# On Process Rate Semantics

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Extract of the:
Open Lectures for PhD Students in Computer Science
**Warsaw 2009-03-12..13**

**http://lucacardelli.name**

# Semantics of Collective Behavior

# “Micromodels”: Continuous Time Markov Chains

- The underlying semantics of stochastic π-calculus (and stochastic interacting automata). Well established in many ways.
  - Automata with rates on transitions.

- “The” correct semantics for chemistry, executable.
  - Gillespie stochastic simulation algorithm

- Lots of advantages
  - Compositional, compact, mechanistic, etc.

- But do not give a good sense of “collective” properties.
  - Yes one can do simulation.
  - Yes one can do program analysis.
  - Yes one can perhaps do modelchecking.
  - But somewhat lacking in “analytical properties” and “predictive power”.

# “Macromodels”: Ordinary Differential Equations

- The classical semantics of collective behavior.
  - E.g. kinetic theory of gasses.
  - They always ask: “How does you automata model relate to the 75 ODE models in the literature?”

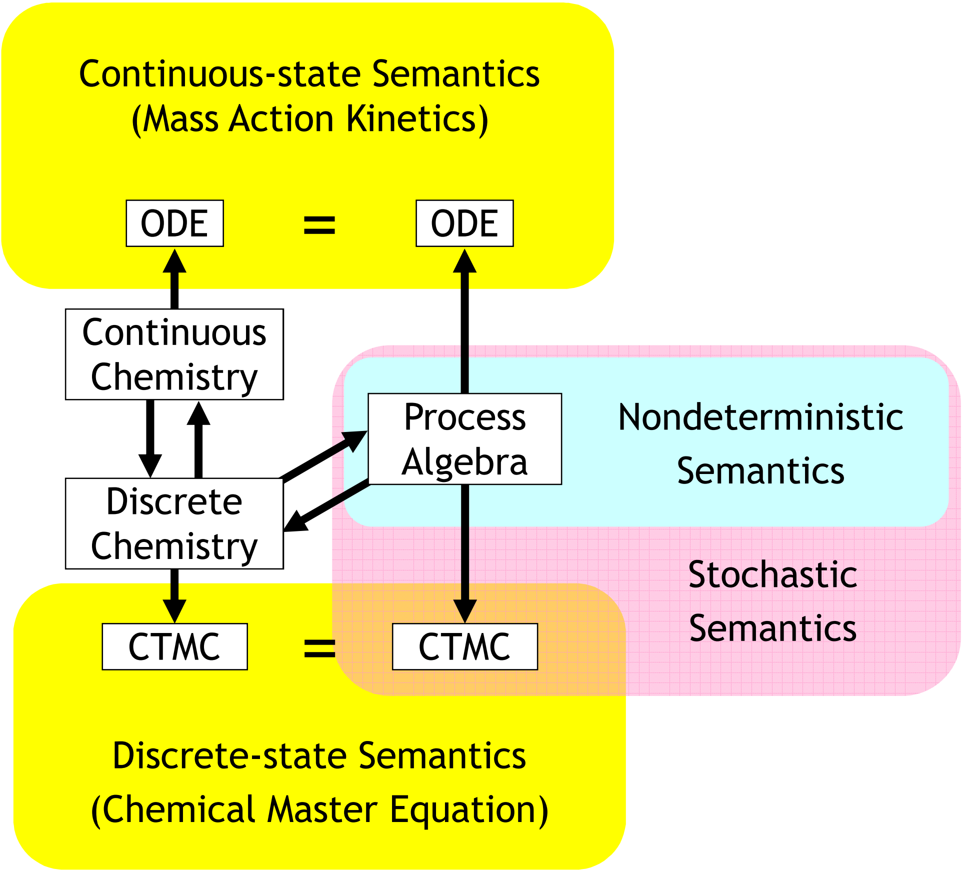
- Going from processes/automata to ODEs directly:
  - *In principle*: just write down the Rate Equation:
    - Let [S] be the “number of processes in state S” as a function of time.
    - Define for each state S:

      d[S]/dt = (rate of change of the number of processes in state S)

      Cumulative rate of transitions from any state S’ to state S, times [S’],
      minus cumulative rate of transitions from S to any state S”, times [S].
  - Fairly intuitive (rate = inflow minus outflow)

- Going to ODEs indirectly through chemistry
  - If we first convert processes to chemical reactions, then we can convert to ODEs by standard means!

# The Two Semantic Sides of Chemistry

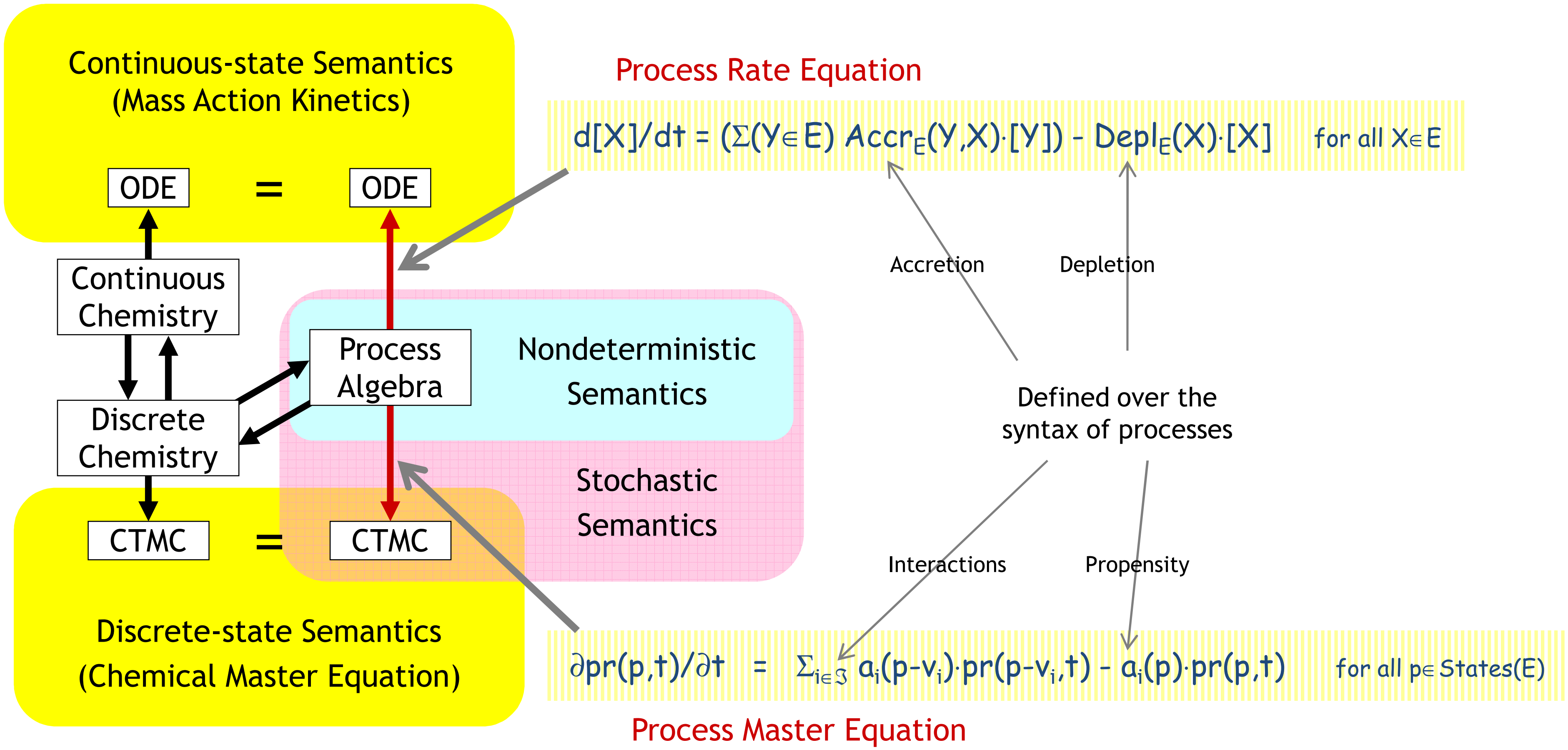


These diagrams commute via appropriate maps.

L. Cardelli: “On Process Rate Semantics” (TCS)

L. Cardelli: “A Process Algebra Master Equation” (QEST’07)

# Quantitative Process Semantics



Continuous-state Semantics
(Mass Action Kinetics)

ODE = ODE

Continuous Chemistry

Discrete Chemistry

Process Algebra

Nondeterministic Semantics

Stochastic Semantics

CTMC = CTMC

Discrete-state Semantics
(Chemical Master Equation)

Process Rate Equation

$d[X]/dt = (\Sigma(Y \in E)\ Accr_E(Y,X) \cdot [Y]) - Depl_E(X) \cdot [X]$ for all $X \in E$

Accretion

Depletion

Defined over the
syntax of processes

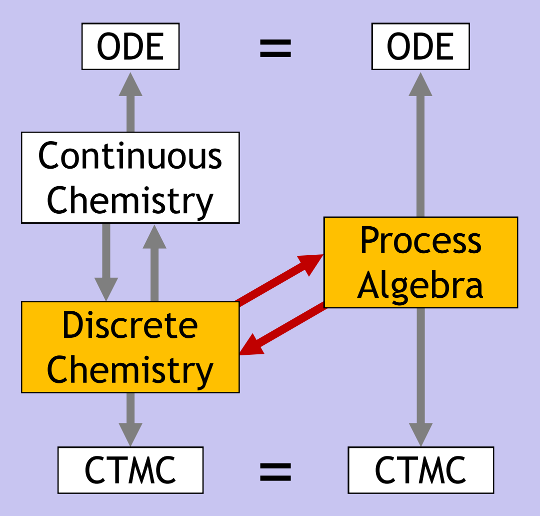
Interactions

Propensity

$\partial pr(p,t)/\partial t = \Sigma_{i \in \mathfrak{I}}\ a_i(p-v_i) \cdot pr(p-v_i,t) - a_i(p) \cdot pr(p,t)$ for all $p \in States(E)$

Process Master Equation

# Stochastic Processes & Discrete Chemistry

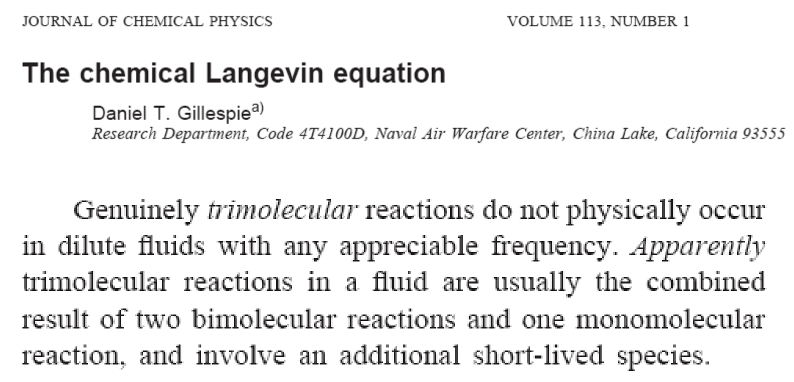


# Chemical Reactions (FSRN)

| | | | | |
|---|---|---|---|---|
| $A \rightarrow^{r} B_1 + \ldots + B_n$ (n≥0) | Unary Reaction | $d[A]/dt = -r[A]$ | Exponential Decay |
| $A_1 + A_2 \rightarrow^{r} B_1 + \ldots + B_n$ (n≥0) | Hetero Reaction | $d[A_i]/dt = -r[A_1][A_2]$ | Mass Action Law |
| $A + A \rightarrow^{r} B_1 + \ldots + B_n$ (n≥0) | Homeo Reaction | $d[A]/dt = -2r[A]^2$ | Mass Action Law |

(assuming $A \neq B_i \neq A_j$ for all i,j)

No other reactions!



JOURNAL OF CHEMICAL PHYSICS VOLUME 113, NUMBER 1

**The chemical Langevin equation**

Daniel T. Gillespie[a)]
*Research Department, Code 4T4100D, Naval Air Warfare Center, China Lake, California 93555*

Genuinely *trimolecular* reactions do not physically occur in dilute fluids with any appreciable frequency. *Apparently* trimolecular reactions in a fluid are usually the combined result of two bimolecular reactions and one monomolecular reaction, and involve an additional short-lived species.

**Chapter IV: Chemical Kinetics**
[David A. Reckhow , CEE 572 Course]

… reactions may be either elementary or non-elementary. Elementary reactions are those reactions that occur exactly as they are written, without any intermediate steps. These reactions almost always involve just one or two reactants. … Non-elementary reactions involve a series of two or more elementary reactions. Many complex environmental reactions are non-elementary. In general, reactions with an overall reaction order greater than two, or reactions with some non-integer reaction order are non-elementary.

**THE COLLISION THEORY OF REACTION RATES** www.chemguide.co.uk

The chances of all this happening if your reaction needed a collision involving more than 2 particles are remote. All three (or more) particles would have to arrive at exactly the same point in space at the same time, with everything lined up exactly right, and having enough energy to react. That's not likely to happen very often!

Trimolecular reactions:

$A + B + C \rightarrow^{r} D$

the measured "r" is an (imperfect) aggregate of e.g.:

$A + B \leftrightarrow AB$

$AB + C \rightarrow D$

Enzymatic reactions:

$S \xrightarrow{E\ r} P$

the "r" is given by Michaelis-Menten (approximated steady-state) laws:

$E + S \leftrightarrow ES$

$ES \rightarrow P + E$

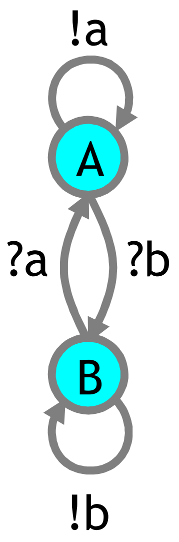
# Chemical Ground Form (CGF)

A stochastic subset of CCS
(no values, no restriction)

E ::= 0 ⁝ X=M, E — Reagents
M ::= 0 ⁝ π;P ⊕ M — Molecules
P ::= 0 ⁝ X | P — Solutions
$\pi ::= \tau_{(r)}$ ⁝ $?a_{(r)}$ ⁝ $!a_{(r)}$ — Actions (delay, input, output)
CGF ::= E,P — Reagents plus Initial Conditions

(To translate chemistry to processes we need a bit more than interacting automata: we may have "+" on the right of →, that is we may need "|" after π.)

⊕ is stochastic choice (vs. + for chemical reactions)
0 is the null solution (P|0 = 0|P = P)
and null molecule (M⊕0 = 0⊕M = M)
Each X in E is a distinct *species*
Each name a is assigned a fixed rate r: $a_{(r)}$

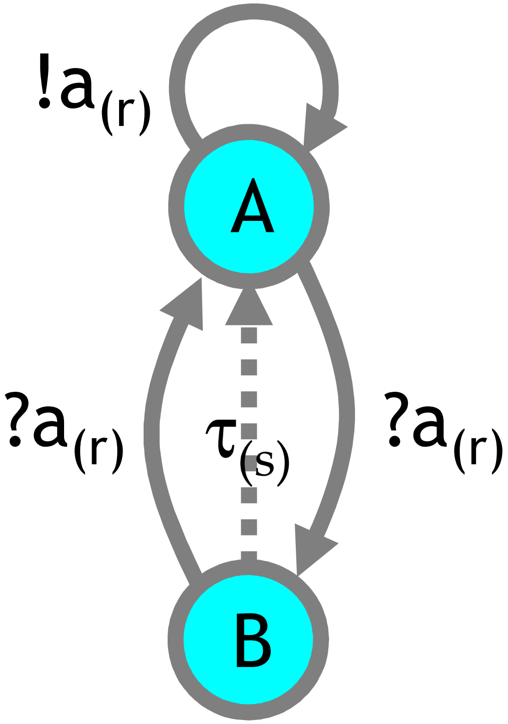


Ex: Interacting Automata
(= finite-control CGFs: they use "|" only in initial conditions):

A = !a;A ⊕ ?b;B — Automaton in state A
B = !b;B ⊕ ?a;A — Automaton in state B
A|A|B|B — Initial conditions: 2A and 2B

# From CGF to Chemistry

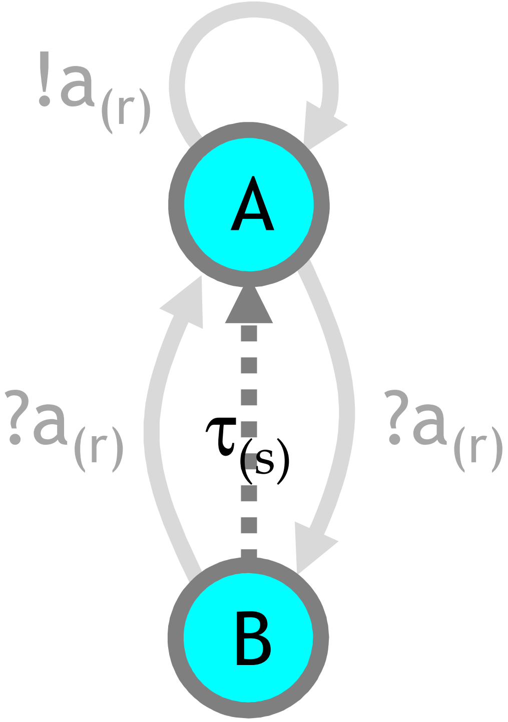
# From CGF to Chemistry (by example)

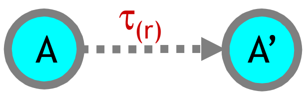


$A = !a_{(r)};A \oplus ?a_{(r)};B$

$B = ?a_{(r)};A \oplus \tau_{(s)};A$

# From CGF to Chemistry (by example)





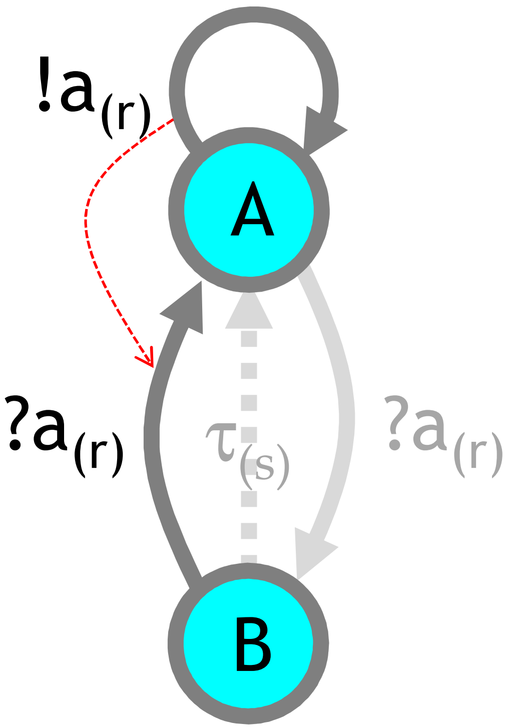
$A \to^{r} A'$

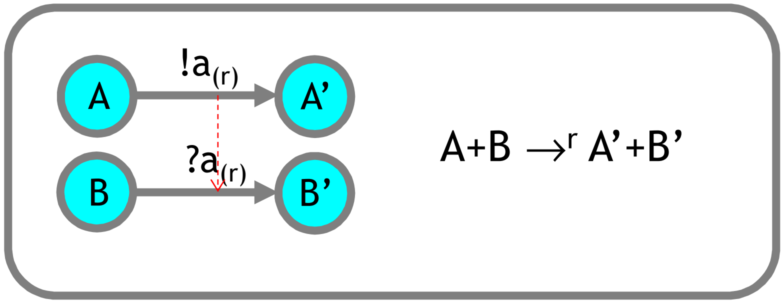
$B \to^{s} A$

$A = !a;A \oplus ?a;B$

$B = ?a;A \oplus \tau_{(s)};A$

# From CGF to Chemistry (by example)





$A+B \to^{r} A'+B'$

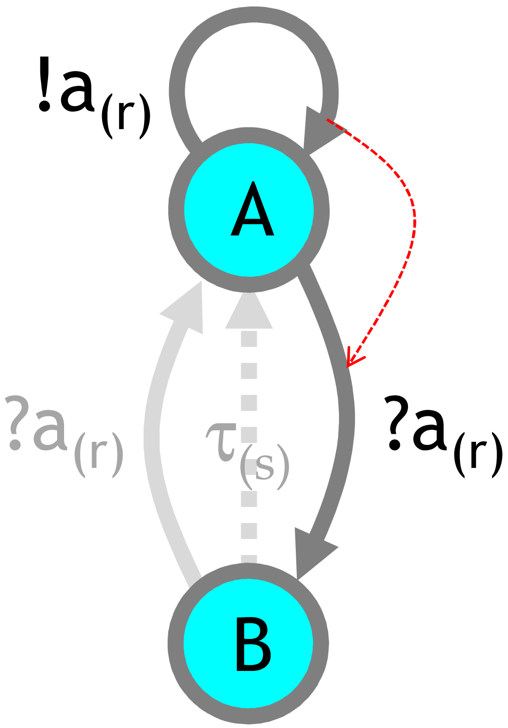
$B \to^{s} A$

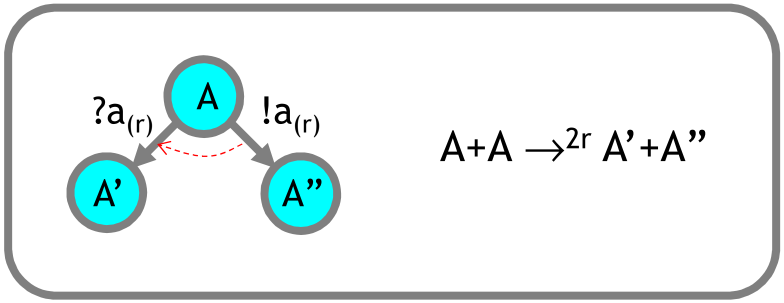
$A+B \to^{r} A+A$

$A = !a;A \oplus ?a;B$

$B = ?a;A \oplus \tau_{(s)};A$

# From CGF to Chemistry (by example)





$A+A \rightarrow^{2r} A'+A''$

$B \rightarrow^{s} A$

$A+B \rightarrow^{r} A+A$

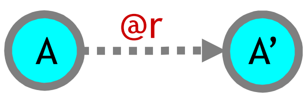
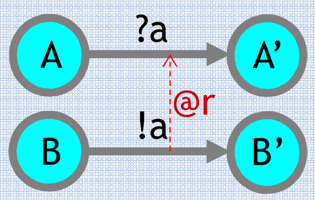
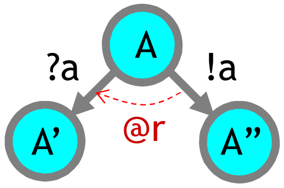
$A+A \rightarrow^{2r} A+B$

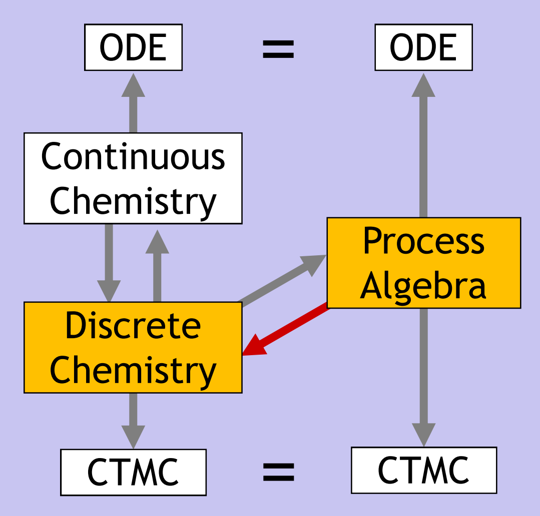
Double rate for homeo reactions

$A = !a;A \oplus ?a;B$

$B = ?a;A \oplus \tau_{(s)};A$

# From CGF to Chemistry (by example)

| Interacting Automata → | Discrete Chemistry |
|---|---|
| initial states<br>$A \mid A \mid \ldots \mid A$ | initial quantities<br>$\#A_0$ |
|  | $A \to^{r} A'$ |
|  | $A+B \to^{r} A'+B'$ |
|  | $A+A \to^{2r} A'+A''$ |



# From CGF to Chemistry: Ch(E)

| | |
|---|---|
| $E ::= 0 \;\vdots\; X=M, E$ | Reagents |
| $M ::= 0 \;\vdots\; \pi;P \oplus M$ | Molecules |
| $P ::= 0 \;\vdots\; X \mid P$ | Solutions |
| $\pi ::= \tau_{(r)} \;\vdots\; ?a_{(r)} \;\vdots\; !a_{(r)}$ | Interactions (delay, input, output) |
| $CGF ::= E,P$ | Reagents plus Initial Conditions |

$E.X.i \overset{\text{def}}{=}$ the i-th Å-summand of the molecule M associated with the X reagent of E

Chemical reactions for E,P: (N.B.: <...> are reaction tags to obtain multiplicity of reactions, and P is P with all the | changed to +)

$$
\begin{aligned}
&Ch(E) := \\
&\quad \{(\langle X.i\rangle: X \to^{r} P) \;\textit{s.t.}\; E.X.i = \tau_{(r)};P\} \cup \\
&\quad \{(\langle X.i,Y.j\rangle: X + Y \to^{r} P + Q) \;\textit{s.t.}\; X \neq Y,\ E.X.i = ?a_{(r)};P,\ E.Y.j = !a_{(r)};Q\} \cup \\
&\quad \{(\langle X.i,X.j\rangle: X + X \to^{2r} P + Q) \;\textit{s.t.}\; E.X.i = ?a_{(r)};P,\ E.X.j = !a_{(r)};Q\}
\end{aligned}
$$

Initial conditions for P:

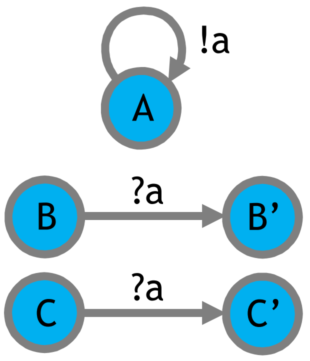
$$Ch(P) := \quad P$$

# Entangled vs Detangled

Entangled

$a: A+B \rightarrow^{r} A+B'$

$a: A+C \rightarrow^{r} A+C'$



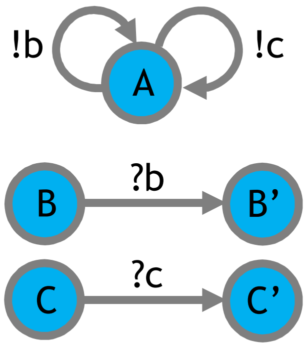
(a@r)

A = !a;A
B = ?a;B'
C = ?a;C'
B' = 0
C' = 0

Entangled: Two reactions on one channel

$b: A+B \rightarrow^{r} A+B'$

$c: A+C \rightarrow^{r} A+C'$



(b@r)
(c@r)

A = !b;A ⊕ !c;A
B = ?b;B'
C = ?c;C'
B' = 0
C' = 0

Detangled: Two reactions on two separate channels

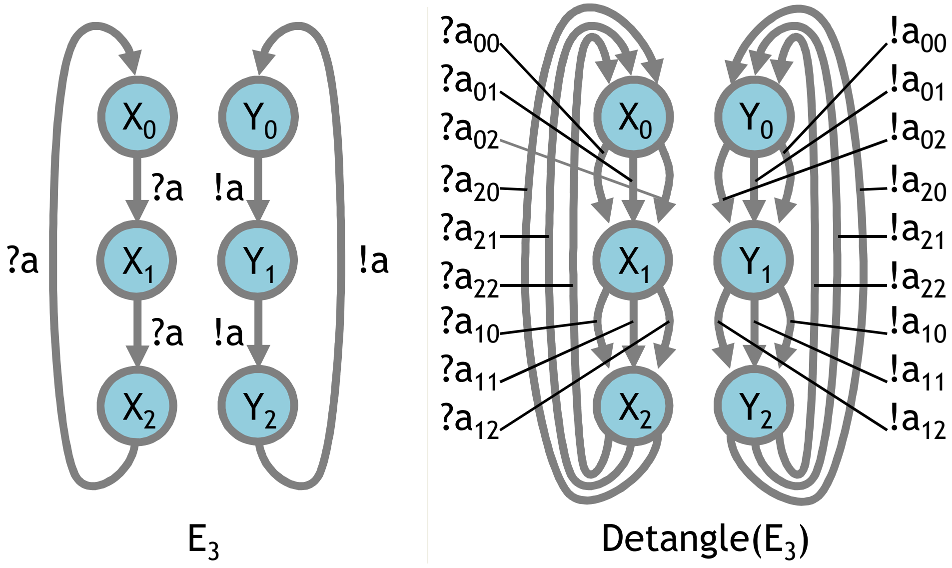
We need a semantics of automata that identifies automata that have the "same chemistry".

