Two Notions of Flux in Biochemical Reaction Networks

J. F. Lynch

Workshop on Logic and Systems Biology 2016

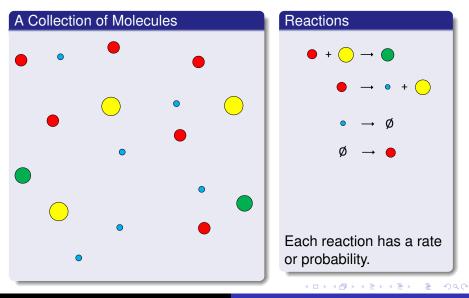
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Biochemical Reaction Networks

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Classical Chemical Kinetics

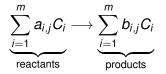


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Two Notions of Flux in Biochemical Reaction Networks

Assume there are chemical species (compounds) C_1, \ldots, C_m and *n* reactions.

For j = 1, ..., n, reaction j has the general form



The reactants consist of $a_{i,j}$ instances of each species C_i . The products consist of $b_{i,j}$ instances of each species C_i .

When the reaction occurs (instantaneously), the reactants are replaced by the products.

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The Stoichiometric Matrix

The effect of each reaction on each species is summarized by the stoichiometric matrix:

$$S = \begin{bmatrix} b_{11} - a_{11} & \dots & b_{1n} - a_{1n} \\ \vdots & \ddots & \vdots \\ b_{m1} - a_{m1} & \dots & b_{mn} - a_{mn} \end{bmatrix}$$

Let p_i be the population size of species C_i for i = 1, ..., m. For any j = 1, ..., n, let $e_j = 1$ and $e_k = 0$ for $k \neq j$. Then

$$\begin{bmatrix} p_1 \\ \vdots \\ p_m \end{bmatrix} + S \begin{bmatrix} e_1 \\ \vdots \\ e_n \end{bmatrix}$$

is the vector of population sizes after one occurence of reaction *j*.

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It follows that for any $r_1, \ldots, r_n \in \mathbb{N}$

$$\begin{bmatrix} p_1 \\ \vdots \\ p_m \end{bmatrix} + S \begin{bmatrix} r_1 \\ \vdots \\ r_n \end{bmatrix}$$

is the vector of population sizes after r_j occurrences of reaction j for j = 1, ..., n.

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Two Models of Mass-Action Kinetics

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States are vectors $[p_1, \ldots, p_m]^T$ over \mathbb{N} . Each p_i is the population size of species C_i .

Each reaction *j* has a base rate $\rho_j \in [0, \infty)$:

Let
$$k_j = \sum_{i=1}^{m} a_i$$
 be the total number of reactants of reaction j ,
 $V =$ volume of container

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For any choice of reactants for reaction *j*, in the absence of any other reaction, the time *t* until they participate in reaction *j* is an exponential rv with rate parameter ρ_i/V^{k_j-1} :

- The probability that reaction *j* occurs once within time Δt is $(\rho_j/V^{k_j-1})\Delta t + o(\Delta t)$ as $\Delta t \rightarrow 0$.
- The pdf of t is

$$(\rho_j/V^{k_j-1})e^{-(\rho_j/V^{k_j-1})t}$$

The cdf of t is

$$1 - e^{-(\rho_j/V^{k_j-1})t}$$

Let μ_j be the number of ways of choosing the reactants for reaction *j*.

Then in the absence of any other reaction, the time *t* until reaction *j* occurs is an exponential rv with rate parameter $\mu_j \rho_j / V^{k_j-1}$ (sometimes called the propensity of the reaction).

Examples

- Suppose reaction *j* is $C_5 \rightarrow 3C_1 + C_4$. Then the propensity is $p_5\rho_j$.
- If reaction *j* is $C_5 + C_7 \longrightarrow 3C_1 + C_4$ then the propensity is $p_5 p_7 \rho_j / V$.
- If reaction *j* is $2C_5 \longrightarrow 3C_1 + C_4$ then the propensity is $p_5(p_5 - 1)\rho_j/(2V)$.

