Stochastic Chemical Reaction Networks

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Krishnamurthy and Smith; J Phys A: Math and Theor. (2017); Smith and Krishnamurthy; PRE (2017); Smith and Krishnamurthy; J Phys A: Math and Theor. (2021)

Examples

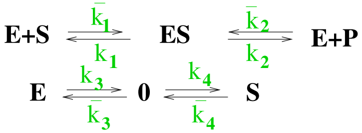
Enzyme kinetics

$$\mathbf{E+S} \underset{k_1}{\overset{\bar{k}_1}{\rightleftarrows}} \mathbf{ES} \underset{k_2}{\overset{\bar{k}_2}{\leftrightarrows}} \mathbf{E+P}$$

$$\mathbf{E} \underset{\bar{k}_3}{\overset{k_3}{\rightleftarrows}} \mathbf{0} \underset{\bar{k}_4}{\overset{k_4}{\rightleftarrows}} \mathbf{S}$$

Examples

Enzyme kinetics



Modelling:

• Deterministically in terms of concentrations of the species and products

$$\frac{d[S]}{dt} = -\overline{k_1}[E][S] + k_1[ES] + k_4 - \overline{k_4}[S]$$

Examples

Enzyme kinetics

$$\mathbf{E+S} \underset{k_1}{\overset{\bar{k}_1}{\rightleftharpoons}} \mathbf{ES} \underset{k_2}{\overset{\bar{k}_2}{\leftrightharpoons}} \mathbf{E+P}$$

$$\mathbf{E} \underset{\bar{k}_3}{\overset{k_3}{\rightleftharpoons}} \mathbf{0} \underset{\bar{k}_4}{\overset{k_4}{\rightleftharpoons}} \mathbf{S}$$

Modelling:

- Deterministically in terms of concentrations of the species and products
- Stochastically (if numbers are low)
- Diffusion approximations
- Hybrid[1]

[1] Asymptotic analysis of Multiscale approximations to reaction networks, **Ball** *et al*, Annals Appl. Prob. (2006)

Examples

CRN's in ecology (Lotka-Volterra)

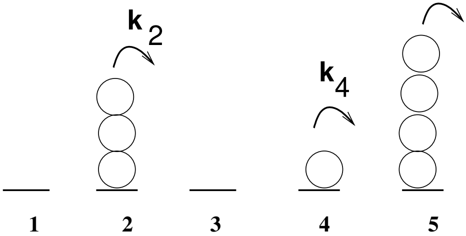
$$\mathbf{X} \longrightarrow \mathbf{2X}$$

$$\mathbf{X+Y} \longrightarrow \mathbf{2Y}$$

$$\mathbf{Y} \longrightarrow \mathbf{0}$$

Examples

CRN's in physics (the zero-range process)

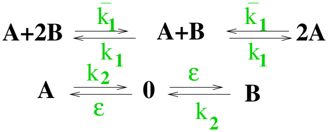


$$S_1 \xrightarrow{k_1} S_2 \xrightarrow{k_2} S_3 \xrightarrow{k_3} S_4 \xrightarrow{k_4} S_5$$

Stochastic models: two examples

$$A \underset{\varepsilon}{\overset{\alpha}{\rightleftharpoons}} 2A \underset{\varepsilon}{\overset{\beta}{\leftrightharpoons}} 3A$$

Stochastic models: two examples



(Stochastic) Mass action kinetics

$$\mathrm{A} \underset{\epsilon}{\overset{\alpha}{\rightleftharpoons}} 2\mathrm{A}$$

- A converts to $2\ \mathrm{A}$ at a rate $\alpha \mathrm{n}_a$
- $2\mathrm{A}$ converts to A at a rate $\epsilon \mathrm{n}_a(\mathrm{n}_a - 1)$

(Stochastic) Mass action kinetics

$$2\mathrm{B} + \mathrm{A} \underset{k_1}{\overset{\bar{k}_1}{\rightleftharpoons}} \mathrm{A} + \mathrm{B}$$

