Reaction Network Modeling

Molecular Programming tutorial
ASE 2015

Chemical Reaction Networks

A mathematical model.

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A programming language for molecular programming in a well-mixed solution.

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"Computing in soup"

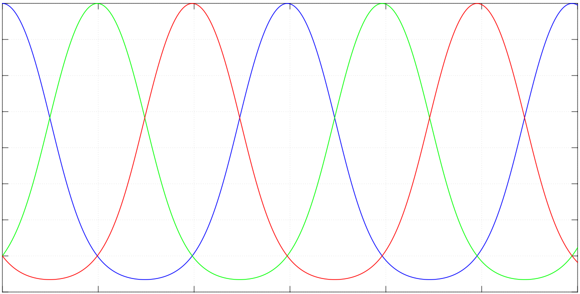
Essentially equivalent to

- Population protocols
- Petri nets
- Vector addition systems

Chemical Reaction Networks

Example: A three-phase oscillator ($\approx$ Lotka-Volterra)

$$X + Y \xrightarrow{k} 2Y$$
$$Y + Z \xrightarrow{k} 2Z$$
$$Z + X \xrightarrow{k} 2X$$



Four types of CRN research

1. Descriptive (20th century): Use CRNs to describe/explain chemical/biochemical processes.

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2. Mathematical (20th century): Use algebra, analysis, and probability to analyze structure and dynamics of CRNs.

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    (a) Write down an (abstract) CRN that does something cool.

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4. Systematic prescriptive (21st century):

   Replace (c) with uniform translation into DNA strand displacement systems.

   Soloveichik, Seelig, and Winfree 2010

reaction network $\longrightarrow$ strand displacement system $\longrightarrow$ DNA strands

programming language	assembly language	machine language

Chen, Dalchau, Srinivas, Phillips, Cardelli, Soloveichik, and Seelig 2013.

"Real programmers code in chemistry!"

Soloveichik, 2011

The CRN Model

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A reaction over a finite set $S \subseteq \mathbf{S}$ is a triple

$$\rho = (\mathbf{r}, \mathbf{p}, k) \in \mathbb{N}^S \times \mathbb{N}^S \times (0, \infty)$$

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with $\mathbf{r} \neq \mathbf{p}$.

$$\begin{aligned} \mathbf{r} = \mathbf{r}(\rho) &= \text{ reactant vector of } \rho \\ \mathbf{p} = \mathbf{p}(\rho) &= \text{ product vector of } \rho \\ k = k(\rho) &= \text{ rate constant of } \rho \end{aligned}$$

The CRN Model

Example: Let $S = \{X, Y, Z\}$. The intuitive notation

$$X + Z \xrightarrow{k} 2Y + Z$$

refers to the formal reaction $(\mathbf{r}, \mathbf{p}, k)$, where

$$\mathbf{r}(X) = \mathbf{r}(Z) = 1, \;\; \mathbf{r}(Y) = 0,$$
$$\mathbf{p}(X) = 0, \;\; \mathbf{p}(Y) = 2, \;\; \mathbf{p}(Z) = 1.$$

The CRN Model

The two most widely used semantics (operational meanings) ascribed to a CRN $N = (S, R)$.

1. Deterministic mass action

   A state is a vector $\mathbf{x} \in [0, \infty)^S$.

   $\mathbf{x}(Y) =$ the concentration of Y in state $\mathbf{x}$.

   Behavior of N governed by autonomous polynomial ODEs.

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Used to model systems with many molecules of each species.

Law of Mass Action (deterministic)

The rate of a reaction depends on its rate constant and the state!

