# Thermodynamics of Biochemical Reaction Networks: Information, Accuracy and Speed

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BIRS, July 28, 2020

Motivation
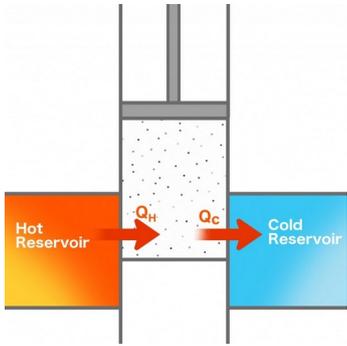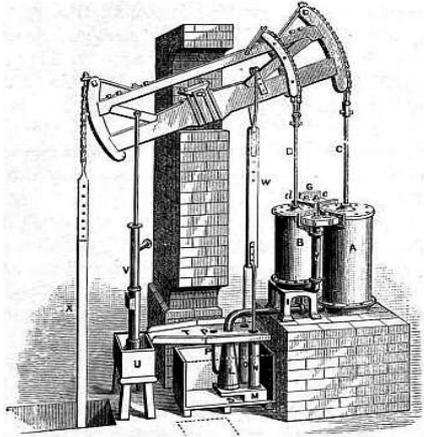
Classical thermodynamics Stochastic thermodynamics
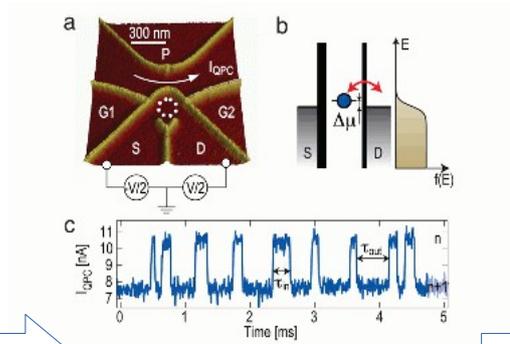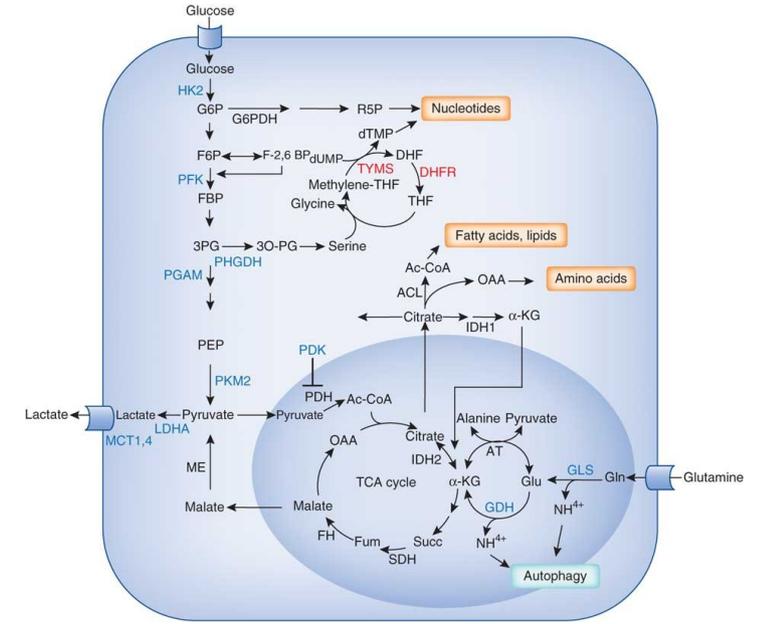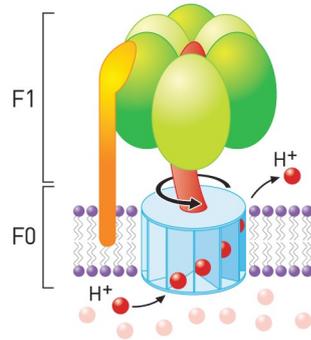
Thermodynamics of
Chemical Reaction Networks

$\bullet\bullet\bullet$

2
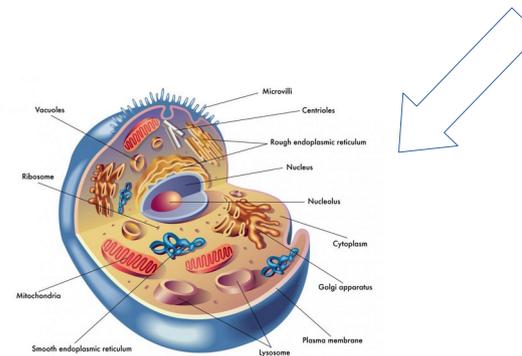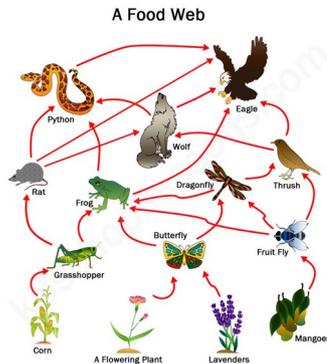
Outline

I) Deterministic description of Open CNRs

      - First and Second Law

      - Role of Topology

      - Role of Information

II) Dissipative Self-Assembly

III) Stochastic description and Accuracy

IV) Conclusions and Perspectives

I) Deterministic description of CRNs

Closed CRN:

$$d_t[\mathbf{Z}] = \mathbb{S}\,\mathbf{J}$$

Open CRN:

Internal $\quad d_t[\mathbf{X}] = \mathbb{S}^X\,\mathbf{J}$

Chemostatted $\quad d_t[\mathbf{Y}] = \mathbb{S}^Y\,\mathbf{J} + \mathbf{I}$

$$\parallel$$

$\mathbb{0}$ in autonomous CRNs
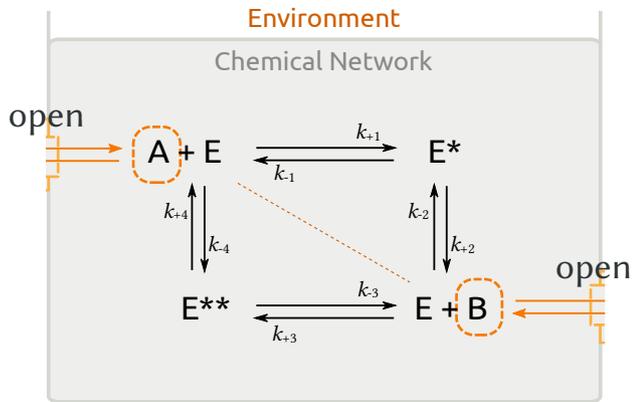
$$\mathbf{J} = \mathbf{J}_+ - \mathbf{J}_- = \begin{pmatrix} k_{+1}[A][E] \\ k_{+2}[E^*] \\ k_{+3}[B][E] \\ k_{+4}[E^{**}] \end{pmatrix} - \begin{pmatrix} k_{-1}[E^*] \\ k_{-2}[B][E] \\ k_{-3}[E^{**}] \\ k_{-4}[A][E] \end{pmatrix}$$

Mass action kinetics $\quad \mathbf{J}_\pm = \mathbf{k}_\pm[\mathbf{Z}]^{\cdot \boldsymbol{\nu}_\pm}$

$$[\mathbf{Z}] = \begin{pmatrix} [\mathbf{X}] \\ [\mathbf{Y}] \end{pmatrix} = \begin{pmatrix} [E] \\ [E^*] \\ [E^{**}] \\ [A] \\ [B] \end{pmatrix}$$

Stoichiometric matrix (topology)

$$\mathbb{S} = \begin{pmatrix} \mathbb{S}^X \\ \mathbb{S}^Y \end{pmatrix} = \begin{pmatrix} -1 & 1 & -1 & 1 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \\ -1 & 0 & 0 & 1 \\ 0 & 1 & -1 & 0 \end{pmatrix}$$

Chemical Potential $\quad \boldsymbol{\mu} = \boldsymbol{\mu}^\circ + RT\ln[\mathbf{Z}]$

Local Detailed Balance $\quad \ln\dfrac{\mathbf{k}_+}{\mathbf{k}_-} = -\dfrac{\boldsymbol{\mu}^\circ \cdot \mathbb{S}}{RT}$

Closed CRN relax to equilibrium $\quad \mathbf{J}^{eq} = \mathbf{J}_+^{eq} - \mathbf{J}_-^{eq} = \mathbb{0}$

4

First and Second Law

CRN Enthalpy:

$$H = \boldsymbol{h}^\circ \cdot [\mathbf{Z}]$$

CRN Entropy:

total concentration

$$S = (\boldsymbol{s}^\circ - R\ln[\mathbf{Z}]) \cdot [\mathbf{Z}] + R[Z]$$

Chemical Work $\dot{W}_{\text{chem}}$

1$^{\text{st}}$ law
Enthalpy Balance

$$d_t H = \boldsymbol{h}^\circ \cdot \mathbb{S}\mathbf{J} + \boldsymbol{h}_Y \cdot \mathbf{I} = \boldsymbol{h}^\circ \cdot \mathbb{S}\mathbf{J} + T\boldsymbol{s}_Y \cdot \mathbf{I} + \boldsymbol{\mu}_Y \cdot \mathbf{I}$$