We approximate the stochastic dynamics by its average behavior.

Let $\pi_j = \mu_j \rho_j / V^{k_j-1}$ be the propensity of reaction *j*. Since the probability that reaction *j* occurs once within time Δt is $\pi_j \Delta t + o(\Delta t)$ as $\Delta t \rightarrow 0$, the average rate of reaction *j* is π_j . We also replace the population sizes p_1, \ldots, p_m by concentrations c_1, \ldots, c_m :

$$c_i = p_i / V$$
 for $i = 1, ..., m$

This accomplishes two things:

- It scales the state variables to more manageable ranges.
- It removes the dependency of reaction rates on V (when V is large).

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A Deterministic Continuous State Model

Example

If reaction *j* is $2C_5 \rightarrow 3C_1 + C_4$, then $\pi_j = p_5(p_5 - 1)\rho_j/(2V)$. Each occurrence of reaction *j* increases c_1 by 3/V. Therefore the rate of change of c_1 due to reaction *j* is

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ho_j}{2}. \end{aligned}$$

The factor $c_5^2 \rho_j / 2$ is the flux of reaction *j*.

In general, the propensity $\pi_j = \mu_j \rho_j / V^{k_j-1}$ is a polynomial of degree k_j in the variables p_1, \ldots, p_m with only one term of degree k_j . Therefore

$$\lim_{V\to\infty}\pi_j/V=\varphi_j$$

is a monomial in c_1, \ldots, c_m of degree k_i .

 φ_j is the flux of reaction *j*,

the average rate of the reaction in a unit of volume (for large V).

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A Deterministic Continuous State Model

Since $b_{ij} - a_{ij}$ is the net effect of reaction *j* on the population of species C_i , $(b_{ij} - a_{ij})\varphi_j$ is the average rate of change of c_i due to reaction *j*.

Therefore $\sum_{j=1}^{n} (b_{ij} - a_{ij})\varphi_j(t)$ is the average rate of change of c_i .

It can be shown that for large V, with high probability the stochastic dynamics is close to its average behavior¹.

So we can approximate the discrete stochastic model with a deterministic continuous model:

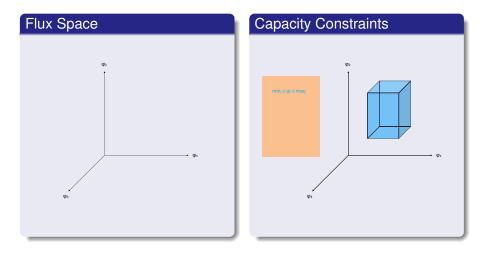
$$\begin{bmatrix} \frac{dc_1}{dt} \\ \vdots \\ \frac{dc_m}{dt} \end{bmatrix} = S \begin{bmatrix} \varphi_1 \\ \vdots \\ \varphi_n \end{bmatrix}$$

¹T. G. Kurtz, Limit Theorems for Sequences of Jump Markov Processes Approximating Ordinary Differential Processes, *J. App. Prob.* 8 (1971)

Flux Plays a Central Role in Systems Biology²

²B. Ø. Palsson, Systems Biology, Cambridge (2007) + CO + CE

Constraint-Based Flux Analysis

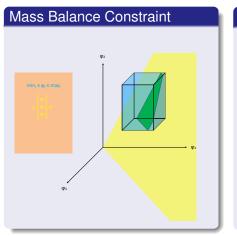


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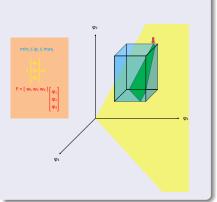
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Constraint-Based Flux Analysis



Optimize Objective Function



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Finding dominant fluxes

Large $\varphi_j \Longrightarrow$ reaction *j* is "important."