Example. In state $\mathbf{x}$, the reactions

$$\rho_1 \equiv X + Z \xrightarrow{a} 2Y + Z$$

and

$$\rho_2 \equiv 2Y + Z \xrightarrow{b} X + Z$$

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$$rate_{\mathbf{x}}(\rho_2) = b\mathbf{x}(Y)^2\mathbf{x}(Z).$$

Example (continued). The CRN

$$X + Z \xrightarrow{a} 2Y + Z$$
$$2Y + Z \xrightarrow{b} X + Z$$

is governed by the system

$$\frac{dx}{dt} = -axz + by^2z$$
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$$\begin{aligned} \frac{dx}{dt} &= -axz + by^2 z \\ \frac{dy}{dt} &= 2axz - 2by^2 z \\ \frac{dz}{dt} &= 0 \quad (Z \text{ is a catalyst.}) \end{aligned}$$

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What is robustness here?

The CRN Model

Klinge, Lathrop, and Lutz 2015: Uniform translation of a nondeterministic finite automaton M into a deterministic mass action CRN N.

- N simulates M
- size(N) linear in size(M)
- N robust with respect to
  - input signal
  - initial concentrations
  - output
  - rate constants of reactions
- Proof, not simulation.

The CRN Model

2. Stochastic mass action

   A state is a vector $\mathbf{x} \in \mathbb{N}^S$.
   $\mathbf{x}(Y) =$ the count of Ys in state $\mathbf{x}$.
   Behavior is governed by continuous time Markov chains.

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Used to model systems in which small counts of molecules are significant.

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Theorem (Kurtz 1972). Roughly stated, deterministic mass action is the limiting case of stochastic mass action as populations and volumes go to infinity.

The CRN Model

The computational power of stochastic mass action CRNs.

- Angluin, Aspnes, and Eisenstat 2006;
  Chen, Doty, and Soloveichik 2012:

  Stable computation (correctness on all paths) can only compute semilinear predicates and functions.

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- The known simulation is not robust.

The CRN Model

Recall For $\lambda \in (0, \infty)$, the exponential distribution with rate λ is the probability measure on $[0, \infty)$ given by the c.d.f.

$$F_\lambda : [0, \infty) \to [0, 1]$$
$$F_\lambda(t) = 1 - e^{-\lambda t}$$

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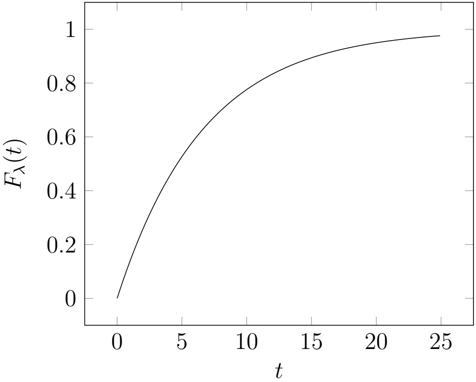

A continuous-time Markov chain (CTMC) is an ordered triple

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$$\Delta(Q) = \{\text{probability measures on } Q\}.$$

Semantics of a CTMC $C = (Q, \lambda, \pi)$.

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- state(0) is chosen according to π.
- For each state $q \in Q$,

$$\lambda_q = \sum_{r \in Q} \lambda(q, r)$$

is the rate out of q.

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  When C does move to a new state, this state is r with probability

$$p(q, r) = \frac{\lambda(q, r)}{\lambda_q}.$$

Stochastic mass action semantics of a CRN $N = (S, R)$
$\equiv$ semantics of the CTMC $C = (Q, \lambda, \pi)$ defined as follows

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- $Q = \mathbb{N}^S$

- $\pi \in \Delta(Q)$ is how you want to initialize the species counts in N.

- Still need $\lambda : \mathbb{N}^S \times \mathbb{N}^S \to [0, \infty)$.

