Fluctuation and thermodynamic uncertainty relations in deterministic chemical reaction networks

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[KY and Ito, PRL, 2021] see also [KY, Kolchinsky, Dechant, and Ito, arXiv:2205.15227]

Chemical reaction network

- Chemical reaction networks

$$\nu_{1,\rho}X_1 + \cdots + \nu_{N,\rho}X_N \underset{-\rho}{\overset{\rho}{\rightleftharpoons}} \nu'_{1,\rho}X_1 + \cdots + \nu'_{N,\rho}X_N$$

described by the deterministic rate equation

$$\frac{dc_\alpha}{dt} = \sum_\rho (\nu'_{\alpha\rho} - \nu_{\alpha\rho})(\mathcal{K}_\rho(c) - \mathcal{K}_{-\rho}(c))$$

$\mathcal{K}_{\pm\rho}(c) \geq 0$: reaction rate, which can be nonlinear

- The theoretical frameworks of deterministic CRNs and stochastic jump processes resemble each other

- Approach based on the analogy has worked, especially to understand the CRN side e.g., Schnakenberg theory [Polettini & Esposito, J. Phys. Chem. 2014], information thermodynamics [Penocchio, *et al.*, arXiv:2204.02815] (see also [KY, Kolchinsky, Dechant, and Ito, arXiv:2205.15227], where we derive several results integrating the two frameworks)

Similarity 1) Equations of motion

- Rate equation $d_t c = \mathbb{S}J(c)$
  - c: concentration
  - $\mathbb{S}$: stoichiometric matrix; $\mathbb{S}_{\alpha\rho} = \nu'_{\alpha\rho} - \nu_{\alpha\rho}$
  - $J(c)$: reaction current; $J_\rho(c) = \mathcal{K}_\rho(c) - \mathcal{K}_{-\rho}(c)$
- Master equation $d_t p = BJ(p)$
  - p: probability
  - B: incidence matrix of the directed graph of states and transitions given by $B_{i,(jk)} = \delta_{ik} - \delta_{ij}$
  - J: probability current $J_{ij}(p) = k_{ij}p_i - k_{ji}p_j$

Similarity 2) Thermodynamics

- Affinity/Thermodynamic force

  CRN: $F_\rho(c) = T \ln \frac{\mathcal{K}_\rho(c)}{\mathcal{K}_{-\rho}(c)}$ $(R = 1)$

  Jump process: $F_{ij}(p) = T \ln \frac{k_{ij} p_i}{k_{ji} p_j}$ $(k_{\mathrm{B}} = 1)$

- Entropy production rate:

$$\sigma = \frac{1}{T} J^{\mathsf{T}} F = \sum_{\rho} (\mathcal{K}_\rho - \mathcal{K}_{-\rho}) \ln \frac{\mathcal{K}_\rho}{\mathcal{K}_{-\rho}} \text{ or } \sum_{i<j} (k_{ij} p_i - k_{ji} p_j) \ln \frac{k_{ij} p_i}{k_{ji} p_j}$$

Difference: Fluctuates or not

- In stochastic thermodynamics,
  fluctuations (typically evaluated by the variance) play a central role.
  e.g., fluctuation theorem, thermodynamic uncertainty relation

- But absent in deterministic CRNs

Q. Aren't there any counterparts that can bring some insights to CRNs?

Results

- $D_{\alpha\beta}(c) := (1/2)\sum_\rho \mathbb{S}_{\alpha\rho}\mathbb{S}_{\beta\rho}(\mathcal{K}_\rho(c) + \mathcal{K}_{-\rho}(c))$ plays the role of a diffusivity in deterministic CRNs (previously known (e.g., [Ge and Qian, Chem. Phys. 2016]) but has not been utilized effectively)

- TUR [KY and Ito, PRL 2021; KY, *et al.*, arXiv:2205.15227]

$$\sigma \geq \max_{\psi \in \mathbb{R}^N} \frac{1}{\psi^\mathsf{T} D(c) \psi} \left(\psi^\mathsf{T} \frac{dc}{dt}\right)^2 \quad \text{(arXiv)}$$
$$\underset{\psi_\beta = \delta_{\alpha\beta}}{\geq} \max_\alpha \frac{(d_t c_\alpha)^2}{D_{\alpha\alpha}} \quad \text{(PRL)}$$

- Speed limit $\tau \geq \dfrac{|c(0) - c(\tau)|^2}{\bar{D}\Sigma}$ [KY and Ito, PRL 2021]

$\rightarrow$ Why is D a diffusion coefficient matrix?

