathscr{F}^X_t$, $\mathscr{F}^Y_t$, and $\mathscr{F}^{XY}_t$, rather than relying on a representation that depends on the current state of Z. This is done by changing the propensity functions of the reaction counters $R^X_t(\nu_X)$, $R^Y_t(\nu_Y)$ to stochastic processes, that depend on the history of the respective marginal system. Abusing notation, we say that $R^X_t(\nu_X)$ has the $\mathscr{F}^{XY}$-intensity process[39] $\lambda^X(\nu_X)$ and the $\mathscr{F}^X$-intensity $\hat{\lambda}^X(\nu_X)$ with

$$\begin{aligned} \lambda^X_t(\nu_X) =& \mathbb{E}\left[\lambda^X(\nu_X, Z(t-)) \mid \mathscr{F}^{XY}_t\right] \\ \hat{\lambda}^X_t(\nu_X) =& \mathbb{E}\left[\lambda^X(\nu_X, Z(t-)) \mid \mathscr{F}^{X}_t\right]. \end{aligned}$$

Analogously, $R^Y_t(\nu_Y)$ has the $\mathscr{F}^{XY}$-intensity $\lambda^Y(\nu_Y)$ and the $\mathscr{F}^X$-intensity $\hat{\lambda}^Y(\nu_Y)$ with

$$\begin{aligned} \lambda^Y_t(\nu_Y) =& \mathbb{E}\left[\lambda^Y(\nu_Y, Z(t-) \mid \mathscr{F}^{XY}_t\right] \\ \hat{\lambda}^Y_t(\nu_Y) =& \mathbb{E}\left[\lambda^Y(\nu_Y, Z(t-) \mid \mathscr{F}^{Y}_t\right]. \end{aligned}$$

Applying Theorem 4.2 in[32] we express the mutual information with initial condition $(X(0), Y(0)) = (x_0, y_0)$ as

$$\begin{aligned} &\mathbb{I}(X_{[0,t)}; Y_{[0,t)}) \\ &= \sum_{\nu_X \in \mathscr{V}_X} \int_0^t \mathbb{E}\left[\phi(\lambda^X_s(\nu_X)) - \phi(\hat{\lambda}^X_s(\nu_X))\right] \mathrm{d}s \\ &\quad + \sum_{\nu_Y \in \mathscr{V}_Y} \int_0^t \mathbb{E}\left[\phi(\lambda^Y_s(\nu_Y)) - \phi(\hat{\lambda}^Y_s(\nu_Y))\right] \mathrm{d}s, \end{aligned}$$

where $\phi(a) := \ln(a)\, \mathbb{1}_{(0,\infty)}(a)$ with $a \geq 0$ and $\mathbb{1}$ denoting the indicator function of the measurable set in its lower index. As mentioned above, the MI naturally decomposes into structurally equivalent parts, which we identify as the directed informations

$$\begin{aligned} \mathbb{I}(X_{[0,t)} \to Y_{[0,t)}) &= \sum_{\nu_Y \in \mathscr{V}_Y} \int_0^t \mathbb{E}\left[\phi(\lambda^Y_s(\nu_Y)) - \phi(\hat{\lambda}^Y_s(\nu_Y))\right] \mathrm{d}s, \\ \mathbb{I}(Y_{[0,t)} \to X_{[0,t)}) &= \sum_{\nu_X \in \mathscr{V}_X} \int_0^t \mathbb{E}\left[\phi(\lambda^X_s(\nu_X)) - \phi(\hat{\lambda}^X_s(\nu_X))\right] \mathrm{d}s. \end{aligned} \tag{5}$$

A formal proof of this identification is given in Appendix A.

Our expressions particularly allow for the cases, where $\mathscr{S}^X \cap \mathscr{S}^Y \neq \emptyset$. Consider, for instance, the case, where $\mathscr{S}^X = \mathscr{S}^Y$. Then, $\mathscr{F}^{XY} = \mathscr{F}^X = \mathscr{F}^Y$ and consequently, $\mathbb{I}(X_{[0,t)}; Y_{[0,t)}) = 0$ as the intensities satisfy $\lambda^X_s(\nu_X) = \hat{\lambda}^X_s(\nu_X)$ and $\lambda^Y_s(\nu_Y) = \hat{\lambda}^Y_s(\nu_Y)$ for all $\nu_X \in \mathscr{V}_X$, $\nu_Y \in \mathscr{V}_Y$ and all $s \geq 0$.

Moreover, our expression accommodates simultaneous changes in X and Y, a scenario previously discussed as complex[21,22]. The challenge arises from the existence of different probability density representations for the joint process (X,Y). For $\mathscr{S}_X \cap \mathscr{S}_Y = \emptyset$ one might intuitively describe the joint process by projecting the change vectors to the coordinates of the joint subsystem, similar to the reduction described in Definition 1. This yields the following stochastic equation for the joint subsystems

$$\begin{pmatrix} X(t) \\ Y(t) \end{pmatrix} = \begin{pmatrix} X(0) \\ Y(0) \end{pmatrix} + \sum_{\nu_{XY} \in \mathscr{V}_{XY}} \nu_{XY} \, R^{XY}_t(\nu_{XY})$$

However, the path probability density in this description may differ in the number of reaction counters and thereby in the dimension of trajectory space representation, compared to the product probability density. In the product measure, simultaneous changes in X and Y, for instance, those arising from a conversion $X \to Y$ are treated as individual changes in both X and Y. In contrast, the above representation of the joint system accounts for such a change only once, and not twice. The path probability densities of the joint and the product measure do not match in terms of the dimension of the path-space representations. To address this dimensionality mismatch in our derivation of the MI and DI expressions, we resolve the issue by splitting the single counting process for simultaneous changes into two separate counting processes, one for X and one for Y.

Interestingly, when reducing to marginal change vectors on the subsystems, reactions that simultaneously affect both X

and Y can merge with those that affect only X or Y individually. For example, consider the species X, Y, A with the reactions $\emptyset \to \mathsf{X}$, $\mathsf{Y} \to \mathsf{X}$, $\mathsf{A}+\mathsf{X} \to 2\mathsf{X}$, $\mathsf{Y} \to \emptyset$, $\emptyset \to \mathsf{Y}$. We identify the process X with the dynamics of the X copy number, and analogously for Y. The reactions in the set $\{\emptyset \to \mathsf{X}, \mathsf{Y} \to \mathsf{X}, \mathsf{A}+\mathsf{X} \to 2\mathsf{X}\}$ are X-indistinguishable with $\nu_X = 1$ and those in $\{\mathsf{Y} \to \mathsf{X}, \mathsf{Y} \to \emptyset\}$ are Y-indistinguishable with $\nu_Y = -1$. Consequently, $R^X(1)$ and $R^Y(-1)$ exhibit both simultaneous and individual jumps.

IV. STOCHASTIC THERMODYNAMICS

A. Closed Stochastic Chemical Reaction Networks

A chemical reaction network is considered closed if it does not exchange molecules with the external environment and if it does not change the number of molecules of any of the chemical species that make up the solvent. A closed thermodynamic system may exchange heat with its environment. We interpret the solvent as a heat bath which maintains a constant temperature T.

The zeroth law of thermodynamics for chemical reaction networks dictates that a closed, microscopically reversible CRN that accounts for all solute species will always relax to equilibrium[31]. Equilibrium statistical mechanics further requires that the equilibrium distribution of a closed chemical reaction network is (i) a Gibbs-Boltzmann distribution $\pi(z) = \lim_{t\to\infty} \mathbb{P}(Z(t) = z) \propto e^{-\beta g(z)}$, where $g(z)$ is the Gibbs free energy of the state z and $\beta = (k_\mathrm{B}T)^{-1}$, and (ii) it satisfies detailed balance

$$\lambda_m^+(z)\,\pi(z) = \lambda_m^-(z+\nu_m)\,\pi(z+\nu_m) \tag{6}$$

for all admissible states z and all microscopically reversible reactions $\mathscr{R}_m$[31]. Plugging the Boltzmannn distribution into (6) yields the local detailed balance condition, or thermodynamic consistency relation, for closed CRNs[31]:

$$\ln\left(\frac{\lambda_m^+(z)}{\lambda_m^-(z+\nu_m)}\right) = -\beta\left(g(z+\nu_m) - g(z)\right) \tag{7}$$

for all admissible states z and all microscopically reversible reactions $\mathscr{R}_m$. Equation (7) relates kinetic and energetic constants, and therefore it is also satisfied during the transient nonequilibrium and independent of the initial conditions.

However, the consistency relation can be broken if reactions are not elementary. The equilibrium Gibbs free energy $g(z)$ of a state z can also be derived using equilibrium statistical mechanics of ideal dilute solutions[31]. It is crucial to ensure that all solute species are accounted for in such derivations. The fundamental assumption in equilibrium statistical mechanics and stochastic thermodynamics of discrete-state CRNs is that the Gibbs energy of the system Z is sufficiently described by the mesoscopic state z. This implies that fluctuations in the microscopic states constituting the mesoscopic state z have a negligible impact on the Gibbs free energy of the system. Significant changes in the system's energy occur only instantaneously due to reactions. Any reaction coordinate of a potentially non-elementary reaction that does not decay instantaneously must be accounted for as a species of the CRN. Perturbations of the well-mixed system due to reactions are disregarded by assuming instantaneous diffusion in a finite volume. Consequently, the model assumptions of stochastic thermodynamics align with the kinetic discrete-state Markov process model.