- $2\mathrm{B} + \mathrm{A}$ converts to $\mathrm{A} + \mathrm{B}$ at rate $\bar{k}_1 \mathrm{n}_b(\mathrm{n}_b - 1)\mathrm{n}_a$
- $\mathrm{A} + \mathrm{B}$ converts to $2\mathrm{B} + \mathrm{A}$ at rate $k_1 \mathrm{n}_a \mathrm{n}_b$

Other kinetics

- Michaelis Menton kinetics $\rightarrow \frac{k_1 \mathrm{n}}{k_2+\mathrm{n}}$
- Hill-type kinetics $\rightarrow \frac{\mathrm{n}^m}{k+\mathrm{n}^m}$

- Modeling via Master equations

$$A \underset{\varepsilon}{\overset{\alpha}{\rightleftharpoons}} 2A \underset{\varepsilon}{\overset{\beta}{\leftrightharpoons}} 3A$$

$$\begin{aligned}\dot{\rho}_{\mathrm{n}} = \ & \rho_{\mathrm{n}-1}\left[\alpha(\mathrm{n}-1)+\epsilon \mathrm{n}\,(\mathrm{n}-1)\right] \\ & +\rho_{\mathrm{n}+1}\left[\epsilon(\mathrm{n}+1)\mathrm{n}+\beta(\mathrm{n}+1)\mathrm{n}\,(\mathrm{n}-1)\right] \\ & -\rho_{\mathrm{n}}\left[\epsilon \mathrm{n}(\mathrm{n}+1)+\beta \mathrm{n}(\mathrm{n}-1)\,(\mathrm{n}-2)+\epsilon \mathrm{n}(\mathrm{n}-1)+\alpha \mathrm{n}\right].\end{aligned}$$

- Solve for ρ_{n} or alternately for moments $\langle \mathrm{n}^{\mathrm{k}} \rangle$
- We will only talk about steady states here.

Anderson and Kurtz, *Stochastic Analysis of Biochemical Systems (2015)*

$$A \underset{\varepsilon}{\overset{\alpha}{\rightleftharpoons}} 2A \underset{\varepsilon}{\overset{\beta}{\leftrightharpoons}} 3A$$

- Equation for the first moment

$$\langle \dot{n} \rangle = \alpha \langle n \rangle - \beta \left\langle \frac{n!}{(n-3)!} \right\rangle$$

- Equation for the second moment

$$\langle \dot{n}^2 \rangle = 2\alpha \langle n^2 \rangle + \alpha \langle n \rangle + 2\epsilon \left\langle \frac{n!}{(n-2)!} \right\rangle + \beta \left\langle \frac{n!}{(n-3)!} \right\rangle - 2\beta \langle n^2 (n-1)(n-2) \rangle$$

- Factorial Moments

$$\mathrm{n}_p^{\underline{k_p}} \equiv \frac{\mathrm{n}_p!}{(\mathrm{n}_p - k_p)!} \qquad ;\ k_p \leq \mathrm{n}_p$$

$$\equiv 0 \qquad ;\ k_p > \mathrm{n}_p.$$

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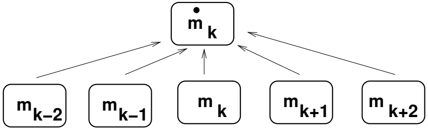
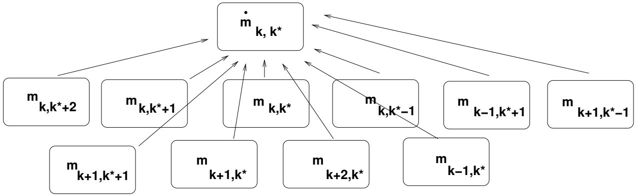
$$\left\langle \mathrm{n}^{\underline{k}} \right\rangle \equiv \left\langle \prod_p \mathrm{n}_p^{\underline{k_p}} \right\rangle.$$

- For more than one species $k \equiv [k_p]$ and $\mathrm{n} \equiv [\mathrm{n}_p]$.