No traditional process algebra equivalence is like this!

Entangled automata lead to more compact models than in chemistry.

Detangled automata are in simple correspondence with chemistry.

# Entangled vs detangled



(closely related to
Pi(Ch(E$_3$)) )

# Chemical Parametric Form (CPF)

| | |
|---|---|
| $E ::= 0 \;\vdots\; X(\mathbf{p})=M, E$ | Reagents |
| $M ::= 0 \;\vdots\; \pi;P \oplus M$ | Molecules |
| $P ::= 0 \;\vdots\; X(\mathbf{p}) \mid P$ | Solutions |
| $\pi ::= \tau_{(r)} \;\vdots\; ?a_{(r)}(\mathbf{p}) \;\vdots\; !a_{(r)}(\mathbf{p})$ | Actions |
| $CPF ::= E,P$ | with initial conditions |

$\oplus$ is stochastic choice (vs. + for chemical reactions)
0 is the null solution ($P|0 = 0|P = P$)
and null molecule ($M\oplus 0 = 0\oplus M = M$)
Each X in E is a distinct *species*
**p** are vectors of names
**p** are vectors of distinct names when in binding position
Each free name a in E is assigned a fixed rate r: $a_{(r)}$

Not bounded-state systems.
Not finite-control systems.
But still finite-species systems.

A translation from CPF to CGF exists
(expanding all possible instantiation of parameters from the initial conditions)

An incremental translation algorithm exists
(expanding on demand from initial conditions)

Example:

$Neg(a,b) = ?a;\ Inh(a,b) \oplus \tau_e;\ (Tr(b) \mid Neg(a,b))$
$Inh(a,b) = \tau_h;\ Neg(a,b)$
$Tr(b) = !b;\ Tr(b) \oplus \tau_d;\ 0$
$Neg(x,x)$

# CPF to CGF: Handling Parameters

Consider first the CPF subset with no communication (pure ?a, !a).

**Grounding** (replace parameters with constants)

where $X/\mathbf{p}$ is a name in bijection with $\langle X,\mathbf{p}\rangle$
(each $X/\mathbf{p}$ is seen as a separate *species*)

$$/(\pi_1;P_1 \oplus \dots \oplus \pi_n;P_n) =_{def} \pi_1;/(P_1) \oplus \dots \oplus \pi_n;/(P_n)$$
$$/(X_1(\mathbf{p}_1) \mid \dots \mid X_n(\mathbf{p}_n)) =_{def} X_1/\mathbf{p}_1 \mid \dots \mid X_n/\mathbf{p}_n$$

$$E ::= X_1(\mathbf{p}_1)=M_1, \dots, X_n(\mathbf{p}_n)=M_n$$
$$M ::= \pi_1;P_1 \oplus \dots \oplus \pi_n;P_n$$
$$P ::= X_1(\mathbf{p}_1) \mid \dots \mid X_n(\mathbf{p}_n)$$
$$\pi ::= \tau_r \quad ?a \quad !a$$

Let N be the set of free names occurring in E.

$E_G$ is the **Parametric Explosion** of E (still a finite species system)
computed by replacing parameters with all combinations of free names in E

$$E_G := \{(X/\mathbf{q} = /(M\{\mathbf{p}\leftarrow\mathbf{q}\})) \text{ s.t. } (X(\mathbf{p}) = M) \in E \text{ and } \mathbf{q} \in N^{\#\mathbf{p}}\}$$
$$P_G := /P$$ (simply ground the given initial conditions once)

$E_G$ is a CGF! To obtain the chemical reactions $Ch_P(E)$, just compute $Ch_G(E_G)$

$$Ch_P(E) = Ch_G(E_G)$$

# CPF to CGF: Handling Communication

## Grounding (replace parameters with constants)

just one main change: now also convert each input parameter into a ground choice of all possible inputs

N is the set of free names in E,P

#**p** is the length of **p**

n/**p** is a name in bijection with <n,**p**>

X/**p** is a name in bijection with <X,**p**>

(each X/**p** is seen as a separate *species*)

$$
\begin{aligned}
&E \ ::= X_1(\mathbf{p}_1)=M_1,\ \dots,\ X_n(\mathbf{p}_n)=M_n\\
&M \ ::= \pi_1;P_1 \oplus \dots \oplus \pi_n;P_n\\
&P \ ::= X_1(\mathbf{p}_1) \mid \dots \mid X_n(\mathbf{p}_n)\\
&\pi \ ::= \tau_r \quad ?a(\mathbf{p}) \quad !a(\mathbf{p})
\end{aligned}
$$

$$
\begin{aligned}
&/_N(\tau_r;P) = \tau_r;\ /_N(P)\\
&/_N(!a_{(r)}(\mathbf{p});P) = !a/\mathbf{p}_{(r)};\ /_N(P)\\
&/_N(?a_{(r)}(\mathbf{p});P) = \oplus(\mathbf{q}\in N^{\#\mathbf{p}}) \text{ of } ?a/\mathbf{q}_{(r)};\ /_N(P\{\mathbf{p}\leftarrow\mathbf{q}\})\\
&/_N(\pi_1;P_1 \oplus \dots \oplus \pi_n;P_n) = /_N(\pi_1;P_1) \oplus \dots \oplus /_N(\pi_n;P_n)\\
&/_N(X_1(\mathbf{p}_1) \mid \dots \mid X_n(\mathbf{p}_n)) = X_1/\mathbf{p}_1 \mid \dots \mid X_n/\mathbf{p}_n
\end{aligned}
$$

$E_G$ is again the **Parametric Explosion** of E

$E_G := \{(X/\mathbf{q} = /_N(M\{\mathbf{p}\leftarrow\mathbf{q}\}))\ \text{s.t.}\ (X(\mathbf{p}) = M) \in E \text{ and } \mathbf{q} \in N^{\#\mathbf{p}}\}$

$P_G := /_N(P)$ (simply ground the given initial conditions once)

$Ch(E) = Ch_G(E_G)$

$E_G$ is a again a CGF!

# CPF to CGF Translation. Ex: Neg(x,x)

E =

Neg(a,b) = ?a; Inh(a,b) $\oplus$ $\tau_e$; (Tr(b) | Neg(a,b))
Inh(a,b) = $\tau_h$; Neg(a,b)
Tr(b) = !b; Tr(b) $\oplus$ $\tau_d$; 0
Neg(x,x)

----- initialization -----

$E_c$:= { Neg/x,x = ?x; Inh/x,x $\oplus$ $\tau_e$; (Tr/x | Neg/x,x)}

----- iteration 1 -----

C := {Neg/x,x $\to^{e}$ Tr/x + Neg/x,x }

$E_c$:= { Neg/x,x = ?x; Inh/x,x $\oplus$ $\tau_e$; (Tr/x | Neg/x,x)
Tr/x = !x; Tr/x $\oplus$ $\tau_d$; 0}

----- iteration 2 -----

C := {Neg/x,x $\to^{e}$ Tr/x + Neg/x,x
Tr/x $\to^{d}$ 0
Tr/x + Neg/x,x $\to^{\rho(x)}$ Tr/x + Inh/x,x }

$E_c$:= { Neg/x,x = ?x; Inh/x,x $\oplus$ $\tau_e$; (Tr/x | Neg/x,x)
Tr/x = !x; Tr/x $\oplus$ $\tau_d$; 0
Inh/x,x = $\tau_h$; Neg/x,x}

----- iteration 3 -----

C := {Neg/x,x $\to^{e}$ Tr/x + Neg/x,x
Tr/x $\to^{d}$ 0
Tr/x + Neg/x,x $\to^{\rho(x)}$ Tr/x + Inh/x,x
Inh/x,x $\to^{h}$ Neg/x,x}

$E_c$:= no change

----- termination -----

Neg/x,x $\to^{e}$ Tr/x + Neg/x,x
Tr/x $\to^{d}$ 0
Tr/x + Neg/x,x $\to^{\rho(x)}$ Tr/x + Inh/x,x
Inh/x,x $\to^{h}$ Neg/x,x
Neg/x,x

# From Chemistry to CGF

# From Chemistry to CGF (by example)

x: $B \rightarrow^{s} A$

b: $A+B \rightarrow^{r} A+A$

c: $A+A \rightarrow^{2r} A+B$

Unique reaction names

|  | $x_{(s)}$ | $b_{(r)}$ | $c_{(r)}$ |
|---|---|---|---|
| A |  |  |  |
| B |  |  |  |

Reactions names

Half-rate for homeo reactions

Species

# From Chemistry to CGF (by example)

x: $B \rightarrow^{s} A$

b: $A+B \rightarrow^{r} A+A$

c: $A+A \rightarrow^{2r} A+B$

| | $x_{(s)}$ | $b_{(r)}$ | $c_{(r)}$ |
|---|---|---|---|
| A | | | |
| B | $\tau$;A | | |

1: Fill the matrix by columns:

Degradation reaction $v_i$: $X \rightarrow_{k_i} P_i$

add $\tau;P_i$ to $<X,v_{ij}>$.

# From FSRN to CGF (by example)

x: $B \rightarrow^{s} A$

b: $A+B \rightarrow^{r} A+A$

c: $A+A \rightarrow^{2r} A+B$

|  | $x_{(s)}$ | $b_{(r)}$ | $c_{(r)}$ |
|---|---|---|---|
| A |  | ?;A\|A |  |
| B | τ;A | !;0 |  |

1: Fill the matrix by columns:

Degradation reaction $v_i$: $X \rightarrow k_i\ P_i$

add $\tau;P_i$ to $<X,v_{ij}>$.

Hetero reaction $v_i$: $X+Y \rightarrow k_i\ P_i$

add $?;P_i$ to $<X,v_i>$ and $!;0$ to $<Y,v_i>$

# From FSRN to CGF (by example)

x: $B \rightarrow^{s} A$

b: $A+B \rightarrow^{r} A+A$

c: $A+A \rightarrow^{2r} A+B$

|   | $x_{(s)}$ | $b_{(r)}$ | $c_{(r)}$ |
|---|---|---|---|
| A |  | ?;A\|A | ?;A\|B<br>!;0 |
| B | $\tau$;A | !;0 |  |

1: Fill the matrix by columns:

Degradation reaction $v_i$: $X \rightarrow^{k_i} P_i$

add $\tau;P_i$ to $<X,v_{ij}>$.

Hetero reaction $v_i$: $X+Y \rightarrow^{k_i} P_i$

add $?;P_i$ to $<X,v_i>$ and $!;0$ to $<Y,v_i>$

Homeo reaction $v_i$: $X+X \rightarrow^{k_i} P_i$

add $?;P_i$ and $!;0$ to $<X,v_i>$

# From FSRN to CGF (by example)

x: $B \rightarrow^{s} A$

b: $A+B \rightarrow^{r} A+A$

c: $A+A \rightarrow^{2r} A+B$

| | $x_{(s)}$ | $b_{(r)}$ | $c_{(r)}$ |
|---|---|---|---|
| A | | ?;A\|A | ?;A\|B<br>!;0 |
| B | τ;A | !;0 | |

1: Fill the matrix by columns:

Degradation reaction $v_i$: $X \rightarrow k_i \; P_i$

add $\tau;P_i$ to $\langle X,v_{ij} \rangle$.

Hetero reaction $v_i$: $X+Y \rightarrow k_i \; P_i$

add $?;P_i$ to $\langle X,v_i \rangle$ and $!;0$ to $\langle Y,v_i \rangle$

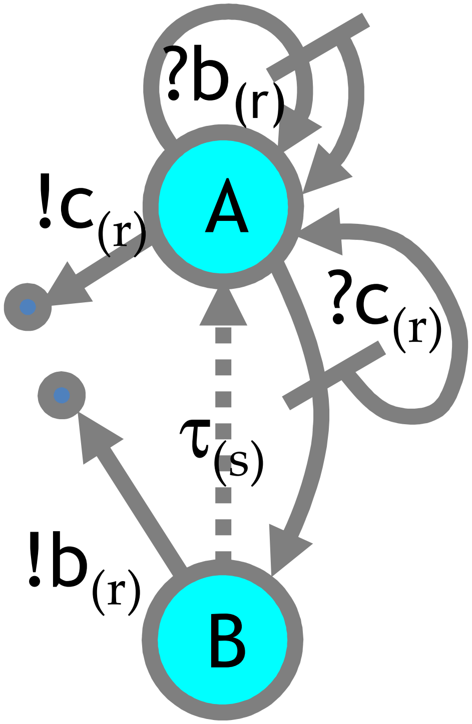
Homeo reaction $v_i$: $X+X \rightarrow k_i \; P_i$

add $?;P_i$ and $!;0$ to $\langle X,v_i \rangle$

2: Read the result by rows:

$A = ?b_{(r)};(A|A) \oplus ?c_{(r)};(A|B) \oplus !c_{(r)};0$

$B = \tau_{(s)};A \oplus !b_{(r)};0$



# From FSRN to CGF (by example)

$x: \quad B \rightarrow^{s} A$

$b: \quad A+B \rightarrow^{r} A+A$

$c: \quad A+A \rightarrow^{2r} A+B$

|   | $x_{(s)}$ | $b_{(r)}$ | $c_{(r)}$ |
|---|---|---|---|
| A |  | ?;A | ?;A\|B<br>!;0 |
| B | τ;A | !;A |  |

1: Fill the matrix by columns:

Degradation reaction $v_i$: $X \rightarrow k_i \; P_i$

add $\tau;P_i$ to $<X,v_{ij}>$.

Hetero reaction $v_i$: $X+Y \rightarrow k_i \; P_i$

add $?;P_i$ to $<X,v_i>$ and $!;0$ to $<Y,v_i>$

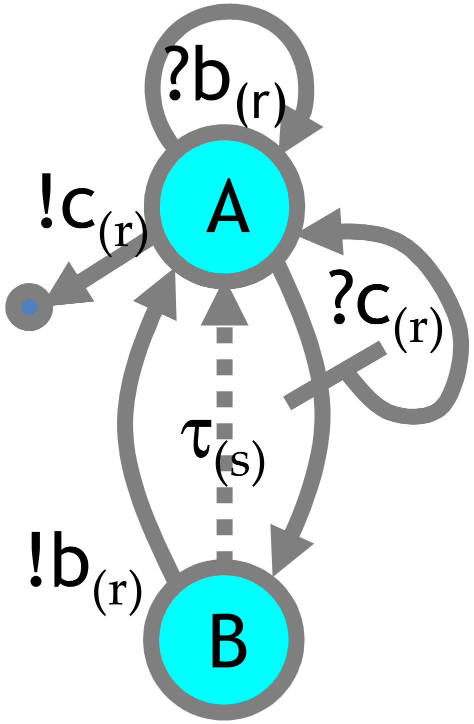
Homeo reaction $v_i$: $X+X \rightarrow k_i \; P_i$

add $?;P_i$ and $!;0$ to $<X,v_i>$

2: Read the result by rows:

$A = ?b_{(r)};A \;\oplus\; ?c_{(r)};(A|B) \;\oplus\; !c_{(r)};0$

$B = \tau_{(s)};A \;\oplus\; !b_{(r)};A$



# From FSRN to CGF (by example)

x: $B \to^{s} A$

b: $A+B \to^{r} A+A$

c: $A+A \to^{2r} A+B$

| | $x_{(s)}$ | $b_{(r)}$ | $c_{(r)}$ |
|---|---|---|---|
| A | | ?;A | ?;B<br>!;A |
| B | $\tau$;A | !;A | |

1: Fill the matrix by columns:

Degradation reaction $v_i$: $X \to_{k_i} P_i$

add $\tau;P_i$ to $<X,v_{ij}>$.

Hetero reaction $v_i$: $X+Y \to_{k_i} P_i$

add $?;P_i$ to $<X,v_i>$ and $!;0$ to $<Y,v_i>$

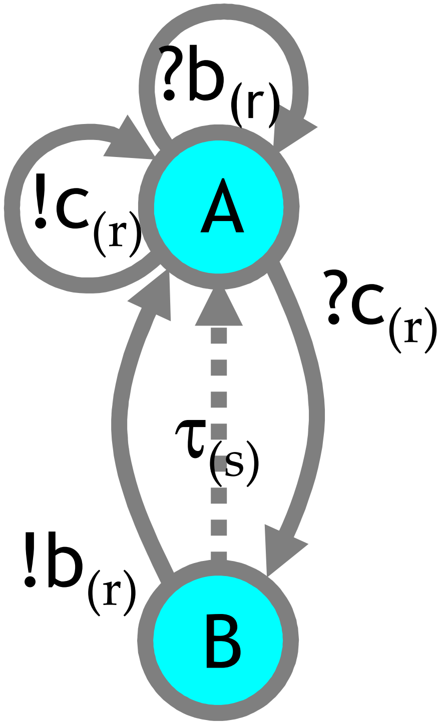
Homeo reaction $v_i$: $X+X \to_{k_i} P_i$

add $?;P_i$ and $!;0$ to $<X,v_i>$

2: Read the result by rows:

$A = ?b_{(r)};A \oplus ?c_{(r)};B \oplus !c_{(r)};A$

$B = \tau_{(s)};A \oplus !b_{(r)};A$



# From Chemistry to Automata (by example)

$v_1$: $A+B \rightarrow_{k_1} C+C$

$v_2$: $A+C \rightarrow_{k_2} D$

$v_3$: $C \rightarrow_{k_3} E+F$

$v_4$: $F+F \rightarrow_{k_4} B$

Interaction Matrix

channels and rates
(1 per reaction)

Half-rate for
homeo reactions

definitions
(1 per species)

| | $v_{1(k1)}$ | $v_{2(k2)}$ | $v_{3(k3)}$ | $v_{4(k4/2)}$ |
|---|---|---|---|---|
| A | $?;(C \mid C)$ | $?;D$ | | |
| B | $!;0$ | | | |
| C | | $!;0$ | $\tau;(E \mid F)$ | |
| D | | | | |
| E | | | | |
| F | | | | $?;B$<br>$!;0$ |

1: Fill the matrix by columns:

Degradation reaction $v_i$: $X \rightarrow k_i\ P_i$

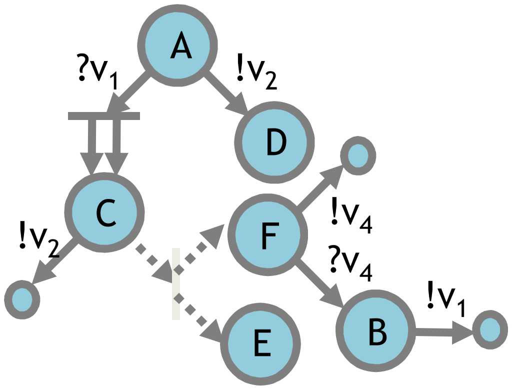
add $\tau;P_i$ to $<X,v_{ij}>$.

Hetero reaction $v_i$: $X+Y \rightarrow k_i\ P_i$

add $?;P_i$ to $<X,v_i>$ and $!;0$ to $<Y,v_i>$

Homeo reaction $v_i$: $X+X \rightarrow k_i\ P_i$

add $?;P_i$ and $!;0$ to $<X,v_i>$



2: Read the result by rows:

$A = ?v_{1(k1)};(C|C) \oplus ?v_{2(k2)};D$

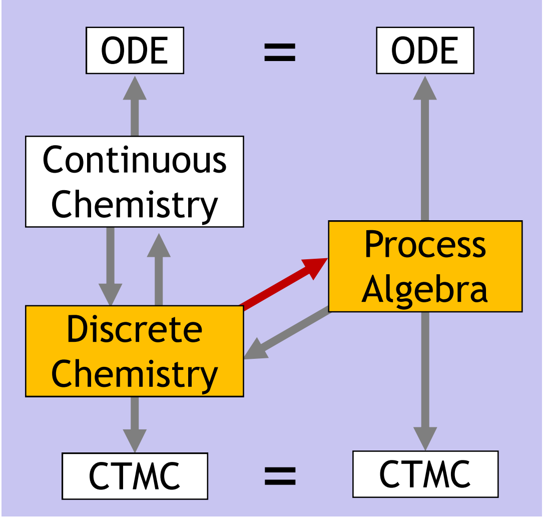
$B = !v_{1(k1)};0$

$C = !v_{2(k2)};0 \oplus \tau_{k3};(E|F)$

$D = 0$

$E = 0$

$F = ?v_{4(k4/2)};B \oplus !v_{4(k4/2)};0$



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

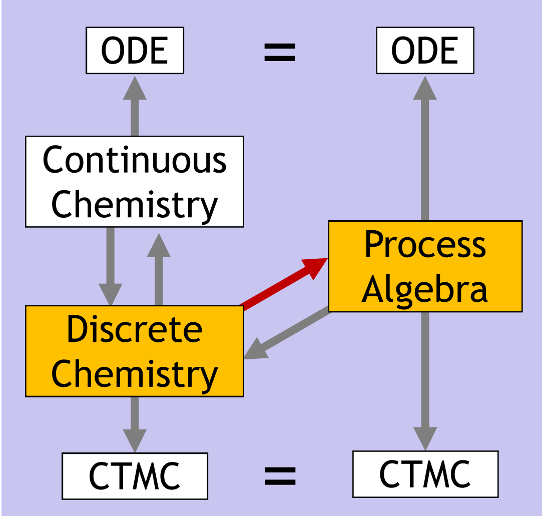
# From Chemistry to CGF: Pi(C)

$v:\quad X \to^{r} Y_1 + \ldots + Y_n + 0$ Unary Reaction

$v:\quad X_1 + X_2 \to^{r} Y_1 + \ldots + Y_n + 0$ Binary Reaction

From uniquely-labeled (v:) chemical reactions C to a CGF Pi(C):

$$\begin{aligned} Pi(C) \;=\; \{(X = \;& \oplus((v\!: X \to^{k} P)\in C)\ \mathit{of}\ (\tau_{(k)};P) && \oplus \\ & \oplus((v\!: X+Y \to^{k} P)\in C \text{ and } Y\neq X)\ \mathit{of}\ (?v_{(k)};P) && \oplus \\ & \oplus((v\!: Y+X \to^{k} P)\in C \text{ and } Y\neq X)\ \mathit{of}\ (!v_{(k)};0) && \oplus \\ & \oplus((v\!: X+X \to^{k} P)\in C)\ \mathit{of}\ (?v_{(k/2)};P \oplus !v_{(k/2)};0) && ) \\ & s.t.\ X \text{ is a species in } C\} \end{aligned}$$



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

# Some Syntactic Properties

- C and Ch(Pi(C)) have the same reactions
  - (and their reaction labels are in bijection)

- Def: E is detangled if each channel appears once as ?a and once as !a.

- If C is a system of chemical reactions then Pi(C) is detangled.
  - (hence chemical reactions embed into a subclass of CGFs)

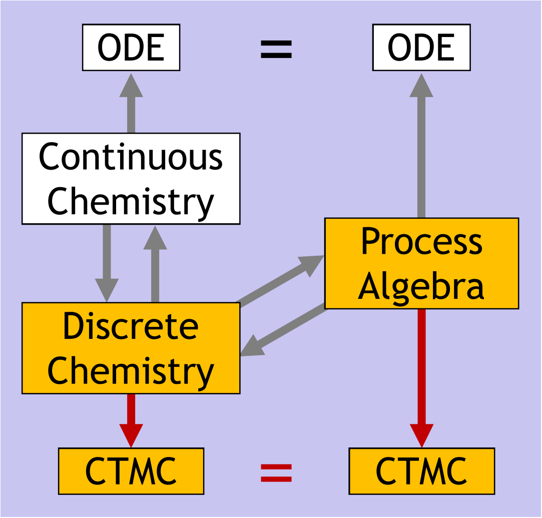
- Hence for any E, we have that Pi(Ch(E)) is detangled.
  - (E and Pi(Ch(E)) are “equivalent” CGFs, but that has to be shown later)

- Def: E,P is automata form if “|” occurs only (other than “|0”) in P.

- Def: Detangle(E) is defined from Pi(Ch(E)) by replacing any occurrence pairs $?a_{(r)};(X|Y|0)$ and $!a_{(r)};0$ with $?a_{(r)};(X|0)$ and $!a_{(r)};(Y|0)$.