Heat Flow $\dot{Q}$

2$^{\text{nd}}$ law
Entropy Balance

$$\dot{\Sigma} = d_t S - \dot{Q}/T$$

Entropy change in (thermal & chemical) reservoirs

Entropy production:
(total entropy change)

$$T\dot{\Sigma} = -\boldsymbol{\mu} \cdot \mathbb{S}\mathbf{J} = (\mathbf{J}_+ - \mathbf{J}_-) \cdot RT\ln\frac{\mathbf{J}_+}{\mathbf{J}_-} \geqslant 0$$

Topology: Conservation Laws & Cycles
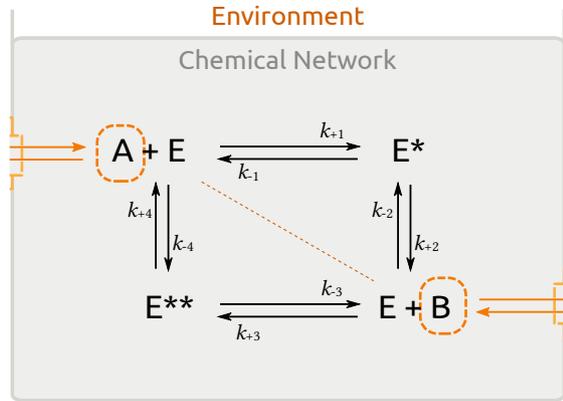
$$\mathbb{S} = \begin{pmatrix} -1 & 1 & -1 & 1 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \\ \hline -1 & 0 & 0 & 1 \\ 0 & 1 & -1 & 0 \end{pmatrix} \begin{matrix} \mathbb{S}^X \\ \\ \\ \mathbb{S}^Y \end{matrix}$$

Closed CRN:

● Conservation Laws: $L_\lambda = \ell_\lambda \cdot [\mathbf{Z}]$

$$\ell_\lambda \cdot \mathbb{S} = 0$$

$\ell_1 = \begin{pmatrix} 1 & 1 & 1 & 0 & 0 \end{pmatrix}$ $L_1 = [E] + [E^*] + [E^{**}]$

$\ell_2 = \begin{pmatrix} 0 & 1 & 1 & 1 & 1 \end{pmatrix}$ $L_2 = [E^*] + [E^{**}] + [A] + [B]$

Open CRN:

● Conservation Laws: $L_\lambda = \ell_\lambda \cdot [\mathbf{X}]$

$$\ell_\lambda \cdot \mathbb{S}^X = 0$$

$L_1 = [E] + [E^*] + [E^{**}]$

Broken conservation law!

● Cycles: $\mathbb{S}\, \mathbf{c}_\alpha = 0$

$$\mathbf{c} = \begin{pmatrix} 1 & 1 & 1 & 1 \end{pmatrix}^T$$

● Cycles: $\mathbb{S}^X \mathbf{c}_\alpha = 0$

$$\mathbf{c} = \begin{pmatrix} 1 & 1 & 1 & 1 \end{pmatrix}^T$$

Emergent cycle!

$$\mathbf{c}_\epsilon = \begin{pmatrix} 1 & 1 & 0 & 0 \end{pmatrix}^T$$

$$\begin{matrix} 0 & = & 0 & + & 0 \\ 1 & = & 1 & + & 0 \\ 2 & = & 1 & + & 1 \end{matrix}$$

$$\#Y = \#\lambda_b + \#\mathbf{c}_\epsilon$$

6

[Polettini & Esposito, *J. Chem. Phys.* **141**, 024117 (2014)]

Topology shapes Entropy Production

$$0 = 0 + 0$$
$$1 = 1 + 0$$
$$2 = 2 + 0$$
$$2 = 1 + 1$$
$$3 = 3 + 0$$
$$3 = 2 + 1$$
$$3 = 1 + 2$$

Broken conservation laws   Emergent cycles

Chemostats $\longleftarrow$ $\boxed{\#Y = \#\lambda_b + \#c_\epsilon}$

Nonconservative Work

$(\mu_B - \mu_A)\, I_B$

c_ϵ Cycle Affinities $\longleftarrow \mathcal{A}_\epsilon \cdot \mathcal{J}_\epsilon \longrightarrow$ Cycle Currents

$-\boldsymbol{\mu}_Y \cdot \mathbb{S}^Y\, c_\epsilon$

$\mathcal{A}_\epsilon = 0 \ \ \forall \epsilon$

Detailed Balanced CRN

$$\boxed{T\dot{\Sigma} \ \ = \ \ \dot{W}_d \ \ + \ \ \dot{W}_{nc} \ \ - \ \ d_t \mathcal{G} \ \ \geqslant 0}$$

Driving Work

$$\dot{W}_d = -\sum_{\lambda_b} \left[\partial_t f_{\lambda_b}(\boldsymbol{\mu}_{Y_b}) \right] L_{\lambda_b}$$
$$= -\left[\partial_t \mu_A \right] L_2$$

NonEq semigrand Gibbs free energy

$$\mathcal{G} \ = \ H - TS - \sum_{\lambda_b} f_{\lambda_b}(\boldsymbol{\mu}_{Y_b})\, L_{\lambda_b}$$
$$= \ H - TS - \mu_A\, L_2$$

[Rao & Esposito. *New J. Phys.* **20**, 023007 (2018)]
[Falasco, Rao & Esposito, *Phys. Rev. Lett.* **121**, 108301 (2018)]

Information and the Work Principle

$$\mathcal{G} = \mathcal{G}_{\text{eq}} + \text{RT} \, \mathcal{L}\left([\mathbf{X}]\big|[\mathbf{X}]_{\text{eq}}\right)$$

Equilibrium of open CRN
$\mathcal{A}_\epsilon = 0 \;\; \forall \epsilon$

"Relative entropy"

$$= [\mathbf{X}] \cdot \ln \frac{[\mathbf{X}]}{[\mathbf{X}]_{\text{eq}}} - \left([X] - [X]_{\text{eq}}\right) \geqslant 0$$

$$W_{\text{d}} + W_{\text{nc}} \geqslant \Delta\mathcal{G}_{\text{eq}} + \text{RT} \, \Delta\mathcal{L}\left([\mathbf{X}]\big|[\mathbf{X}]_{\text{eq}}\right)$$

$\text{RT} \, \mathcal{L}$
- Min work to generate a NonEq distrib
- Max work that can be extracted from a NonEq distrib

... in Reaction-Diffusion

$$d_t[\mathbf{X}]_\mathbf{r} = -\nabla \cdot \mathbf{J}_\mathbf{r}^X + \mathbb{S}^X \mathbf{j_r}$$

$$d_t[\mathbf{Y}]_\mathbf{r} = -\nabla \cdot \mathbf{J}_\mathbf{r}^Y + \mathbb{S}^Y \mathbf{j_r} + \mathbf{I_r}$$

Diffusion   Reactions   Exchange

Mass-action kinetics

$$\mathbf{j}_\mathbf{r}^{\pm} = \mathbf{k}_{\pm}[\mathbf{Z}]_\mathbf{r}^{\circ \boldsymbol{\nu}_{\pm}}$$

Diffusion: Fick's Law

$$\mathbf{J_r} = -\mathbb{D}\nabla[\mathbf{Z}]_\mathbf{r}$$

Diffusion coefficients

$$\boxed{W_d + W_{nc} = \Delta \mathcal{G}_{eq} + RT\,\Delta\mathcal{L} + T\Sigma}$$

$$\geqslant 0$$

$$= \int_\mathcal{V} d\mathbf{r} \left[[\mathbf{Z}]_\mathbf{r} \circ \ln \frac{[\mathbf{Z}]_\mathbf{r}}{[\mathbf{Z}]_{eq}} - ([\mathbf{Z}]_\mathbf{r} - [\mathbf{Z}]_{eq}) \right] \geqslant 0$$

Spacial structuring takes work:

$$\mathcal{L}\left([\mathbf{Z}]_{patt} \big| [\mathbf{Z}]_{eq}\right) \geqslant \mathcal{L}\left([\bar{\mathbf{Z}}] \big| [\mathbf{Z}]_{eq}\right)$$
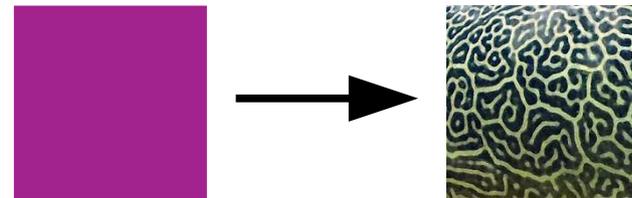
Cost of Chemical Waves

$$T\dot{\sigma} = \dot{w}_{\mathrm{nc}} - \partial_t \mathbb{g} - \nabla \cdot J^{\mathbb{g}x}$$