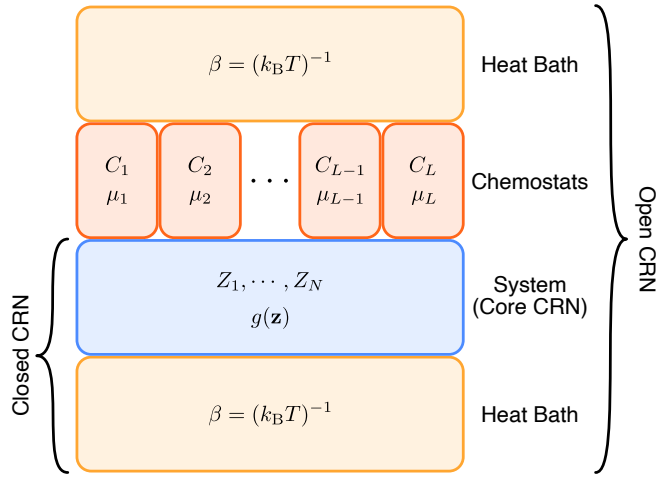


FIG. 2: Visualization of an open CRN, where the core system Z is coupled to a number of chemostat species C. Each horizontal layer can exchange energy with its vertically adjacent layers.

B. Open Chemical Reaction Networks – Coupling to Chemostats

An open CRN allows the exchange of molecules with external reservoirs. In the following, we assume that the core system Z is coupled to L chemostats $\mathsf{C}_1, \ldots, \mathsf{C}_L$ via the solvent, as illustrated in Figure 2. We assume that the copy number of chemostat molecules in the solvent is sufficiently high to be represented by their real-valued concentrations $c = (c_1, \ldots, c_L)$, which are held constant over time by an external agent. In our case, this external agent is a biological cell that strives to maintain homeostasis. Others have discussed chemostats that vary in time according to a predetermined deterministic protocol[30,31,40]. The coupled system follows the stoichiometric balance equations

$$\mathscr{R}_m: \quad \sum_{l=1}^{L} r_l^{(m)}\mathsf{C}_l + \sum_{n=1}^{N} a_n^{(m)}\mathsf{Z}_n \quad \underset{\lambda_m^-}{\overset{\lambda_m^+}{\rightleftharpoons}} \quad \sum_{l=1}^{L} s_l^{(m)}\mathsf{C}_l + \sum_{n=1}^{N} b_n^{(m)}\mathsf{Z}_n,$$

where $\gamma_m = s^{(m)} - r^{(m)}$ is the stoichiometric change vector of the chemostat species associated with $\mathscr{R}_m$. Immediately after each reaction, the chemostat is assumed to correct the copy number of all chemostat species. Consequently, the propensity functions of the coupled reactions maintain the form (1) with the adjustment that the stochastic rate constants now depend on the chemostat concentrations insofar as they incorpo-

rate a deterministic law of mass action

$$k_m^+(c) = \kappa_m^+ \frac{V \prod_{n=1}^N a_n^{(m)}!}{\prod_{n=1}^N V^{a_n^{(m)}}} \prod_{l=1}^L c_l^{r_l^{(m)}},$$
$$k_m^-(c) = \kappa_m^- \frac{V \prod_{n=1}^N b_n^{(m)}!}{\prod_{n=1}^N V^{b_n^{(m)}}} \prod_{l=1}^L c_l^{s_l^{(m)}},$$

where the units of the deterministic rate constants κ_m^+, κ_m^- are adapted accordingly. Therefore, the probability evolution is still described by (2). For a time-varying protocol, the propensity functions become explicitly time-dependent through the concentration values, resulting in a time-inhomogeneous Markov jump process. The generalization to stochastic protocols by describing the chemostats via a continuous-state stochastic process is straightforward. However, the feedback from the core system must be negligible to maintain the validity of the chemostat assumption.

To describe the energetics of each reaction $\mathscr{R}_m$ we denote by μ_l the chemical potential of C_l, i.e., the energy associated with a single molecule of species C_l. Reaction $\mathscr{R}_m$, starting from state z, is associated with a change in the Gibbs free energy of the state

$$\Delta g^{(m)}(z) = g(z+\nu_m) - g(z) = -\Delta g^{(-m)}(z+\nu_m)$$

and the chemical work $W_{\text{chem}}^{(m)}$ done on the system by the chemostat

$$W_{\text{chem}}^{(\pm m)} = \mp \sum_l (s_l^{(m)} - r_l^{(m)})\mu_l,$$

where $(-m)$ denotes the reverse reaction. Hence the energy dissipated into the environment per reaction is

$$\Delta Q^{(\pm m)}(z) = W_{\text{chem}}^{(\pm m)} - \Delta g^{(\pm m)}(z) \tag{8}$$

with $\Delta Q^{(-m)}(z+\nu_m) = -\Delta Q^{(m)}(z)$. Intuitively, the dissipated energy is the chemical work done on the system but not stored in the system's state. Let $0 < \tau_1^{(\pm m)} < \tau_2^{(\pm m)} < \cdots \leq t$ be the random times, when reaction $\mathscr{R}_m$ happens in forward or backward direction. Then the energy dissipated by the random trajectory $Z_{[0,t]} := \{Z(s) : 0 \leq s \leq t\}$ of the open CRN within the time interval $(0,t]$ is

$$q(t) = \sum_{m=1}^M \left\{ \left(\sum_{k:0<\tau_k^{(m)} \leq t} \Delta Q^{(m)}(Z(\tau_k^{(m)}-)) \right) + \left(\sum_{k:0<\tau_k^{(-m)} \leq t} \Delta Q^{(-m)}(Z(\tau_k^{(-m)}-)) \right) \right\} \tag{9}$$

where $Z(t-) = \lim_{s\uparrow t} Z(s)$ denotes the left limit in time, such that $Z(\tau_k^{(m)}-)$ is the state of the CRN just before the k-th occurrence of reaction $\mathscr{R}_m$ in forward direction[30]. We rewrite (9) via stochastic integrals of the reaction counting processes

$$q(t) = \sum_{m=1}^M \left\{ \int_0^t \Delta Q^{(m)}(Z(s-))\, \mathrm{d}R_m^+(s) + \int_0^t \Delta Q^{(-m)}(Z(s-))\, \mathrm{d}R_m^-(s) \right\}.$$

Thus the mean energy dissipation rate $\dot{Q}(t) = \frac{\mathrm{d}}{\mathrm{d}t}\mathbb{E}[q(t)]$ of the open CRN is

$$\dot{Q}(t) = \sum_z \sum_{m=1}^M \Delta Q^{(m)}(z)\, (\lambda_m^+(z)p(z,t) - \lambda_m^-(z+\nu_m)p(z+\nu_m,t)), \tag{10}$$

as we show in the following proof.

Proof of (10). By the use of the Poisson process definition in[39] (Page 27) the expectations of the stochastic integrals can be rewritten as expectations of Lebesgue/Riemann integrals

$$\begin{aligned}\mathbb{E}[q(t)] &= \sum_{m=1}^M \mathbb{E}\left[\int_0^t \Delta Q^{(m)}(Z(s-))\, \mathrm{d}R_m^+(s) + \int_0^t \Delta Q^{(-m)}(Z(s-))\, \mathrm{d}R_m^-(s) \right] \\ &= \sum_{m=1}^M \mathbb{E}\left[\int_0^t \Delta Q^{(m)}(Z(s))\lambda_m^+(Z(s))\, \mathrm{d}s + \int_0^t \Delta Q^{(-m)}(Z(s))\lambda_m^-(Z(s))\, \mathrm{d}s \right],\end{aligned}$$

where the expectation of q is taken over the distribution of all trajectories $Z_{[0,t]}$. By exchanging the expectation with the integral via Fubini's theorem and taking the derivative we obtain

$$\dot{Q}(t) = \sum_{m=1}^M \{\mathbb{E}[\Delta Q^{(m)}(Z(t))\lambda_m^+(Z(t))] + \mathbb{E}[\Delta Q^{(-m)}(Z(t))\lambda_m^-(Z(t))]\}.$$

Evaluating the expectations yields

$$\dot{Q}(t) = \sum_z \sum_{m=1}^M (\Delta Q^{(m)}(z)\lambda_m^+(z) + \Delta Q^{(-m)}(z)\lambda_m^-(z))p(z,t).$$

Equation (10) then follows by shifting the order of summation of the last term and using the property of Equation (8). □

Defining the forward, the backward, and the net probability fluxes $J_m^+(z,t) = \mathbb{P}(Z(t)=z)\,\lambda_m^+(z)$, $J_m^-(z,t) = \mathbb{P}(Z(t)=z+\nu_m)\,\lambda_m^-(z+\nu_m)$, and $J_m(z,t) = J_m^+(z,t) - J_m^-(z,t)$, respectively, of reaction $\mathscr{R}_m$, we can rewrite (10) as

$$\dot{Q}(t) = \sum_z \sum_{m=1}^M \Delta Q^{(m)}(z)\, J_m(z,t).$$

In a similar fashion we represent the chemical work done on the trajectory $Z_{[0,t]}$ by

$$w(t) = \sum_{m=1}^M W_{\text{chem}}^{(m)}(R_m^+(t) - R_m^-(t)),$$

which gives rise to the mean rate of chemical work

$$\dot{W}(t) = \frac{\mathrm{d}}{\mathrm{d}t}\mathbb{E}[w(t)] = \sum_z \sum_{m=1}^{M} W_{\mathrm{chem}}^{(m)} J_m(z,t),$$

by following the steps in the proof of (10). $\dot{W}(t)$ can also be understood as the amount of energy required to maintain the chemostat concentrations, i.e., the energy expenditure of the external agent.