- If E is in automata form then Detangle(E) is (detangled and) in automata form
  - (but Pi(Ch(E)) may not be)

# Discrete-State Semantics



# Discrete Semantics of Reactions

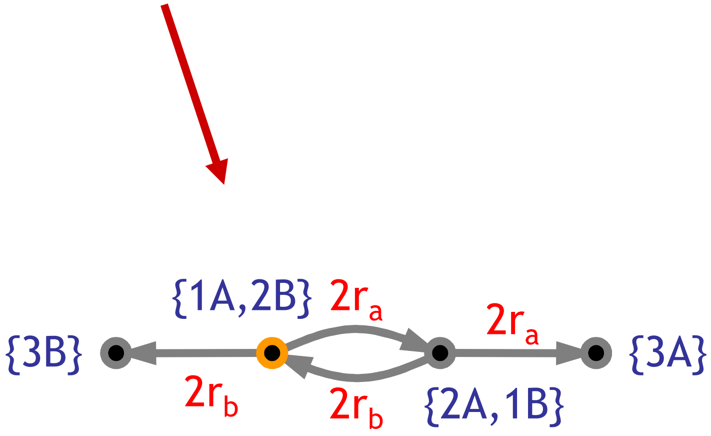
Syntax:

$A+B \to^{r} A+A$

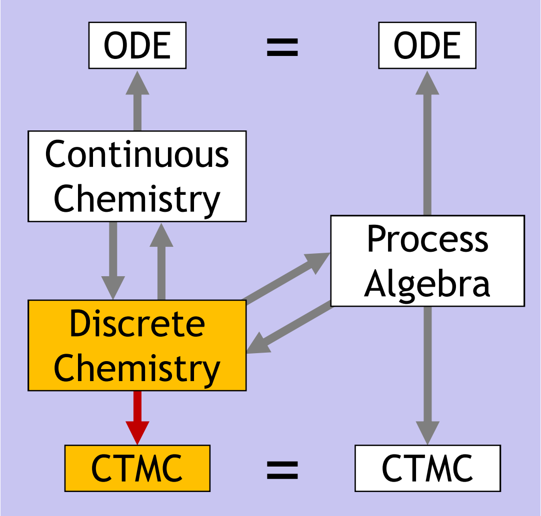
$A+B \to^{r} B+B$

$A+B+B$

Semantics:



CTMC



ODE = ODE

Continuous Chemistry

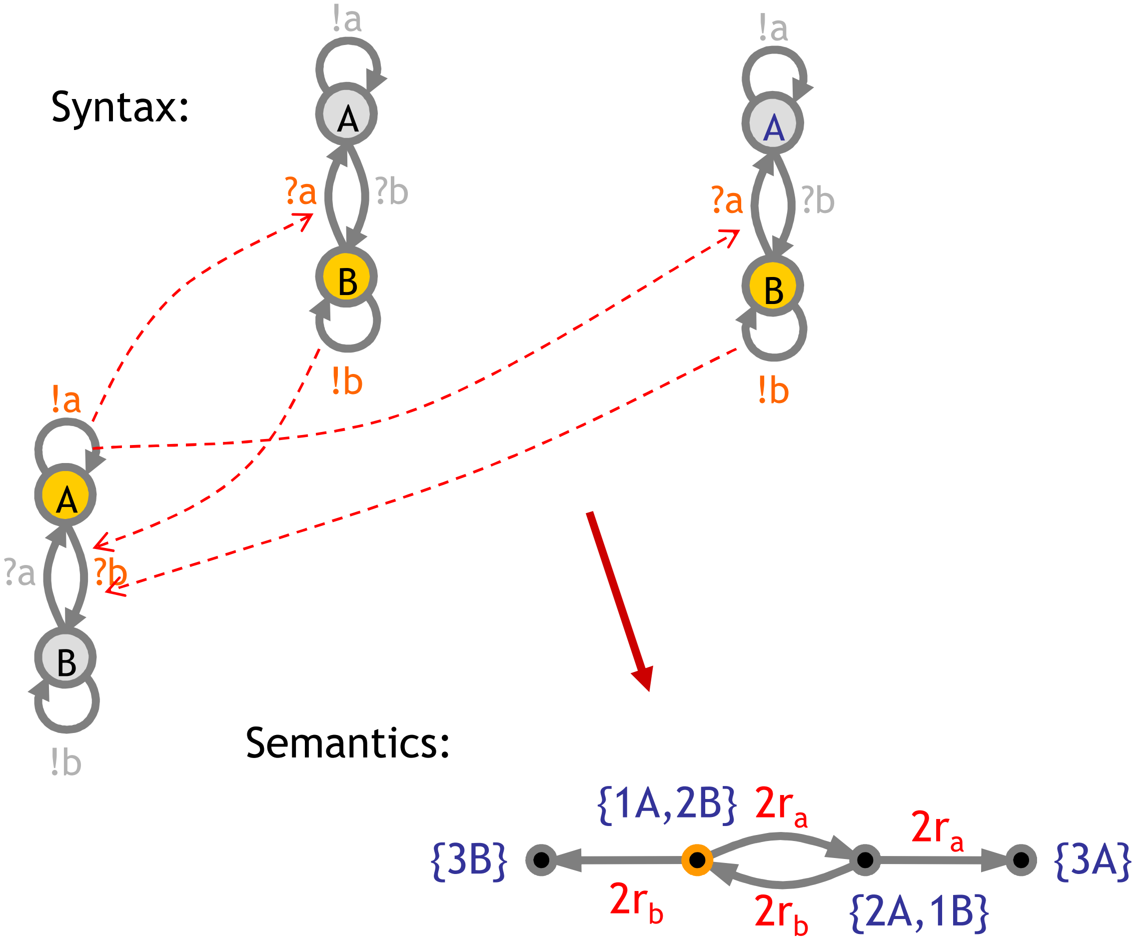
Process Algebra

Discrete Chemistry

CTMC = CTMC

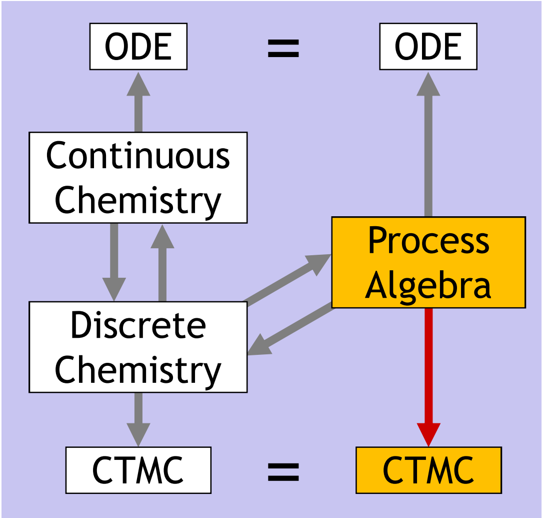
# Discrete Semantics of Reagents

Syntax:



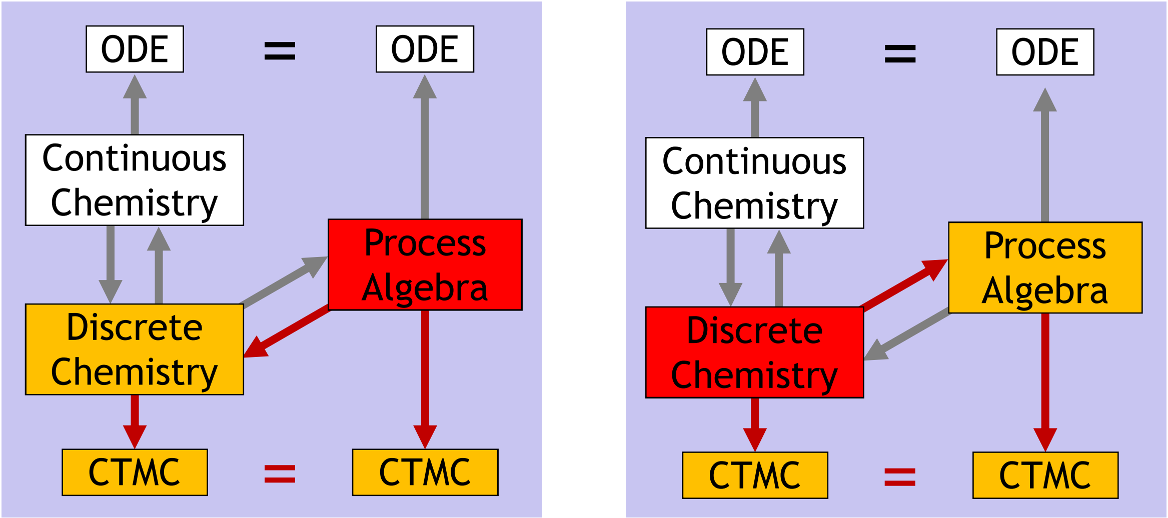
Semantics:

CTMC



# Discrete State Equivalence

- Def: ♒ is equivalent CTMC’s (isomorphic graphs with same rates).
- Thm: E ♒ Ch(E)
- Thm: C ♒ Pi(C)



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

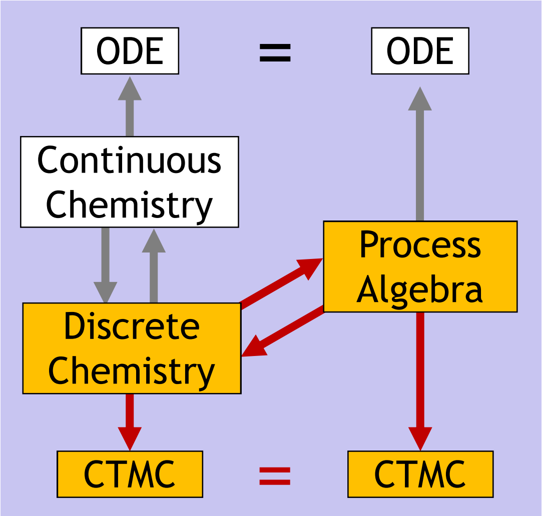
- For each E there is an E’ ♒ E that is detangled (E’ = Pi(Ch(E)))
- For each E in automata form there is an an E’ ♒ E that is detangled and in automata form (E’ = Detangle(E)).

# Interacting Automata = Discrete Chemistry

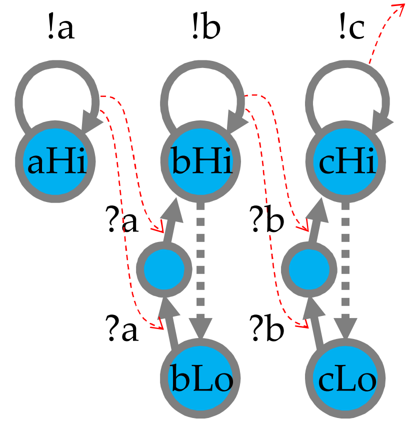
This is enough to establish that the process algebra is really faithful to the chemistry.

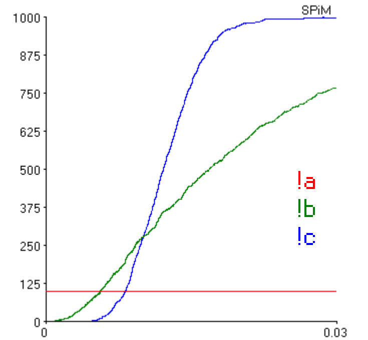
But CTMC are not the "ultimate semantics" because there are still questions of when two different CTMCs are actually equivalent (e.g. "lumping").

The "ultimate semantics" of chemistry is the *Chemical Master Equation* (derivable from the Chapman-Kolmogorov equation of the CTMC).



# Exercise 1

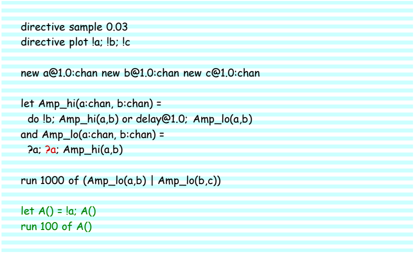




100×aHi, 1000×bLo, 1000×cLo, rates=1.0

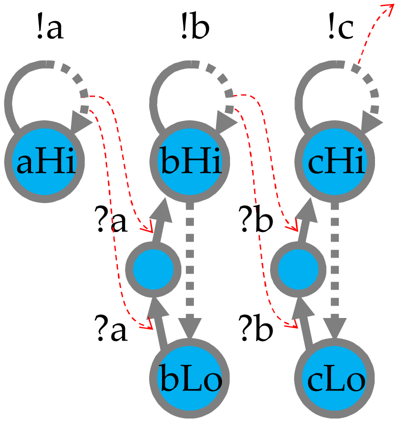
Second-Oder Regime cascade:
a signal amplifier (MAPK)

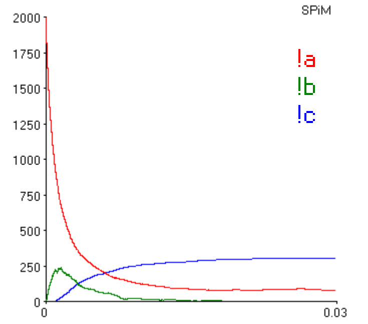
aHi > 0 ⇒ cHi = max



```
directive sample 0.03
directive plot !a; !b; !c

new a@1.0:chan new b@1.0:chan new c@1.0:chan

let Amp_hi(a:chan, b:chan) =
  do !b; Amp_hi(a,b) or delay@1.0;  Amp_lo(a,b)
and Amp_lo(a:chan, b:chan) =
  ?a; ?a; Amp_hi(a,b)

run 1000 of (Amp_lo(a,b) | Amp_lo(b,c))

let A() = !a; A()
run 100 of A()
```

Write these automata in CGF and translate them to chemical reactions.

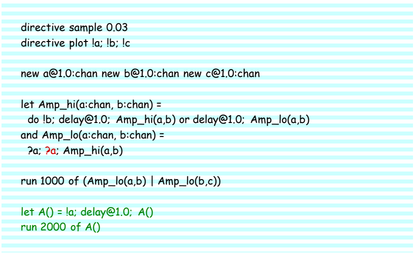




2000×aHi, 1000×bLo, 1000×cLo, rates=1.0

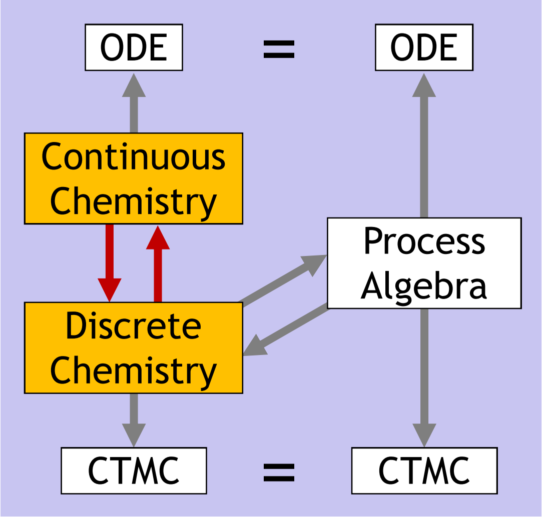
Zero-Oder Regime cascade:
a signal *divider!*

aHi = max ⇒ cHi = 1/3 max

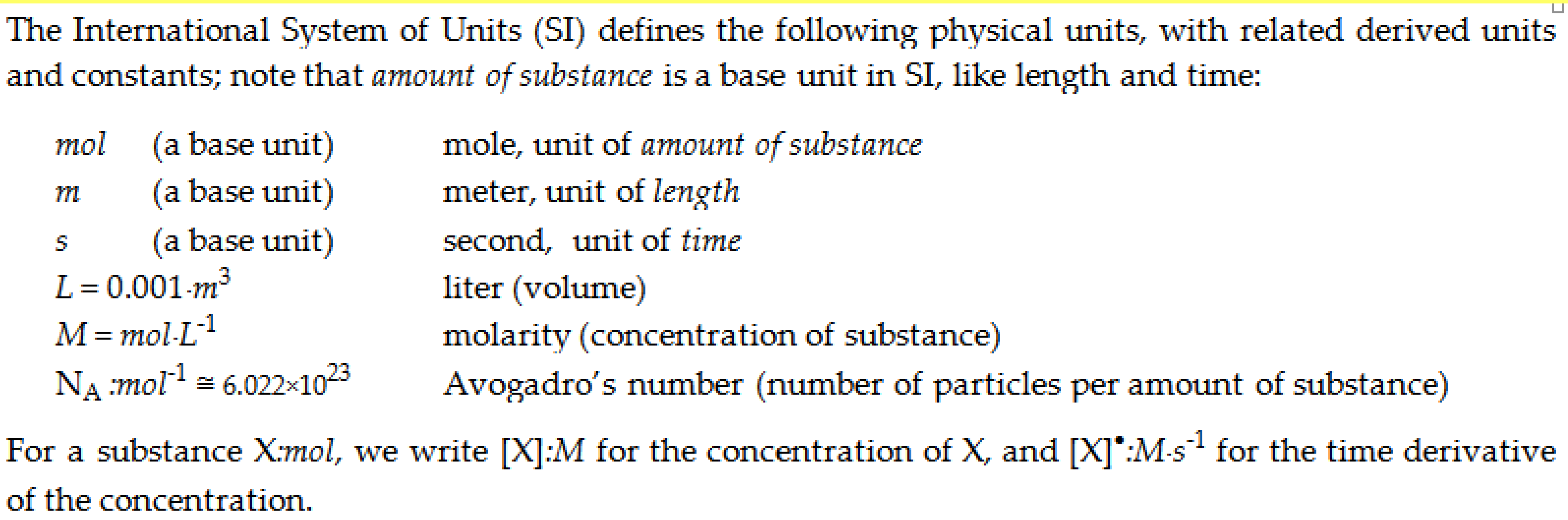


```
directive sample 0.03
directive plot !a; !b; !c

new a@1.0:chan new b@1.0:chan new c@1.0:chan

let Amp_hi(a:chan, b:chan) =
  do !b; delay@1.0;  Amp_hi(a,b) or delay@1.0;  Amp_lo(a,b)
and Amp_lo(a:chan, b:chan) =
  ?a; ?a; Amp_hi(a,b)

run 1000 of (Amp_lo(a,b) | Amp_lo(b,c))

let A() = !a; delay@1.0;  A()
run 2000 of A()
```

# Discrete vs Continuous Chemistry



# The "Type System" of Chemistry



The International System of Units (SI) defines the following physical units, with related derived units and constants; note that *amount of substance* is a base unit in SI, like length and time:

| | | |
|---|---|---|
| $mol$ | (a base unit) | mole, unit of *amount of substance* |
| $m$ | (a base unit) | meter, unit of *length* |
| $s$ | (a base unit) | second, unit of *time* |
| $L = 0.001{\cdot}m^3$ | | liter (volume) |
| $M = mol{\cdot}L^{-1}$ | | molarity (concentration of substance) |
| $N_A : mol^{-1} \cong 6.022{\times}10^{23}$ | | Avogadro's number (number of particles per amount of substance) |

For a substance $X{:}mol$, we write $[X]{:}M$ for the concentration of X, and $[X]^{\bullet}{:}M{\cdot}s^{-1}$ for the time derivative of the concentration.

A continuous chemical system (C,V) is a system of chemical reactions C plus a vector of initial concentrations $V_X$: M, one for each species X.

The rates of unary reactions have dimension $s^{-1}$.

The rates of binary reactions have dimension $M^{-1}s^{-1}$.

(because in both cases the rhs of an ODE should have dimension $M{\cdot}s^{-1}$).

## Relating Concentration to Number of Molecules

For a given volume of solution V, the volumetric factor $\gamma$ of dimension $M^{-1}$ is:

$\gamma : M^{-1} = N_A V$ where $N_A{:}mol^{-1}$ and $V{:}L$

$\#X / \gamma : M =$ concentration of X molecules

$\gamma{\cdot}[X] : 1 =$ total number of X molecules (rounded to an integer).

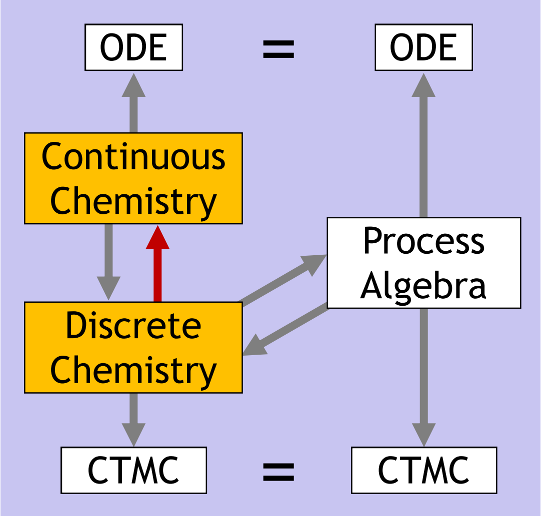
# The Gillespie Conversion

| Discrete Chemistry | Continuous Chemistry | $\gamma = N_A V$ | $:M^{-1}$ |
|---|---|---|---|
| initial quantities<br>$\#A_0$ | initial concentrations<br>$[A]_0$ | with $[A]_0 = \#A_0/\gamma$ | |
| $A \overset{r}{\dashrightarrow} A'$ | $A \xrightarrow{k} A'$ | with $k = r$ | $:s^{-1}$ |
| $A+B \overset{r}{\dashrightarrow} A'+B'$ | $A+B \xrightarrow{k} A'+B'$ | with $k = r\gamma$ | $:M^{-1}s^{-1}$ |
| $A+A \overset{r}{\dashrightarrow} A'+A''$ | $A+A \xrightarrow{k} A'+A''$ | with $k = r\gamma/2$ | $:M^{-1}s^{-1}$ |

V = interaction volume
$N_A$ = Avogadro's number

Think $\gamma = 1$
i.e. $V = 1/N_A$

$M = mol{\cdot}L^{-1}$
molarity (concentration)



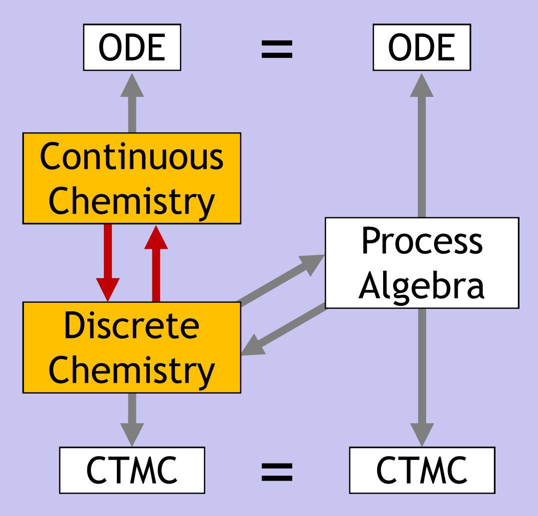
# $\mathrm{Cont}_\gamma$ and $\mathrm{Disc}_\gamma$

### 4.2–3 Definition: $Cont_\gamma$ and $Disc_\gamma$

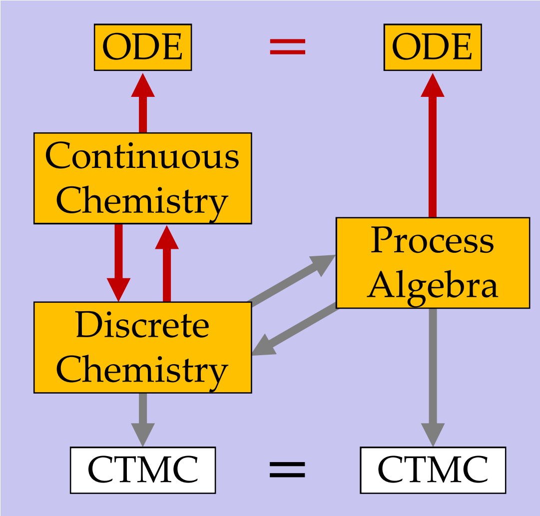
For a volumetric factor $\gamma{:}M^{-1}$, we define a translation $Cont_\gamma$ from a discrete chemical systems (C,P), with species X and initial molecule count $\#X_0 = \#X(P)$, to a continuous chemical systems (C,V) with initial concentration $[X]_0 = V_X$. The translation $Disc_\gamma$ is its inverse, up to a rounding error $\lceil \gamma[X]_0 \rceil$ in converting concentrations to molecule counts. Since $\gamma$ is a global conversion constant, we later usually omit it as a subscript.

| | | | | |
|---|---|---|---|---|
| $Cont_\gamma(X \to^r P)$ | $= X \to^k P$ | with $k = r$, | $r{:}s^{-1}$ | $k{:}s^{-1}$ |
| $Cont_\gamma(X+Y \to^r P)$ | $= X+Y \to^k P$ | with $k = r\gamma$ | $r{:}s^{-1}$ | $k{:}M^{-1}s^{-1}$ |
| $Cont_\gamma(X+X \to^r P)$ | $= X+X \to^k P$ | with $k = r\gamma/2$ | $r{:}s^{-1}$ | $k{:}M^{-1}s^{-1}$ |
| $Cont_\gamma(\#X_0)$ | $= [X]_0$ | with $[X]_0 = \#X_0/\gamma$ | $X_0{:}mol$ | $[X]_0{:}M$ |
| $Disc_\gamma(X \to^k P)$ | $= X \to^r P$ | with $r = k$, | $k{:}s^{-1}$ | $r{:}s^{-1}$ |
| $Disc_\gamma(X+Y \to^k P)$ | $= X+Y \to^r P$ | with $r = k/\gamma$ | $k{:}M^{-1}s^{-1}$ | $r{:}s^{-1}$ |
| $Disc_\gamma(X+X \to^k P)$ | $= X+X \to^r P$ | with $r = 2k/\gamma$ | $k{:}M^{-1}s^{-1}$ | $r{:}s^{-1}$ |
| $Disc_\gamma([X]_0)$ | $= \#X_0$ | with $\#X_0 = \lceil \gamma[X]_0 \rceil$ | $[X]_0{:}M$ | $X_0{:}mol$ |

$$\mathrm{Ch}_\gamma \ := \ \mathrm{Cont}_\gamma \circ \mathrm{Ch}$$



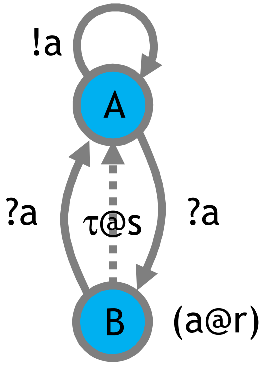
# Continuous-State Semantics



# Same Semantics

Could chemistry itself be that semantics?

No: different sets of reactions can have the same behavior!