Fisher waves

$$X + Y \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} 2X$$

Murray, Mathematical
Biology I. (Springer 2002)

$$\partial_t x = k_{+1}xy - k_{-1}x^2 + D\partial_r^2 x$$

$$\dot{w}_{\mathrm{nc}} = 0$$

Brusselator

$$Y_1 \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} X_1$$

$$X_1 + Y_2 \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} X_2 + Y_3$$
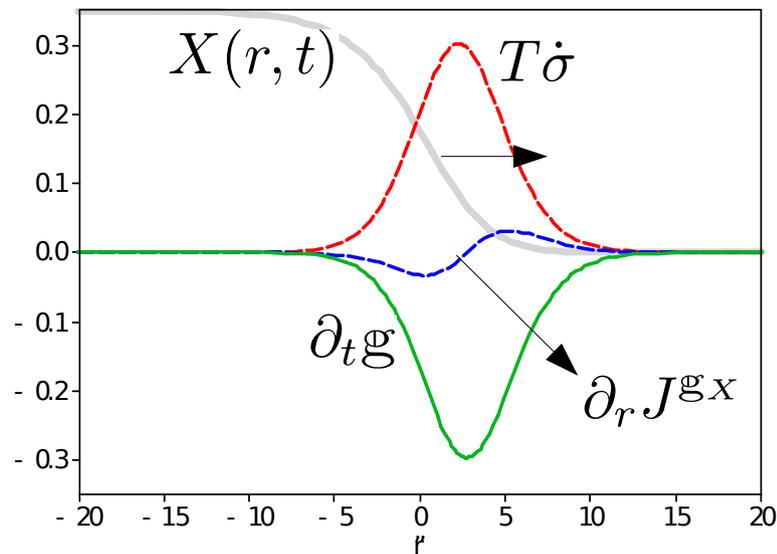
Auchmuty & Nicolis, Bull.
Math. Biol. **38**, 325 (1976)

$$2X_1 + X_2 \underset{k_{-3}}{\overset{k_{+3}}{\rightleftharpoons}} 3X_1$$

$$X_1 \underset{k_{-4}}{\overset{k_{+4}}{\rightleftharpoons}} Y_4$$

$$T\dot{\Sigma} = -\mathrm{d}_t \mathbb{G} = RTc\,x_{\mathrm{eq}} \quad \sim \quad \text{Amplitude} \atop \text{Speed}$$

[Avanzini, Falasco & Esposito, *J. Chem. Phys.* **151**, 234103 (2019)]
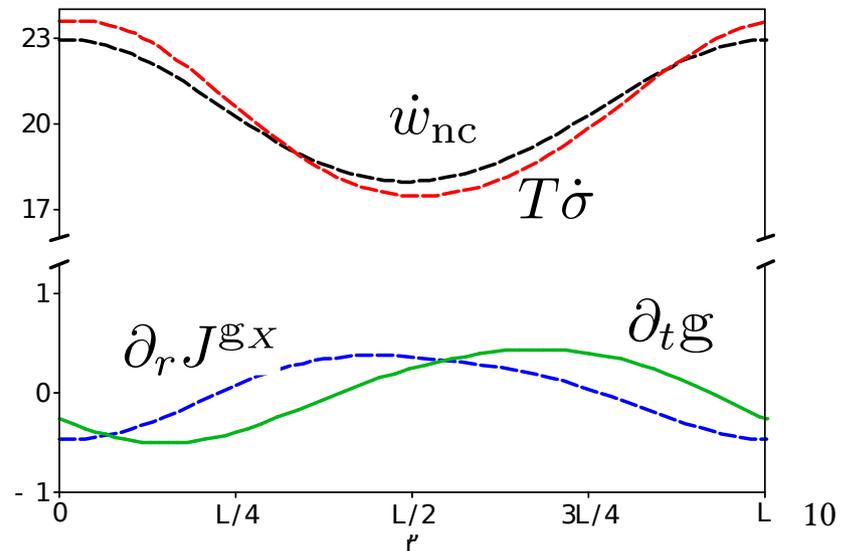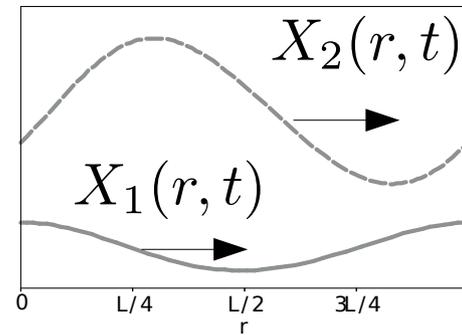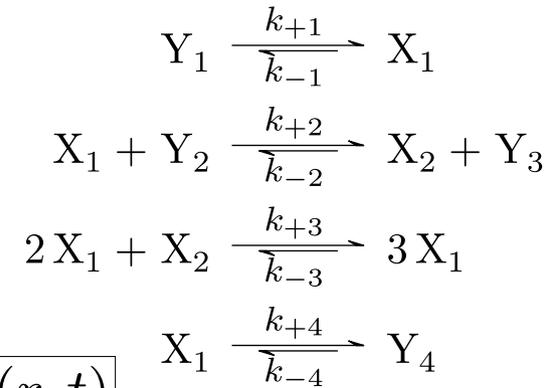
Chemical Cloaking and its Cost

- Pristine concentration gradient of Z :

- Impermeable object distorting the gradient:

- Preventing the object from distorting the gradient using the CRN:

$$A + Z \; \underset{k_-}{\overset{k_+}{\rightleftharpoons}} \; B + 2Z$$
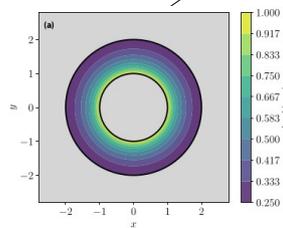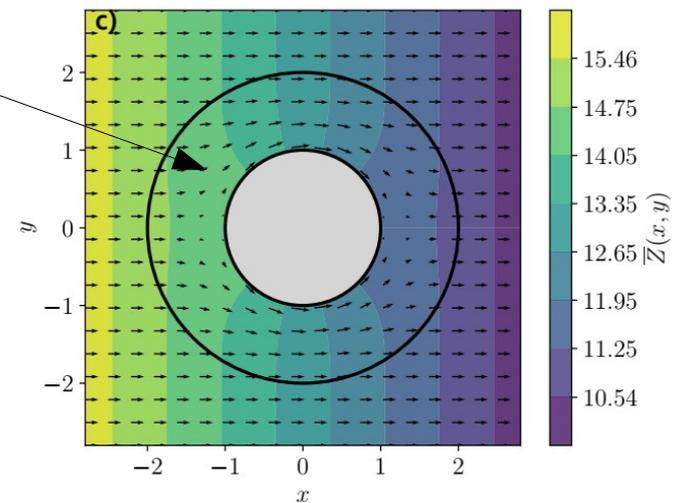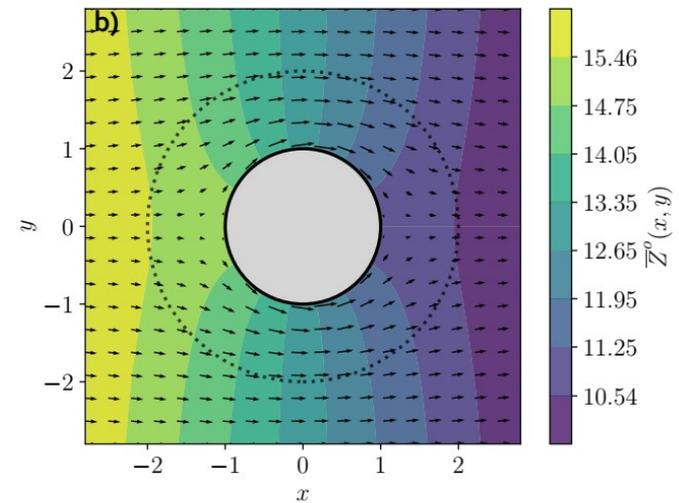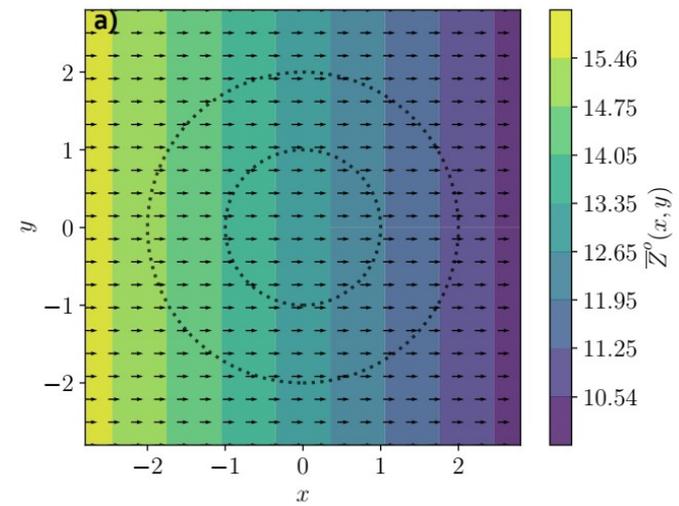
Chemostats
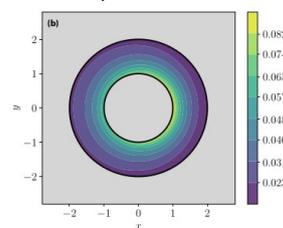
Significant part of the energy comes from the gradient!