In open CRNs the thermodynamic consistency relation

$$\ln\left(\frac{\lambda_m^+(z)}{\lambda_m^-(z+\nu_m)}\right) = \beta \Delta Q^{(m)}(z) \tag{11}$$

for all admissible states z and all reversible reactions $\mathscr{R}_m$ generalizes the local detailed balance (7)[31]. To show consistency in the deterministic limit, we use the macroscopic limit of the Gibbs free energy of the state and the propensity functions for a large volume V

$$\begin{aligned}
g(V\tilde{z}) \approx & V \sum_{n=1}^{N} \int_0^{\tilde{z}_n} (g_n^\circ + \beta^{-1}\ln(y_n))\,\mathrm{d}y_n \\
\Delta g^{(m)}(V\tilde{z}) \approx & \nu_m (V^{-1}\nabla_{\tilde{z}}) g(V\tilde{z}) \\
= & \sum_{n=1}^{N} (b_n^{(m)} - a_n^{(m)})(g_n^\circ + \beta^{-1}\ln(\tilde{z}_n)) \\
\lambda_m^+(V\tilde{z}) \approx & \kappa_m^+ V \left(\prod_{l=1}^{L} c_l^{r_l^{(m)}}\right)\left(\prod_{n=1}^{N} \tilde{z}_n^{a_n^{(m)}}\right), \\
\lambda_m^-(V\tilde{z}) \approx & \kappa_m^- V \left(\prod_{l=1}^{L} c_l^{s_l^{(m)}}\right)\left(\prod_{n=1}^{N} \tilde{z}_n^{b_n^{(m)}}\right),
\end{aligned}$$

where g_n° is the standard Gibbs free energy of species n, $\tilde{z} = V^{-1}z$, $\nabla_{\tilde{z}}$ denotes the gradient operator w.r.t. the components of $\tilde{z}$, and we assumed independence of the chemical potentials of distinct species, i.e., an ideal dilute solution. Further we identify $\mu_l = \mu_l^\circ + \beta^{-1}\ln(c_l)$, with standard potential energy μ_l°, and observe that $-W_{\mathrm{chem}}^{(\pm m)}$ precisely represents the change in Gibbs free energy of the chemostat species in the macroscopic limit. Thus, if the species $\mathsf{C}_1,\ldots,\mathsf{C}_L$ and the core system were to form a closed system, the macroscopic limit of $-\Delta Q^{(m)}(z)$ would exactly correspond to the change in macroscopic Gibbs free energy of the total system upon the occurrence of reaction $\mathscr{R}_m$ in forward direction. So in the macroscopic limit the thermodynamic consistency relation for open CRNs (11), i.e.,

$$\ln\left(\frac{\lambda_m^+(V\tilde{z})}{\lambda_m^-(V\tilde{z})}\right) = \beta\left(\sum_l (s_l^{(m)} - r_l^{(m)})\mu_l - \Delta g^{(m)}(V\tilde{z})\right), \tag{12}$$

is consistent with (7). Substituting the definitions of $\Delta g^{(m)}(V\tilde{z})$ and μ_l in Equation (12) yields the well known relation for the macroscopic rate constants[?]

$$\begin{aligned}
\ln(K_{\mathrm{eq}}^{(m)}) = & \ln\left(\frac{\kappa_m^+}{\kappa_m^-}\right) \\
= & -\sum_{l=1}^{L} (s_l^{(m)} - r_l^{(m)})\beta\mu_l^\circ \\
& - \sum_{n=1}^{N} (b_n^{(m)} - a_n^{(m)})\beta g_n^\circ,
\end{aligned} \tag{13}$$

where $K_{\mathrm{eq}}^{(m)}$ is the equilibrium constant of reaction $\mathscr{R}_m$. Consistency in the mesoscopic limit can be established by dropping the chemostat assumptions on the chemostat species and noting that the sum of the potential of the chemostat species and g represents the mesoscopic Gibbs free energy of the total system. This total Gibbs free energy and the respective mesoscopic rates then satisfy Eq. (7).

C. Relation of Entropy Production Rate and Energy Dissipation

Plugging (11) into (10) reexpresses the mean energy dissipation rate (in units of $k_{\mathrm{B}}T$)

$$\beta\dot{Q}(t) = \sum_z \sum_{m=1}^{M} \ln\left(\frac{\lambda_m^+(z)}{\lambda_m^-(z+\nu_m)}\right) J_m(z,t) \tag{14}$$

based only on the kinetic parameters of the open CRN. Now (14) is further identified as the (Shannon) entropy flow into the environment[30,31] $\frac{\mathrm{d}}{\mathrm{d}t}H^{\mathrm{env}}(t) = \beta\dot{Q}(t)$. The mean entropy production $H^{\mathrm{tot}}(t)$ of the whole system, consisting of the core system and its environment, during the interval $[0,t]$ is given as

$$H^{\mathrm{tot}}(t) := \int_0^t \left(\frac{\mathrm{d}}{\mathrm{d}s}H[Z(s)] + \frac{\mathrm{d}}{\mathrm{d}s}H^{\mathrm{env}}(s)\right)\mathrm{d}s, \tag{15}$$

where $H[Z(t)] = -\sum_z p(z,t)\ln(p(z,t))$ is the (Shannon) entropy of the core system at time $t \geq 0$. Using the CME (2) we express the derivative of the entropy of the core system as

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}H[Z(t)] = & -\sum_z (\ln(p(z,t)) + 1)\,\partial_t p(z,t) \\
= & \sum_z \sum_{m=1}^{M} \ln\left(\frac{p(z,t)}{p(z+\nu_m,t)}\right) J_m(z,t).
\end{aligned}$$

Thus the entropy production rate is given by

$$\frac{\mathrm{d}}{\mathrm{d}t}H^{\mathrm{tot}}(t) = \sum_z \sum_{m=1}^{M} \ln\left(\frac{J_m^+(z,t)}{J_m^-(z,t)}\right) J_m(z,t). \tag{16}$$

At stationarity, we have $\lim_{t\to\infty} H[Z(t)] = -\sum_z \pi(z)\ln(\pi(z))$, implying $\lim_{t\to\infty}\frac{\mathrm{d}}{\mathrm{d}t}H[Z(t)] = 0$. Consequently,

$$e_p := \lim_{t\to\infty}\frac{\mathrm{d}}{\mathrm{d}t}H^{\mathrm{tot}}(t) = \lim_{t\to\infty}\frac{\mathrm{d}}{\mathrm{d}t}H^{\mathrm{env}}(t) = \lim_{t\to\infty}\beta\dot{Q}(t),$$

i.e., the entropy production rate in the NESS quantifies the mean energy dissipation rate of the core chemical reaction network into the environment.

Thus far, we have provided the mean energy dissipation rate for an unspecified coupling to chemostat species and unspecified chemostat concentrations, based solely on the knowledge of the stochastic rate constants and the change vectors ν_m of the core system. Since the deterministic rate constants are constrained by the change vectors γ_m and the concentrations c of the chemostat species, as described by Equation (13), the stochastic rate constants must also satisfy the relation

$$\frac{k_m^+}{k_m^-} = K_{\mathrm{eq}}^{(m)} \left(\prod_{n=1}^{N} V^{b_n^{(m)} - a_n^{(m)}} \right) \left(\prod_{l=1}^{L} c^{r_l^{(m)} - s_l^{(m)}} \right).$$

D. Entropy Production Rate of a Finite Conversion Networks

Much of the literature on the entropy production rate uses a description based on the infinitesimal generator matrix $\mathbf{\Lambda}$ of a CTMC instead of a reaction network description[29,30,35]. A connection between the two pictures is established by using a one-hot coding of the reaction network, which then describes a set of microscopically reversible conversion reactions.

Let Z be N-dimensional with a finite state space $\mathscr{Z} = \{e_1, \dots, e_N\} \subset \{0,1\}^N$, where e_i is the unit vector with a one at position i, and the generator matrix $\Lambda \in \mathbb{R}_{\geq 0}^{N \times N}$. Further, the set of reactions be $\mathscr{R} := \{(i,j) \in \{1,\dots,N\}^2 \colon j > i, \Lambda_{ij} > 0\}$ with associated stoichiometric change vectors $\nu_{(i,j)} = e_j - e_i$. For $i < j$ we define the reversible conversion reaction

$$\begin{aligned} &\mathscr{R}_{(i,j)} : \quad Z_i \underset{\lambda^-_{(i,j)}}{\overset{\lambda^+_{(i,j)}}{\rightleftharpoons}} Z_j \quad \text{with} \\ &\lambda^+_{(i,j)}(z) = \Lambda_{ij} \mathbf{1}(z = e_i), \\ &\lambda^-_{(i,j)}(z) = \Lambda_{ji} \mathbf{1}(z = e_j). \end{aligned} \tag{17}$$

In the context of an open CRN, this definition implies that each reaction $\mathscr{R}_{(i,j)}$ is associated with a unique change vector of chemostat species. By (16) we obtain

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t} H^{\mathrm{tot}}(t) = &\sum_{i=1}^{N} \sum_{(k,j) \in \mathscr{R}} \ln \left(\frac{p(e_i,t)\, \lambda^+_{(k,j)}(e_k)}{p(e_i + e_j - e_k, t)\, \lambda^-_{(k,j)}(e_j)} \right) \\ &\times \left(\lambda^+_{(k,j)}(e_k) p(e_i,t) - \lambda^-_{(k,j)}(e_j) p(e_i + e_j - e_k, t) \right) \end{aligned}$$

and hence substituting (17) yields

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t} H^{\mathrm{tot}}(t) = &\sum_{i=1}^{N} \sum_{j \colon j > i} \ln \left(\frac{p(e_i,t)\, \Lambda_{ij}}{p(e_j,t)\, \Lambda_{ji}} \right) \\ &\times \left(\Lambda_{ij}\, p(e_i,t) - \Lambda_{ji}\, p(e_j,t) \right). \end{aligned} \tag{18}$$

We emphasize that the description of the system via the generator matrix is less general than the reaction-based description. In particular, the traditional notion (18) of the entropy production rate is inconsistent with the case, where of parallel reactions channels. We call $\mathscr{R}_{m_1}$ and $\mathscr{R}_{m_2}$ parallel, if $\nu_{m_1} = \nu_{m_2}$, but $\gamma_{m_1} \neq \gamma_{m_2}$. The generator matrix merges the rates of the two reactions, as they are indistinguishable from the perspective of the core network only. For example, any two-state Markov process satisfies detailed balance w.r.t. the rates in the generator matrix, i.e., $\ln(\pi(1)\Lambda_{12}/\pi(2)\Lambda_{21}) = 0$ and $e_p = 0$ in the notion of (18). In Sec. V A, however, we describe a two-state Markov process exhibiting a NESS via the reaction-based description.