Law of Mass Action (stochastic)

Intuition: The rate of a unary reaction

$$\rho \equiv X \xrightarrow{k} \text{<anything>}$$

in a state $\mathbf{x} \in \mathbb{N}^S$ is

$$rate_{\mathbf{x}}(\rho) = k\mathbf{x}(X).$$

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The rate of a binary reaction

$$\rho \equiv X + Y \xrightarrow{k} \text{<anything>}$$

in a state $\mathbf{x} \in \mathbb{N}^S$ and volume V is

$$rate_{\mathbf{x}}(\rho) = \begin{cases} k\mathbf{x}(X)\mathbf{x}(Y)/V & \text{if } X \neq Y \\ k\mathbf{x}(X)(\mathbf{x}(X) - 1)/V & \text{if } X = Y \end{cases}$$

The rate of a reaction $\rho = (\mathbf{r}, \mathbf{p}, k)$ in a state $\mathbf{x} \in \mathbb{N}^S$ is

$$\mathsf{rate}_{\mathbf{x}}(\rho) = \frac{k}{V^{\|\mathbf{r}\|-1}} \prod_{Y \in S} \frac{\mathbf{x}(Y)!}{(\mathbf{x}(Y) - \mathbf{r}(Y))!},$$

where V is the volume of the solution and

$$\|\mathbf{r}\| = \sum_{Y \in S} \mathbf{r}(Y).$$

Gillespie, 1977

In the CTMC $C = (\mathbb{N}^S, \lambda, \pi)$ for a CRN $N = (S, R)$ we define the rate matrix $\lambda : Q \times Q \to [0, \infty)$ by

$$\lambda(\mathbf{x}, \mathbf{y}) = \sum \left\{ rate_{\mathbf{x}}(\rho) \mid \rho \in R \; takes \; \mathbf{x} \; to \; \mathbf{y} \right\}.$$

We have now completely specified the most often-used semantics (kinetics) for CRNs, namely,

deterministic mass action

and

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Caution: These are sometimes called

mass action

and

stochastic,

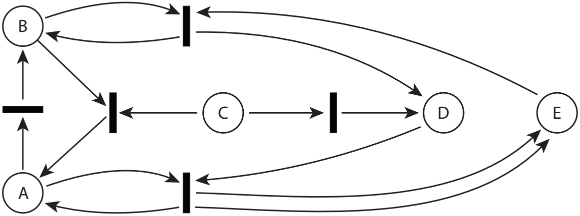
respectively.

Relating CRNs to Other Models

1. Petri nets (Petri 1962).

   A Petri net is a directed bipartite graph whose vertices are places (circles) and transitions (bars).

   Example (CSWB 2009)



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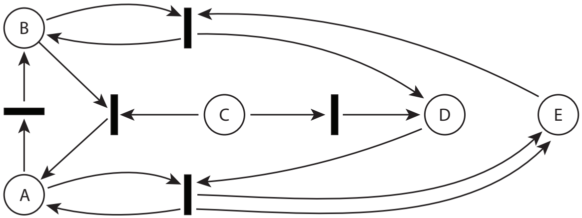
A transition is enabled if there is a token available for each of its incoming edges.

In this case, the transition may fire, causing these tokens to be removed and tokens to be placed at the targets of its outgoing edges.

Relating CRNs to Other Models

It is routine to check that the Petri net



has the same behavior as the CRN

$$A \to B \qquad A + D \to A + 2E$$
$$C \to D \qquad B + E \to B + D$$
$$B + C \to A$$

Relating CRNs to Other Models

2. Vector addition systems (Karp and Miller 1969)

   Fix $n \in \mathbb{Z}^+$ and a finite set V of vectors $\mathbf{v} \in \mathbb{Z}^n$.
   Consider walks in $\mathbb{N}^n$ that start at a location $\mathbf{x}_0 \in \mathbb{N}^n$ and proceed in steps, each of which adds a vector in V to the current location, leading to a new location in $\mathbb{N}^n$.

Relating CRNs to Other Models

Example (CSWB 2009) The CRN

$$A \to B \qquad A + D \to A + 2E$$
$$C \to D \qquad B + E \to B + D$$
$$B + C \to A$$

is equivalent to the vector addition system

A	B	C	D	E	F	G
(-1	1	0	0	0	0	0)
(0	0	-1	1	0	0	0)
(1	-1	-1	0	0	0	0)
(-1	0	0	-1	0	1	0)
(1	0	0	0	2	-1	0)
(0	-1	0	0	-1	0	1)
(0	1	0	1	0	0	-1)

Relating CRNs to Other Models

3. Population protocols (Angluin, Aspnes, and Eisenstat 2008)

   These are essentially CRNs in which every reaction has exactly two reactants and two products.