Avanzini, Falasco, Esposito, PRE **101**, 060102(R) (2020)

II) Dissipative Self-Assembly
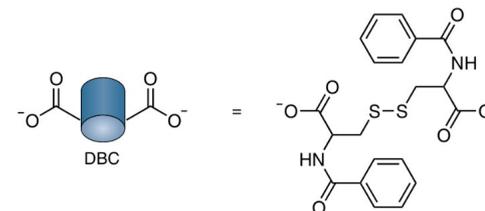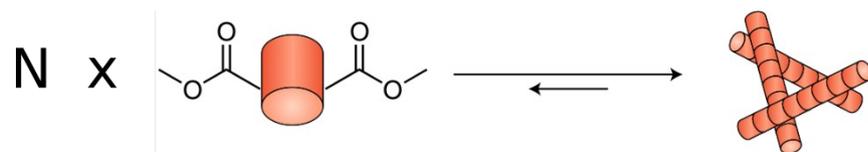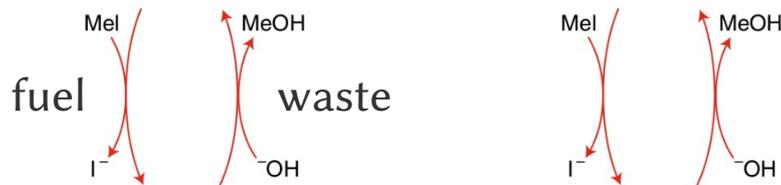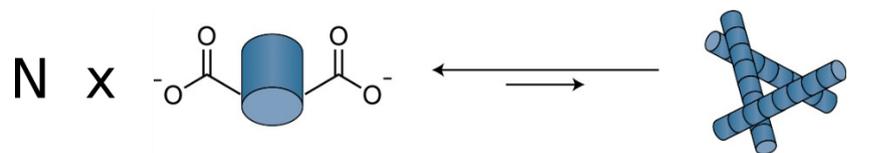

Boekhoven et al (2010)
Angew. Chem. Int. Ed. **49**, 4825
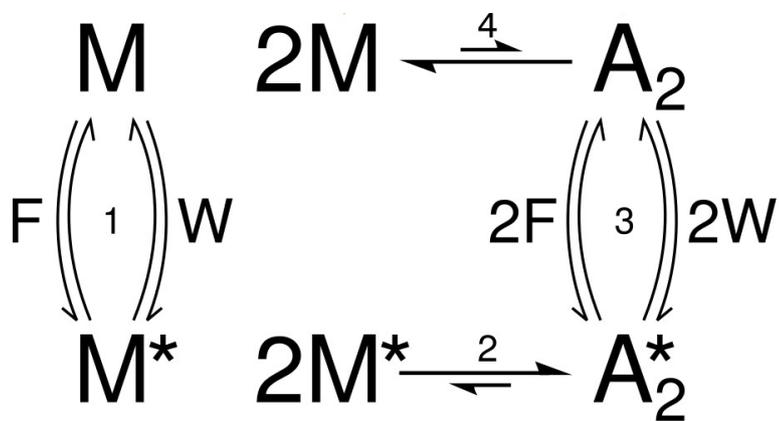
Ragazzon G. & Prins L. (2018)
Nature Nanotech. **13**, 882

[Penocchio, Rao & Esposito, *Nature Com.* **10**, 3865 (2019)]

Energy Storage
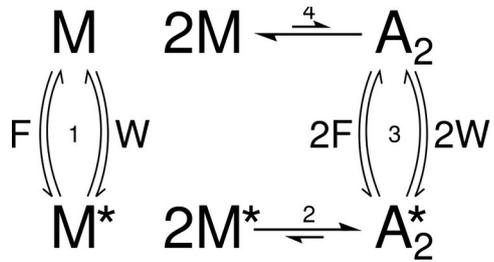
Analyzing open chemical systems as thermodynamic machines
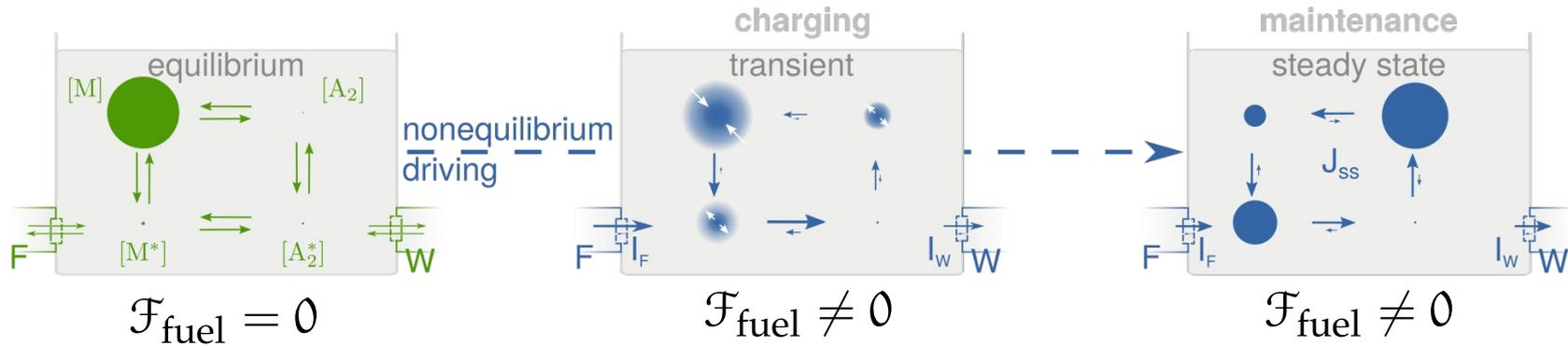
$$T\Sigma = \mathcal{W}_{\text{fuel}} - \Delta\mathcal{G} \geqslant 0$$

$$\underbrace{I_F \cdot (\mu_F - \mu_W) = I_F \cdot \mathcal{F}_{\text{fuel}}}$$

$$\eta_{\text{es}} = \frac{\Delta\mathcal{G}}{\mathcal{W}_{\text{fuel}}} = 1 - \frac{T\Sigma}{\mathcal{W}_{\text{fuel}}} \leqslant 1$$