E. Relation of entropy production and time reversibility

Thus far we have considered the mean entropy production $H^{\mathrm{tot}}(t)$ by the whole system during the interval $[0,t]$ as defined in Equation (15). There is, however, also a trajectory-wise notion of the entropy production. Noting that the entropy of the core system at time $t \geq 0$ can be written as $H[Z(t)] = \mathbb{E}[-\ln(p(Z(t),t))]$ we regard $-\ln(p(Z(t),t))$ as the entropy of Z at time $t \geq 0$. Consequently, the entropy change of the core system between initial and final state of the random trajectory $Z_{[0,t]}$ is

$$h^{\mathrm{sys}}(t) := \ln \left(\frac{p(Z(0),0)}{p(Z(t),t)} \right). \tag{19}$$

For later convenience we rewrite Eq. (19) via integrals. Since $-\ln(p(Z(t),t))$ evolves continuously during intervals, where Z is constant, and has stochastic updates upon reactions, we obtain

$$\begin{aligned} h^{\mathrm{sys}}(t) = &- \int_0^t \partial_s \ln(p(Z(s),s))\, \mathrm{d}s \\ &+ \sum_{m=1}^{M} \int_0^t \ln \left(\frac{p(Z(s-),s)}{p(Z(s-) + \nu_m, s)} \right) \mathrm{d}R_m^+(s) \\ &+ \sum_{m=1}^{M} \int_0^t \ln \left(\frac{p(Z(s-),s)}{p(Z(s-) - \nu_m, s)} \right) \mathrm{d}R_m^-(s), \end{aligned}$$

where by the use of the chemical master equation (2) we may substitute

$$\begin{aligned} &\int_0^t \partial_s \ln(p(Z(s),s))\, \mathrm{d}s \\ &= \sum_{m=1}^{M} \int_0^t \Bigg\{ \lambda_m^+(Z(s) - \nu_m) \frac{p(Z(s) - \nu_m, s)}{p(Z(s),s)} \\ &\qquad - (\lambda_m^+(Z(s)) + \lambda_m^-(Z(s))) \\ &\qquad + \lambda_m^-(Z(s) + \nu_m) \frac{p(Z(s) + \nu_m, s)}{p(Z(s),s)} \Bigg\}\, \mathrm{d}s. \end{aligned}$$

We further have $\mathbb{E}\left[\int_0^t \partial_s \ln(p(Z(s),s))\, \mathrm{d}s\right] = 0$ as we show later in this Section. The trajectory-wise entropy flow into the environment during $[0,t]$ is defined as $h^{\mathrm{env}}(t) = \beta q(t)$ and substituting with Eq. (11), such that

$$\begin{aligned} h^{\mathrm{env}}(t) := \sum_{m=1}^{M} \Bigg\{ &\int_0^t \ln \left(\frac{\lambda_m^+(Z(s-))}{\lambda_m^-(Z(s-) + \nu_m)} \right) \mathrm{d}R_m^+(s) \\ &+ \int_0^t \ln \left(\frac{\lambda_m^-(Z(s-))}{\lambda_m^+(Z(s-) - \nu_m)} \right) \mathrm{d}R_m^-(s) \Bigg\}. \end{aligned}$$

Finally, the total entropy production of the trajectory $Z_{[0,t]}$ is

$$h^{\text{tot}}(t) := h^{\text{sys}}(t) + h^{\text{env}}(t)$$

and following the steps in the proof of (10) yields

$$H^{\text{tot}}(t) = \mathbb{E}[h^{\text{tot}}(t)].$$

We now turn to the discussion of time-reversibility. Consider an interval $[0,t]$ and define the time reversed reaction counters $\tilde{R}_m^+(\tau) := \tilde{R}_m^-(t) - \tilde{R}_m^-(t-\tau)$ and $\tilde{R}_m^-(\tau) := \tilde{R}_m^+(t) - \tilde{R}_m^+(t-\tau)$ for all $\tau \in [0,t]$. The time reversed process $\tilde{Z}(\tau) = Z(t-\tau)$ then obeys

$$\tilde{Z}(\tau) = \tilde{Z}(0) + \sum_{m=1}^{M} \nu_m (\tilde{R}_m^+(\tau) - \tilde{R}_m^-(\tau))$$

for all $\tau \in [0,t]$. To derive the propensity functions for the time-reversed counting processes, we employ a useful trick by leveraging mesoscopic consistency. If we consider the entire system as a closed CRN and treat the chemostat assumption as an approximation, the combined CRN (Z,C), without the chemostat approximation, would be a Markov jump process devoid of parallel reaction channels. In this scenario, it is well known that the propensity functions for the time-reversed CRN are given by

$$\begin{aligned}
&\tilde{\lambda}_m^{\pm}(z,c,\tau) \\
=&\lim_{h\searrow 0} \mathbb{P}(\tilde{Z}(\tau+h) = z \pm \nu_m, \tilde{C}(\tau+h) = c \pm \frac{\gamma_m}{V} \mid \dots \\
&\dots \tilde{Z}(\tau) = z, \tilde{C}(\tau) = c) \\
=&\lim_{h\searrow 0} \mathbb{P}(Z(t-\tau) = z, C(t-\tau) = c \mid \dots \\
&\dots Z(t-\tau-h) = z \pm \nu_m, C(t-\tau-h) = c \pm \frac{\gamma_m}{V}) \\
&\times \frac{\mathbb{P}(Z(t-\tau-h) = z \pm \nu_m, C(t-\tau-h) = c \pm \frac{\gamma_m}{V})}{\mathbb{P}(Z(t-\tau) = z, C(t-\tau) = c)} \\
=&\lambda_m^{\mp}(z \pm \nu_m, c \pm \frac{\gamma_m}{V}) \frac{\mathbb{P}(\tilde{Z}(\tau) = z \pm \nu_m, \tilde{C}(\tau) = c \pm \frac{\gamma_m}{V})}{\mathbb{P}(\tilde{Z}(\tau) = z, \tilde{C}(\tau) = c)}.
\end{aligned}$$

Reestablishing the chemostat assumptions then yields

$$\tilde{\lambda}_m^{\pm}(z,\tau) = \lambda^{\mp}(z \pm \nu_m) \frac{\mathbb{P}(\tilde{Z}(\tau) = z \pm \nu_m)}{\mathbb{P}(\tilde{Z}(\tau) = z)}.$$

We now turn to the concepts of reversibility.

Definition 2. *A stationary Markov process Z is called reversible, if $Z_{[0,t]} \overset{d}{=} \tilde{Z}_{[0,t]}$ (equality in distribution) for all $t \geq 0$.*

However, this definition is not entirely consistent with thermodynamics in the presence of parallel reaction channels, as the trajectories of Z lack information about which specific channel was utilized. It can therefore not account for the reversal of the interactions with a chemostat as we exemplify in Sec. V A. Therefore we generalize the definition.

Definition 3. *A stationary Markov CRN Z is called thermodynamically reversible, if $X_{[0,t]} \overset{d}{=} \tilde{X}_{[0,t]}$ (equality in distribution) for all $t \geq 0$, where*

$$\begin{aligned}
X_{[0,t]} &:= \left\{Z(0), (R_m^+(s), R_m^-(s)) \colon m \in \{1,\dots,M\}, s \in [0,t]\right\}, \\
\tilde{X}_{[0,t]} &:= \left\{\tilde{Z}(0), (\tilde{R}_m^+(s), \tilde{R}_m^-(s)) \colon m \in \{1,\dots,M\}, s \in [0,t]\right\}.
\end{aligned}$$

Since the KL-divergence quantifies the divergence of distributions and vanishes in the case of equality. It can thus be regarded as a quantification of the degree of irreversibility. It hold that

$$\mathbb{D}_{\text{KL}}(X_{[0,t]} \| \tilde{X}_{[0,t]}) = 0$$

for all $t \geq 0$ if and only if Z is thermodynamically reversible. The KL-divergence between counting processes is defined via the corresponding Radon-Nikodym derivative[41] of the forward process w.r.t. the time reversed process, such that

$$\begin{aligned}
&\mathbb{D}_{\text{KL}}(X_{[0,t]} \| \tilde{X}_{[0,t]}) \\
=&\mathbb{D}_{\text{KL}}\left(Z(0) \| \tilde{Z}(0)\right) \\
&+ \mathbb{D}_{\text{KL}}\left((R_m^+(s), R_m^-(s))_{s\in[0,t], m\in\mathscr{R}} \| (\tilde{R}_m^+(s), \tilde{R}_m^-(s))_{s\in[0,t], m\in\mathscr{R}}\right),
\end{aligned}$$

where $\mathbb{D}_{\text{KL}}\left(Z(0) \| \tilde{Z}(0)\right) = \sum_z p(z,0) \ln\left(\frac{p(z,0)}{p(z,t)}\right)$ and

$$\begin{aligned}
&\mathbb{D}_{\text{KL}}\left((R_m^+(s), R_m^-(s))_{s\in[0,t], m\in\mathscr{R}} \| (\tilde{R}_m^+(s), \tilde{R}_m^-(s))_{s\in[0,t], m\in\mathscr{R}}\right) \\
=&\sum_{m=1}^{M} \mathbb{E}\left[\int_0^t \tilde{\lambda}_m^+(Z(s),s) + \tilde{\lambda}_m^-(Z(s),s) - \lambda_m^+(Z(s)) - \lambda_m^-(Z(s)) \, \mathrm{d}s\right] \\
&+ \sum_{m=1}^{M} \mathbb{E}\left[\int_0^t \ln\left(\frac{\lambda_m^+(Z(s-))}{\tilde{\lambda}_m^+(Z(s-),s)}\right) \mathrm{d}R_m^+(s)\right] \\
&+ \sum_{m=1}^{M} \mathbb{E}\left[\int_0^t \ln\left(\frac{\lambda_m^-(Z(s-))}{\tilde{\lambda}_m^-(Z(s-),s)}\right) \mathrm{d}R_m^-(s)\right]
\end{aligned}$$