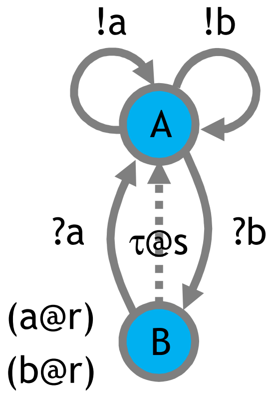
$A = !a;A \oplus ?a;B$

$B = ?a;A \oplus \tau_{(s)};A$

$B \xrightarrow{s} A$

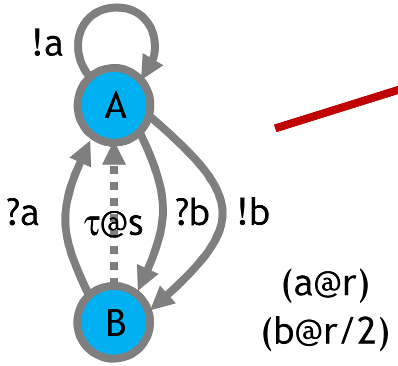
$A+B \xrightarrow{r} A+A$

$A+A \xrightarrow{2r} A+B$



$A = !a;A \oplus !b;A \oplus ?b;B$

$B = ?a;A \oplus \tau_{(s)};A$



$A = !a;A \oplus !b;B \oplus ?b;B$

$B = ?a;A \oplus \tau_{(s)};A$

$B \xrightarrow{s} A$

$A+B \xrightarrow{r} A+A$

$A+A \xrightarrow{r} B+B$

Different reactions,
but they induce the
same ODEs

# From Reactions to ODEs (Law of Mass Action)

$v_1$: $A+B \rightarrow_{k_1} C+C$

$v_2$: $A+C \rightarrow_{k_2} D$

$v_3$: $C \rightarrow_{k_3} E+F$

$v_4$: $F+F \rightarrow_{k_4} B$

Write the coefficients by columns

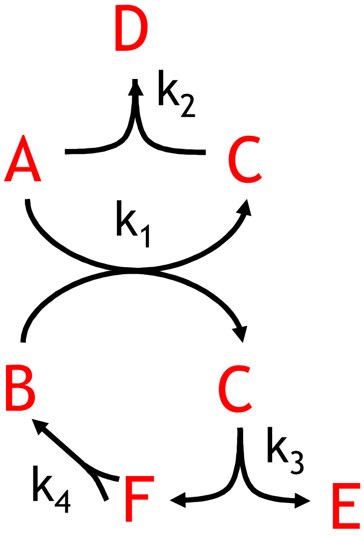
Stoichiometric Matrix

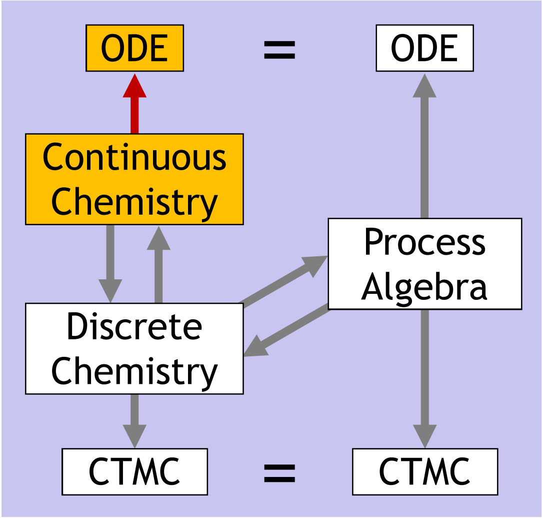
reactions

species

| N | $v_1$ | $v_2$ | $v_3$ | $v_4$ |
|---|---|---|---|---|
| A | -1 | -1 | | |
| B | -1 | | | 1 |
| C | 2 | -1 | -1 | |
| D | | 1 | | |
| E | | | 1 | |
| F | | | 1 | -2 |

X





Quantity changes

Stoichiometric matrix

Rate laws

$$d[X]/dt = N \cdot l$$

$$d[A]/dt = -l_1 - l_2$$
$$d[B]/dt = -l_1 + l_4$$
$$d[C]/dt = 2l_1 - l_2 - l_3$$
$$d[D]/dt = l_2$$
$$d[E]/dt = l_3$$
$$d[F]/dt = l_3 - 2l_4$$

Read the concentration changes from the rows

E.g. $d[A]/dt = -k_1[A][B] - k_2[A][C]$

Set a rate law for each reaction

(Degradation/Hetero/Homeo)

| | l |
|---|---|
| $l_1$ | $k_1[A][B]$ |
| $l_2$ | $k_2[A][C]$ |
| $l_3$ | $k_3[C]$ |
| $l_4$ | $k_4[F]^2$ |

X: chemical species

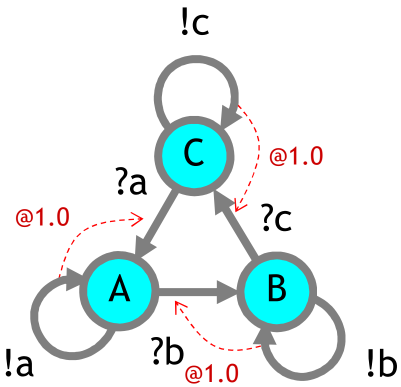
[-]: quantity of molecules

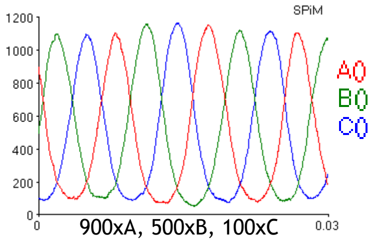
l: rate laws

k: kinetic parameters

N: stoichiometric matrix

# From Processes to ODEs via Chemistry!





900xA, 500xB, 100xC

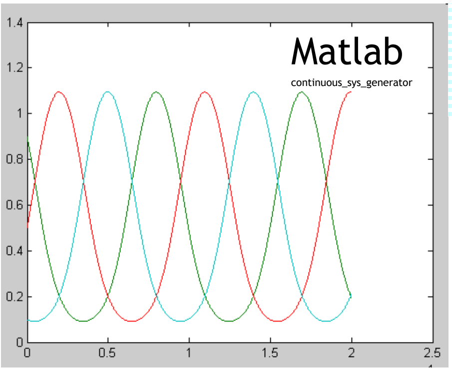
```
directive sample 0.03 1000
directive plot A(); B(); C()

new a@1.0:chan new b@1.0:chan new
c@1.0:chan
let A() = do !a;A() or ?b; B()
and B() = do !b;B() or ?c; C()
and C() = do !c;C() or ?a; A()

run (900 of A() | 500 of B() | 100 of C())
```

$$A = !a_{(s)};A \oplus ?b_{(s)};B$$
$$B = !b_{(s)};B \oplus ?c_{(s)};C$$
$$C = !c_{(s)};C \oplus ?a_{(s)};A$$

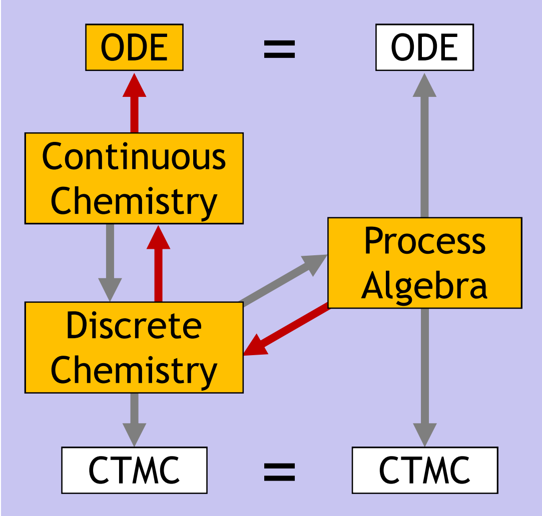
$$A+B \to^{s} B+B$$
$$B+C \to^{s} C+C$$
$$C+A \to^{s} A+A$$

$$d[A]/dt = -s[A][B]+s[C][A]$$
$$d[B]/dt = -s[B][C]+s[A][B]$$
$$d[C]/dt = -s[C][A]+s[B][C]$$

$(\gamma = 1)$



```
interval/step [0:0.001:20.0]
(A)     dx1/dt = - x1*x2 + x3*x1        0.9
(B)     dx2/dt = - x2*x3 + x1*x2        0.5
(C)     dx3/dt = - x3*x1 + x2*x3        0.1
```


ODE = ODE

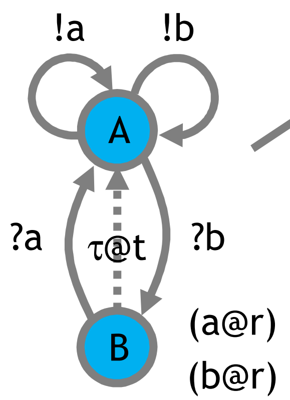
Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

# From Processes to ODEs via Chemistry!



$\tau: B \xrightarrow{t} A$

$a: A+B \xrightarrow{r} A+A$

$b: A+A \xrightarrow{2r} A+B$

(discrete reactions)

$B \xrightarrow{t} A$

$A+B \xrightarrow{r\gamma} A+A$

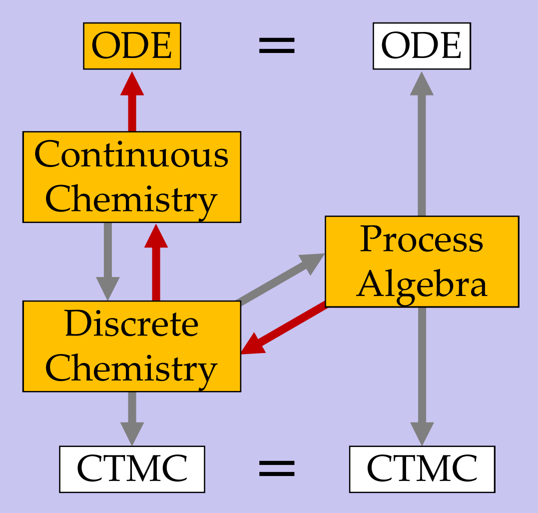
$A+A \xrightarrow{r\gamma} A+B$

(continuous reactions)

lose 1A at rate $r\gamma$

$d[A]/dt = t[B] + r\gamma[A][B] - r\gamma[A]^2$

$d[B]/dt = -t[B] - r\gamma[A][B] + r\gamma[A]^2$



ODE = ODE

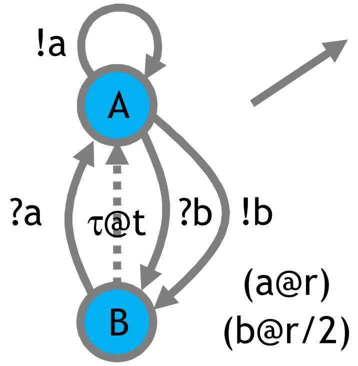
Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

Different chemistry but same ODEs, hence equivalent automata



$\tau: B \xrightarrow{t} A$

$a: A+B \xrightarrow{r} A+A$

$b: A+A \xrightarrow{r} B+B$

(discrete reactions)

$B \xrightarrow{t} A$

$A+B \xrightarrow{r\gamma} A+A$

$A+A \xrightarrow{r\gamma/2} B+B$

(continuous reactions)

lose 2A at rate $r\gamma/2$

$d[A]/dt = t[B] + r\gamma[A][B] - r\gamma[A]^2$

$d[B]/dt = -t[B] - r\gamma[A][B] + r\gamma[A]^2$

# Processes Rate Equation

Process Rate Equation for Reagents E in volume $\gamma$

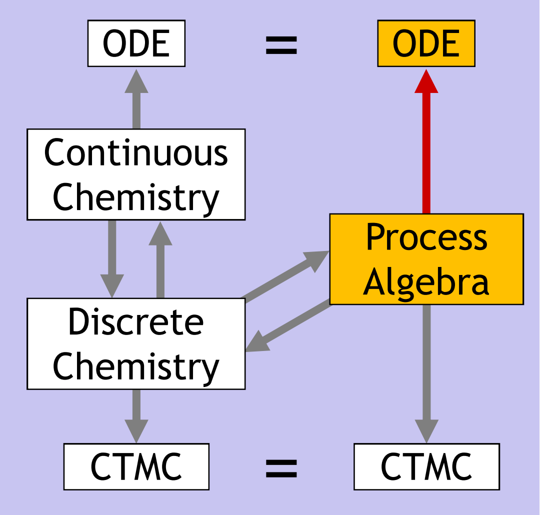
$$d[X]/dt = (\Sigma(Y \in E)\ \mathrm{Accr}_E(Y,X) \cdot [Y]) - \mathrm{Depl}_E(X) \cdot [X]$$
for all $X \in E$

"The change in process concentration (!!) for X at time t is:
the sum over all possible (kinds of) processes Y of:
the concentration at time t of Y
times the accretion from Y to X
minus the concentration at time t of X
times the depletion of X to some other Y"

$\mathrm{Depl}_E(X) =$
$\Sigma(i\!: E.X.i=\tau_{(r)};P)\ r\ +$
$\Sigma(i\!: E.X.i=?a_{(r)};P)\ r\gamma \cdot \mathrm{OutsOn}_E(a)\ +$
$\Sigma(i\!: E.X.i=!a_{(r)};P)\ r\gamma \cdot \mathrm{InsOn}_E(a)$

$\mathrm{Accr}_E(Y, X) =$
$\Sigma(i\!: E.Y.i=t_{(r)};P)\ \#X(P) \cdot r\ +$
$\Sigma(i\!: E.Y.i=?a_{(r)};P)\ \#X(P) \cdot r\gamma \cdot \mathrm{OutsOn}_E(a)\ +$
$\Sigma(i\!: E.Y.i=!a_{(r)};P)\ \#X(P) \cdot r\gamma \cdot \mathrm{InsOn}_E(a)$

$\mathrm{InsOn}_E(a) = \Sigma(Y \in E)\ \#\{Y.i \mid E.Y.i=?a_{(r)};P\} \cdot [Y]$
$\mathrm{OutsOn}_E(a) = \Sigma(Y \in E)\ \#\{Y.i \mid E.Y.i=!a_{(r)};P\} \cdot [Y]$



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

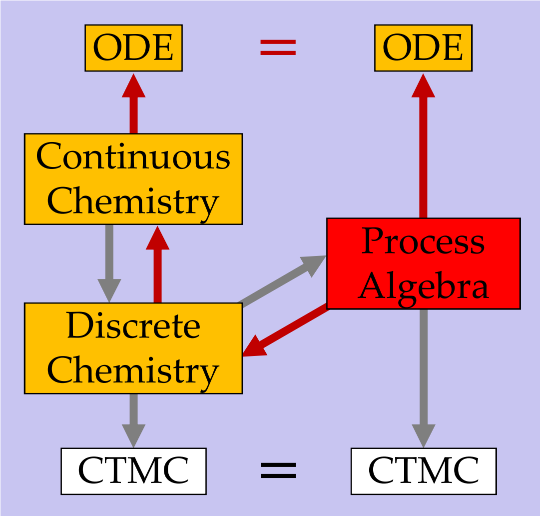
$X = \tau_{(r)};0 \;\longrightarrow\; d[X]/dt = -r[X]$

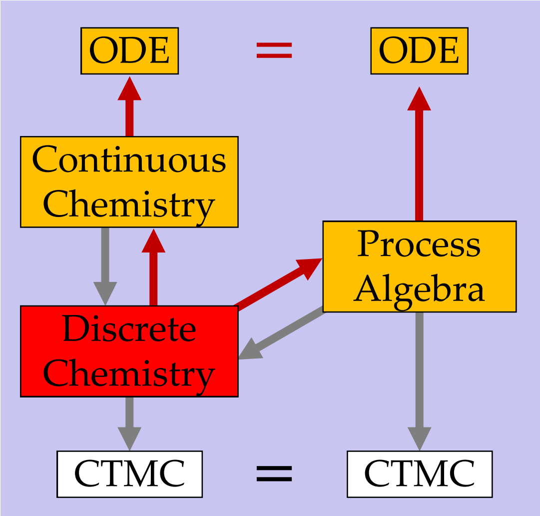
$X = ?a_{(r)};0$
$Y = !a_{(r)};0 \;\longrightarrow\; d[X]/dt = -r\gamma[X][Y]$, $d[Y]/dt = -r\gamma[X][Y]$

$X = ?a_{(r)};0 \oplus !a_{(r)};0 \;\longrightarrow\; d[X]/dt = -2r\gamma[X]^2$

# Continuous State Equivalence

- Def: ≈ is equivalence of polynomials over the field of reals.
- Thm: E ≈ Cont(Ch(E))
- Thm: Cont(C) ≈ Pi(C)

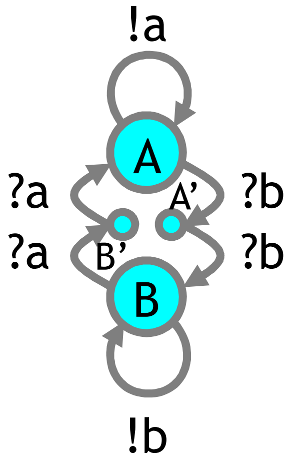


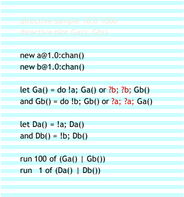


- For each E there is an E’ ≈ E that is detangled (E’ = Pi(Ch(E)))
- For each E in automata form there is an an E’ ≈ E that is detangled and in automata form (E’ = Detangle(E)).

# Exercise 2

Q: What does this do?





```
directive sample 10.0 1000
directive plot Ga(); Gb()

new a@1.0:chan()
new b@1.0:chan()

let Ga() = do !a; Ga() or ?b; ?b; Gb()
and Gb() = do !b; Gb() or ?a; ?a; Ga()

let Da() = !a; Da()
and Db() = !b; Db()

run 100 of (Ga() | Gb())
run  1 of (Da() | Db())
```

$A = !a_{(r)};A \oplus ?b;A' \quad A' = ?b;B$

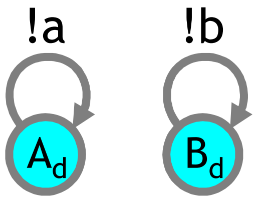
$B = !b_{(r)};B \oplus ?a;B' \quad B' = ?a;A$

$A_d = !a_{(r)};A_d$

$B_d = !b_{(r)};B_d$

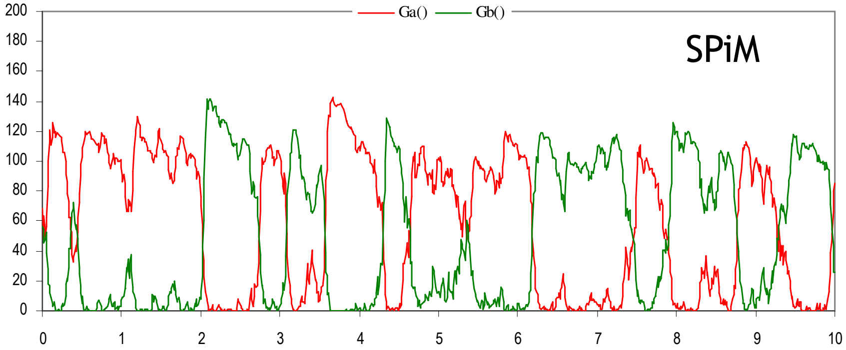
Derive the ODEs from these “Hysteric Groupies” automata. Either by going through the chemical reactions and the Law of Mass Action (easier), or directly from the Process Rate Equation.

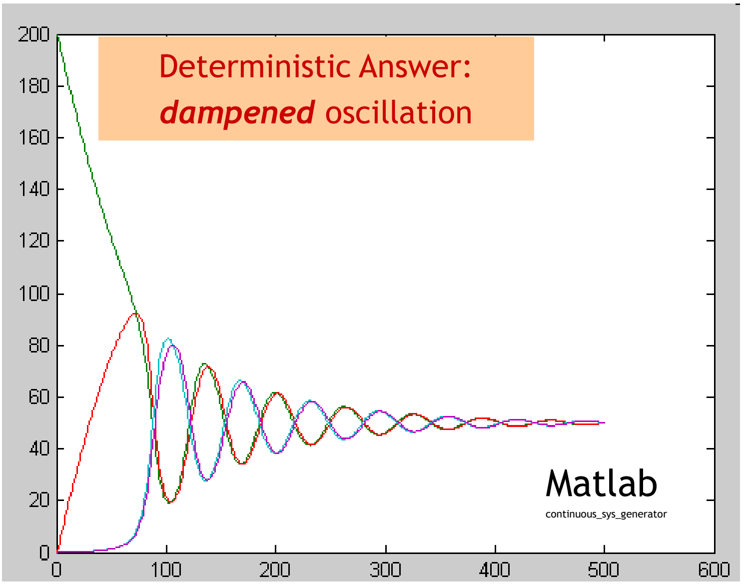
Doping



ODE predicts dampened oscillation, while the stochasic system keeps oscillating at max level.

Stochastic Answer:
**robust** quasi-oscillation





Deterministic Answer:
***dampened*** oscillation

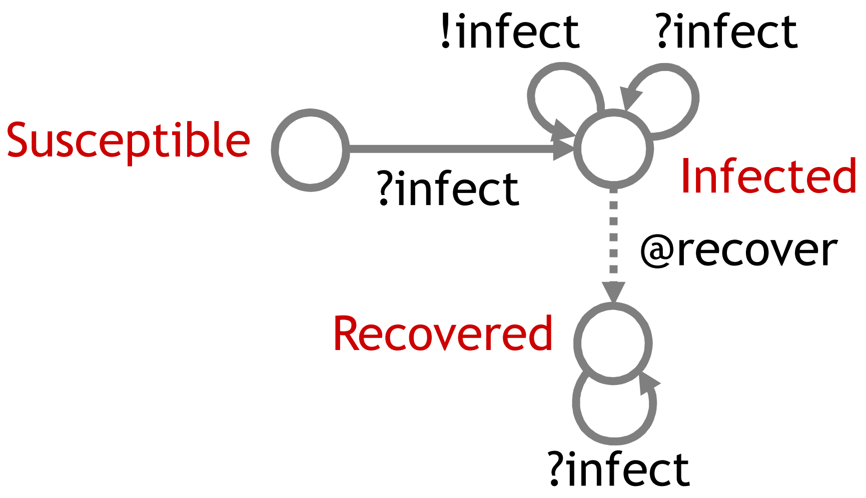
# Epidemics

Non-Chemical Mass Action

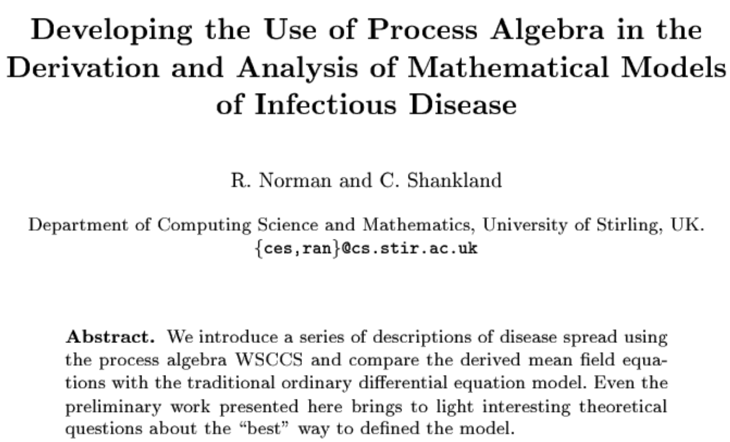
Kermack, W. O. and McKendrick, A. G. "**A Contribution to the Mathematical Theory of Epidemics.**" *Proc. Roy. Soc. Lond. A* **115**, 700-721, 1927.

http://mathworld.wolfram.com/Kermack-McKendrickModel.html

# Epidemics



```
directive sample 500 0 1000
directive plot Recovered(); Susceptible(); Infected()

new infect @0.001:chan()
val recover = 0.03

let Recovered() =
  ?infect; Recovered()

and Susceptible() =
  ?infect; Infected()

and Infected() =
  do !infect; Infected()
  or ?infect; Infected()
  or delay@recover; Recovered()

run (200 of Susceptible() | 2 of Infected())
```

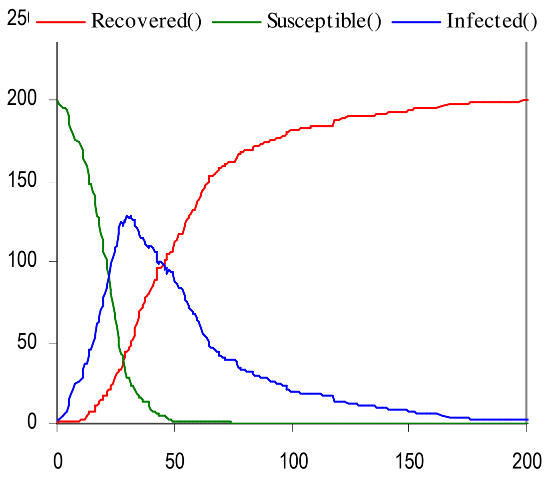


Developing the Use of Process Algebra in the Derivation and Analysis of Mathematical Models of Infectious Disease

R. Norman and C. Shankland

Department of Computing Science and Mathematics, University of Stirling, UK.
{ces,ran}@cs.stir.ac.uk

**Abstract.** We introduce a series of descriptions of disease spread using the process algebra WSCCS and compare the derived mean field equations with the traditional ordinary differential equation model. Even the preliminary work presented here brings to light interesting theoretical questions about the "best" way to defined the model.



# ODEs

$S = ?i_{(t)};I$
$I = !i_{(t)};I \oplus ?i_{(t)};I \oplus t_r;R$
$R = ?i_{(t)};R$

Differentiating Processes!

$S + I \xrightarrow{t\gamma} I + I$
$I + I \xrightarrow{t\gamma} I + I$
$I \xrightarrow{r} R$
$R + I \xrightarrow{t\gamma} R + I$

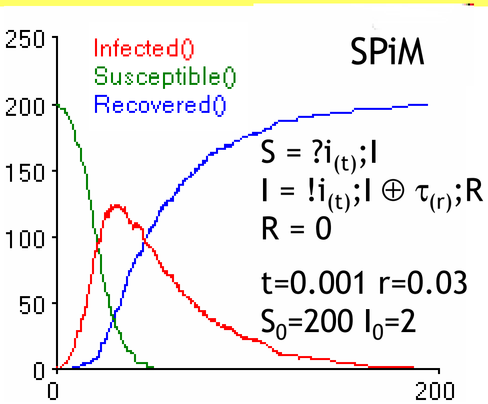
“useless” reactions

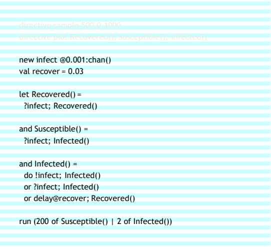
$d[S]/dt = -t\gamma[S][I]$
$d[I]/dt = t\gamma[S][I]-r[I]$
$d[R]/dt = r[I]$

Automata produce the standard ODEs!