- (Factorial) Moment Hierarchy



- (Factorial) Moment Hierarchy



Solution of Moment hierarchies:

- If the system is in equilibrium (detailed balance)

Solution of Moment hierarchies:

- If the system has *deficiency* $\delta = 0$

The notion of Deficiency

$$\delta = \mathcal{C} - l - s$$

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$$\mathbf{A+2B} \underset{k_1}{\overset{\bar{k}_1}{\rightleftharpoons}} \mathbf{A+B} \underset{k_1}{\overset{\bar{k}_1}{\leftrightharpoons}} \mathbf{2A+B}$$

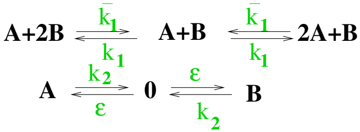
$$\mathbf{A} \underset{\varepsilon}{\overset{k_2}{\rightleftharpoons}} \mathbf{0} \underset{k_2}{\overset{\varepsilon}{\rightleftharpoons}} \mathbf{B}$$

$$A \rightarrow \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

$$B \rightarrow \begin{bmatrix} 0 \\ 1 \end{bmatrix}$$

The notion of Deficiency

$$\delta = \mathcal{C} - l - s$$



$$\begin{bmatrix} 0 \\ -1 \end{bmatrix}; \begin{bmatrix} +1 \\ 0 \end{bmatrix}; \begin{bmatrix} -1 \\ 0 \end{bmatrix}; \begin{bmatrix} 0 \\ +1 \end{bmatrix}$$

$\mathcal{C} = 6,\ l = 2,\ s = 2 \Rightarrow \delta = 2$

The Deficiency zero theorem

Theorem

If a CRN is weakly reversible then, for mass action kinetics, the rate equations will have precisely one steady state, within each positive stoichiometric compatibility class. This steady state is asymptotically stable .

Feinberg and Horn *1977*; Horn and Jackson *1972*; Feinberg*1979,1987*

Anderson-Craciun-Kurtz (ACK) Theorem

Theorem

If a CRN modeled deterministically satisfies the condition of the deficiency zero theorem, then the stochastically modeled mass action system has a product-form stationary distribution .

Anderson, Craciun and Kurtz, *2010*

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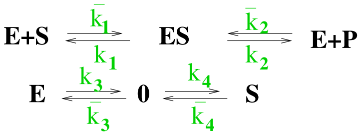

$$\rho(n_1, n_2, n_3, n_4) = \Pi_i e^{-c_i} \frac{c_i^{n_i}}{n_i!}$$

Deficiency is easy to compute even for very complicated networks

Taken from the supplementary material of Eloundou-Mbebi, et al. Nat Commun 7, 13255 (2016).

network	NADH	NAD	NADP	NADPH	ATP	ADP	AMP	number of metabolites satisfying necessary condition for ACR	number of metabolites	number of reactions*	deficiency
M acetivorans iMB745								250	715	892	138
M barkeri iAF692								204	628	741	92
E coli Carbon								5	48	104	27
E coli Core	c	c	c		c			14	52	114	26
E coli iJO1366								322	1805	3243	768
M pneumoniae iJW145								85	214	321	58
M tuberculosis iNJ661								309	826	1085	209
T maritima								143	491	627	104
P putida iJN746								247	909	1314	172
A niger								765	1177	1505	309
C reinhardtii AM303			c,h		h,m,c			133	220	294	58
Arabidopsis core	c,h	c,h,p,m	m	cm,c				292	407	624	110
M musculus								1719	2110	1144	291
H sapiens		m	c,m	c,r				1735	2766	2993	794

Supplementary Table 2: **Metabolic networks for which ACR is tested.** (h=chloroplast; c=cytosol; m=mitochondria; p=peroxisome; f=flagellum). The table includes the compartments of the energy related metabolites, the number of metabolites which do not violate the necessary condition, the number of metabolites, reactions, and the deficiency of the network. * Blocked reactions are removed from the model as they preclude the existence of positive steady state. The number of reactions refer to that in the models modiefied in such way and in which reversible reactions were split into two irreversible reactions.