Now note that

$$\begin{aligned}
&\int_0^t \partial_s \ln(p(Z(s),s)) \, \mathrm{d}s \\
=&\sum_{m=1}^{M} \int_0^t \tilde{\lambda}_m^+(Z(s),s) + \tilde{\lambda}_m^-(Z(s),s) - \lambda_m^+(Z(s)) - \lambda_m^-(Z(s)) \, \mathrm{d}s,
\end{aligned}$$

but also

$$\begin{aligned}
&\mathbb{E}\left[\int_0^t \tilde{\lambda}_m^+(Z(s),s) + \tilde{\lambda}_m^-(Z(s),s) - \lambda_m^+(Z(s)) - \lambda_m^-(Z(s)) \, \mathrm{d}s\right] \\
=&\mathbb{E}\left[\tilde{R}_m^+(t) + \tilde{R}_m^-(t) - R_m^+(t) - R_m^+(t)\right] = 0,
\end{aligned}$$

which proves $\mathbb{E}\left[\int_0^t \partial_s \ln(p(Z(s),s)) \, \mathrm{d}s\right] = 0$. Finally, we obtain

$$\begin{aligned}
&H^{\text{tot}}(t) = \mathbb{E}[h^{\text{tot}}(t)] \\
=&\mathbb{D}_{\text{KL}}\left((R_m^+(s), R_m^-(s))_{s\in[0,t], m\in\mathscr{R}} \| (\tilde{R}_m^+(s), \tilde{R}_m^-(s))_{s\in[0,t], m\in\mathscr{R}}\right)
\end{aligned}$$

by putting everything together and following the steps in the proof of Equation (10). By this relation, some authors[42] have proposed a measure-theoretic definition of the entropy production rate, which can now be generalized for open CRNs.

Definition 4.

$$e_p(t) := \lim_{h \searrow 0} \frac{1}{h} \mathbb{D}_{KL}(X_{[t,t+h]} \| \tilde{X}_{[t,t+h]})$$

is called instantaneous entropy production rate of a CRN and

$$e_p := \lim_{t \to \infty} \frac{1}{t} \mathbb{D}_{KL}(X_{[0,t]} \| \tilde{X}_{[0,t]})$$

is called limiting entropy production rate of a CRN.

It is straight forward to show that these measure-theoretic definitions are consistent with the previously mentioned notions of the entropy production rate. Since $\mathbb{D}_{\mathrm{KL}}(X_{[t,t+h]} \| \tilde{X}_{[t,t+h]}) \geq 0$ for all $t, h \geq 0$, we can use the measure-theoretic definition to obtain the second law for the thermodynamics of open CRNs, i.e.,

$$e_p(t), e_p \geq 0.$$

We conclude by reviewing equivalent conditions for thermodynamic equilibrium of open CRNs.

Theorem 1. *Let Z be stationary with limiting distribution $\pi(z)$. Then the following conditions are equivalent.*

(a) Z is thermodynamically reversible. In particular, $\mathbb{D}_{KL}(X_{[0,t]} \| \tilde{X}_{[0,t]}) = 0$ for all $t \geq 0$ and the time reversed propensities satisfy $\tilde{\lambda}_m^{\pm}(z,t) = \lambda_m^{\pm}(z)$.

(b) $e_p = 0$

(c) Stoichiometric Kolmogorov (Wegscheider) cycle condition: Any closed cycle of states

$$z_0 \xrightarrow{\rho_1 m_1} z_1 \xrightarrow{\rho_2 m_2} \dots \xrightarrow{\rho_j m_j} z_n \xrightarrow{\rho_{n+1} m_{n+1}} z_0,$$

originating from a sequence of reaction channel uses m_j in the directions $\rho_j \in \{+,-\}$, such that $\rho_j \nu_{m_j} = (z_j - z_{j-1})$, satisfies

$$\frac{\lambda_{m_1}^{\rho_1}(z_0)\lambda_{m_2}^{\rho_2}(z_1)\cdots\lambda_{m_{n+1}}^{\rho_{n+1}}(z_n)}{\lambda_{m_{n+1}}^{-\rho_{n+1}}(z_0)\lambda_{m_n}^{-\rho_n}(z_n)\cdots\lambda_{m_1}^{-\rho_1}(z_1)} = 1.$$

(d) Z satisfies the detailed balance condition

$$\lambda_m^{+}(z)\pi(z) = \lambda_m^{-}(z+\nu_m)\pi(z+\nu_m)$$

for all z and all $m \in \mathscr{R}$.

The stoichiometric cycle condition, when combined with the thermodynamic consistency relation, is analogous to the path-independence property of conservative force fields. This relation essentially verifies whether the forces acting on the system originate from a potential or contain nonconservative component.

A proof for Theorem 1 is given in Appendix B.

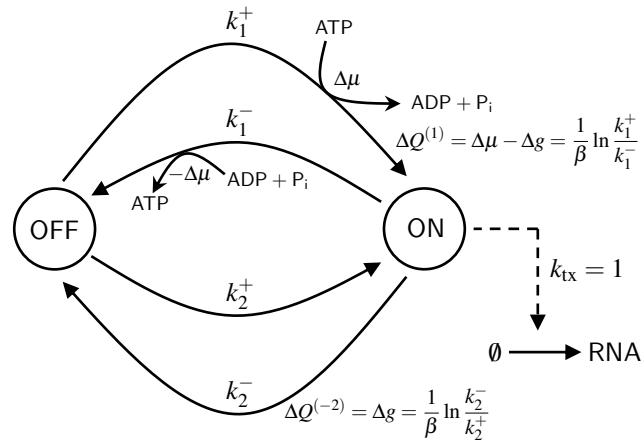


FIG. 3: State transition diagram of a two-state promoter model with two microscopically reversible reaction channels. The first reaction channel involves ATP hydrolysis and is therefore coupled to the chemostats of ATP, ADP and P_i.

V. CASE STUDIES

The initial hypothesis was that a cell's information processing capacity is constrained by its energy dissipation. In Section IV C we demonstrated that the energy dissipation rate at the NESS equals the entropy production rate. Here, using two minimal nonequilibrium promoter models, we show that the maximum directed information rate (DIR) of the channel from the promoter's transcriptional activity X to the RNA copy number Y increases as the upper bound on the entropy production rate e_p is raised. This finding supports our initial hypothesis within the context of gene regulation.

A. Models

Consider a two-state Markov jump process with states OFF and ON, which modulate transcriptional activity by switching between the transcription rates 0 and k_{tx}. For simplicity, we set $k_{\mathrm{tx}} = 1$ in our analysis, thereby fixing the system's time scale. The state transition diagram of this model, along with transition rates and thermodynamic assumptions, is shown in Fig. 3. The model features a pair of parallel reaction channels: the first channel involves ATP hydrolysis with $\Delta\mu = \mu_{\mathsf{ADP+P_i}} - \mu_{\mathsf{ATP}}$ and is coupled to corresponding chemostats, while the second reaction channel is thermally driven and not coupled to a chemostat. We denote the Gibbs free energy difference between the states by $\Delta g = g(\mathsf{ON}) - g(\mathsf{OFF})$. The entropy production rate at the NESS is

$$e_p = J \ln\left(\frac{k_1^+ k_2^-}{k_2^+ k_1^-}\right) \tag{20}$$

with net probability flux $J = \frac{k_1^+ k_2^- - k_2^+ k_1^-}{k_1^+ + k_1^- + k_2^+ + k_2^-}$, as we show in appendix **??**.

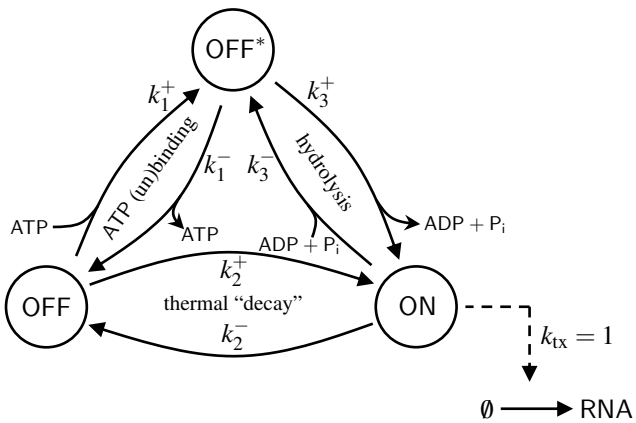


FIG. 4: State transition diagram of a three-state promoter model with three microscopically reversible reaction channels. The upper path from OFF to ON involves ATP hydrolysis. Hence, OFF* is the intermediate of a non-elementary hydrolysis reaction.

The three-state promoter model in Figure 4 extends the two-state model by adding an intermediate state, OFF*, which represents a step in a non-elementary reaction involving ATP hydrolysis. In this model, the first reaction channel handles ATP binding and unbinding between OFF and OFF*, while the second channel accounts for the actual ATP hydrolysis, driving the transition from OFF* to ON. The third reaction allows direct transition between OFF and ON and is not coupled to any chemostat species. Thermodynamically, the three-state promoter is characterized by

$$\begin{aligned}\Delta Q^{(3)} =& -\mu_{\mathsf{ADP+P_i}} - \Delta g^{(3)} = \frac{1}{\beta}\ln\frac{k_3^+}{k_3^-},\\ \Delta g :=& \Delta g^{(2)} = \Delta g^{(1)} + \Delta g^{(3)} \text{ and}\\ \Delta Q^{(-2)} =& \Delta g = \frac{1}{\beta}\ln\frac{k_2^-}{k_2^+}.\end{aligned}$$

The EPR satisfies

$$e_p = J\ln\left(\frac{k_1^+k_3^+k_2^-}{k_1^-k_3^-k_2^+}\right)$$

with $J = k_2^-\pi(ON) - k_2^+\pi(OFF)$, which is related to the general form of the EPR for circular state transition diagrams[35].