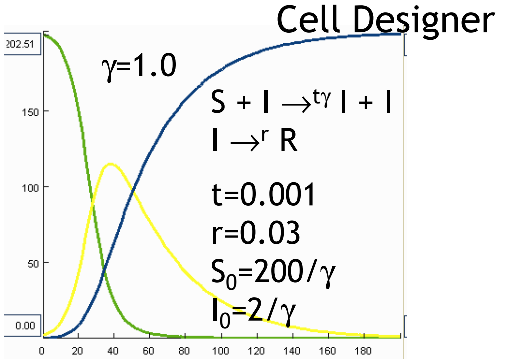
$$\frac{dS}{dt} = -aIS$$
$$\frac{dI}{dt} = aIS - bI$$
$$\frac{dR}{dt} = bI$$

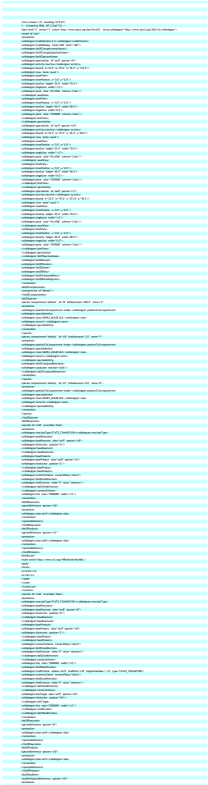
(the Kermack-McKendrick, or SIR model)

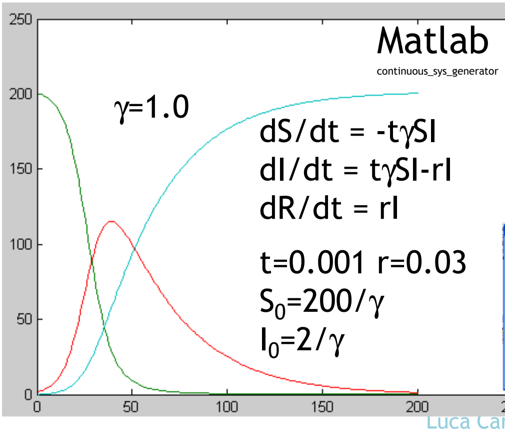


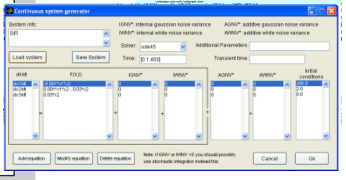


```
directive sample 500.0 1000
directive plot Recovered(); Susceptible(); Infected()

new infect @0.001:chan()
val recover = 0.03

let Recovered() =
  ?infect; Recovered()

and Susceptible() =
  ?infect; Infected()

and Infected() =
  do !infect; Infected()
  or ?infect; Infected()
  or delay@recover; Recovered()

run (200 of Susceptible() | 2 of Infected())
```







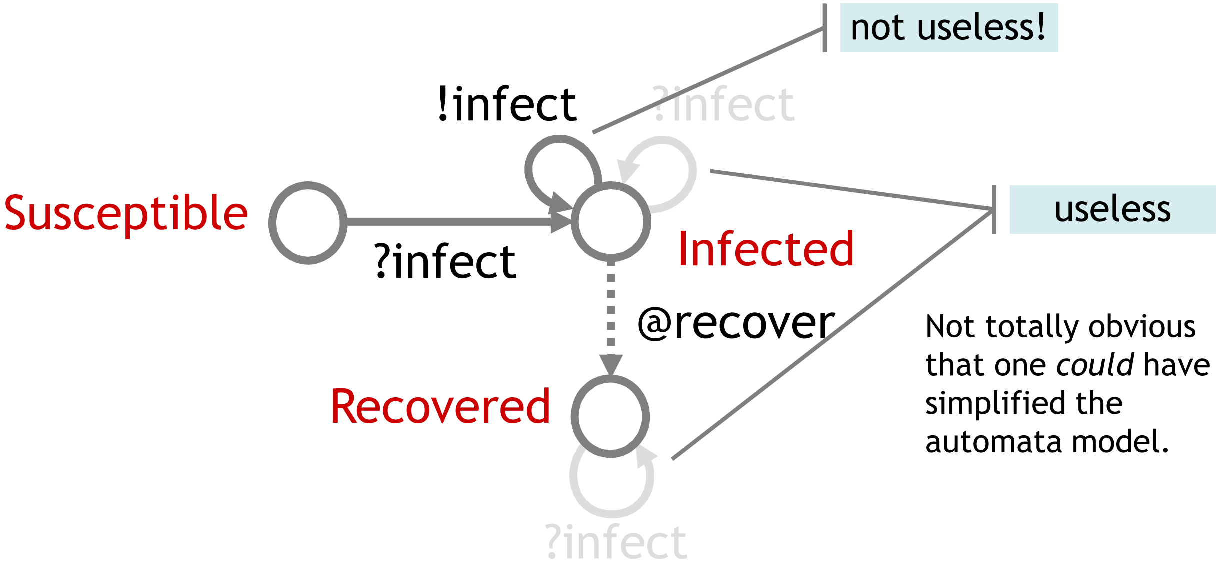


System info: SIR
Solver: ode45
Time: [0:1:400]

| dX/dt | F(X,t) | IGNV* | IWNV* | AGNV* | AWNV* | Initial conditions |
|---|---|---|---|---|---|---|
| dx1/dt | -0.001*x1*x2 | 0 | 0 | 0 | 0 | 200.0 |
| dx2/dt | 0.001*x1*x2 - 0.03*x2 | 0 | 0 | 0 | 0 | 2.0 |
| dx3/dt | 0.03*x2 | 0 | 0 | 0 | 0 | 0.0 |

Note: if IGNV or IWNV >0 you should possibly use stochastic integrator instead this

# Simplified Model



not useless!

useless

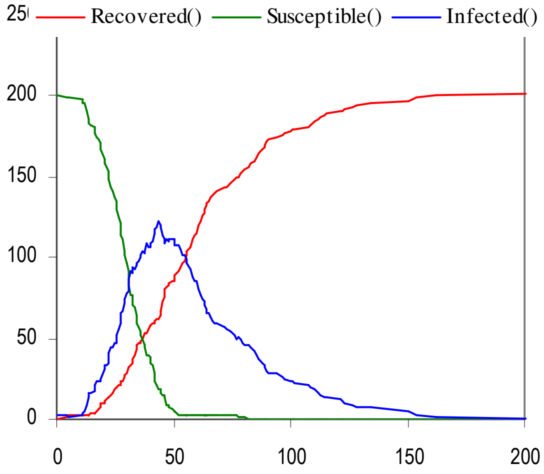
Not totally obvious that one *could* have simplified the automata model.

$$S = ?i_{(t)};I$$
$$I = !i_{(t)};I \oplus \tau_r;R$$
$$R = 0$$

$$S + I \xrightarrow{t\gamma} I + I$$
$$I \xrightarrow{r} R$$

$$d[S]/dt = -t\gamma[S][I]$$
$$d[I]/dt = t\gamma[S][I]-r[I]$$
$$d[R]/dt = r[I]$$

```
directive sample 500.0 1000
directive plot Recovered(); Susceptible(); Infected()

new infect @0.001:chan()
val recover = 0.03

let Recovered() =
  ()

and Susceptible() =
  ?infect; Infected()

and Infected() =
  do !infect; Infected()
  or delay@recover; Recovered()

run (200 of Susceptible() | 2 of Infected())
```

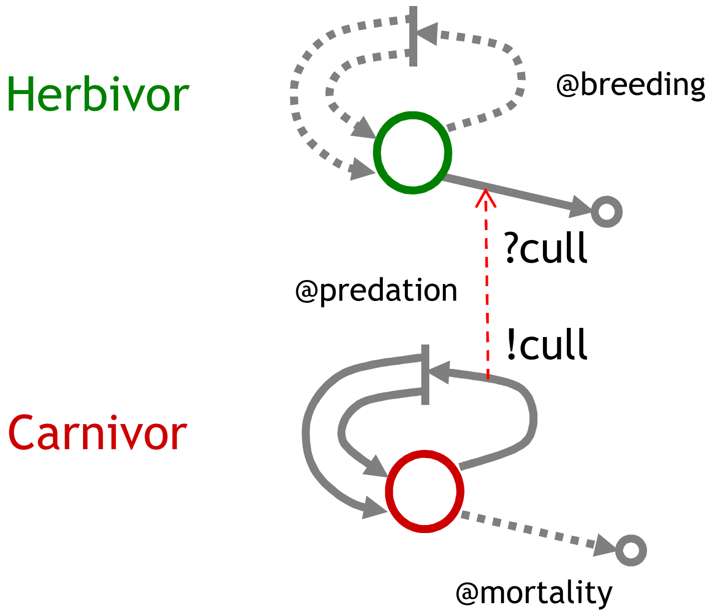


Same ODE, hence equivalent automata models.

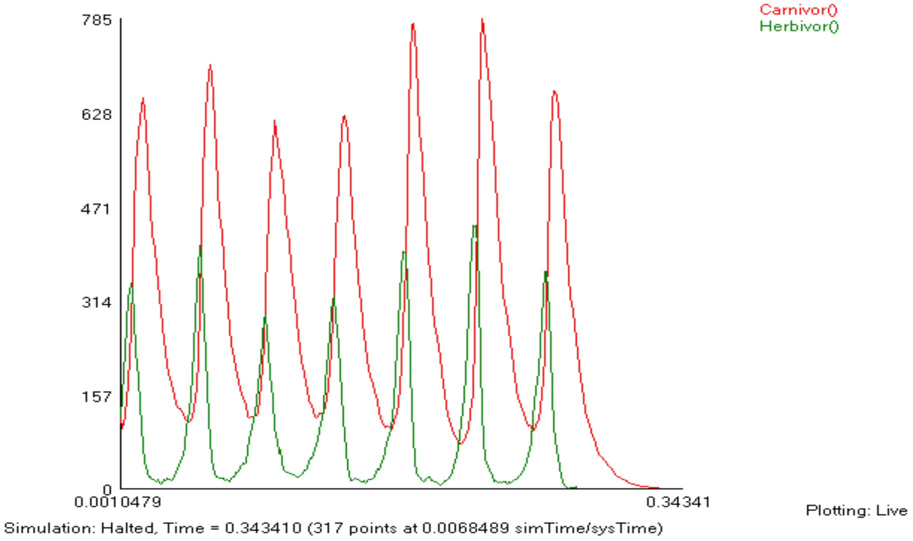
# Lotka-Volterra

Unbounded Systems

# Predator-Prey



```
directive sample 1.0 1000
directive plot Carnivor(); Herbivor()

val mortality = 100.0
val breeding = 300.0
val predation = 1.0
new cull @predation:chan()

let Herbivor() =
  do delay@breeding; (Herbivor() | Herbivor())
  or ?cull; ()

and Carnivor() =
  do delay@mortality; ()
  or !cull; (Carnivor() | Carnivor())

run 100 of Herbivor()
run 100 of Carnivor()
```



An *unbounded*
*state* system!

# Lotka-Volterra in Matlab

$H = \tau_b;(H|H) \oplus ?c_{(p)};0$

$C = \tau_m;0 \oplus !c_{(p)};(C|C)$

$\#H_0, \#C_0$

$H \rightarrow^{b} H + H$

$C \rightarrow^{m} 0$

$H + C \rightarrow^{p\gamma} C + C$

$[H]_0 = \#H_0/\gamma$

$[C]_0 = \#C_0/\gamma$

$d[H]/dt = b[H]-p\gamma[H][C]$

$d[C]/dt = -m[C]+p\gamma[H][C]$

$[H]_0 = \#H_0/\gamma$

$[C]_0 = \#C_0/\gamma$

$m=100.0$

$b=300.0$

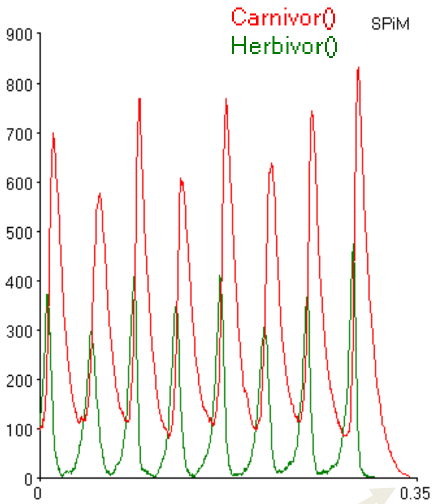
$p=1.0$

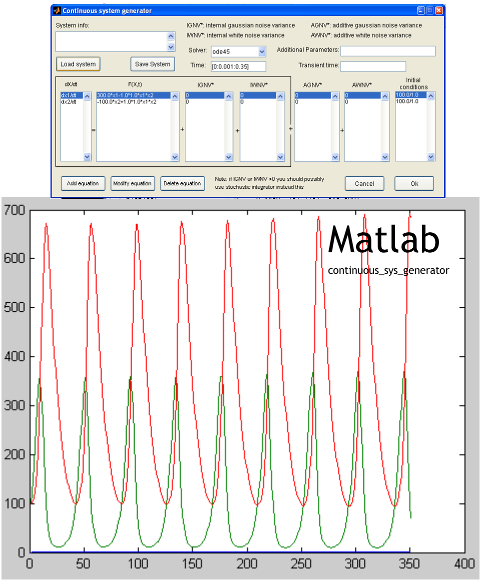
$\gamma=1.0$

$\#H_0 = 100$

$\#C_0 = 100$

```
directive sample 0.35 1000
directive plot Carnivor(); Herbivor()

val mortality = 100.0
val breeding = 300.0
val predation = 1.0
new cull @predation:chan()

let Herbivor() =
  do delay@breeding; (Herbivor() | Herbivor())
  or ?cull; ()

and Carnivor() =
  do delay@mortality; ()
  or !cull; (Carnivor() | Carnivor())

run 100 of Herbivor()
run 100 of Carnivor()
```





Continuous system generator

System info:

IGNV*: internal gaussian noise variance

IWNV*: internal white noise variance

AGNV*: additive gaussian noise variance

AWNV*: additive white noise variance

Solver: ode45

Additional Parameters:

Time: [0:0.001:0.35]

Transient time:

| dX/dt | F(X,t) | IGNV* | IWNV* | AGNV* | AWNV* | Initial conditions |
|---|---|---|---|---|---|---|
| dx1/dt | 300.0*x1-1.0*1.0*x1*x2 | 0 | 0 | 0 | 0 | 100.0/1.0 |
| dx2/dt | -100.0*x2+1.0*1.0*x1*x2 | 0 | 0 | 0 | 0 | 100.0/1.0 |

Note: if IGNV or IWNV >0 you should possibly use stochastic integrator instead this

Matlab

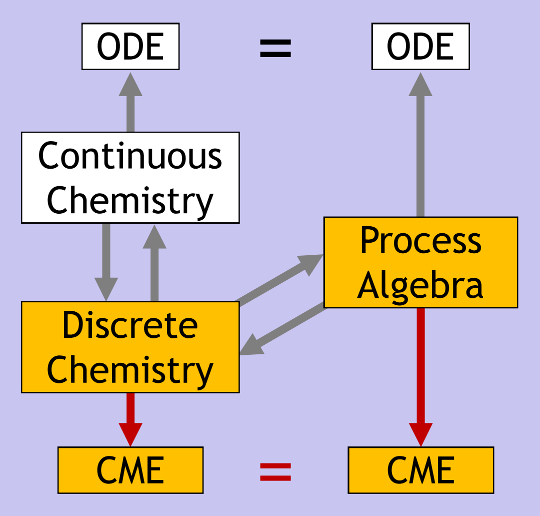
continuous_sys_generator

Extinction

No extinction

Which one is the “right prediction”?

# Master Equation Semantics



# Chemical Master Equation

Chemical Master Equation for a chemical system C

$$\partial pr(s,t)/\partial t \quad = \quad \Sigma_{i\in 1..M}\ a_i(s-v_i)\cdot pr(s-v_i,t) - a_i(s)\cdot pr(s,t) \qquad \text{for all } s\in States(C)$$

Reactions Propensity

"The change of probability at time t of a state is:
 the sum over all possible (kinds of) reactions of:
  the probability at time t of each state leading to this one
   times the propensity of that reaction in that state
  minus the probability at time t of the current state
   times the propensity of each reaction in the current state"

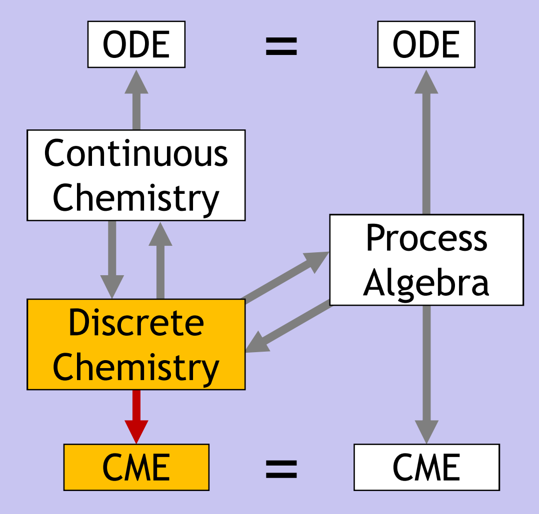
$s\in 1..N\rightarrow Nat$ is a *state* of the system with N chemical species

$pr(s,t) = Pr\{\chi(t)=s \mid \chi(0)=s_0\}$ is the conditional probability of the system $\chi$ being in state s at time t given that it was in state $s_0$ at time 0.

There are 1..M chemical reactions.

$v_i$ is the state change caused by reaction i (as a difference)

$a_i(s) = c_i\cdot h_i(r)$ is the *propensity* of reaction i in state s, defined by a base reaction rate and a state-dependent count of the distinct combinations of reagents. (It depends on the kind of reactions.)


ODE = ODE
Continuous Chemistry
Process Algebra
Discrete Chemistry
CME = CME

# Process Algebra Master Equation

Process Master Equation for a system of reagents E

$$\partial pr(r,t)/\partial t \quad = \quad \Sigma_{i\in\Im}\ a_i(r-v_i)\cdot pr(r-v_i,t)\ -\ a_i(r)\cdot pr(r,t) \qquad \text{for all } r\in States(E)$$

Interactions

Propensity

"The change of probability at time t of a state is:
 the sum over all possible (kinds of) interactions of:
  the probability at time t of each state leading to this one
   times the propensity of that interaction in that state
  minus the probability at time t of the current state
   times the propensity of each interaction in the current state"

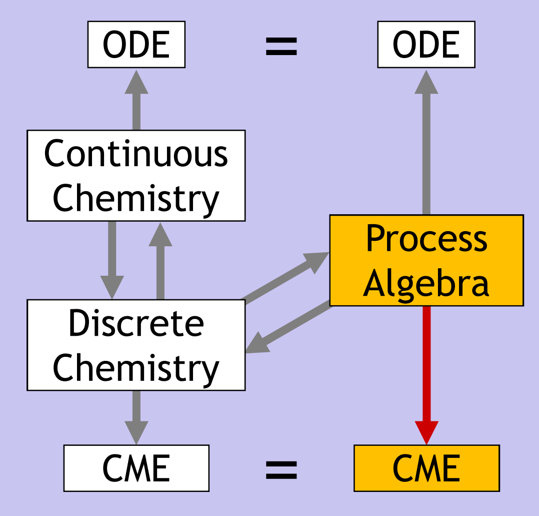
$r\in$ *species*(E)$\rightarrow$Nat is a *state* of the system

$pr(r,t) = Pr\{\chi(t)=r \mid \chi(0)=r_0\}$ is the conditional probability of the system $\chi$ being in state r at time t given that it was in state $r_0$ at time 0.

$\Im$ is the finite set of *possible interactions* arising from a set of reagents E. (All $\tau$ and all ?a/!a pairs in E)

$v_i$ is the state change caused by interaction i (as a difference)

$a_i(r) = r_i\cdot h_i(r)$ is the *propensity* of interaction i in state r, defined by a base rate of interaction and a state-dependent count of the distinct combinations of reagents. (It depends on the kind of interaction.)



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CME = CME

# … details

Process Master Equation for Reagents E

$$\partial pr(r,t)/\partial t \quad = \quad \Sigma_{i\in\Im}\ a_i(r-v_i)\cdot pr(r-v_i,t)\ -\ a_i(r)\cdot pr(r,t) \qquad \text{for all } r\in States(E)$$

$pr(p,t) = Pr\{\mathbf{S}(t)=p \mid \mathbf{S}(0)=p_0\}$ is the conditional probability of the system being in state p (a multiset of molecules) at time t given that it was in state $p_0$ at time 0.

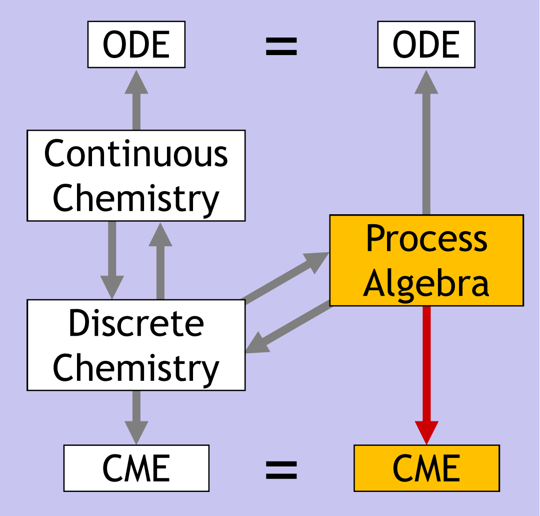
$\Im = \{\{X.i\}\ \textit{s.t.}\ E.X.i = \tau_{(r)};Q\} \cup$
$\{\{X.i,\ Y.j\}\ \textit{s.t.}\ E.X.i = ?n_{(r)};Q \text{ and } E.Y.j = !n_{(r)};R\}$
is the set of possible interactions in E

$v_i$ is the *state change* caused by an interaction $i\in\Im$.

$v_i = -X+Q$ if $i = \{X.i\}\ \textit{s.t.}\ E.X.i = \tau_{(r)};Q$
$v_i = -X-Y+Q+R$ if $i = \{X.i,\ Y.j\}\ \textit{s.t.}\ E.X.i = ?n_{(r)};Q \text{ and } E.Y.j = !n_{(r)};R$

$a_i$ is the *propensity* of interaction i in state p. Here $p^{\#X}$ is the number of X in p.

$a_i(p) = r\cdot p^{\#X}$ if $i = \{X.i\}\ \textit{s.t.}\ E.X.i = \tau_{(r)};Q$
$a_i(p) = r\cdot p^{\#X}\cdot p^{\#Y}$ if $i = \{X.i,\ Y.j\}\ \textit{s.t.}\ X\neq Y \text{ and } E.X.i = ?a_{(r)};Q \text{ and } E.Y.j = !a_{(r)};R$
$a_i(p) = r\cdot p^{\#X}\cdot(p^{\#X}-1)$ if $i = \{X.i,\ X.j\}\ \textit{s.t.}\ E.X.i = ?a_{(r)};Q \text{ and } E.X.j = !a_{(r)};R$



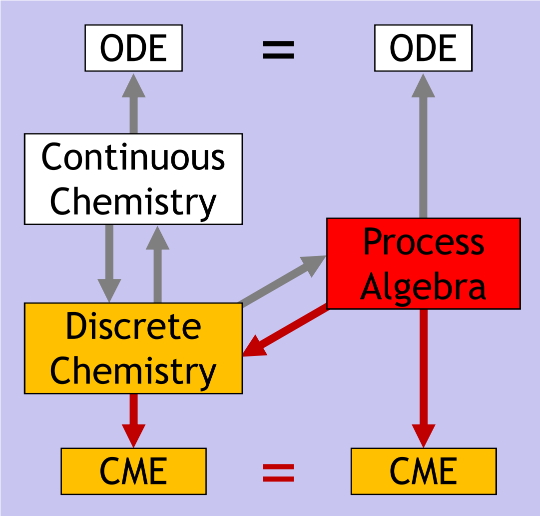
ODE = ODE
Continuous Chemistry
Process Algebra
Discrete Chemistry
CME = CME

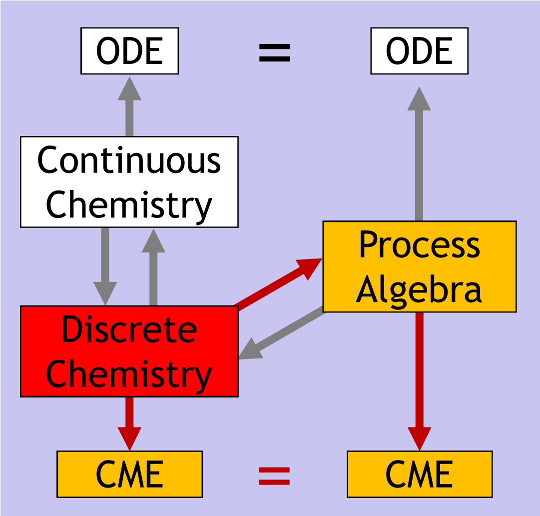
# Equivalence of Master Equations

- Def: ≈ is equivalence of derived Master Equations (they are identical).

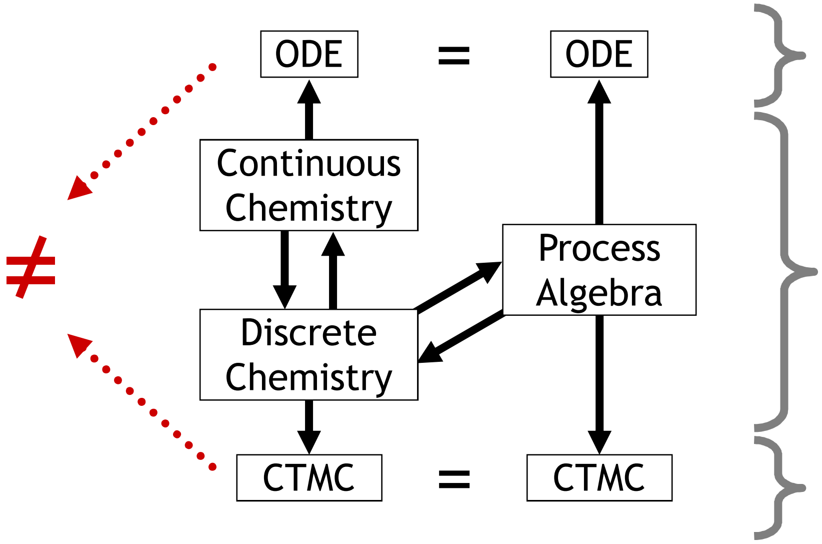
- Thm: E ≈ Ch(E)

- Thm: C ≈ Pi(C)





# GMA ≠ CME



ODE = ODE

Continuous Chemistry

≠

Process Algebra

Discrete Chemistry

CTMC = CTMC

Semantics #1

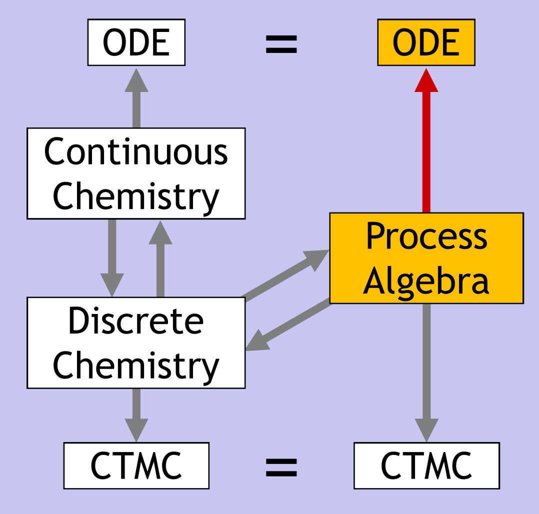
Continuous state space

Syntax

Semantics #2

Discrete state space

# Processes to GMA Directly



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

Process Rate Equation for Reagents E in volume $\gamma$

$$d[X]/dt = (\Sigma(Y \in E)\ Accr_E(Y,X)\cdot[Y]) - Depl_E(X)\cdot[X]$$

for all $X \in E$

"The change in process concentration (!!) for X at time t is:
  the sum over all possible (kinds of) processes Y of:
    the concentration at time t of Y
      times the accretion from Y to X
    minus the concentration at time t of X
      times the depletion of X to some other Y"

$Depl_E(X) =$
  $\Sigma(i: E.X.i=\tau_{(r)};P)\ r\ +$
  $\Sigma(i: E.X.i=?a_{(r)};P)\ r\gamma\cdot OutsOn_E(a)\ +$
  $\Sigma(i: E.X.i=!a_{(r)};P)\ r\gamma\cdot InsOn_E(a)$

$Accr_E(Y, X) =$
  $\Sigma(i: E.Y.i=t_{(r)};P)\ \#X(P)\cdot r\ +$
  $\Sigma(i: E.Y.i=?a_{(r)};P)\ \#X(P)\cdot r\gamma\cdot OutsOn_E(a)\ +$
  $\Sigma(i: E.Y.i=!a_{(r)};P)\ \#X(P)\cdot r\gamma\cdot InsOn_E(a)$

$InsOn_E(a) = \Sigma(Y \in E)\ \#\{Y.i \mid E.Y.i=?a_{(r)};P\}\cdot[Y]$
$OutsOn_E(a) = \Sigma(Y \in E)\ \#\{Y.i \mid E.Y.i=!a_{(r)};P\}\cdot[Y]$

$X = \tau_{(r)};0 \quad \rightarrow \quad d[X]/dt = -r[X]$

$X = ?a_{(r)};0 \quad \rightarrow \quad d[X]/dt = -r\gamma[X][Y]$
$Y = !a_{(r)};0 \qquad\quad d[Y]/dt = -r\gamma[X][Y]$

$X = ?a_{(r)};0 \quad \rightarrow \quad d[X]/dt = -2r\gamma[X]^2$
$\quad \oplus\ !a_{(r)};0$

# Process Algebra Master Equation

Process Master Equation for a system of reagents E

$$\partial pr(r,t)/\partial t \quad = \quad \Sigma_{i\in\Im}\ a_i(r-v_i)\cdot pr(r-v_i,t)\ -\ a_i(r)\cdot pr(r,t) \qquad \text{for all } r\in States(E)$$

Interactions

Propensity

"The change of probability at time t of a state is:
  the sum over all possible (kinds of) interactions of:
    the probability at time t of each state leading to this one
      times the propensity of that interaction in that state
    minus the probability at time t of the current state
      times the propensity of each interaction in the current state"

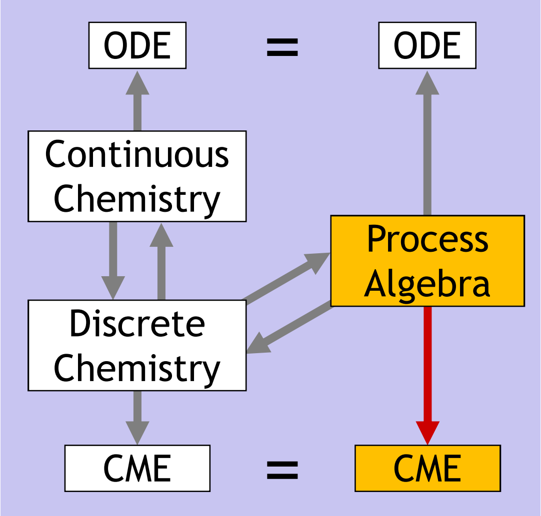
$r\in$ *species*(E)$\rightarrow$Nat is a *state* of the system

$pr(r,t) = Pr\{\chi(t)=r\ |\chi(0)=r_0\}$ is the conditional probability of the system $\chi$ being in state r at time t given that it was in state $r_0$ at time 0.