Sometimes a reaction network can be simplified by removing all "unimportant" reactions.

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Analyzing causality

For $i \in \{1, ..., m\}$ and $j, k \in \{1, ..., n\}$, let

$$\phi_{i,j,k} = b_{i,j}\varphi_j \times \frac{a_{i,k}\varphi_k}{\sum_{l=1}^n a_{i,l}\varphi_l},$$

the flow rate of species i from reaction j to k.

High flow rates \implies strong influences.

Groups of reactions with large mutual flow rates are evidence of "modules" within reaction networks.

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Flux in Discrete Stochastic Systems

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Recall that the flux φ_j of reaction *j* is its average rate in a unit of volume (for large *V*):

$$\varphi_j = \lim_{\substack{\Delta t \to 0 \\ V \to \infty}} \mathbf{E} \left(\frac{N_j[t, t + \Delta t]}{V \Delta t} \right),$$

where $N_j[t, t + \Delta t]$ is the number of times that reaction *j* occurs in the interval $[t, t + \Delta t]$.

So a possible definition of discrete stochastic flux is

$$\mathsf{E}\left(\frac{N_j[t,t+\Delta t]}{V\Delta t}\right) = \frac{\mathsf{E}(N_j[t,t+\Delta t])}{V\Delta t}.$$

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In general, analytic expressions for $\mathbf{E}(N_j[t, t + \Delta t])$ are not known.

It can be estimated by averaging $N_j[t, t + \Delta t]$ over repeated simulations.

 $N_j[t, t + \Delta t]$ can be computed in real time during simulation, or in linear time from the simulation trajectory (the log of the simulation events).

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Kahramanoğulları: More information can be obtained by further processing of the trajectory.

 $F_{i,j,k}[t, t + \Delta t]$ is the number of molecules of species *i* produced by reaction *j* and consumed by reaction *k* in the interval $[t, t + \Delta t]$.

Just as N_j is analogous to φ_j , $F_{i,j,k}$ is analogous to $\phi_{i,j,k}$, the flow rate of species *i* from reaction *j* to *k*.

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Data structures constructed from the simulation:

Simulation trajectory \implies simulation trace Simulation trace \implies simulation configuration

F can be extracted in linear time from the simulation configuration.

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At any time, the state of the system is a finite collection of molecules.

Each molecule belongs to a species.

There are finitely many species A, B, C, \ldots

Each molecule has a unique id $\in \mathbb{N}$.

Ex.: A(k) is the molecule belonging to species A with id k.

Reactions create and remove molecules.

Each new molecule has an id that has never occurred before during the simulation.

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The effect of a reaction can be described by a pair (L, R):

- L = set of molecules removed by the reaction.
- R = set of molecules created by the reaction.

Example

$(\{B(3), C(2)\}, \{D(1)\})$

B(3) and C(2) are destroyed, D(1) is created.

Definition

The trajectory of a simulation is a list of discrete events numbered $1, \ldots, T$:

$$\langle (j_t, L_t, R_t, \tau_t) | t = 1, \ldots, T \rangle$$

where

 j_t = the reaction at event t. (L_t, R_t) = the effect of the reaction. τ_t = the time at which event t occurred.

The initial state is event 0.

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Definition

The trace of a simulation is a directed acyclic graph.

Each vertex has a label of the form $A(k, j, \tau)$ where A(k) is a molecule of species A and id k, created by reaction *j* at time τ .

There are edges $(A(k, j, \tau), B(k', j', \tau'))$ for every pair of vertices such that A(k) is consumed by reaction j' at time τ' .

Definition

The simulation configuration is a directed acyclic multigraph.

Each vertex has a label of the form (j, τ) where

j is a reaction

 τ is a time when reaction *j* occurred.