B. Maximum information under energy constraints

We now formulate the maximization problem and refer to the maximum DIR as the (information) capacity. For the two-state promoter we compute

$$C = \sup_{\substack{0\le\bar{k}^+,\bar{k}^-\\ 0\le e_p(\bar{k}^+,\bar{k}^-)\le r}} \bar{\mathbb{I}}(X\to Y) \tag{21}$$

where $\bar{k}^+ = k_1^+ + k_2^+$, $\bar{k}^- = k_1^- + k_2^-$ are the effective rates of the transitions between OFF and ON.

The physical boundary conditions $-\Delta\mu, k_1^+, k_2^- > 0$ constrain the admissible region of the effective rates:

$$\bar{k}^+ > c_2 e^{-\beta\Delta g}, \quad c_2 > \bar{k}^+ e^{\beta(\Delta g+\Delta\mu)}$$

For this admissible region the EPR is thus expressed in terms of the effective rates via

$$e_p(\bar{k}^+,\bar{k}^-) = -\beta\Delta\mu\frac{\left(\bar{k}^+ - \bar{k}^- e^{-\beta\Delta g}\right)\left(\bar{k}^- e^{-\beta\Delta\mu} - \bar{k}^+ e^{-\beta\Delta g}\right)}{\left(\bar{k}^+ + \bar{k}^-\right)\left(e^{-\beta\Delta\mu}-1\right)}, \tag{22}$$

as we show in appendix C.

The DIR for the model with a two-state promoter has been shown to satisfy[26]

$$\begin{aligned}\bar{\mathbb{I}}(X\to Y) =& \frac{1}{\mathsf{E}[\tau]}(\ln(k_{tx}) + h(\tau) - 1)\\ =& k_{tx}\pi(\mathsf{ON})(\ln(k_{tx}) + h(\tau) - 1)\\ =& k_{tx}\frac{h(\tilde{\tau}) - 1}{\mathsf{E}[\tilde{\tau}]},\end{aligned}$$

where $h(\tau)$ is the differential entropy of the time τ between transcription events in the dynamics of Y. $\tilde{\tau} = k_{tx}\tau$ is its dimensionless version. The probability density of τ is

$$p(\tau = t) = \frac{k_{tx} - w_1}{w_2 - w_1}w_2 e^{-w_2 t} + \frac{w_2 - k_{tx}}{w_2 - w_1}w_1 e^{-w_1 t},$$

which is an affine combination of exponentials and where $w_1, w_2 > 0$ are the roots of $w \mapsto (\bar{k}^- + k_{tx} - w)(\bar{k}^+ - w) - \bar{k}^+\bar{k}^-$ with $w_1 < w_2$.

Figure 5 presents the numerical solution of Equation (**??**) for a fixed value of Equation (21) for fixed value of $-\beta\Delta\mu = 16$, corresponding to the chemical work performed by ATP hydrolysis[43], and a fixed ratio of $-\Delta g/\Delta\mu = 0.5$. In Figure 5a the information capacity is evaluated for different $r > 0$ subject given that $-\Delta g/\Delta\mu = 0.5$. Complementarily, Figure 5b displays a density plot of the e_p in the $(\bar{k}^+,\bar{k}^-)$-plane together with its hyperbolic level sets of and the curve of DIR maximizing effective rates for varying $r > 0$.

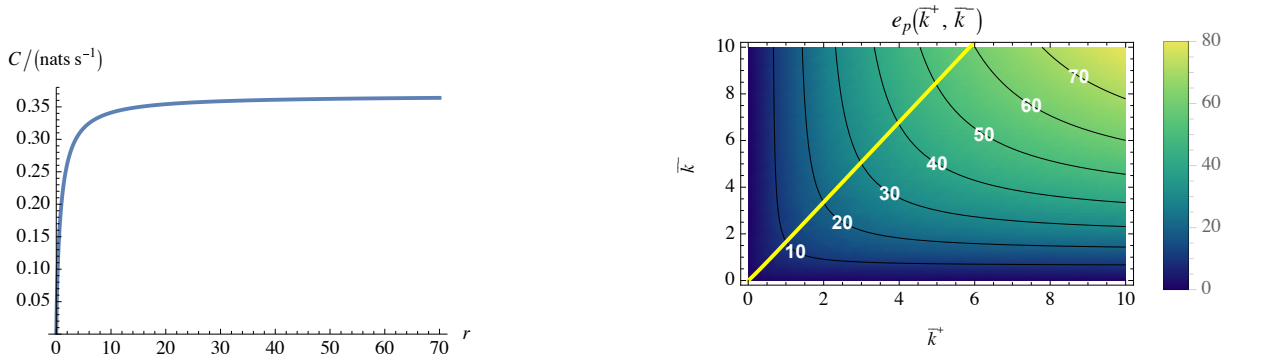
In contrast, Figure 6 shows the information capacity for varying $-\Delta g/\Delta\mu$ and different level sets of e_p. In the range $-\Delta g/\Delta\mu \in [0,1]$ the DIR increases with raised e_p. For $-\Delta g/\Delta\mu \notin [0,1]$ the level set $e_p = 0$ in the $(\bar{k}^+,\bar{k}^-)$-plane crosses the DIR maximizing ratio $\bar{k}^-/\bar{k}^+ = e - 1$. However, $-\Delta g/\Delta\mu < 0$ can be regarded as implausible since ON would then have less Gibbs free energy than OFF. $-\Delta g/\Delta\mu > 1$ on the other hand corresponds to $\Delta Q^{(1)} < 0$, i.e., a chemically driven reaction, which additionally absorbs heat from the environment. Both scenarios are biophysically implausible.

For the three-state promoter we define the capacity problem as

$$C = \sup_{\substack{0\le k_1^+,k_1^-,k_2^-,k_3^+\\ 0\le e_p\le r}} \bar{\mathbb{I}}(X\to Y),$$

where Δg, $\Delta\mu$ and k_{tx} are fixed. The DIR of this model can be shown to have the form[26]

$$\bar{\mathbb{I}}(X\to Y) = k_{tx}\ln(k_{tx})\pi(\mathsf{ON}) + \frac{h(\tau)-1}{\mathsf{E}[\tau]}. \tag{23}$$



(a) Maximum DIR for fixed $-\Delta g/\Delta\mu = 0.5$ as a function of the upper bound $r \geq e_p$.

(b) Maximum DIR as a function of $-\Delta g/\Delta\mu$ for different level sets of e_p.

FIG. 5: Maximum DIR for the two-state promoter model and fixed $-\beta\Delta\mu = 16$ and $-\Delta g/\Delta\mu = 0.5$.

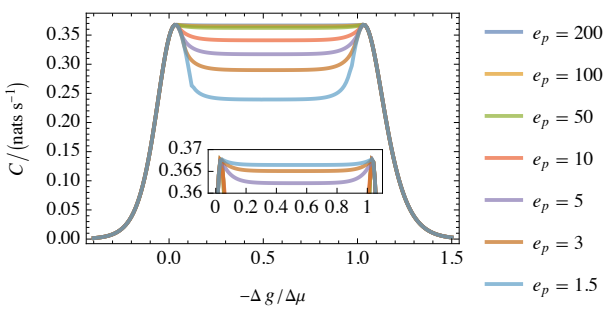


FIG. 6: Maximum DIR of the two-state promoter model with $-\beta\Delta\mu = 16$ as a function of $-\Delta g/\Delta\mu$ for different level sets of e_p.

The corresponding information capacity curves for $k_{\text{tx}} = 1$ in Figure 7 are analogous to the curves of the two-state promoter.

VI. CONCLUSION AND OUTLOOK

In this paper, we explored the relationship between energy dissipation and information processing in cellular systems using Markovian chemical reaction networks. We rigorously reformulated stochastic thermodynamics for open CRNs, linking the energy dissipation rate at the non-equilibrium steady state to the entropy production rate, and identified inconsistencies in traditional formulations when applied to open CRNs.

We extended the mutual information (MI) and directed information (DI) to account for information transmission between arbitrary subnetworks within CRNs. A rigorous derivation of the DI between subnetworks was presented. While suitable channel coding theorems for CRNs are still lacking, the DI is a promising candidate for future research.

Case studies in gene regulation demonstrated that energy dissipation constrains information throughput, with the directed information rate (DIR) increasing with the EPR, supporting the hypothesis that cellular information processing is limited by energy dissipation.

The insights gained here provide a foundation for further research on the energetic limits of information processing capabilities in biological systems, with implications for the design of energy-efficient biological networks.

Appendix A: Directed information between subnetworks of Markovian CRNs

We evaluate the DI between subnetworks via Equation (4). We start by defining relevant filtrations $\mathscr{F}^1$, $\mathscr{F}^2$ that for any fixed $s \geq 0$ and all $t \geq 0$ obey

$$\mathscr{F}_t^{X,2} = \mathscr{F}_s^Y \vee \mathscr{F}_t^X$$

$$\mathscr{F}_t^{Y,2} = \begin{cases} \mathscr{F}_s^Y & \text{for } t < s \\ \mathscr{F}_t^Y & \text{for } t \geq s, \end{cases}$$

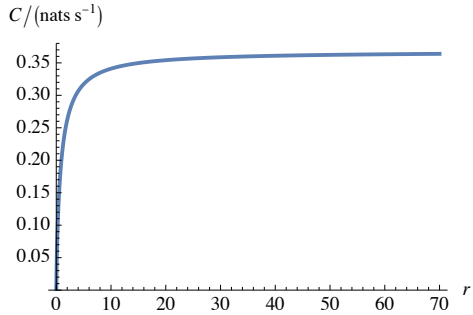
$$\mathscr{F}_t^1 = \begin{cases} \mathscr{F}_t^{X,2} & \text{for } t < s \\ \mathscr{F}_t^{XY} & \text{for } t \geq s, \end{cases}$$

where $\vee$ denotes the join operation for sigma algebras. For all $t \geq s$ we define the probability measures $\mathbb{P}^1_{t,s} = \mathbb{E}[\mathbb{P}^{XY}_{[0,t)} \mid \mathscr{F}_s^Y]$ and $\mathbb{P}^2_{t,s} = \mathbb{E}[\mathbb{P}^X_{[0,t)} \mid \mathscr{F}_s^Y] \otimes \mathbb{E}[\mathbb{P}^Y_{[0,t)} \mid \mathscr{F}_s^Y]$. Then,