   Note that this fixes the total population.

   Example (AAE 2008) The population protocol

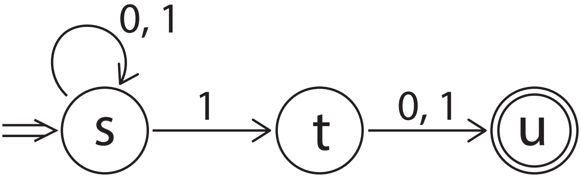
$$X + Y \to X + B \qquad\qquad X + B \to X + X$$
$$X + Y \to Y + B \qquad\qquad Y + B \to Y + Y$$

   computes approximate majority.

A CRN That Simulates an NFA

with Titus Klinge and Jim Lathrop

Let M be the NFA



Objective: Design a CRN N that simulates M in deterministic mass action.

A CRN That Simulates an NFA

M gets its input $w \in \{0, 1\}^*$ sequentially, so N should get its input sequentially.

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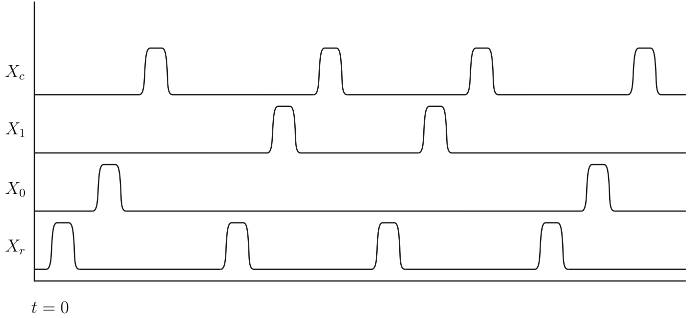
The user will provide an input $w = b_0 b_1 \cdots b_{n-1} \in \{0,1\}^n$ approximately in the square-wave form



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We also have

- state species $Y_s, Y_t, Y_u,$

A CRN That Simulates an NFA

We thus have input species X_0, X_1, X_c, X_r.
We also have

- state species Y_s, Y_t, Y_u,
- portal species Z_s, Z_t, Z_u, and

A CRN That Simulates an NFA

We thus have input species X_0, X_1, X_c, X_r.
We also have

- state species Y_s, Y_t, Y_u,
- portal species Z_s, Z_t, Z_u, and
- dual species $\overline{Y_s}, \overline{Y_t}, \overline{Y_u}, \overline{Z_s}, \overline{Z_t}, \overline{Z_u}$.

Reactions

- For each state q,

$$X_r + Z_q \to X_r + \overline{Z_q}.$$

reset

Reactions

- For each state q,

$$X_r + Z_q \to X_r + \overline{Z_q}. \qquad \text{reset}$$

- For each transition $q \xrightarrow{b} r$,

$$X_b + Y_q + \overline{Z_r} \to X_b + Y_q + Z_q. \qquad \text{compute}$$

Reactions

- For each state q,

$$X_r + Z_q \to X_r + \overline{Z_q}.$$

reset

- For each transition $q \xrightarrow{b} r$,

$$X_b + Y_q + \overline{Z_r} \to X_b + Y_q + Z_q.$$

compute

- For each state q

$$X_c + Z_q + \overline{Y_q} \to X_c + Z_q + Y_q$$
$$X_c + \overline{Z_q} + Y_q \to X_c + \overline{Z_q} + \overline{Y_q}$$

copy

Reactions

- For each state q,

$$2Y_q + \overline{Y_q} \to 3Y_q$$
$$2\overline{Y_q} + Y_q \to 3\overline{Y_q}$$

error correction

Summary

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Thank you!