[Penocchio, Rao & Esposito, *Nature Com.* **10**, 3865 (2019)]
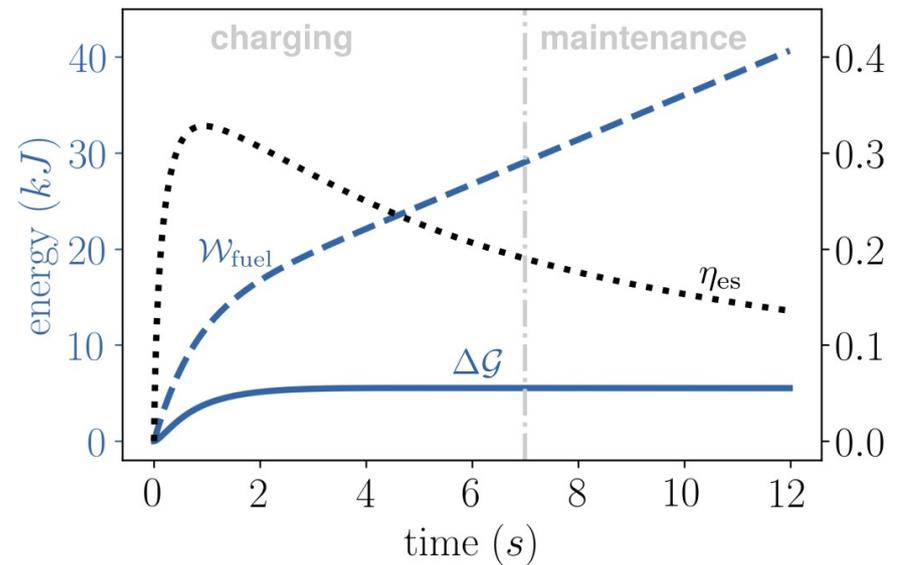
Dissipative Synthesis
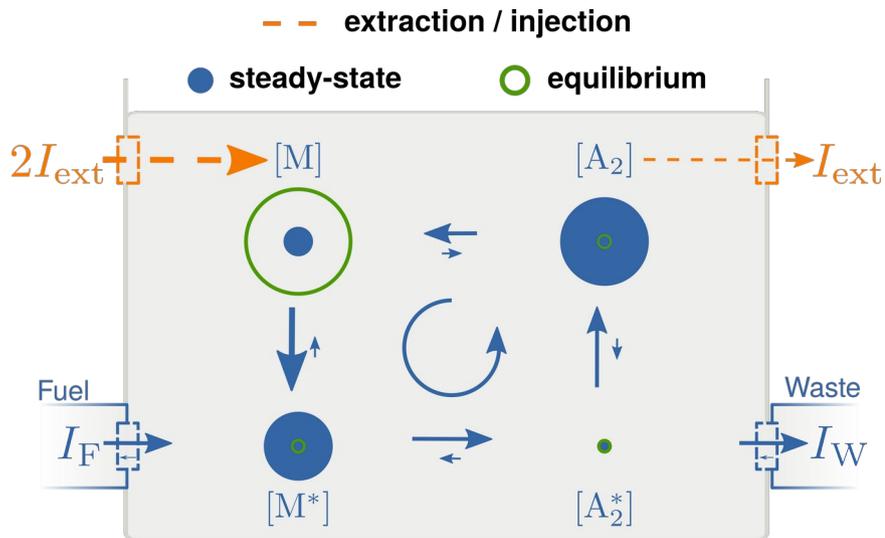
$$T\dot{\Sigma} = \dot{\mathcal{W}}_{\text{fuel}} + \dot{\mathcal{W}}_{\text{ext}} \geqslant 0$$

$$\underbrace{\quad}_{I_F \cdot \mathcal{F}_{\text{fuel}}} \qquad \underbrace{\quad}_{I_{\text{ext}} \cdot (2\mu_M - \mu_{A_2})}$$

$$\underbrace{\quad}_{k_{\text{ext}} \cdot [A_2]}$$

$$\eta_{\text{ds}} = -\frac{\dot{\mathcal{W}}_{\text{ext}}}{\dot{\mathcal{W}}_{\text{fuel}}} = 1 - \frac{T\dot{\Sigma}}{\dot{\mathcal{W}}_{\text{fuel}}} \leq 0$$

linear regime

[Penocchio, Rao & Esposito, *Nature Com.* **10**, 3865 (2019)]
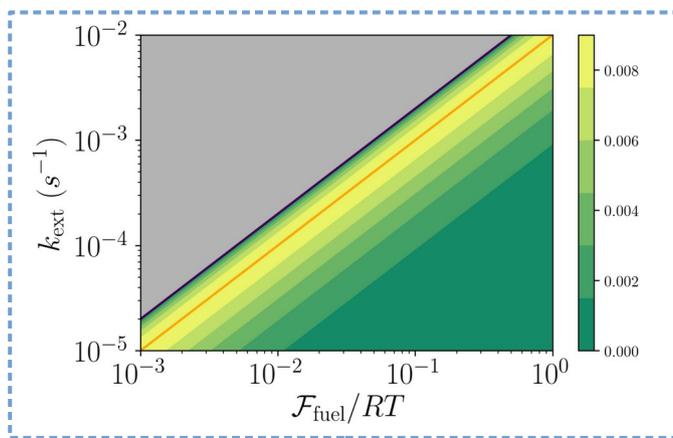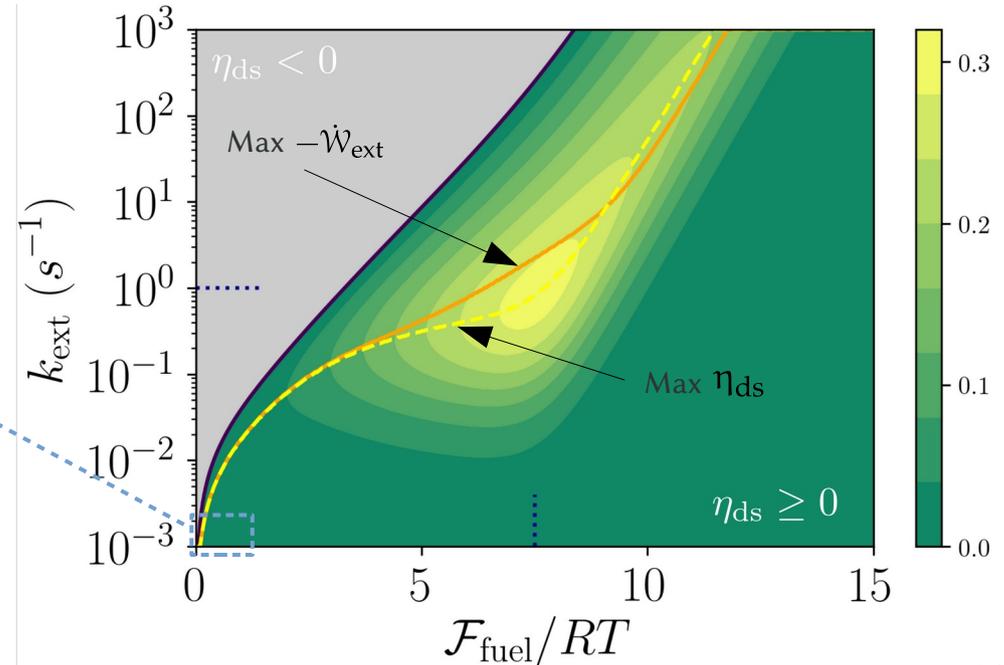
III) Stochastic formulation

- Dynamics: Chemical Master Equation

    - Infinite space of species abundances (n_A , $n_B \cdots$) instead of ($[A]$, $[B] \cdots$)

- Thermodynamics: Stochastic Thermodynamics in Infinite Spaces

    - The structure of thermodynamics is exactly the same

    - Entropy is now the Shannon entropy of the probability of species abundances
    $$S(\boldsymbol{n}) = -k_B \ln p_{\boldsymbol{n}} + \boxed{(s_{\boldsymbol{n}}^\circ \cdot \boldsymbol{n} - \ln \boldsymbol{n}!)}$$
    - Entropy production satisfies a fluctuation relation

    [Rao & Esposito, *J. Chem. Phys.* **149**, 245101 (2018)]

- From stochastic to deterministic description:

    - Linear CRN: full equivalence

    $$\langle \Sigma_{\text{stoch}} \rangle = \Sigma_{\text{det}}$$

    [Polettini, Wachtel & Esposito,
    J. Chem. Phys. **143**, 184103 (2015)]

    - Deficient CRN: equivalence at steady state

    - In general no equivalence, in particular in presence of phase transitions
   [Lazarescu, Cossetto, Falasco & Esposito, *J. Chem. Phys.* **151**, 064117 (2019)]

Accuracy in Dissipative Self-Assembly

Steady-state (long time limit of energy storage)
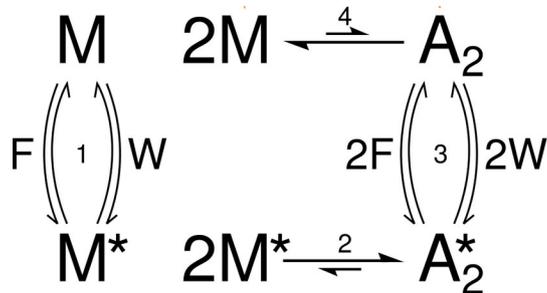
Stochasticity of species

$$SNR = \frac{\text{mean}}{\sqrt{\text{variance}}}$$
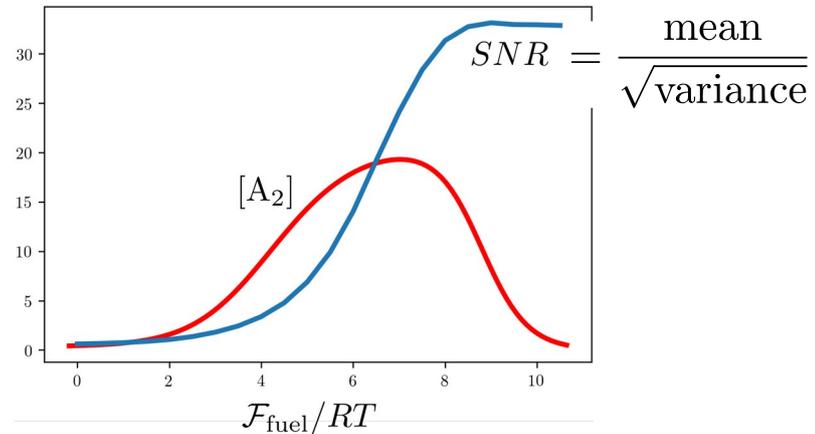
Stochasticity of currents