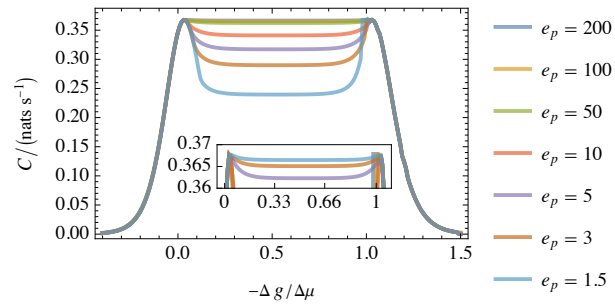
$$\mathbb{I}(Y_{[s,s+h)}; X_{[0,s+h)} \mid Y_{[0,s)}) = \int \mathbb{E}\left[\ln\left(\frac{\mathrm{d}\mathbb{P}^1_{s+h,s}}{\mathrm{d}\mathbb{P}^2_{s+h,s}}\right) \mid \mathscr{F}_s^Y\right] \mathrm{d}\mathbb{P}^Y_{[0,s)}. \tag{A1}$$

With Theorem 4.1 in[32], the conditional expectation in Equation (A1) obeys

$$\begin{aligned} &\mathbb{E}\left[\ln\left(\frac{\mathrm{d}\mathbb{P}^1_{s+h,s}}{\mathrm{d}\mathbb{P}^2_{s+h,s}}\right) \mid \mathscr{F}_s^Y\right] \\ &= \sum_{\nu_X \in \mathscr{V}_X} \int_0^{s+h} \mathbb{E}\left[\phi(\lambda_u^{X,1}(\nu_X)) - \phi(\lambda_u^{X,2}(\nu_X)) \mid \mathscr{F}_s^Y\right] \mathrm{d}u \\ &\quad + \sum_{\nu_Y \in \mathscr{V}_Y} \int_s^{s+h} \mathbb{E}\left[\phi(\lambda_u^{Y,1}(\nu_Y)) - \phi(\lambda_u^{Y,2}(\nu_Y)) \mid \mathscr{F}_s^Y\right] \mathrm{d}u, \end{aligned}$$



(a) Maximum DIR for fixed $-\Delta g/\Delta\mu = 0.5$ as a function of the upper bound $r \geq e_p$.



(b) Maximum DIR as a function of $-\Delta g/\Delta\mu$ for different level sets of e_p.

FIG. 7: Maximum DIR for the three-state promoter model with fixed $-\beta\Delta\mu = 16$.

with newly defined intensity processes

$$\lambda_u^{X,1}(v_X) = \mathbb{E}\left[\lambda^X(v_X, Z(u-)) \mid \mathscr{F}_u^1\right]$$
$$\lambda_u^{X,2}(v_X) = \mathbb{E}\left[\lambda^X(v_X, Z(u-)) \mid \mathscr{F}_u^{X,2}\right]$$

for all $u \geq 0$ and

$$\lambda_u^{Y,1}(v_Y) = \mathbb{E}\left[\lambda^Y(v_Y, Z(u-)) \mid \mathscr{F}_u^1\right]$$
$$\lambda_u^{Y,2}(v_Y) = \mathbb{E}\left[\lambda^Y(v_Y, Z(u-)) \mid \mathscr{F}_u^{Y,2}\right]$$

for all $u \geq s$. Now note that $\mathscr{F}_u^1 = \mathscr{F}_u^{X,2}$ for all $u < s$, such that all v_X the integrals vanish on $[0,s)$. Note also that $\lim_{h\searrow 0} \mathscr{F}_{s+h}^1 = \mathscr{F}_s^{X,2}$, such that $\mathbb{E}\left[\phi(\lambda_s^{X,1}(v_X)) - \phi(\lambda_s^{X,2}(v_X)) \mid \mathscr{F}_s^Y\right] = 0$. Hence,

$$\lim_{h\searrow 0} \frac{1}{h} \int_s^{s+h} \mathbb{E}\left[\phi(\lambda_u^{X,1}(v_X)) - \phi(\lambda_u^{X,2}(v_X)) \mid \mathscr{F}_s^Y\right] \mathrm{d}u = 0$$

Lastly, $\mathscr{F}_u^1 = \mathscr{F}_u^{XY}$ and $\mathscr{F}_u^{Y,2} = \mathscr{F}_u^Y$ for all $u \geq s$, which implies $\lambda_u^{Y,1}(v_Y) = \lambda_u^Y(v_Y)$ and $\lambda_u^{Y,2}(v_Y) = \hat{\lambda}_u^Y(v_Y)$. Concluding, we have

$$\lim_{h\searrow 0} \frac{1}{h} \mathbb{I}(Y_{[s,s+h)}; X_{[0,s+h)} \mid Y_{[0,s)})$$
$$= \sum_{v_Y \in \mathscr{V}_Y} \mathbb{E}\left[\phi(\lambda_s^Y(v_Y)) - \phi(\hat{\lambda}_s^Y(v_Y))\right]$$

such that Equation (5) follows immediately with Equation (4).

Appendix B: Equivalent equilibrium conditions

Proof of Thm. 1. We start showing the equivalence of (b), (c) and (d).
(d) $\implies$ (c): For all j (d) can be rewritten as

$$\lambda_{m_j}^{\rho_j}(z_{j-1})\pi(z_{j-1}) = \lambda_m^{-\rho_j}(z_j)\pi(z_j)$$

with $z_0 = z_{n+1}$. The implication then simply follows by substituting $\lambda_{m_j}^{\rho_j}(z_{j-1})/\lambda_m^{-\rho_j}(z_j) = \pi(z_j)/\pi(z_{j-1})$.
(c) $\implies$ (b): Can be shown via a stoichiometric version of the cycle representation of the entropy production rate[42].
(b) $\implies$ (d): All terms in Equation (16) are non-negative as can be shown by distinguishing the cases $J_m(z,t) \geq 0$ and $J_m(z,t) < 0$. Thus, if $e_p = 0$, then all terms must vanish individually, i.e., $\lim_{t\to\infty} J_m(z,t) = 0$ for all z and $m \in \mathscr{R}$. Thus detailed balance is statisfied.
(a) $\implies$ (b): Apply Definition 4. (d) $\implies$ (a): At stationarity, we have $\mathbb{D}_{\mathrm{KL}}\left(Z(0)\|\tilde{Z}(0)\right) = 0$. Further, the detailed balance condition implies $\tilde{\lambda}_m^{\pm}(z,t) = \lambda_m^{\pm}(z)$ for all $t \geq 0$. Hence, $\ln\left(\lambda_m^+(z)/\tilde{\lambda}_m^+(z,t)\right) = 0$ and, consequently, $\mathbb{D}_{\mathrm{KL}}\left((R_m^+(s), R_m^-(s))_{s\in[0,t],m\in\mathscr{R}} \| (\tilde{R}_m^+(s), \tilde{R}_m^-(s))_{s\in[0,t],m\in\mathscr{R}}\right) = 0$. □

Appendix C: EPR of a non-equilibrium two-state model

To derive the EPR for the two-state model we use Equation (14) for the entropy exchange rate, which is equal to the EPR at the NESS:

$$\begin{aligned}
e_p =& \pi(OFF)k_1^+ \ln\left(\frac{k_1^+}{k_1^-}\right) + \pi(ON)k_1^- \ln\left(\frac{k_1^-}{k_1^+}\right) \\
&+ \pi(OFF)k_2^+ \ln\left(\frac{k_2^+}{k_2^-}\right) + \pi(ON)k_2^- \ln\left(\frac{k_2^-}{k_2^+}\right) \\
=& \ln\left(\frac{k_1^+}{k_1^-}\right)(\pi(OFF)k_1^+ - \pi(ON)k_1^-) \\
&+ \ln\left(\frac{k_2^+}{k_2^-}\right)(\pi(OFF)k_2^+ - \pi(ON)k_2^-) \\
=& \ln\left(\frac{k_1^+}{k_1^-}\right)\frac{(k_1^- + k_2^-)k_1^+ - (k_1^+ + k_2^+)k_1^-}{k_1^+ + k_1^- + k_2^+ + k_2^-} \\
&+ \ln\left(\frac{k_2^+}{k_2^-}\right)\frac{(k_1^- + k_2^-)k_2^+ - (k_1^+ + k_2^+)k_2^-}{k_1^+ + k_1^- + k_2^+ + k_2^-}
\end{aligned}$$

with $\pi(OFF) = \frac{k_1^- + k_2^-}{k_1^+ + k_1^- + k_2^+ + k_2^-}$ and $\pi(ON) = \frac{k_1^+ + k_2^+}{k_1^+ + k_1^- + k_2^+ + k_2^-}$. The stationary distribution is the kernel of the generator matrix corresponding to the model. Simplifying the above expression yields Equation (20).