Understanding from analogy

- Traffic $A_{ij}(p) := k_{ij}p_i + k_{ji}p_j$ in a jump process gives a short-time fluctuation as

$$\mathrm{Var}(\Delta R)(t; t+\Delta t) = \sum_{i<j}(R_i - R_j)^2 A_{ij}(p(t))\Delta t + o(\Delta t)$$

- TUR $\sigma \geq \dfrac{2(d_t\langle R\rangle)^2}{D_R}$ with $D_R := \sum_{i<j}(R_i - R_j)^2 A_{ij}(p(t))$ [Otsubo, *et al.*, PRE 2020]

- If we define $A_\rho(c) := \mathcal{K}_\rho(c) + \mathcal{K}_{-\rho}(c)$, $D_{\alpha\beta}(c) = \dfrac{1}{2}\sum_\rho \mathbb{S}_{\alpha\rho}\mathbb{S}_{\beta\rho}A_\rho(c)$

  $\rightarrow$ analogous to fluctuations

From chemical master/Fokker–Planck equation

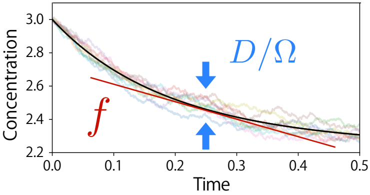
- The system size expansion of the chemical master equation brings the chemical Fokker–Planck equation

$$\frac{\partial}{\partial t}P(c,t) = -\sum_{\alpha}\frac{\partial}{\partial c_\alpha}[f_\alpha(c)P(c,t)] + \frac{1}{\Omega}\sum_{\alpha,\beta}\frac{\partial^2}{\partial c_\alpha \partial c_\beta}[D_{\alpha\beta}(c)P(c,t)]$$

with Ω being the volume parameter and

$$f_\alpha(c) := \sum_{\rho}\mathbb{S}_{\alpha\rho}(\mathcal{K}_\rho(c) - \mathcal{K}_{-\rho}(c)),\ D_{\alpha\beta}(c) = \frac{1}{2}\sum_{\rho}\mathbb{S}_{\alpha\rho}\mathbb{S}_{\beta\rho}(\mathcal{K}_\rho(c) + \mathcal{K}_{-\rho}(c))$$

$\rightarrow$ D is the diffusion coefficient of the chemical FP equation times the volume



Proof of TUR

$$\left(\psi^{\mathsf{T}}\frac{dc}{dt}\right)^2=\left(\sum_\rho[\mathbb{S}^{\mathsf{T}}\psi]_\rho J_\rho(c)\right)^2=\left(\sum_\rho[\mathbb{S}^{\mathsf{T}}\psi]_\rho\frac{J_\rho(c)}{F_\rho(c)/T}F_\rho(c)\right)^2$$

$$\leq\sum_\rho\frac{J_\rho(c)}{F_\rho(c)/T}(c)[\mathbb{S}^{\mathsf{T}}\psi]_\rho^2\sum_{\rho'}\frac{J_{\rho'}(c)}{F_{\rho'}(c)/T}F_{\rho'}(c)^2$$

$$\leq\frac{1}{2}\sum_\rho A_\rho(c)[\mathbb{S}^{\mathsf{T}}\psi]_\rho^2\,\sigma=(\psi^{\mathsf{T}}D\psi)\sigma$$

Where we used

- Cauchy–Schwarz inequality in the second line
- Inequality between log mean and arithmetic mean in the third line

$$\frac{a-b}{\ln(a/b)}\leq\frac{a+b}{2}$$

with $a=\mathcal{K}_\rho(c)$ and $b=\mathcal{K}_{-\rho}(c)$, that is, $\dfrac{J_\rho(c)}{F_\rho(c)/T}\leq\dfrac{A_\rho(c)}{2}$