Thermodynamic Uncertainty Relation $\sqrt{\Sigma/2}$

SNR_4
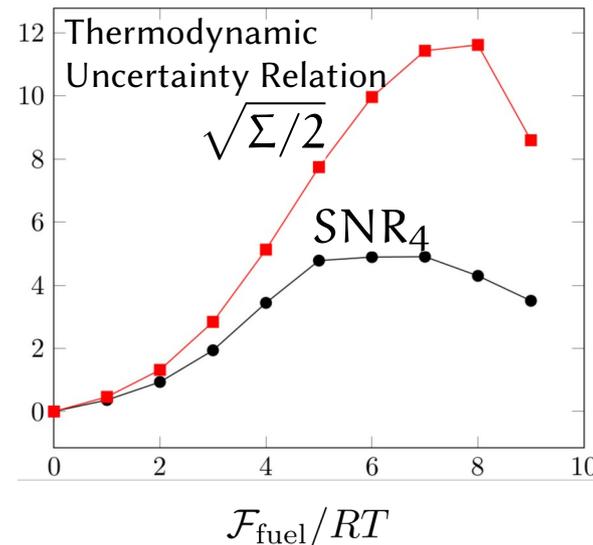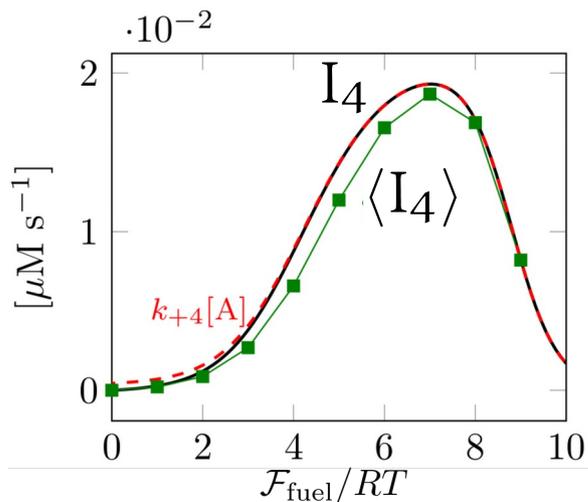
Higher accuracy away from equilibrium

[Falasco, Cossetto, Penocchio, & Esposito, *NJP* **21**, 073005 (2019)]

IV) Conclusions and Perspectives

- Fundamental findings:

    - Topology of a network shapes its thermodynamics

    - Thermo. and Info. are fundamentally related even at deterministic level

- Framework to asses the cost, accuracy and speed of various cellular operations:

    - Energy transduction from molecular motors to metabolism

    - Cost of cellular information processing and computation

- Perspectives:

    - How do energy and information constrain biology at higher levels?

    - Keeping track of energetics at higher levels is a major challenge

Supplementary Material

Thermodynamic Consistent Coarse graining

Correct dynamical coarse grainings can give rise to wrong thermodynamics !

One ϵ

Two ϵ

Emergent cycle ϵ

$$\mathcal{J}_\epsilon = \psi_\epsilon^+ - \psi_\epsilon^-$$

$$\mathcal{A}_\epsilon \overset{?}{=} RT \ln \frac{\psi_\epsilon^+}{\psi_\epsilon^-}$$
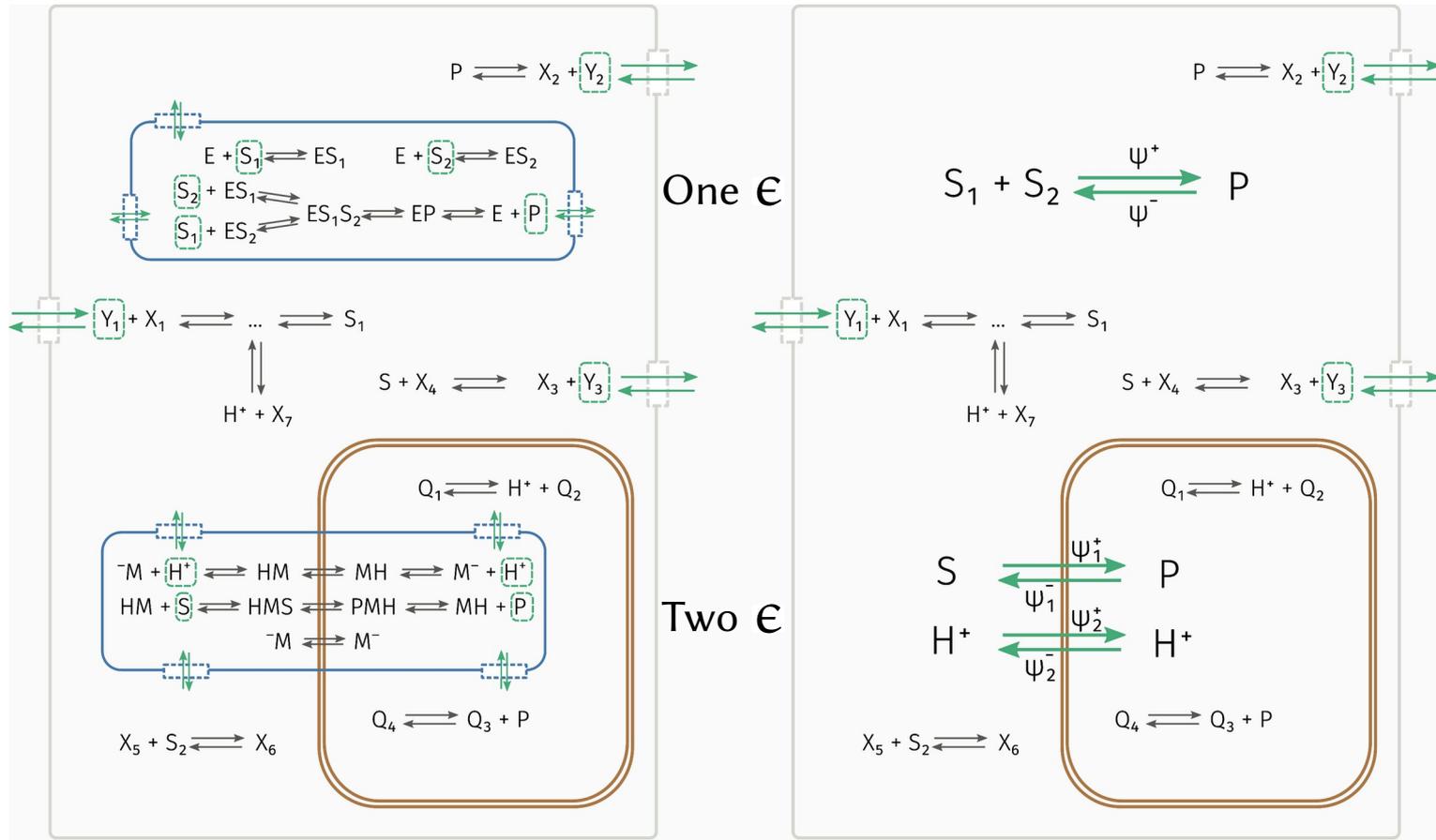
Only if one ϵ

$$\boxed{T\dot{\Sigma} = -\boldsymbol{\mu} \cdot \mathbb{S}_i \mathbf{J}_i} \quad \longrightarrow \quad \boxed{T\dot{\Sigma} = \sum_\epsilon \mathcal{A}_\epsilon \mathcal{J}_\epsilon}$$

Exact at steady-state

EP in the part to coarse-grained

[Wachtel, Rao & Esposito, *New J. Phys.* **20** 042002 (2018)]

Stochastic Dynamics of Open CRNs

State $\begin{pmatrix} n \\ [Y] \end{pmatrix}$

Internal: population

Chemostatted: concentrations

Probability p_n $\qquad$ ρ reactions
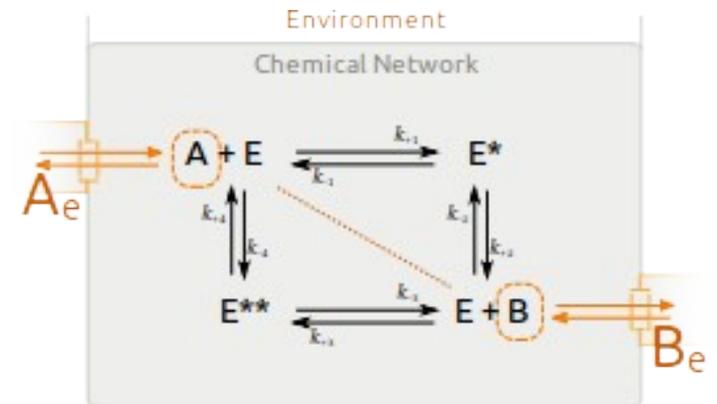
Chemical Master Equation

$$d_t p_n = \sum_\rho \left\{ w_{-\rho}\left(n + \mathbb{S}_\rho\right) p_{n+\mathbb{S}_\rho} - w_\rho\left(n\right) p_n \right\}$$