To obtain the EPR as a function of the effective rates $\overline{k}^+ = k_1^+ + k_2^+$, $\overline{k}^- = k_1^- + k_2^-$, we we express the rates in the state transition diagram via the effective rates and the potential differences Δg, $\Delta\mu$. We have

$$\begin{aligned} k_1^- &= k_1^+ e^{\beta(\Delta g+\Delta\mu)}, \quad k_2^+ = k_2^- e^{-\beta\Delta g}, \\ \overline{k}^- &= k_1^+ e^{\beta(\Delta g+\Delta\mu)} + k_2^-, \quad \overline{k}^+ = k_1^+ + k_2^- e^{-\beta\Delta g}, \end{aligned}$$

which implies

$$k_1^+ = \frac{\overline{k}^+ - \overline{k}^- e^{-\beta\Delta g}}{1-e^{\Delta\mu}}, \quad k_2^- = \frac{\overline{k}^- - \overline{k}^+ e^{\beta(\Delta g+\Delta\mu)}}{1-e^{\Delta\mu}}$$

and therefore also

$$\begin{aligned} k_1^- &= \frac{\overline{k}^+ - \overline{k}^- e^{-\beta\Delta g}}{1-e^{\Delta\mu}} e^{\beta(\Delta g+\Delta\mu)} \\ k_2^+ &= \frac{\overline{k}^- - \overline{k}^+ e^{\beta(\Delta g+\Delta\mu)}}{1-e^{\Delta\mu}} e^{-\beta\Delta g} \end{aligned}$$

The physical boundary conditions $-\Delta\mu, k_1^+, k_2^- > 0$ constrain the admissible region of the effective rates to

$$\overline{k}^+ > \overline{k}^- e^{-\beta\Delta g}, \quad \overline{k}^- > \overline{k}^+ e^{\beta(\Delta g+\Delta\mu)}.$$

For this region we obtain the Equation (22) by substituting the original rates with the above expressions and simplifying.

Appendix D: Interarrival time between transcription events for a three-state promoter

The DI between the promoter dynamics and the RNA copy number has was linked to the differential entropy of the interarrival time in Equation (23). Here, we apply Anderson's filtering theorem for semi Markov processes similarly as described in[26]. Define the state space $E := \{\mathrm{J}, \mathrm{ON}, \mathrm{OFF}^*, \mathrm{OFF}\}$, where J is the jump state, which mimics ON in terms of leaving transitions. The Laplace version of the semi-Markov kernel density is

$$q^*(s) = \begin{pmatrix} \frac{k_{\mathrm{tx}}}{u_{ON}+s} & 0 & \frac{k_3^-}{u_{ON}+s} & \frac{k_2^-}{u_{ON}+s} \\ \frac{k_{\mathrm{tx}}}{u_{ON}+s} & 0 & \frac{k_3^-}{u_{ON}+s} & \frac{k_2^-}{u_{ON}+s} \\ 0 & \frac{k_3^+}{u_{OFF*}+s} & 0 & \frac{k_1^-}{u_{OFF*}+s} \\ 0 & \frac{k_2^+}{u_{OFF}+s} & \frac{k_1^+}{u_{OFF}+s} & 0 \end{pmatrix},$$

where $u_{ON} = k_2^- + k_3^- + k_{\mathrm{tx}}$, $u_{OFF} = k_1^+ + k_2^+$ We filter E to the reduced state space $\{\mathrm{J}\}$ which yields the interarrival time distribution f_τ of the output. Since the geometric series of a 3×3-matrix is hard to evaluate, we do the filtering state by state, from right to left. In the first step we identify

$$\begin{aligned} a^*(s) &= \begin{pmatrix} \frac{k_{\mathrm{tx}}}{u_{ON}+s} & 0 & \frac{k_3^-}{u_{ON}+s} \\ \frac{k_{\mathrm{tx}}}{u_{ON}+s} & 0 & \frac{k_3^-}{u_{ON}+s} \\ 0 & \frac{k_3^+}{u_{OFF*}+s} & 0 \end{pmatrix} \\ b^*(s) &= \left(\frac{k_2^-}{u_{ON}+s}, \frac{k_2^-}{u_{ON}+s}, \frac{k_1^-}{u_{OFF*}+s} \right)^T, \\ c^*(s) &= \left(0, \frac{k_2^+}{u_{OFF}+s}, \frac{k_1^+}{u_{OFF}+s} \right) \text{ and} \\ d^* &= 0. \end{aligned}$$

Thus

$$b^*(s)\,c^*(s) = \begin{pmatrix} 0 & \frac{k_2^+k_2^-}{(u_{OFF}+s)(u_{ON}+s)} & \frac{k_1^+k_2^-}{(u_{OFF}+s)(u_{ON}+s)} \\ 0 & \frac{k_2^+k_2^-}{(u_{OFF}+s)(u_{ON}+s)} & \frac{k_1^+k_2^-}{(u_{OFF}+s)(u_{ON}+s)} \\ 0 & \frac{k_1^-k_2^+}{(u_{OFF*}+s)(u_{OFF}+s)} & \frac{k_1^+k_1^-}{(u_{OFF*}+s)(u_{OFF}+s)} \end{pmatrix}$$

and

$$\begin{aligned} \tilde{q}^*(s) =& a^*(s) + b^*(s)\,c^*(s) \\ =& \begin{pmatrix} \frac{k_{\mathrm{tx}}}{u_{ON}+s} & \frac{k_2^+k_2^-}{(u_{OFF}+s)(u_{ON}+s)} & \frac{k_1^+k_2^- + k_3^-(u_{OFF}+s)}{(u_{OFF}+s)(u_{ON}+s)} \\ \frac{k_{\mathrm{tx}}}{u_{ON}+s} & \frac{k_2^+k_2^-}{(u_{OFF}+s)(u_{ON}+s)} & \frac{k_1^+k_2^- + k_3^-(u_{OFF}+s)}{(u_{OFF}+s)(u_{ON}+s)} \\ 0 & \frac{k_1^-k_2^+ + k_3^+(u_{OFF}+s)}{(u_{OFF*}+s)(u_{OFF}+s)} & \frac{k_1^+k_1^-}{(u_{OFF*}+s)(u_{OFF}+s)} \end{pmatrix} \end{aligned}$$

In the second step we identify

$$\begin{aligned} a^*(s) &= \begin{pmatrix} \frac{k_{\mathrm{tx}}}{u_{ON}+s} & \frac{k_2^+k_2^-}{(u_{OFF}+s)(u_{ON}+s)} \\ \frac{k_{\mathrm{tx}}}{u_{ON}+s} & \frac{k_2^+k_2^-}{(u_{OFF}+s)(u_{ON}+s)} \end{pmatrix}, \\ b^*(s) &= \frac{k_3^-(r_2+s)}{(u_{OFF}+s)(u_{ON}+s)} (1,1)^T, \\ c^*(s) &= \frac{k_3^+(r_1+s)}{(u_{OFF*}+s)(u_{OFF}+s)} (0,1), \\ \sum_{k=0}^{\infty} (d^*(s))^k &= \frac{(u_{OFF*}+s)(u_{OFF}+s)}{(u_{OFF*}+s)(u_{OFF}+s) - k_1^+k_1^-} \end{aligned}$$

with $r_1 := \frac{k_1^-k_2^+}{k_3^+} + u_{OFF}$ and $r_2 := \frac{k_1^+k_2^-}{k_3^-} + u_{OFF}$. We denote the roots of $s \mapsto (u_{OFF*}-s)(u_{OFF}-s) - k_1^+k_1^-$ by w_1, w_2. Then

$$\begin{aligned} & b^*(s) \sum_{k=0}^{\infty} (d^*(s))^k c^*(s) \\ =& \frac{k_3^+k_3^-(r_1+s)(r_2+s)}{(u_{OFF}+s)(u_{ON}+s)(w_1+s)(w_2+s)} \begin{pmatrix} 0 & 1 \\ 0 & 1 \end{pmatrix} \\ & \tilde{\tilde{q}}^*(s) = a^*(s) + b^*(s) \sum_{k=0}^{\infty} (d^*(s))^k c^*(s) \\ =& \begin{pmatrix} \frac{k_{\mathrm{tx}}}{u_{ON}+s} & \frac{k_3^+k_3^-(r_1+s)(r_2+s) + k_2^+k_2^-(w_1+s)(w_2+s)}{(u_{OFF}+s)(u_{ON}+s)(w_1+s)(w_2+s)} \\ \frac{k_{\mathrm{tx}}}{u_{ON}+s} & \frac{k_3^+k_3^-(r_1+s)(r_2+s) + k_2^+k_2^-(w_1+s)(w_2+s)}{(u_{OFF}+s)(u_{ON}+s)(w_1+s)(w_2+s)} \end{pmatrix}. \end{aligned}$$

Denoting the roots of $\mathbb{C} \ni s \mapsto k_3^+k_3^-(r_1-s)(r_2-s) + k_2^+k_2^-(w_1-s)(w_2-s)$ by q_1, q_2 we rewrite

$$\tilde{\tilde{q}}^*(s) = \begin{pmatrix} \frac{k_{\text{tx}}}{u_{ON}+s} & \frac{(k_3^+k_3^-+k_2^+k_2^-)(q_1+s)(q_2+s)}{(u_{OFF}+s)(u_{ON}+s)(w_1+s)(w_2+s)} \\ \frac{k_{\text{tx}}}{u_{ON}+s} & \frac{(k_3^+k_3^-+k_2^+k_2^-)(q_1+s)(q_2+s)}{(u_{OFF}+s)(u_{ON}+s)(w_1+s)(w_2+s)} \end{pmatrix}.$$

For the last filtering step we use that $\frac{a}{b}\frac{1}{1-\frac{a}{b}} = \frac{a}{b-a}$ and $1 + \frac{a}{b-a} = \frac{b}{b-a}$ for any $a \neq b$. We obtain

$$\begin{aligned} f_\tau^*(s) = &\{k_{\text{tx}}(u_{OFF}+s)(w_1+s)(w_2+s)\} \\ &\times \{u_{OFF}+s)(u_{ON}+s)(w_1+s)(w_2+s) \\ &- (k_3^+k_3^- + k_2^+k_2^-)(q_1+s)(q_2+s)^{-1}. \end{aligned}$$

Denote $R(s) := k_{\text{tx}}(u_{OFF}+s)(w_1+s)(w_2+s)$ and let $v_1, \ldots, v_4$ be the roots of $U(s) := (u_{OFF}+s)(u_{ON}+s)(w_1+s)(w_2+s) - (k_3^+k_3^- + k_2^+k_2^-)(q_1+s)(q_2+s)$. Then

$$f_\tau(t) = \sum_{k=1}^{4} \frac{R(v_k)}{U'(v_k)} e^{v_k t}.$$

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