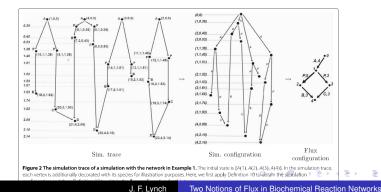
There is an edge from vertex (j, τ) to vertex (j', τ') labeled with *A* if

a molecule belonging to species *A* is produced by reaction *j* at time τ and consumed by reaction *j'* at time τ' .

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Example

 $\begin{array}{l} \mbox{Rules: } 1: A \to P + P, 2: P \to B, 3: P \to C, 4: B + C \to D \\ \mbox{Initial state: } \{A(1), A(2), A(3), A(4)\} \\ \mbox{Simulation trajectory:} \\ \langle (1, \{A(4)\}, \{P(5), P(6)\}, 0.36); (2, \{P(5)\}, \{B(7)\}, 0.40); \ldots; \\ (4, \{B(16), C(19)\}, \{D(23)\}, 2.14) \rangle \end{array}$



Simulation Trajectory \implies Simulation Trace

The trace is extended after each event T = 0, 1, ...

- After event 0, trace consists of vertices *A*(*i*, 0, 0.0) for all *A*(*i*) in the initial state.
- Assume vertices and edges of trace have been constructed for events 0,..., *T* and event *T* + 1 is (*j*_{T+1}, *L*_{T+1}, *R*_{T+1}, τ_{T+1}).

For each $A(i) \in R_{T+1}$, add new vertex $A(i, j_{T+1}, \tau_{T+1})$.

From each vertex $B(k, j_t, \tau_t)$ where $B(k) \in L_{t+1}$, add an edge to all the new vertices.

(Total new edges = $|L_{T+1} \times R_{T+1}|$.)

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Simulation Trace \implies Simulation Configuration

• Project trace vertices to configuration vertices:

 $\pmb{A}(i,j,\tau)\mapsto (j,\tau)$

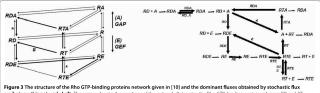
• Project trace edges :

 $(A(i,j, au),B(i',j', au'))\mapsto ((j, au),(j', au'))$ with label A

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analysis on this network. Left: The arrows denote the reactions of the network R denotes the Rho GTP-binding protein, whereas RD and RT denote is GDP and GTP bound forms A and E denote GAP and GET. Thus RPG. For example, denotes the protein complex formed by RD and E. The thick arrows denote the dominant fluxes obtained by the analysis in [10]. **Right:** The dominant fluxes obtained by stochastic flux, analysis include the fluxes marked with a nod exclude the ones marked with $0 \neq 0$ not left. This analysis includes the dominant fluxes obtained by stochastic flux, analysis include the fluxes marked with a nod exclude the ones marked with $0 \neq 0$ not left. This analysis includes also the fluxes used to the enzymes A and E.

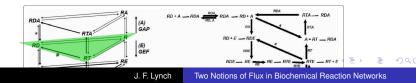
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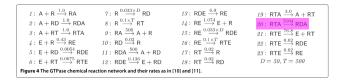
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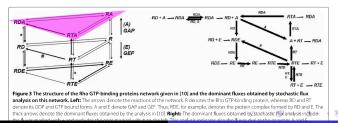
Cycling in the absence of regulatory molecules. R = Rho GTP-binding protein RD = GDP-bound R RT = GTP-bound R





Inhibition by GAP

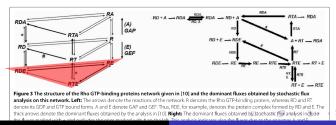




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Activation by GEF





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Some Possibilities for Future Work

- Integrate with statistical methods
 - Confidence intervals for flux values
 - Determining how many repetitions of a simulation are needed to get a given level of accuracy and confidence.
- Extend flux to networks with binding/unbinding reactions (Kappa, BNG)
- General question: For a given range of population sizes, how accurate is the ODE approximation? Where is the combinatorial wall?