$\Im$ is the finite set of *possible interactions* arising from a set of reagents E. (All $\tau$ and all ?a/!a pairs in E)

$v_i$ is the state change caused by interaction i (as a difference)

$a_i(r) = r_i\cdot h_i(r)$ is the *propensity* of interaction i in state r, defined by a base rate of interaction and a state-dependent count of the distinct combinations of reagents. (It depends on the kind of interaction.)



ODE = ODE

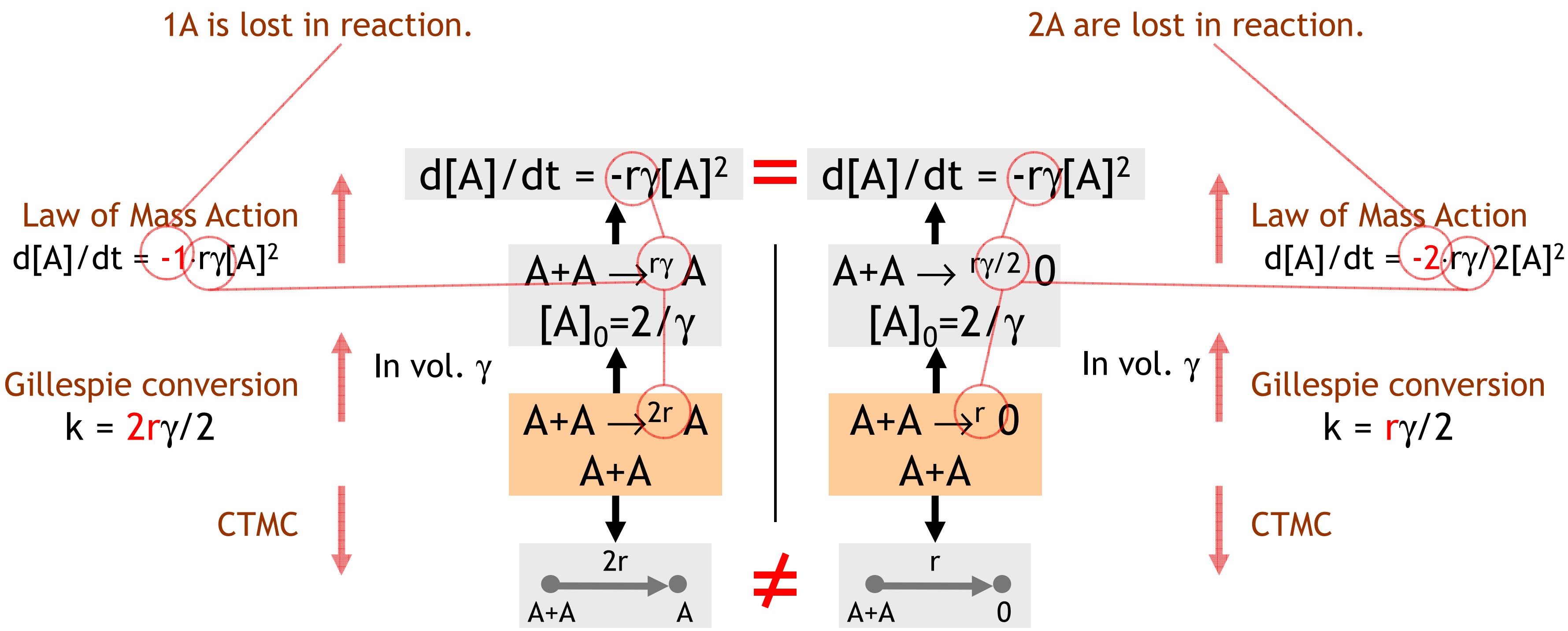
Continuous Chemistry

Process Algebra

Discrete Chemistry

CME = CME

# $A+A \rightarrow^{2r} A$ =? $A+A \rightarrow^{r} 0$



1A is lost in reaction.

2A are lost in reaction.

$d[A]/dt = -r\gamma[A]^2$ = $d[A]/dt = -r\gamma[A]^2$

Law of Mass Action

$d[A]/dt = -1 \cdot r\gamma[A]^2$

$A+A \rightarrow^{r\gamma} A$

$[A]_0=2/\gamma$

$A+A \rightarrow^{r\gamma/2} 0$

$[A]_0=2/\gamma$

Law of Mass Action

$d[A]/dt = -2 \cdot r\gamma/2[A]^2$

Gillespie conversion

$k = 2r\gamma/2$

In vol. $\gamma$

$A+A \rightarrow^{2r} A$

A+A

$A+A \rightarrow^{r} 0$

A+A

In vol. $\gamma$

Gillespie conversion

$k = r\gamma/2$

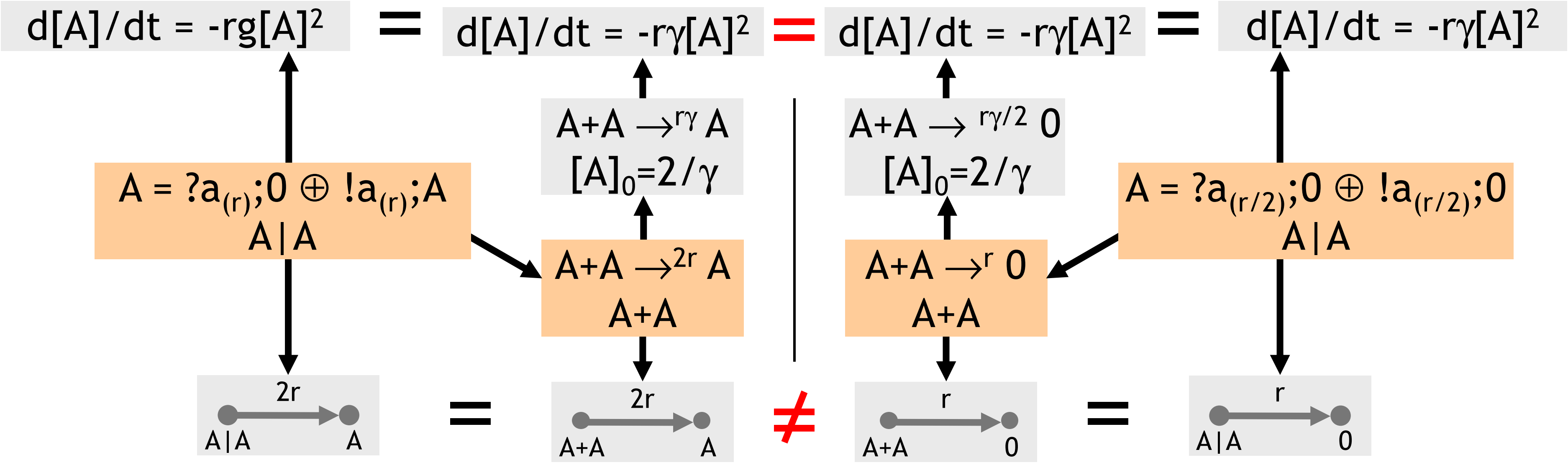
CTMC

≠

CTMC

(For conservation of mass, consider instead $A+A \rightarrow^{2r} A+B$ vs. $A+A \rightarrow^{r} B+B$)

# $A+A \rightarrow^{2r} A$ =? $A+A \rightarrow^{r} 0$



$d[A]/dt = -rg[A]^2$ = $d[A]/dt = -r\gamma[A]^2$ = $d[A]/dt = -r\gamma[A]^2$ = $d[A]/dt = -r\gamma[A]^2$

$A = ?a_{(r)};0 \oplus !a_{(r)};A$
$A|A$

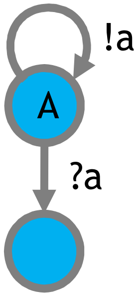
$A+A \rightarrow^{r\gamma} A$
$[A]_0=2/\gamma$

$A+A \rightarrow^{2r} A$
$A+A$

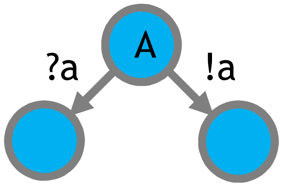
$A+A \rightarrow^{r\gamma/2} 0$
$[A]_0=2/\gamma$

$A+A \rightarrow^{r} 0$
$A+A$

$A = ?a_{(r/2)};0 \oplus !a_{(r/2)};0$
$A|A$

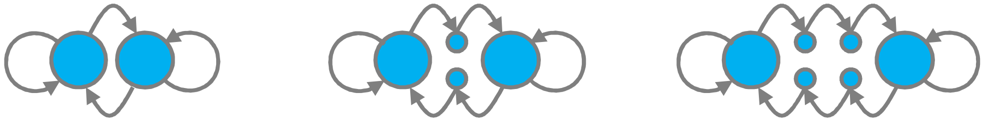


(a@r)

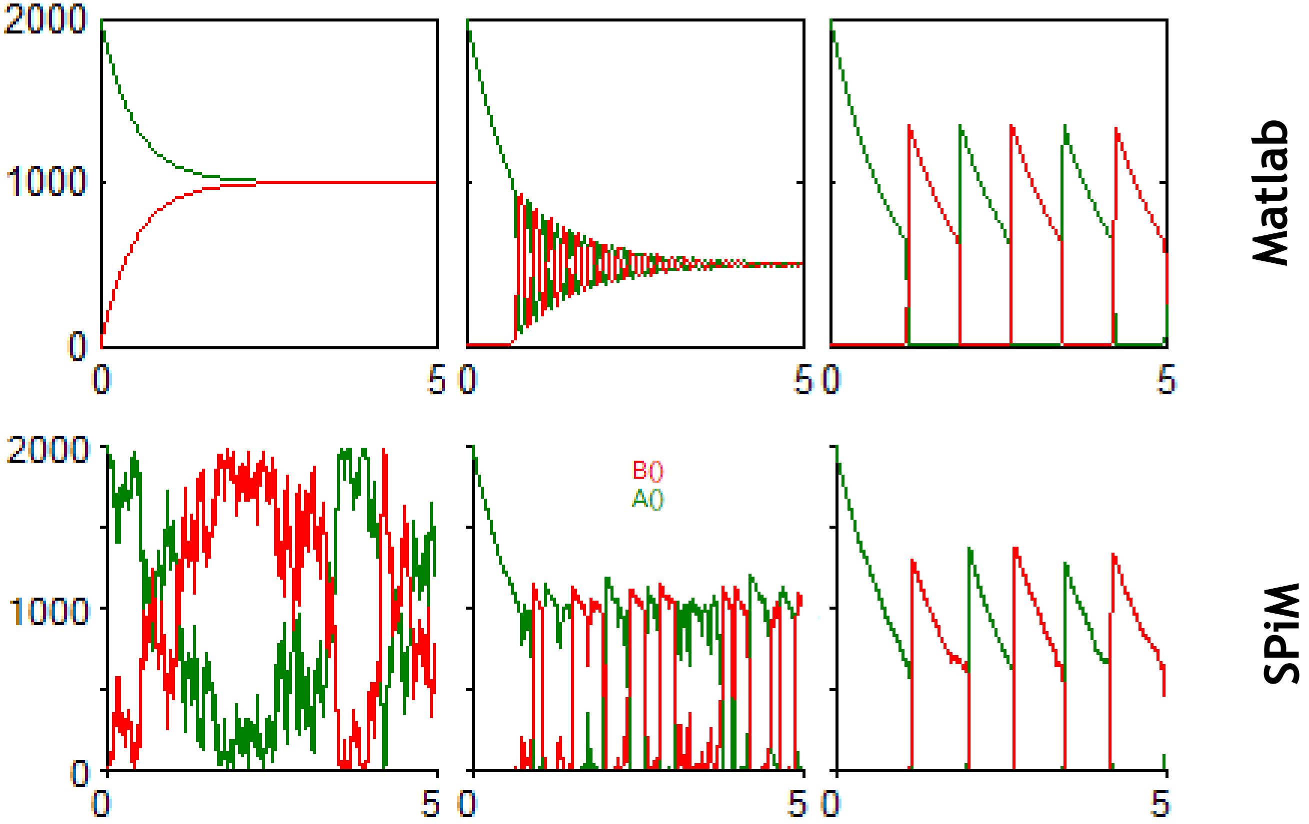


(a@r/2)

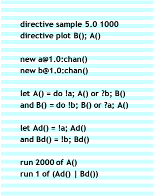
# Continuous vs. Discrete Groupies



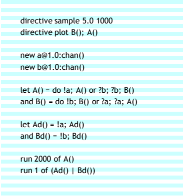
(all with doping)



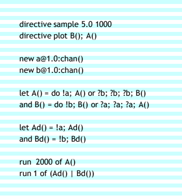
$2000{\times}A\ ,\ 0{\times}B\ ,\ 1{\times}A_d\ ,\ 1{\times}B_d\ ,\ r = 1.0$



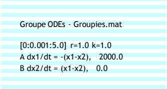
```
directive sample 5.0 1000
directive plot B(); A()

new a@1.0:chan()
new b@1.0:chan()

let A() = do !a; A() or ?b; B()
and B() = do !b; B() or ?a; A()

let Ad() = !a; Ad()
and Bd() = !b; Bd()

run 2000 of A()
run 1 of (Ad() | Bd())
```



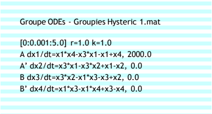
```
directive sample 5.0 1000
directive plot B(); A()

new a@1.0:chan()
new b@1.0:chan()

let A() = do !a; A() or ?b; ?b; B()
and B() = do !b; B() or ?a; ?a; A()

let Ad() = !a; Ad()
and Bd() = !b; Bd()

run 2000 of A()
run 1 of (Ad() | Bd())
```



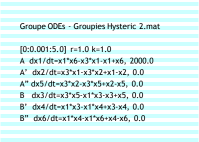
```
directive sample 5.0 1000
directive plot B(); A()

new a@1.0:chan()
new b@1.0:chan()

let A() = do !a; A() or ?b; ?b; ?b; B()
and B() = do !b; B() or ?a; ?a; ?a; A()

let Ad() = !a; Ad()
and Bd() = !b; Bd()

run  2000 of A()
run 1 of (Ad() | Bd())
```



```
Groupe ODEs - Groupies.mat

[0:0.001:5.0]  r=1.0 k=1.0
A dx1/dt = -(x1-x2),    2000.0
B dx2/dt = (x1-x2),    0.0
```

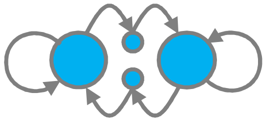


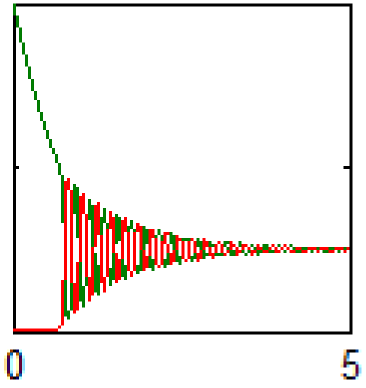
```
Groupe ODEs - Groupies Hysteric 1.mat

[0:0.001:5.0]  r=1.0 k=1.0
A dx1/dt=x1*x4-x3*x1-x1+x4, 2000.0
A' dx2/dt=x3*x1-x3*x2+x1-x2, 0.0
B dx3/dt=x3*x2-x1*x3-x3+x2, 0.0
B' dx4/dt=x1*x3-x1*x4+x3-x4, 0.0
```



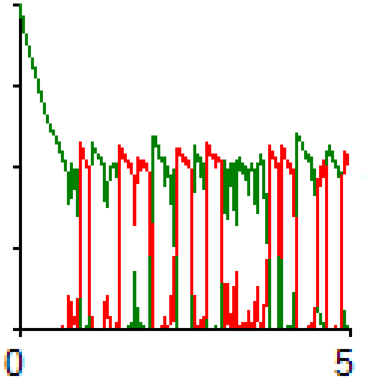
```
Groupe ODEs - Groupies Hysteric 2.mat

[0:0.001:5.0]  r=1.0 k=1.0
A  dx1/dt=x1*x6-x3*x1-x1+x6, 2000.0
A'  dx2/dt=x3*x1-x3*x2+x1-x2, 0.0
A" dx5/dt=x3*x2-x3*x5+x2-x5, 0.0
B   dx3/dt=x3*x5-x1*x3-x3+x5, 0.0
B'  dx4/dt=x1*x3-x1*x4+x3-x4, 0.0
B"  dx6/dt=x1*x4-x1*x6+x4-x6, 0.0
```

# Scientific Predictions





After a while, all 4 states are almost equally occupied.

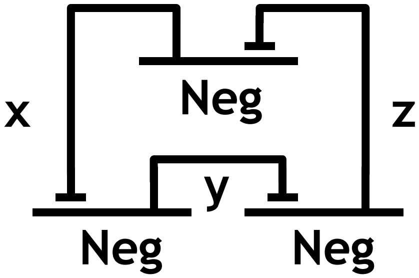


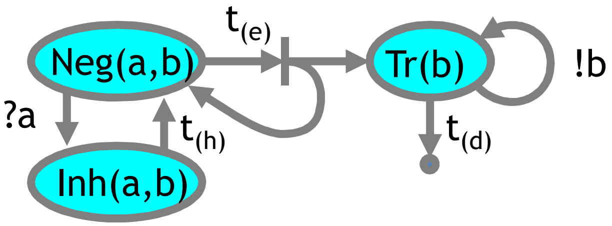
The 4 states are almost never equally occupied.

# And Yet It Moves

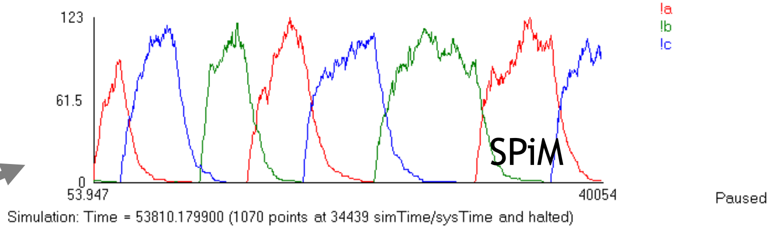
R.Blossey, L.Cardelli, A.Phillips:
**Compositionality, Stochasticity and Cooperativity in Dynamic Models of Gene Regulation** (HFSP Journal)

## The Repressilator





## A fine stochastic oscillator over a wide range of parameters.



Simulation: Time = 53810.179900 (1070 points at 34439 simTime/sysTime and halted)

## Parametric representation

$$Neg(a,b) = ?a; Inh(a,b) \oplus \tau_e; (Tr(b) \mid Neg(a,b))$$
$$Inh(a,b) = \tau_h; Neg(a,b)$$
$$Tr(b) = !b; Tr(b) \oplus \tau_g; 0$$
$$Neg(x_{(r)},y_{(r)}) \mid Neg(y_{(r)},z_{(r)}) \mid Neg(z_{(r)},x_{(r)})$$

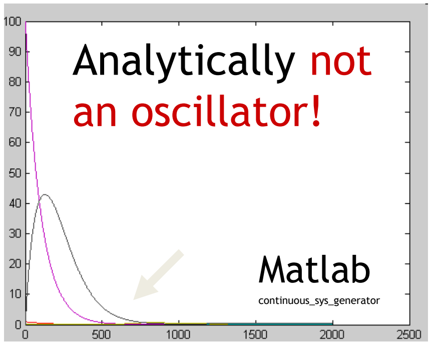
```
directive sample 50000.0 1000
directive plot !a; !b; !c

val dk = 0.001    (* Decay rate *)
val inh = 0.001   (* Inhibition rate *)
val cst = 0.1     (* Constitutive rate *)

let tr(p:chan()) = do !p; tr(p) or delay@dk

let neg(a:chan(), b:chan()) =
  do ?a; delay@inh; neg(a,b)
  or delay@cst; (tr(b) | neg(a,b))

val bnd = 1.0     (* Protein binding rate *)
new a@bnd:chan() new b@bnd:chan() new
c@bnd:chan()
run (neg(c,a) | neg(a,b) | neg(b,c))
```

$d[Neg/x,y]/dt = -r[Tr/x][Neg/x,y] + h[Inh/x,y]$
$d[Neg/y,z]/dt = -r[Tr/y][Neg/y,z] + h[Inh/y,z]$
$d[Neg/z,x]/dt = -r[Tr/z][Neg/z,x] + h[Inh/z,x]$
$d[Inh/x,y]/dt = r[Tr/x][Neg/x,y] - h[Inh/x,y]$
$d[Inh/y,z]/dt = r[Tr/y][Neg/y,z] - h[Inh/y,z]$
$d[Inh/z,x]/dt = r[Tr/z][Neg/z,x] - h[Inh/z,x]$
$d[Tr/x]/dt = e[Neg/z,x] - g[Tr/x]$
$d[Tr/y]/dt = e[Neg/x,y] - g[Tr/y]$
$d[Tr/z]/dt = e[Neg/y,z] - g[Tr/z]$

$Neg/x,y \to^{e} Tr/y + Neg/x,y$
$Neg/y,z \to^{e} Tr/z + Neg/y,z$
$Neg/z,x \to^{e} Tr/x + Neg/z,x$
$Tr/x + Neg/x,y \to^{r} Tr/x + Inh/x,y$
$Tr/y + Neg/y,z \to^{r} Tr/y + Inh/y,z$
$Tr/z + Neg/z,x \to^{r} Tr/z + Inh/z,x$
$Inh/x,y \to^{h} Neg/x,y$
$Inh/y,z \to^{h} Neg/y,z$
$Inh/z,x \to^{h} Neg/z,x$
$Tr/x \to^{g} 0$
$Tr/y \to^{g} 0$
$Tr/z \to^{g} 0$
$Neg/x,y + Neg/y,z + Neg/z,x$

simplifying (N is the quantity of each of the 3 gates)

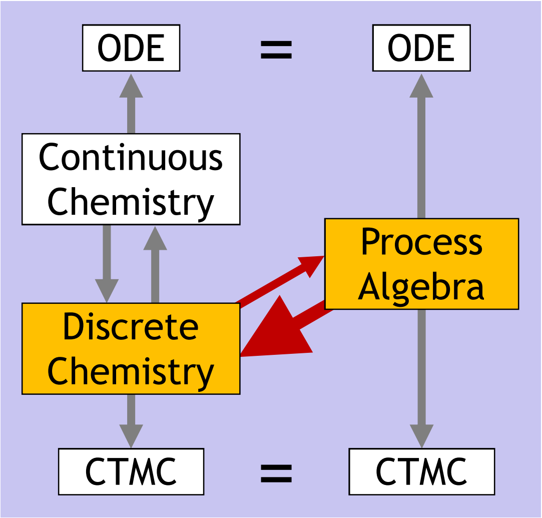
$d[Neg/x,y]/dt = hN - (h+r[Tr/x])[Neg/x,y]$
$d[Neg/y,z]/dt = hN - (h+r[Tr/y])[Neg/y,z]$
$d[Neg/z,x]/dt = hN - (h+r[Tr/z])[Neg/z,x]$
$d[Tr/x]/dt = e[Neg/z,x] - g[Tr/x]$
$d[Tr/y]/dt = e[Neg/x,y] - g[Tr/y]$
$d[Tr/z]/dt = e[Neg/y,z] - g[Tr/z]$



Analytically not an oscillator!

```
interval/step [0:10:20000]          N=1, r=1.0, e=0.1, h=0.001, g=0.001
(Neg/x,y) dx1/dt = 0.001 - (0.001 + x4)*x1           1.0
(Neg/x,y) dx2/dt = 0.001 - (0.001 + x5)*x2           1.0
(Neg/x,y) dx3/dt = 0.001 -    (0.001 + x6)*x3        1.0
(Tr/x)           dx4/dt = 0.1*x3 - 0.001*x4                  100.0
(Tr/y)           dx5/dt = 0.1*x1 - 0.001*x5                  0
(Tr/z)           dx6/dt = 0.1*x2 - 0.001*x6                  0
```

# Model Compactness



# $n^2$ Scaling Problems

- $E_n$ has 2n variables (nodes) and 2n terms (arcs).
- $Ch(E_n)$ has 2n species and $n^2$ reactions.