Stochastic Reaction Rates $\qquad w_\rho(n) = k_\rho [Y]^{\cdot \nu_\rho^Y} \dfrac{n!}{(n - \nu_\rho)!}$

Local Detailed Balance $\quad \ln \dfrac{w_\rho(n)}{w_{-\rho}(n + \mathbb{S}_\rho)} = -\beta \left[\left(g_{n+\mathbb{S}_\rho} - g_n\right) + \mu_Y \cdot \mathbb{S}_\rho^Y \right]$

$$g_n = \mu^\circ \cdot n + k_B T \ln n!$$

0th Law: Closed CN are Detailed-balanced $\qquad p_n^{\text{eq}} \propto e^{-\beta g_n}$

Stochastic Thermodynamics of CRNs

Stochastic Trajectory: $\mathfrak{n}_t \equiv n_0 \to n_1 \to \ldots \to n_t$ for given protocol π_t

Enthalpy: $H(n) = h^\circ \cdot n$
Entropy: $S(n) = -\ln p_n + (s_n^\circ \cdot n - \ln n!)$

reminder $S = (s^\circ - T \ln[\mathbf{Z}]) \cdot [\mathbf{Z}] + R[Z] + S_0$

Enthalpy Balance

Chemical Work   Entropy Flow

$$\Delta H[\mathfrak{n}_t] = \boxed{W_c[\mathfrak{n}_t]} + \boxed{Q[\mathfrak{n}_t]}$$

$$\| \qquad\qquad \geqslant$$

$$\int_{t_0}^t d\tau\, \boldsymbol{\mu}_Y \cdot \mathbf{I}^Y \qquad Q^{rct}[\mathfrak{n}_t] + T \int_{t_0}^t d\tau\, s_Y \cdot \mathbf{I}^Y$$

$$\underbrace{\qquad\qquad}_{\text{Heat Flow}} \quad \underbrace{\qquad\qquad\qquad}_{\substack{\text{Entropy exchanged} \\ \text{with the chemostats}}}$$

Entropy Balance

$$T\Delta S[\mathfrak{n}_t] = Q[\mathfrak{n}_t] + \boxed{T\Sigma[\mathfrak{n}_t]}$$

$$\geqslant$$

Entropy change · · · Entropy change in the reservoirs · · · Entropy production

$$k_B T \ln \frac{p_{n_0}(t_0)\, \mathcal{P}[\mathfrak{n}_t|\pi]}{p_{n_t}(t)\, \mathcal{P}[\mathfrak{n}_t^\dagger|\pi^\dagger]}$$

[Rao & Esposito, *J. Chem. Phys.* **149**, 245101 (2018)]

Stochastic Thermodynamics I

$$T\Sigma[\mathfrak{n}_t] = W_{\text{chem}}[\mathfrak{n}_t] - \Delta G[\mathfrak{n}_t]$$

$$W_{\text{chem}} = \int d\tau \, \boldsymbol{\mu}^Y(\tau) \cdot \mathbf{I}(\tau)$$

$$\langle G \rangle = \sum_{\boldsymbol{n}} p_{\boldsymbol{n}} \left[g_{\boldsymbol{n}} + k_B T \ln p_{\boldsymbol{n}} \right] = G_{\text{eq}} + k_B T \, \mathcal{D}\left(p | p_{\text{eq}}\right)$$

Relative Entropy $\quad \mathcal{D}\left(p | p_{\text{eq}}\right) = \sum_{\boldsymbol{n}} p_{\boldsymbol{n}} \ln \frac{p_{\boldsymbol{n}}}{p_{\boldsymbol{n}}^{\text{eq}}} \geqslant 0$

Stochastic Thermodynamics II

$$T\Sigma[\mathfrak{n}_t] = W_d[\mathfrak{n}_t] + W_{nc}[\mathfrak{n}_t] - \Delta\mathcal{G}[\mathfrak{n}_t]$$

$$W_d[\mathfrak{n}_t] = -\int d\tau \sum_{\lambda_b} \left[\partial_t f_{\lambda_b}(\boldsymbol{\mu}_{Y_p}(\tau))\right] \left[\boldsymbol{\ell}^{\lambda_b} \cdot \boldsymbol{n}_\tau\right]$$

$$W_{nc}[\mathfrak{n}_t] = \int d\tau \, \mathcal{F}_{Y_f}(\tau) \cdot \sum_\rho (-\mathbb{S}_\rho^{Y_f}) j_\rho(\tau)$$

$$\langle \mathcal{G} \rangle = \sum_{\boldsymbol{n}} p_{\boldsymbol{n}} \left[g_{\boldsymbol{n}} - \sum_{\lambda_b} f_{\lambda_b} \, L_{\boldsymbol{n}}^{\lambda_b} + k_B T \ln p_{\boldsymbol{n}}\right] = \mathcal{G}_{eq} + k_B T \, \mathcal{D}\left(p \middle| p_{eq}\right)$$

Relative Entropy $\quad \mathcal{D}\left(p \middle| p_{eq}\right) = \sum_{\boldsymbol{n}} p_{\boldsymbol{n}} \ln \frac{p_{\boldsymbol{n}}}{p_{\boldsymbol{n}}^{eq}} \geqslant 0$

23

[Rao & Esposito, *J. Chem. Phys.* **149**, 245101 (2018)]

Detailed Fluctuation Theorem

noneq: $\mathfrak{g}_n(\pi_t)$

relaxation: $\{\mathcal{F}_y = 0\}$

forward: π_τ

backward: $\pi_\tau^\dagger$

equilibrium: $\mathfrak{g}_n(\pi_0)$

equilibrium: $\mathfrak{g}_n(\pi_t)$
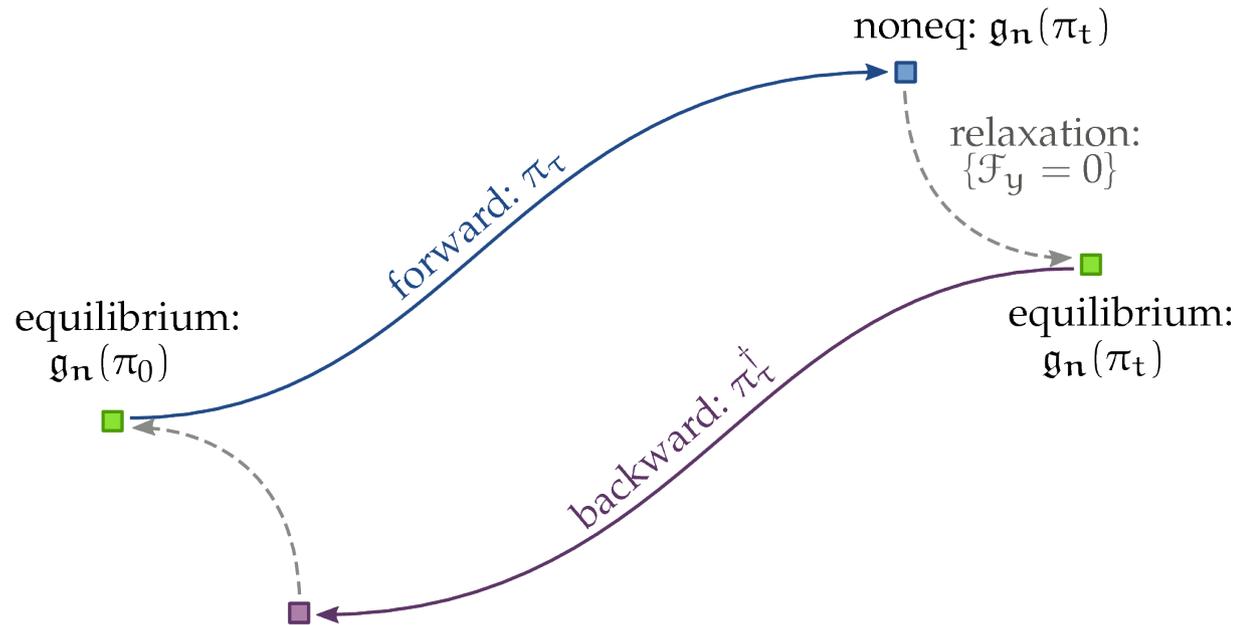
$$\frac{P_t(W_d, W_{nc})}{P_t^\dagger(-W_d, -W_{nc})} = \exp\left\{\beta\left(W_d + W_{nc} - \Delta \mathcal{G}_{eq}\right)\right\}$$