Summary

- We discussed that $D_{\alpha\beta}(c) = \frac{1}{2}\sum_{\rho} \mathbb{S}_{\alpha\rho}\mathbb{S}_{\beta\rho}(\mathcal{K}_{\rho}(c) + \mathcal{K}_{-\rho}(c))$ evaluates the (potential) "fluctuation" of a CRN

- It provides the TUR

$$\sigma \geq \sigma^{\mathrm{ex}} \geq \frac{1}{\psi^{\mathsf{T}} D(c)\psi}\left(\psi^{\mathsf{T}}\frac{dc}{dt}\right)^2$$

and the speed limit

$$\tau \geq \frac{|c(0) - c(\tau)|^2}{\bar{D}\Sigma}$$

* Please see our paper [KY and S. Ito, PRL 2021] for a bit more details, and [KY, Kolchinsky, Dechant, and Ito, arXiv:2205.15227] for several topics, such as decomposition of the EPR and optimal transport in jump processes & CRNs.

Master equation

- Master equation $d_t p = BJ(p)$

  p: probability

  B: incidence matrix of the directed graph of states and transitions given by $B_{i,(jk)} = \delta_{ik} - \delta_{ij}$

  J: probability current $J_{ij}(p) = k_{ij} p_i - k_{ji} p_j$

  $\because)\ \sum_{j<k} B_{i,(jk)} J_{jk} = \sum_{j(<i)} J_{ji} - \sum_{k(>i)} J_{ik} = \sum_{j(\neq i)} J_{ji}$

Open CRN

- α is open $\overset{def}{\iff}$ $d_t c_\alpha = [\mathbb{S}J(c)]_\alpha + \mathcal{J}_\alpha = 0$ by an external flow $\mathcal{J}$
- The TUR can be stated more generally as

$$\sigma \geq \frac{1}{\psi^\mathsf{T} D(c)\psi} \left(\psi^\mathsf{T} f(c)\right)^2$$

with $f_\alpha(c) = \sum_\rho \mathbb{S}_{\alpha\rho} J_\rho(c)$ regardless of whether α is closed or open

- Specifically, in a steady state c^{ss}, $f_\alpha(c^{\mathrm{ss}}) = 0$ if α is closed, and $f_\alpha(c^{\mathrm{ss}}) = -\mathcal{J}_\alpha$ if open, thus

$$\sigma^{\mathrm{ss}} \geq \frac{1}{\psi^\mathsf{T} D(c^{\mathrm{ss}})\psi} \left(\psi^\mathsf{T} \mathcal{J}\right)^2$$

Keizer's Fluctuation–Dissipation relation

[Ge and Qian, Chem. Phys. 2016]

- Let c^{ss} be a complex balanced steady state
- Define

$$\Gamma_{\alpha\beta}(c) := \frac{\partial f_\alpha}{\partial c_\beta}(c), \quad g_{\alpha\beta}(c) := \frac{1}{RT}\frac{\partial^2 G}{\partial c_\alpha \partial c_\beta} = \frac{\delta_{\alpha\beta}}{c_\alpha}$$

- Then, we have

$$-2D(c^{\mathrm{ss}}) = \Gamma(c^{\mathrm{ss}})g(c^{\mathrm{ss}})^{-1} + g(c^{\mathrm{ss}})^{-1}\Gamma(c^{\mathrm{ss}})^{\mathsf{T}}$$

cf. Lyapunov equation for a stochastic linear system $d_t x = Hx + \Xi$, with $\langle \Xi_i(t)\Xi_j(t')\rangle = 2\mathcal{D}_{ij}\delta(t-t')$

$$\frac{d}{dt}\mathfrak{S}(t) = H\mathfrak{S}(t) + \mathfrak{S}(t)H^{\mathsf{T}} + 2\mathcal{D}$$

$$\mathfrak{S}_{ij}(t) = \langle [x_i(t) - \langle x_i(t)\rangle][x_j(t) - \langle x_j(t)\rangle]\rangle$$