Results for the Steady-states of $\delta \neq 0$ networks

- $\phi(z) \equiv \sum_{\mathrm{n}} \left(\prod_{p=1}^{P} z_p^{\mathrm{n}_p} \right) \rho_{\mathrm{n}}$
-

$$\frac{\partial}{\partial \tau} \phi(z) = -\mathcal{L}\left(z, \frac{\partial}{\partial z} \right) \phi(z)\,.$$

Results for the Steady-states of $\delta \neq 0$ networks

$$\frac{\partial}{\partial \tau} \left\langle \mathrm{n}^{\underline{k_p}}_{p} \right\rangle = \sum_{j=0}^{k_p} \left(\begin{array}{c} k_p \\ j \end{array} \right) (Y_p)^{\underline{j}} \mathcal{A} E \left[\psi \left(\mathrm{n}^{\underline{y_p + k - j}} \right) \right]$$

Results for the Steady-states of $\delta \neq 0$ networks

$$\frac{\partial}{\partial \tau} \left\langle \mathrm{n}_{\underline{p}}^{\underline{k_p}} \right\rangle = \sum_{j=0}^{k_p} \left(\begin{array}{c} k_p \\ j \end{array} \right) (\mathrm{Y}_p)^{\underline{j}} \mathcal{A} E \left[\psi \left(\mathrm{n}^{\underline{y_p + k - j}} \right) \right]$$

$$\begin{aligned}(\mathrm{Y}_p)^{\underline{1}} = Y &\rightarrow \left[\begin{array}{ccc} 1 & 2 & 3 \end{array} \right] \\ (\mathrm{Y}_p)^{\underline{2}} &\rightarrow \left[\begin{array}{ccc} 0 & 2 & 6 \end{array} \right] \\ (\mathrm{Y}_p)^{\underline{3}} &\rightarrow \left[\begin{array}{ccc} 0 & 0 & 6 \end{array} \right]\end{aligned}$$

$$\mathcal{A} = \left[\begin{array}{ccc} -\alpha & \epsilon & 0 \\ \alpha & -2\epsilon & \beta \\ 0 & \epsilon & -\beta \end{array} \right]$$

$$\psi \left(\mathrm{n}^{\underline{y_p}} \right) = \left[\begin{array}{c} n^{\underline{1}} \\ n^{\underline{2}} \\ n^{\underline{3}} \end{array} \right]$$

In the Steady State

$$0 = \sum_{j=0}^{k} \binom{k}{j} (Y_p)^{\underline{j}} \mathcal{A} E \left[\psi \left(\mathrm{n}^{\underline{y_p + k - j}} \right) \right]$$

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- If $\delta = 0$, all steady states lie in $\ker(\mathcal{A})$
- if $\mathcal{A}E[\psi(\mathrm{n})] = 0$, entire moment hierarchy is satisfied.

In the Steady State

$$0 = \sum_{j=0}^{k} \binom{k}{j} (Y_p)^{\underline{j}} \mathcal{A} E \left[\psi \left(\mathrm{n}^{\underline{y_p + k - j}} \right) \right]$$

- How can we satisfy the moment hierarchy if $\delta \neq 0$?

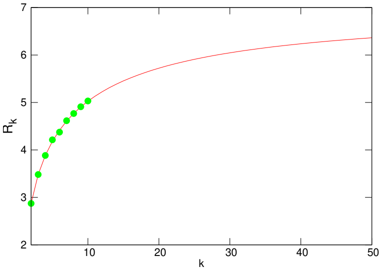
Steady-State Recursions

- Define $R_k \equiv \frac{\langle \underline{\mathrm{n}^{k}} \rangle}{\langle \underline{\mathrm{n}^{k-1}} \rangle}$

$$R_k = \frac{(k-1)\left(\frac{\alpha}{\beta} + \frac{\epsilon}{\beta}(k-2)\right)}{(k-1)\left(2R_{k+1} + (k-2) - \frac{\epsilon}{\beta}\right) + R_{k+2}R_{k+1} - \frac{\alpha}{\beta}}$$

Steady-State Recursions

$\alpha = 100$, $\beta = 10$, $\epsilon = 70$. For large k, R_k saturates to $\epsilon/\beta = 7$.



Some open questions

- More implications of deficiency
- Applicability to quasi steady states
- Large deviation approximations
- Methods for larger networks?