Initial state $\quad p_n^{eq} \propto e^{-\beta \mathfrak{g}_n}$

[Rao & Esposito, *J. Chem. Phys.* **149**, 245101 (2018)]

Deficiency and Complex-Balanced CRNs

Deficiency

$$\delta = \dim \ker \mathbb{S}^X - \dim \ker \partial^{\text{open}}$$

$$\delta = 0 \quad \Rightarrow \quad \text{Complex-Balanced CN}$$

Complex-Balanced Steady State $[\bar{\mathbf{X}}]$

Multi-Poisson SS distribution $\quad \bar{p}_{\boldsymbol{n}} = \mathcal{N} \dfrac{\boldsymbol{\lambda}^{\cdot \boldsymbol{n}}}{\boldsymbol{n}!}$

Example: *nondeficient*

$$m = 0 \Rightarrow \delta = 0$$

Example: *deficient*

$$2\,E \xleftrightarrow{\;3\;} \varnothing \xleftrightarrow{\;1\;} N$$

$$N + m\,E \xleftrightarrow{\;2\;} (m+2)\,E$$

$$m \geqslant 1 \Rightarrow \delta = 1$$

[Horn & Jackson, 1972], [Feinberg, 1972], [Anderson, Craciun, Kurtz, 2010]
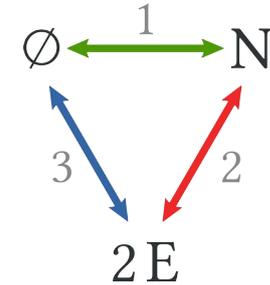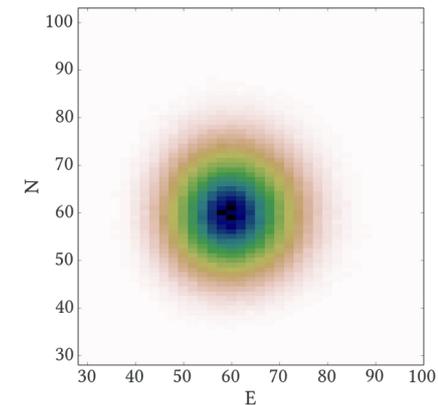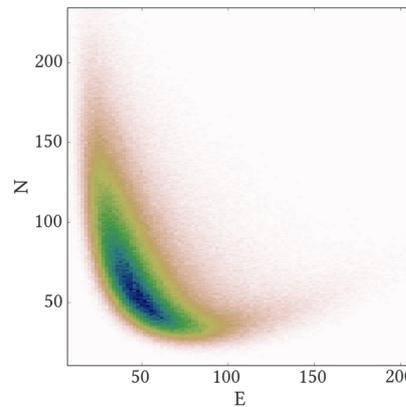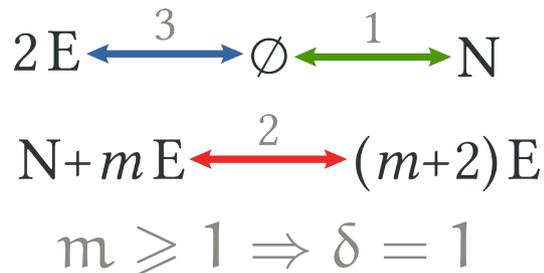
Thermo of Complex-Balanced CRNs

Average Stochastic Entropy Production

=

Deterministic Entropy Production

$$\left\langle \dot{\Sigma}_{\text{stoch}} \right\rangle = \dot{\Sigma}_{\text{det}}$$

[Polettini, Wachtel & Esposito, *J. Chem. Phys.* **143**, 184103 (2015)]
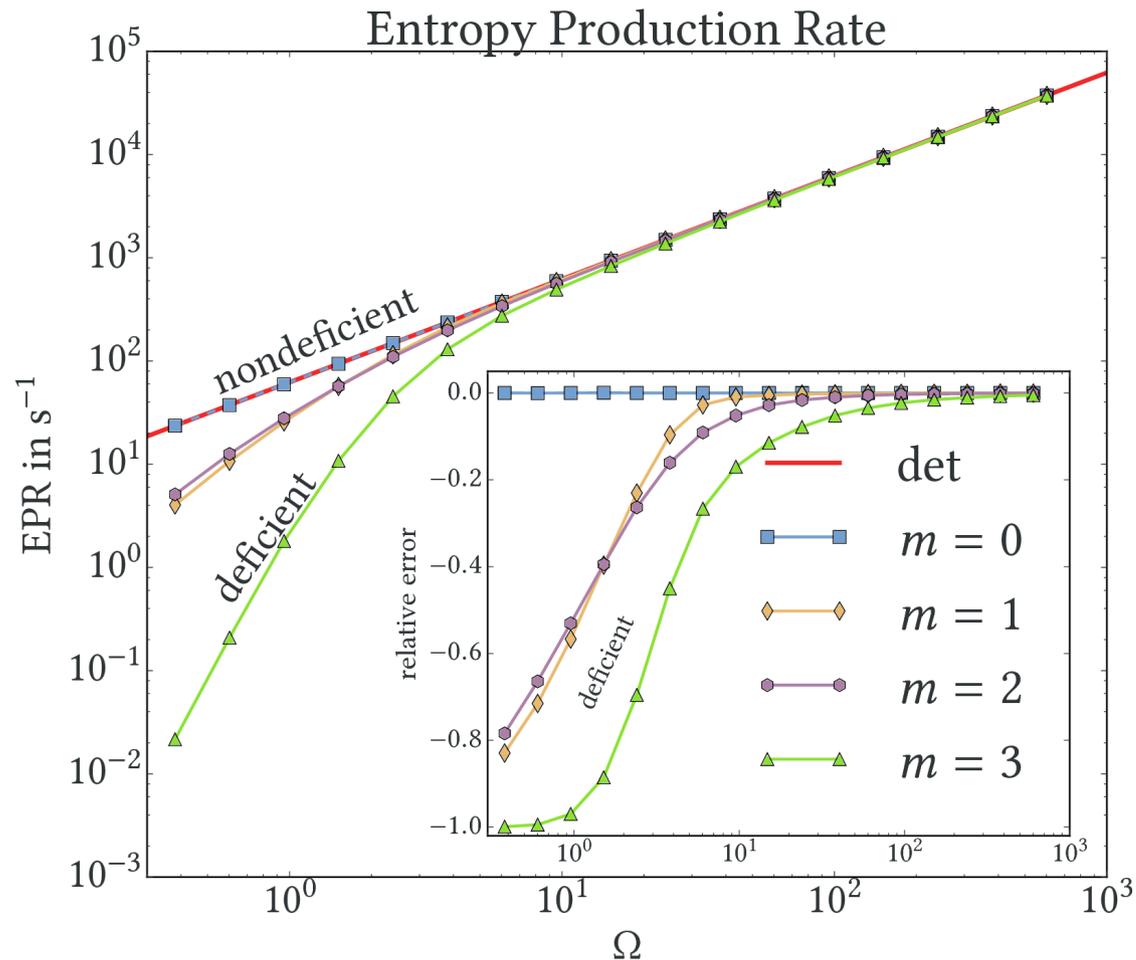
Thermo of Complex-Balanced CRNs

Adiabatic—Nonadiabatic decomposition of the deterministic entropy production

$$\mathrm{T}\dot{\Sigma} = \underbrace{-\bar{\boldsymbol{\mu}} \cdot \mathbb{S}\mathbf{J}}_{\substack{\textit{Adiabatic} \\ \dot{\Sigma}_\mathrm{a} \geqslant 0}} \underbrace{- \mathrm{d}_\mathrm{t}[\boldsymbol{X}] \cdot \mathrm{RT}\, \ln \frac{[\boldsymbol{X}]}{[\bar{\boldsymbol{X}}]}}_{\substack{\textit{Nonadiabatic} \\ \dot{\Sigma}_\mathrm{na} \geqslant 0}} \geqslant 0$$

$$= \underbrace{-\mathrm{RT}\, \mathrm{d}_\mathrm{t}\mathcal{L}\left([\boldsymbol{X}] \| [\bar{\boldsymbol{X}}]\right)}_{\textit{Relaxation}} + \underbrace{\mathrm{RT}\mathrm{d}_\mathrm{t}[\bar{\mathrm{X}}] - [\boldsymbol{X}] \cdot \mathrm{d}_\mathrm{t}\bar{\boldsymbol{\mu}}_\mathrm{X}}_{\substack{\dot{\Sigma}_\mathrm{d} \\ \textit{Driving}}}$$

Landauer Principle III

$$\Sigma_\mathrm{a} + \Sigma_\mathrm{d} = \mathrm{RT}\Delta\mathcal{L} + \Sigma$$
$$\geqslant 0$$

[Rao & Esposito, *Phys. Rev. X* **6**, 041064 (2016)]