- The stoichiometric matrix has size $2n \cdot n^2 = 2n^3$.
- The ODEs have 2n variables and $2n(n+n) = 4n^2$ terms

(number of variables times number of accretions plus depletions when sums are distributed)

$E_3$

$X_0 = ?a_{(r)};X_1$
$X_1 = ?a_{(r)};X_2$
$X_2 = ?a_{(r)};X_0$
$Y_0 = !a_{(r)};Y_1$
$Y_1 = !a_{(r)};Y_2$
$Y_2 = !a_{(r)};Y_0$

$Ch(E_3)$

$a_{00}: X_0+Y_0 \to^r X_1+Y_1$
$a_{01}: X_0+Y_1 \to^r X_1+Y_2$
$a_{02}: X_0+Y_2 \to^r X_1+Y_0$
$a_{10}: X_1+Y_0 \to^r X_2+Y_1$
$a_{11}: X_1+Y_1 \to^r X_2+Y_2$
$a_{12}: X_1+Y_2 \to^r X_2+Y_0$
$a_{20}: X_2+Y_0 \to^r X_0+Y_1$
$a_{21}: X_2+Y_1 \to^r X_0+Y_2$
$a_{22}: X_2+Y_2 \to^r X_0+Y_0$

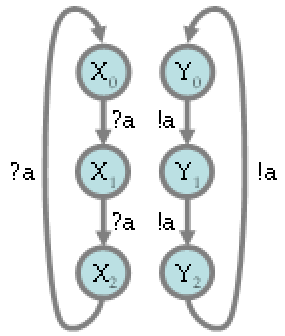
$StoichiometricMatrix(Ch(E_3))$

| | $a_{00}$ | $a_{01}$ | $a_{02}$ | $a_{10}$ | $a_{11}$ | $a_{12}$ | $a_{20}$ | $a_{21}$ | $a_{22}$ |
|---|---|---|---|---|---|---|---|---|---|
| $X_0$ | -1 | -1 | -1 | | | | +1 | +1 | +1 |
| $X_1$ | +1 | +1 | +1 | -1 | -1 | -1 | | | |
| $X_2$ | | | | +1 | +1 | +1 | -1 | -1 | -1 |
| $Y_0$ | -1 | | +1 | -1 | | +1 | -1 | | +1 |
| $Y_1$ | +1 | -1 | | +1 | -1 | | +1 | -1 | |
| $Y_2$ | | +1 | -1 | | +1 | -1 | | +1 | -1 |

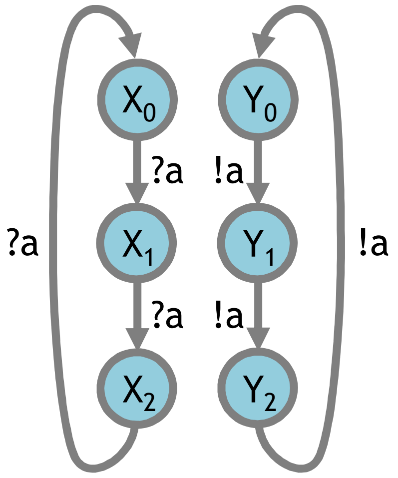
$ODE(E_3)$

$$d[X_0]/dt = -r[X_0][Y_0] - r[X_0][Y_1] - r[X_0][Y_2] + r[X_2][Y_0] + r[X_2][Y_1] + r[X_2][Y_2]$$
$$d[X_1]/dt = -r[X_1][Y_0] - r[X_1][Y_1] - r[X_1][Y_2] + r[X_0][Y_0] + r[X_0][Y_1] + r[X_0][Y_2]$$
$$d[X_2]/dt = -r[X_2][Y_0] - r[X_2][Y_1] - r[X_2][Y_2] + r[X_1][Y_0] + r[X_1][Y_1] + r[X_1][Y_2]$$
$$d[Y_0]/dt = -r[X_0][Y_0] - r[X_1][Y_0] - r[X_2][Y_0] + r[X_0][Y_2] + r[X_1][Y_2] + r[X_2][Y_2]$$
$$d[Y_1]/dt = -r[X_0][Y_1] - r[X_1][Y_1] - r[X_2][Y_1] + r[X_0][Y_0] + r[X_1][Y_0] + r[X_2][Y_0]$$
$$d[Y_2]/dt = -r[X_0][Y_2] - r[X_1][Y_2] - r[X_2][Y_2] + r[X_0][Y_1] + r[X_1][Y_1] + r[X_2][Y_1]$$

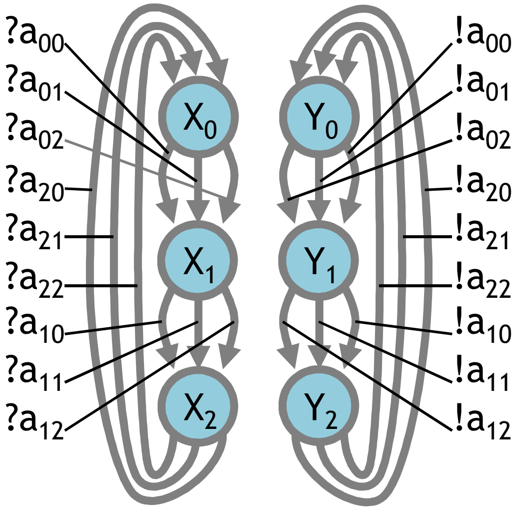
$E_3$



# Entangled vs detangled



$E_3$



Detangle($E_3$)

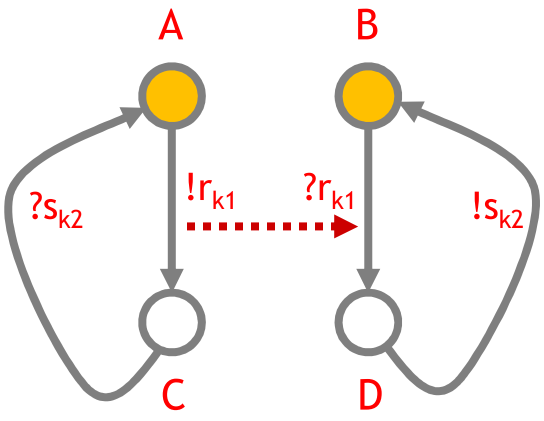
(closely related to
Pi(Ch($E_3$)) )

# Model Maintenance

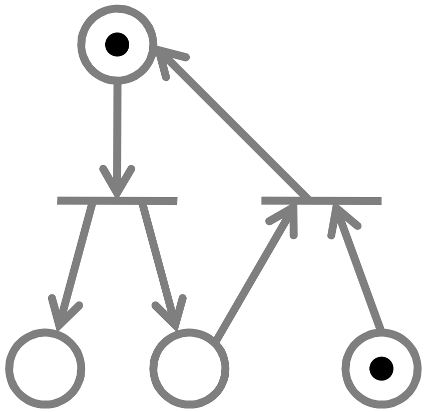
- Biology (unlike much of chemistry) is combinatorial
  - Biochemical systems have many regular repeated components
  - Components interact and combine in complex combinatorial ways
  - Components have local state
  - A biochemical system is vastly more compact that its potential state space

- One may have to expand the state space during analysis, but must not do it during description

- There is a good way:
  - Describe biochemical systems compositionally
  - Each component with its own state and interactions
  - ... as Nature intended...



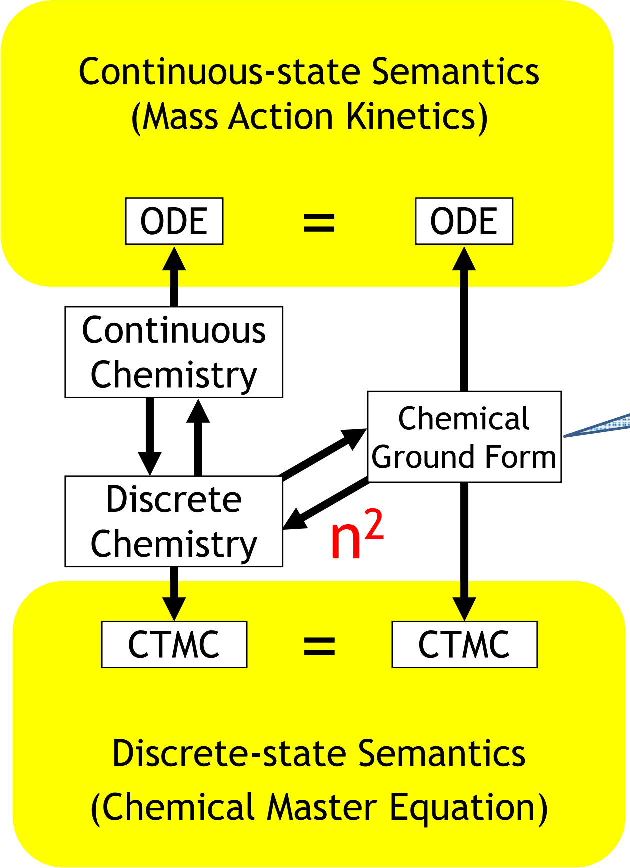
Or



Or ...

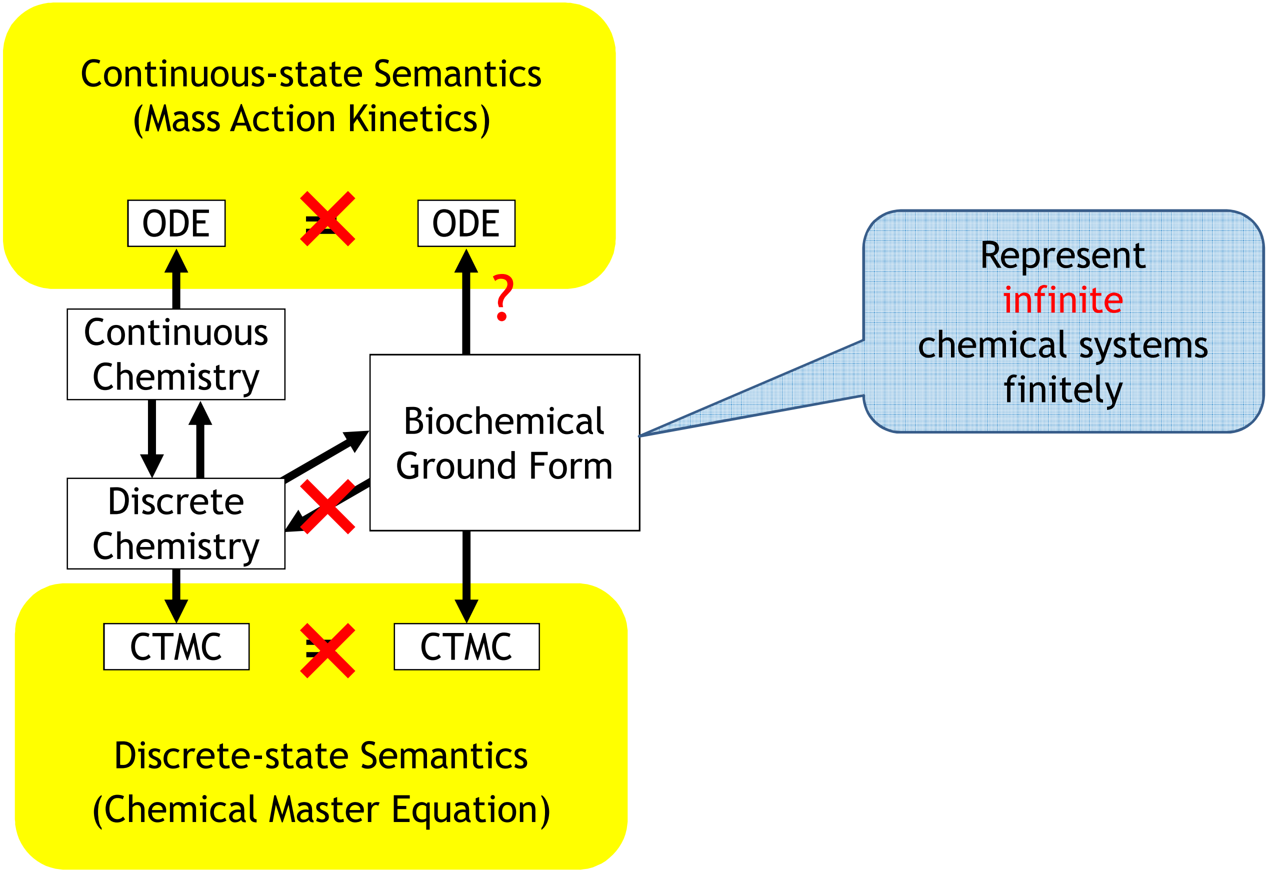
# Chemistry *and Beyond*

# Process Algebra is ‘Bigger’ than Chemistry



Represent combinatorial chemical systems compactly

# Process Algebra is 'Bigger' than Chemistry



Continuous-state Semantics
(Mass Action Kinetics)

ODE = ODE

?

Continuous Chemistry

Discrete Chemistry

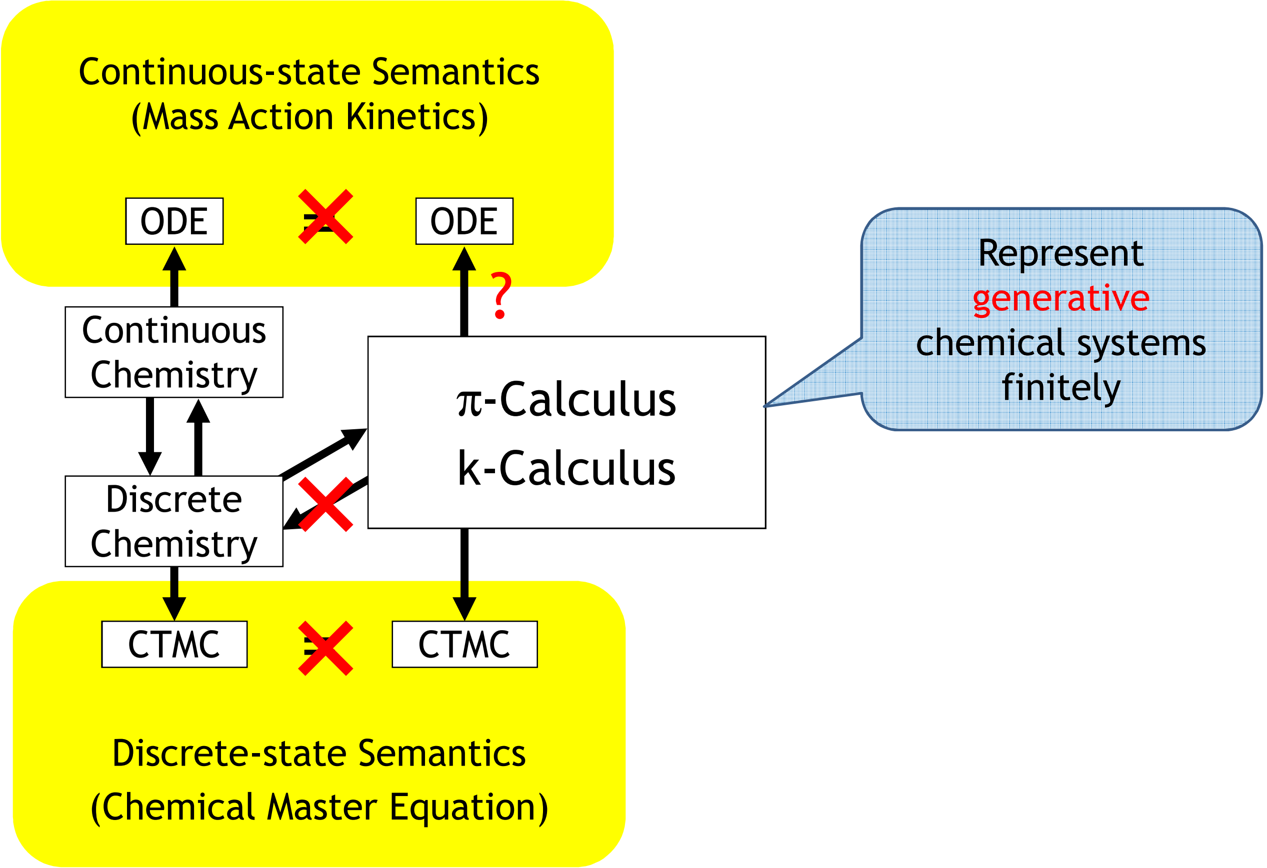
Biochemical Ground Form

CTMC = CTMC

Discrete-state Semantics
(Chemical Master Equation)

Represent
infinite
chemical systems
finitely

# Process Algebra is ‘Bigger’ than Chemistry



Continuous-state Semantics
(Mass Action Kinetics)

ODE ≠ ODE

?

Continuous Chemistry

Discrete Chemistry

π-Calculus
k-Calculus

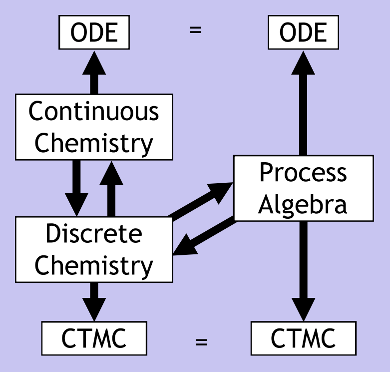
Represent generative chemical systems finitely

CTMC ≠ CTMC

Discrete-state Semantics
(Chemical Master Equation)

# Conclusions

# Conclusions



- Process Algebra
  - An extension of automata theory to populations of interacting automata
  - Modeling the behavior of individuals in an arbitrary environment
  - Compositionality (combining models by juxtaposition)

- Connections between modeling approaches
  - Connecting the discrete/concurrent/stochastic/molecular approach
  - to the continuous/sequential/deterministic/population approach

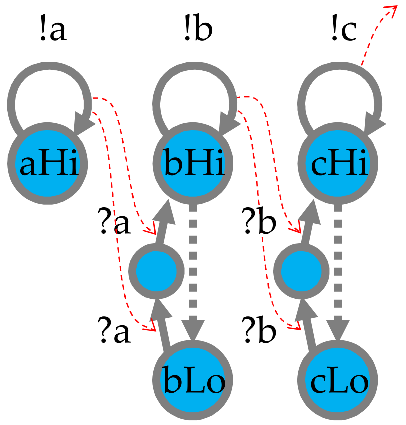
- Connecting syntax with semantics
  - Syntax = model presentation (equations/programs/diagrams/blobs etc.)
  - Semantics = state space (generated by the syntax)

- Ultimately, connections between analysis techniques
  - We need (and sometimes have) good semantic techniques to analyze state spaces (e.g. calculus, but also increasingly modelchecking)
  - But we need equally good syntactic techniques to structure complex models (e.g. compositionality) and analyze them (e.g. process algebra)

- A bright future for Computer Science and Logic in modern Biology
  - Biology needs good analysis techniques for discrete systems analysis (modal logics, modelchecking, causality analysis, abstract interpretation, …)

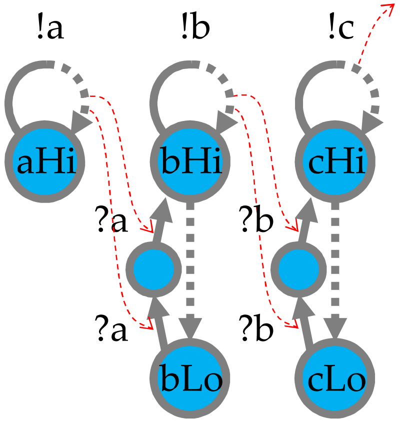
# Exercise 1a Solution

$\mathrm{aHi} = {!a}_{(1.0)};\mathrm{aHi}$
$\mathrm{bLo} = {?a}_{(1.0)};\ \mathrm{bMd}$
$\mathrm{bMd} = {?a}_{(1.0)};\ \mathrm{bHi}$
$\mathrm{bHi} = {!b}_{(1.0)};\ \mathrm{bHi} \oplus \tau_{(1.0)};\ \mathrm{bLo}$
$\mathrm{cLo} = {?b}_{(1.0)};\ \mathrm{cMd}$
$\mathrm{cMd} = {?b}_{(1.0)};\ \mathrm{cHi}$
$\mathrm{cHi} = {!c}_{(1.0)};\ \mathrm{cHi} \oplus \tau_{(1.0)};\ \mathrm{cLo}$



$\mathrm{aHi} + \mathrm{bLo} \rightarrow^{1.0} \mathrm{aHi} + \mathrm{bMd}$
$\mathrm{aHi} + \mathrm{bMd} \rightarrow^{1.0} \mathrm{aHi} + \mathrm{bHi}$
$\mathrm{bHi} \rightarrow^{1.0} \mathrm{bLo}$
$\mathrm{bHi} + \mathrm{cLo} \rightarrow^{1.0} \mathrm{bHi} + \mathrm{cMd}$
$\mathrm{bHi} + \mathrm{cMd} \rightarrow^{1.0} \mathrm{bHi} + \mathrm{cHi}$
$\mathrm{cHi} \rightarrow^{1.0} \mathrm{cLo}$

# Exercise 1b Solution



$\mathrm{aHi} = !a_{(1.0)};\mathrm{aR}$
$\mathrm{aR} = \tau_{(1.0)};\ \mathrm{aHi}$
$\mathrm{bLo} = ?a_{(1.0)};\ \mathrm{bMd}$
$\mathrm{bMd} = ?a_{(1.0)};\ \mathrm{bHi}$
$\mathrm{bHi} = !b_{(1.0)};\ \mathrm{bR} \oplus \tau_{(1.0)};\ \mathrm{bLo}$
$\mathrm{bR} = \tau_{(1.0)};\ \mathrm{bHi}$
$\mathrm{cLo} = ?b_{(1.0)};\ \mathrm{cMd}$
$\mathrm{cMd} = ?b_{(1.0)};\ \mathrm{cHi}$
$\mathrm{cHi} = !c_{(1.0)};\ \mathrm{cR} \oplus \tau_{(1.0)};\ \mathrm{cLo}$
$\mathrm{cR} = \tau_{(1.0)};\ \mathrm{cHi}$

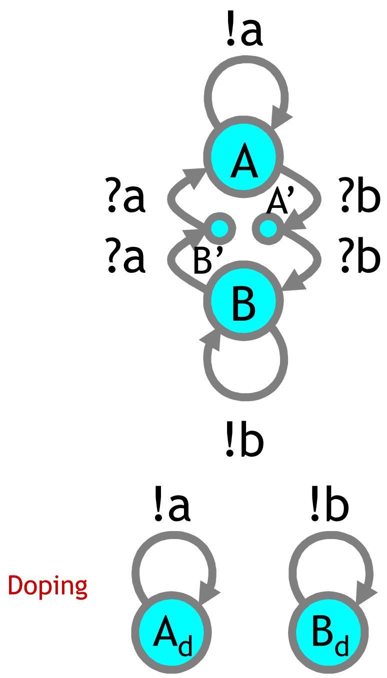
$\mathrm{aHi} + \mathrm{bLo} \rightarrow^{1.0} \mathrm{aR} + \mathrm{bMd}$
$\mathrm{aHi} + \mathrm{bMd} \rightarrow^{1.0} \mathrm{aR} + \mathrm{bHi}$
$\mathrm{aR} \rightarrow^{1.0} \mathrm{aHi}$
$\mathrm{bHi} \rightarrow^{1.0} \mathrm{bLo}$
$\mathrm{bHi} + \mathrm{cLo} \rightarrow^{1.0} \mathrm{bR} + \mathrm{cMd}$
$\mathrm{bHi} + \mathrm{cMd} \rightarrow^{1.0} \mathrm{bR} + \mathrm{cHi}$
$\mathrm{bR} \rightarrow^{1.0} \mathrm{bHi}$
$\mathrm{cHi} \rightarrow^{1.0} \mathrm{cLo}$

Note: no reaction from cHi to cR etc. because there is nothing (here) to interact with c.

The chemical system is incomplete (it does not say how cHi would behave in a bigger system), while the automata already specify what would happen (if we remove the red bits above we obtain the same reactions).

# Exercise 2 Solution

Q: What does this do?



```
directive sample 10.0 1000
directive plot Ga(); Gb()

new a@1.0:chan()
new b@1.0:chan()

let Ga() = do !a; Ga() or ?b; ?b; Gb()
and Gb() = do !b; Gb() or ?a; ?a; Ga()

let Da() = !a; Da()
and Db() = !b; Db()

run 100 of (Ga() | Gb())
run  1 of (Da() | Db())
```

$$A = !a_{(r)};A \oplus ?b;A' \qquad A' = ?b;B$$
$$B = !b_{(r)};B \oplus ?a;B' \qquad B' = ?a;A$$

$$A_d = !a_{(r)};A_d$$
$$B_d = !b_{(r)};B_d$$

$$A+B \to^r A+B' \qquad A+B' \to^r A+A$$
$$B+A \to^r B+A' \qquad B+A' \to^r B+B$$

$$A+B_d \to^r A'+B_d \qquad A'+B_d \to^r B+B_d$$
$$B+A_d \to^r B'+A_d \qquad B'+A_d \to^r A+A_d$$

$$d[A]/dt = r[A][B']-r[B][A]-r[A][B_d]+r[B'][A_d]$$
$$d[A']/dt = r[B][A]-r[B][A']+r[A][B_d]-r[A'][B_d]$$
$$d[B]/dt = r[B][A']-r[A][B]-r[B][A_d]+r[A'][B_d]$$
$$d[B']/dt = r[A][B]-r[A][B']+r[B][A_d]-r[B'][A_d]$$

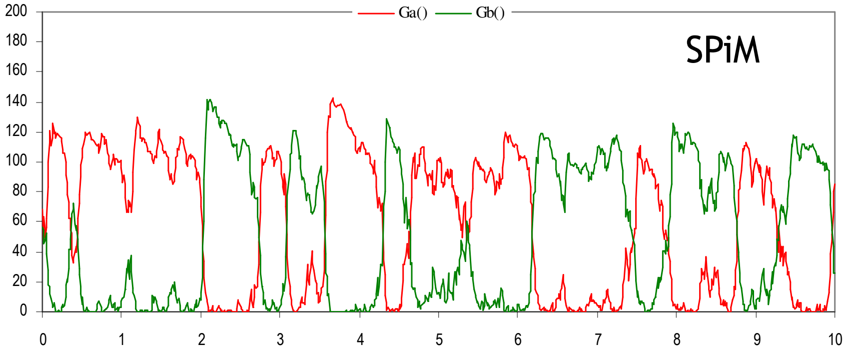
$$d[A_d]/dt = 0$$
$$d[B_d]/dt = 0$$

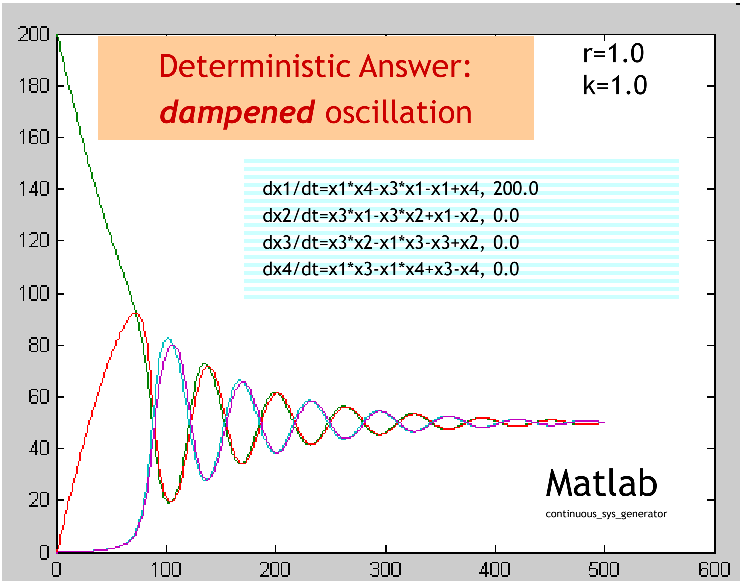
$$d[A]/dt = r[A][B']-r[B][A]-rk[A]+rk[B']$$
$$d[A']/dt = r[B][A]-r[B][A']+rk[A]-rk[A']$$
$$d[B]/dt = r[B][A']-r[A][B]-rk[B]+rk[A']$$
$$d[B']/dt = r[A][B]-r[A][B']+rk[B]-rk[B']$$

$[A_d]$,$[B_d]$ are constant; assume them both = k

ODE predicts dampened oscillation, while the stochasic system keeps oscillating at max level.

Stochastic Answer:
**robust** quasi-oscillation



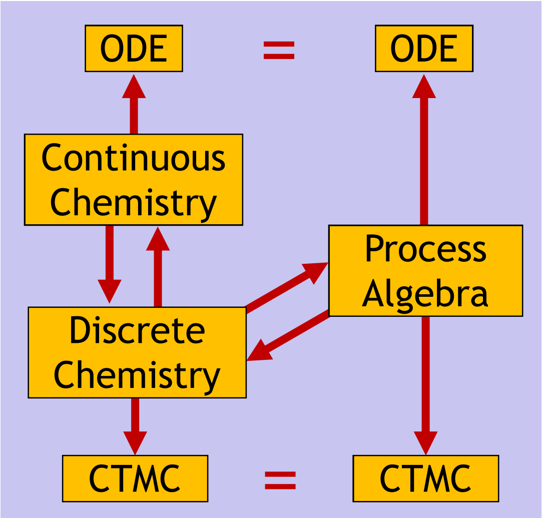


Deterministic Answer:
***dampened*** oscillation

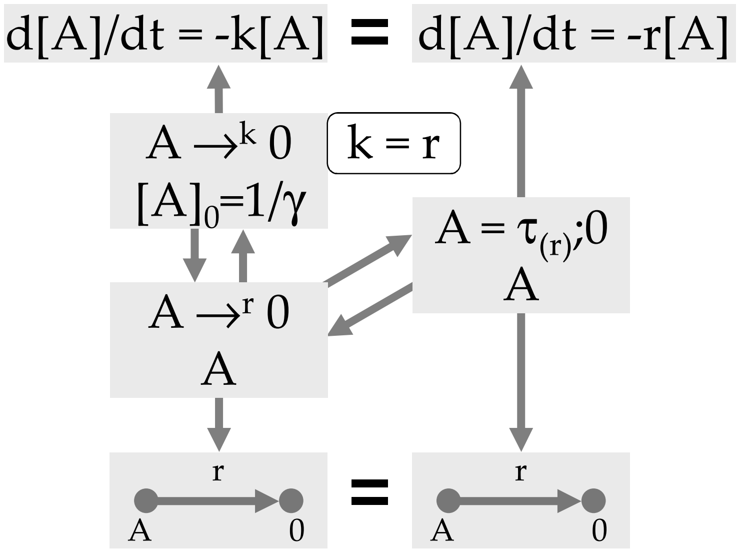
r=1.0
k=1.0

```
dx1/dt=x1*x4-x3*x1-x1+x4, 200.0
dx2/dt=x3*x1-x3*x2+x1-x2, 0.0
dx3/dt=x3*x2-x1*x3-x3+x2, 0.0
dx4/dt=x1*x3-x1*x4+x3-x4, 0.0
```

# Summary


ODE
=
ODE
Continuous Chemistry
Process Algebra
Discrete Chemistry
CTMC
=
CTMC

# Unary Reactions



$d[A]/dt = -k[A]$ **=** $d[A]/dt = -r[A]$

$A \to^{k} 0$

$[A]_0 = 1/\gamma$

$k = r$

$A = \tau_{(r)};0$

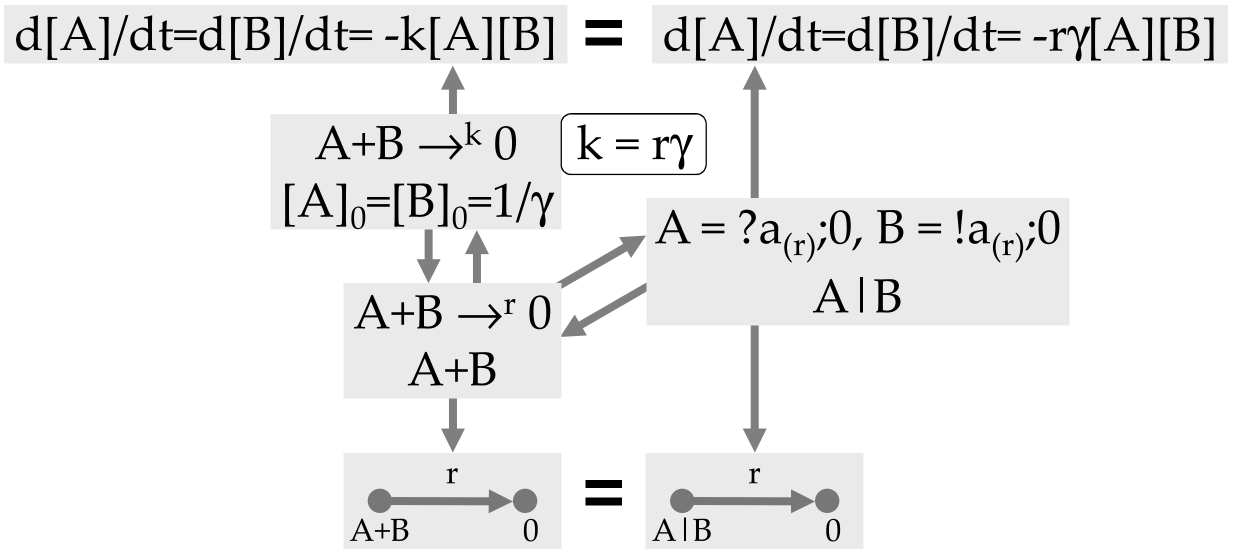
$A$

$A \to^{r} 0$

$A$

○┈▸∘ Unary Reaction

# Hetero Reactions



$d[A]/dt=d[B]/dt= -k[A][B]$ = $d[A]/dt=d[B]/dt= -r\gamma[A][B]$

$A+B \to^{k} 0$

$[A]_0=[B]_0=1/\gamma$

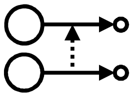
$\boxed{k = r\gamma}$

$A = ?a_{(r)};0,\ B = !a_{(r)};0$

$A|B$

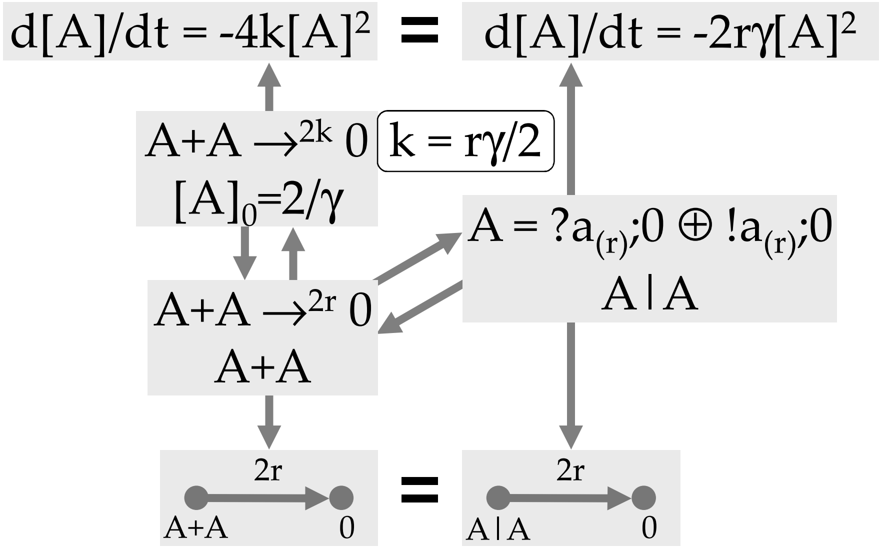
$A+B \to^{r} 0$

$A+B$



Hetero Reaction

# Homeo Reactions



$d[A]/dt = -4k[A]^2$ **=** $d[A]/dt = -2r\gamma[A]^2$

$A+A \rightarrow^{2k} 0$

$[A]_0=2/\gamma$

$\boxed{k = r\gamma/2}$

$A = ?a_{(r)};0 \oplus !a_{(r)};0$

$A|A$

$A+A \rightarrow^{2r} 0$

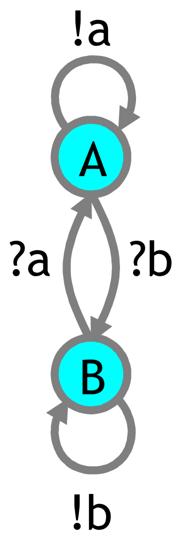
$A+A$

Homeo Reaction

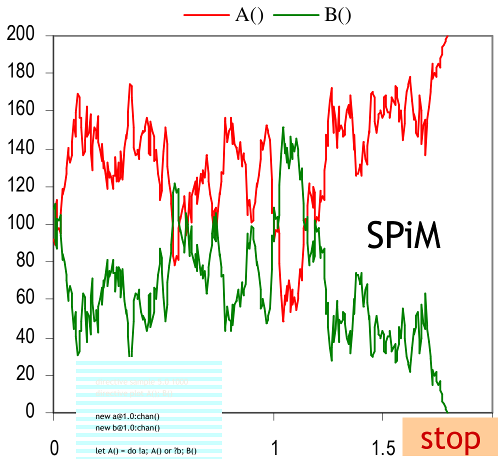
# Groupies ODEs

# Groupies ODE

Q: What does this do?



Stochastic Answer: **bistable** system



```
directive sample 5.0 1000
directive plot A(); B()

new a@1.0:chan()
new b@1.0:chan()

let A() = do !a; A() or ?b; B()
and B() = do !b; B() or ?a; A()

run 100 of (A() | B())
```

Same rate r

$$A = !a_{(r)};A \oplus ?b_{(r)};B$$
$$B = !b_{(r)};B \oplus ?a_{(r)};A$$

$$A+B \rightarrow^{r} A+A$$
$$B+A \rightarrow^{r} B+B$$

$$d[A]/dt = \cancel{r[A][B]-r[B][A]}$$
$$d[B]/dt = \cancel{r[B][A]-r[A][B]}$$

$$d[A]/dt = 0$$
$$d[B]/dt = 0$$

Deterministic Answer: ***constant*** system

ODE predicts stability $\dot{[A]}=0$ for any value of [A], while the stochastic system is stable only when [A] is either 0 or Max.

Different rates r,s

$$A = !a_{(r)};A \oplus ?b_{(s)};B$$
$$B = !b_{(s)};B \oplus ?a_{(r)};A$$

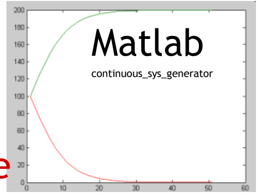
$$A+B \rightarrow^{r} A+A$$
$$B+A \rightarrow^{s} B+B$$

$$d[A]/dt = r[A][B]-s[B][A]$$
$$d[B]/dt = s[B][A]-r[A][B]$$

$$d[A]/dt = (r-s)[A][B]$$
$$d[B]/dt = (s-r)[B][A]$$

Deterministic Answer: ***monostable*** systems

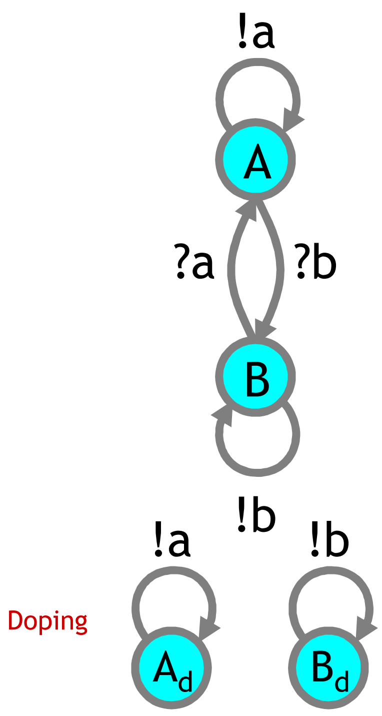
ODE predicts A will always "win", if r>s, and B will always loose. The stochastic system can have either outcome (with different probabilities).



```
[0:0.01:0.5]
dx1/dt = 0.1*x1*x2,   100
dx2/dt = -0.1*x1*x2, 100
```

# Doped Groupies ODEs

Q: What does this do?



$$A = !a_{(r)};A \oplus ?b_{(r)};B \qquad A_d = !a_{(r)};A_d$$
$$B = !b_{(r)};B \oplus ?a_{(r)};A \qquad B_d = !b_{(r)};B_d$$

```
directive sample 10.0 1000
directive plot Ga(); Gb(); Da(); Db()

new a@1.0:chan()
new b@1.0:chan()

let Ga() = do !a; Ga() or ?b; Gb()
and Gb() = do !b; Gb() or ?a; Ga()

let Da() = !a; Da()
and Db() = !b; Db()

run  1 of (Da() | Db())
run 100 of (Ga() | Gb())
```

$$A+B \to^{r} A+A \qquad A+B_d \to^{r} B+B_d$$
$$B+A \to^{r} B+B \qquad B+A_d \to^{r} A+A_d$$

$$d[A]/dt = \cancel{r[A][B]-r[B][A]}-r[A][B_d]+r[B][A_d] \qquad d[A_d]/dt = 0$$
$$d[B]/dt = \cancel{r[B][A]-r[A][B]}-r[B][A_d]+r[A][B_d] \qquad d[B_d]/dt = 0$$

$$d[A]/dt = -rk([A]-[B])$$
$$d[B]/dt = rk([A]-[B])$$

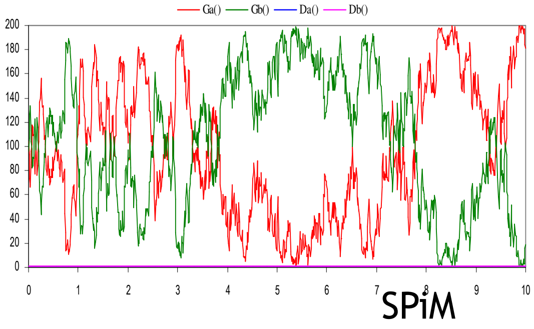
At $[B]=0$: $d[A]/dt=-rk[A]$, $d[B]/dt=rk[A]$

At $[A]\approx[B]$: $d[A]/dt=d[B]/dt\approx 0$

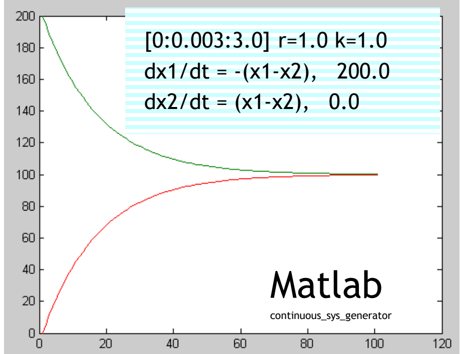
At $[A]=[B]$: $d[A]/dt=d[B]/dt=0$

$[A_d]$,$[B_d]$ are constant; assume them both = k

Stochastic Answer:
**bounded random walk**



Deterministic Answer:
convergence and ***stability***



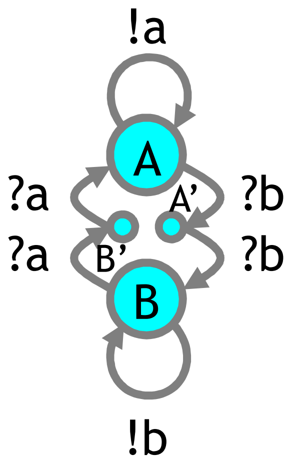
```
[0:0.003:3.0] r=1.0 k=1.0
dx1/dt = -(x1-x2),   200.0
dx2/dt = (x1-x2),   0.0
```

ODE predicts converging stable equilibrium at [A]=[B] instead of the total chaos observed in the stochastic system!

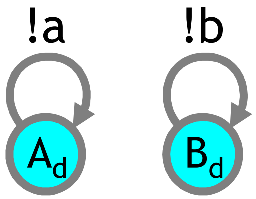
For k=0 (no dope), predicts deadlock $d[A]/dt=d[B]/dt=0$ but at any value of [A], which is definitely not true in the stochastic system.

# Hysteric Groupies ODEs

Q: What does this do?



Doping



```
directive sample 10.0 1000
directive plot Ga(); Gb()

new a@1.0:chan()
new b@1.0:chan()

let Ga() = do !a; Ga() or ?b; ?b; Gb()
and Gb() = do !b; Gb() or ?a; ?a; Ga()

let Da() = !a; Da()
and Db() = !b; Db()

run 100 of (Ga() | Gb())
run  1 of (Da() | Db())
```

$$A = !a_{(r)};A \oplus ?b;A' \quad A' = ?b;B$$
$$B = !b_{(r)};B \oplus ?a;B' \quad B' = ?a;A$$

$$A_d = !a_{(r)};A_d$$
$$B_d = !b_{(r)};B_d$$

$$A+B \xrightarrow{r} A+B' \quad A+B' \xrightarrow{r} A+A$$
$$B+A \xrightarrow{r} B+A' \quad B+A' \xrightarrow{r} B+B$$

$$A+B_d \xrightarrow{r} A'+B_d \quad A'+B_d \xrightarrow{r} B+B_d$$
$$B+A_d \xrightarrow{r} B'+A_d \quad B'+A_d \xrightarrow{r} A+A_d$$

$$d[A]/dt = r[A][B']-r[B][A]-r[A][B_d]+r[B'][A_d]$$
$$d[A']/dt = r[B][A]-r[B][A']+r[A][B_d]-r[A'][B_d]$$
$$d[B]/dt = r[B][A']-r[A][B]-r[B][A_d]+r[A'][B_d]$$
$$d[B']/dt = r[A][B]-r[A][B']+r[B][A_d]-r[B'][A_d]$$

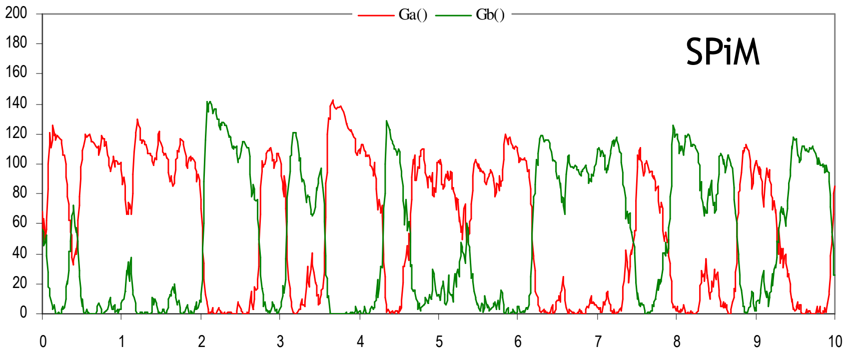
$$d[A_d]/dt = 0$$
$$d[B_d]/dt = 0$$

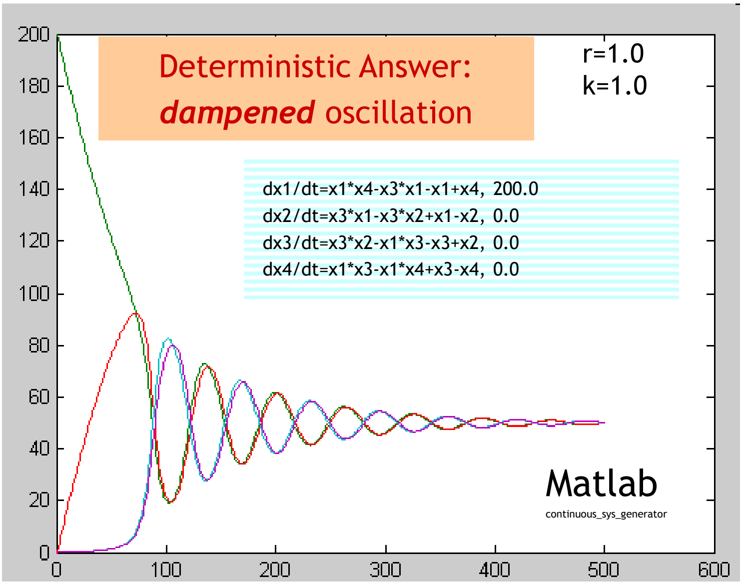
$$d[A]/dt = r[A][B']-r[B][A]-rk[A]+rk[B']$$
$$d[A']/dt = r[B][A]-r[B][A']+rk[A]-rk[A']$$
$$d[B]/dt = r[B][A']-r[A][B]-rk[B]+rk[A']$$
$$d[B']/dt = r[A][B]-r[A][B']+rk[B]-rk[B']$$

$[A_d]$,$[B_d]$ are constant;
assume them both = k

ODE predicts dampened oscillation, while the stochasic system keeps oscillating at max level.

Stochastic Answer:
**robust** quasi-oscillation



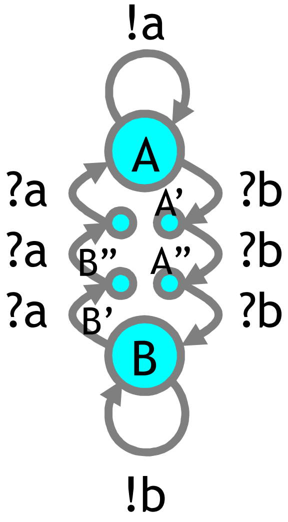


Deterministic Answer:
***dampened*** oscillation

```
dx1/dt=x1*x4-x3*x1-x1+x4, 200.0
dx2/dt=x3*x1-x3*x2+x1-x2, 0.0
dx3/dt=x3*x2-x1*x3-x3+x2, 0.0
dx4/dt=x1*x3-x1*x4+x3-x4, 0.0
```

# Hysteric Groupies ODEs

Q: What does this do?



```
directive sample 10.0 1000
directive plot Ga(); Gb()

new a@1.0:chan()
new b@1.0:chan()

let Ga() = do !a; Ga() or ?b; ?b; ?b; Gb()
and Gb() = do !b; Gb() or ?a; ?a; ?a; Ga()

let Da() = !a; Da()
and Db() = !b; Db()

run 100 of (Ga() | Gb())
run  1 of (Da() | Db())
```

$A = !a_{(r)};A \oplus ?b;A'$ $\quad A' = ?b;A''$ $\quad A'' = ?b;B$

$B = !b_{(r)};B \oplus ?a;B'$ $\quad B' = ?a;B''$ $\quad B'' = ?a;A$

$A_d = !a_{(r)};A_d$

$B_d = !b_{(r)};B_d$

$A+B \to^{r} A+B'$ $\quad A+B' \to^{r} A+B''$ $\quad A+B'' \to^{r} A+A$

$B+A \to^{r} B+A'$ $\quad B+A' \to^{r} B+A''$ $\quad B+A'' \to^{r} B+B$

$A+B_d \to^{r} A'+B_d$ $\quad A'+B_d \to^{r} A''+B_d$ $\quad A''+B_d \to^{r} B+B_d$

$B+A_d \to^{r} B'+A_d$ $\quad B'+A_d \to^{r} B''+A_d$ $\quad B''+A_d \to^{r} A+A_d$

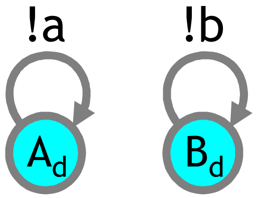
$$
\begin{aligned}
d[A]/dt &= r[A][B'']-r[B][A]-r[A][B_d]+r[B''][A_d]\\
d[A']/dt &= r[B][A]-r[B][A']+r[A][B_d]-r[A'][B_d]\\
d[A'']/dt &= r[B][A']-r[B][A'']+r[A'][B_d]-r[A''][B_d]\\
d[B]/dt &= r[B][A'']-r[A][B]-r[B][A_d]+r[A''][B_d]\\
d[B']/dt &= r[A][B]-r[A][B']+r[B][A_d]-r[B'][A_d]\\
d[B'']/dt &= r[A][B']-r[A][B'']+r[B'][A_d]-r[B''][A_d]
\end{aligned}
$$

$$
\begin{aligned}
d[A_d]/dt &= 0\\
d[B_d]/dt &= 0
\end{aligned}
$$

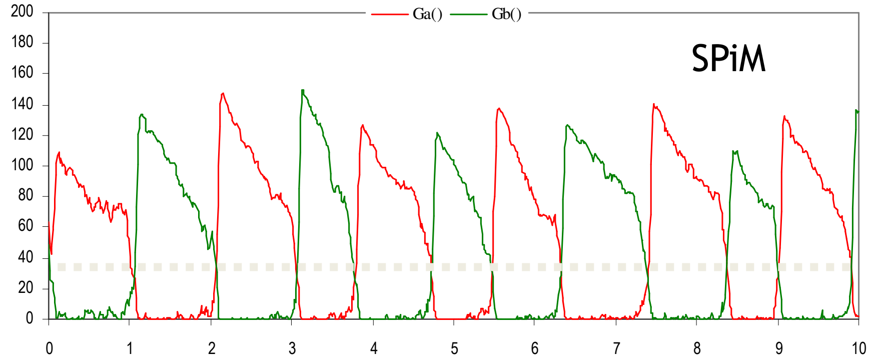
$$
\begin{aligned}
d[A]/dt &= r[A][B'']-r[B][A]-rk[A]+rk[B'']\\
d[A']/dt &= r[B][A]-r[B][A']+rk[A]-rk[A']\\
d[A'']/dt &= r[B][A']-r[B][A'']+rk[A']-rk[A'']\\
d[B]/dt &= r[B][A'']-r[A][B]-rk[B]+rk[A'']\\
d[B']/dt &= r[A][B]-r[A][B']+rk[B]-rk[B']\\
d[B'']/dt &= r[A][B']-r[A][B'']+rk[B']-rk[B'']
\end{aligned}
$$

$[A_d]$,$[B_d]$ are constant;
assume them both = k

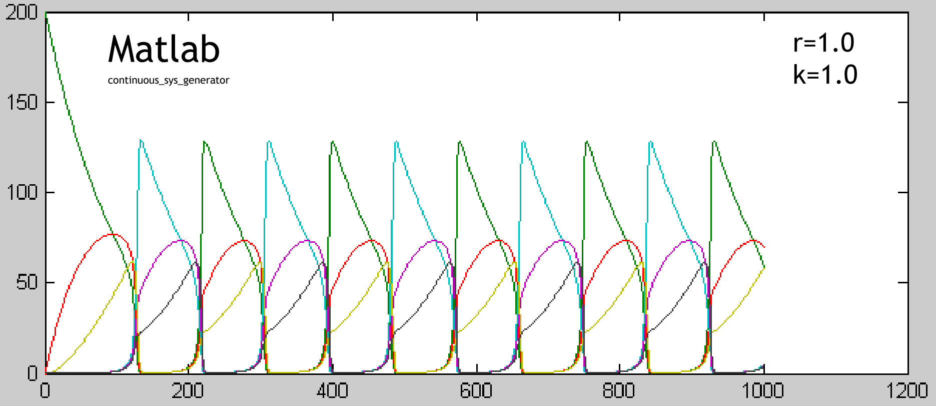
Doping



Stochastic Answer:
**robust** oscillation



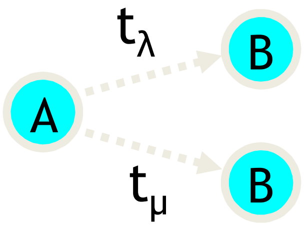
```
A  dx1/dt=x1*x6-x3*x1-x1+x6, 200.0
A'  dx2/dt=x3*x1-x3*x2+x1-x2, 0.0
A" dx5/dt=x3*x2-x3*x5+x2-x5, 0.0
B   dx3/dt=x3*x5-x1*x3-x3+x5, 0.0
B'  dx4/dt=x1*x3-x1*x4+x3-x4, 0.0
B"  dx6/dt=x1*x4-x1*x6+x4-x6, 0.0
```



# --Laws by ODEs

# Choice Law by ODEs

$t_{\lambda};B$ Å $t_{\mu};B$ = $t_{\lambda+\mu};B$

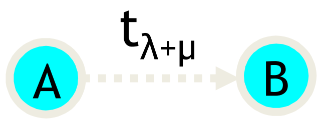


$A = t_{\lambda};B$ Å $t_{\mu};B$

$A$ ®$^{\lambda}$ $B$
$A$ ®$^{\mu}$ $B$

$$[A]^{\cdot} = -\lambda[A] - \mu[A]$$
$$[B]^{\cdot} = \lambda[A] + \mu[A]$$

=

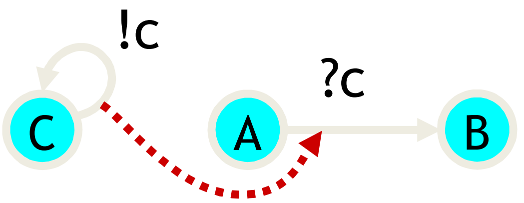


$A = t_{\lambda+\mu};B$

$A$ ®$^{\lambda+\mu}$ $B$

$$[A]^{\cdot} = -(\lambda+\mu)[A]$$
$$[B]^{\cdot} = (\lambda+\mu)[A]$$

# Idle Interaction Law by ODEs



A = ?c;B
C = !c;C

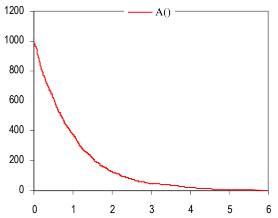
A+C ®$^r$ B+C

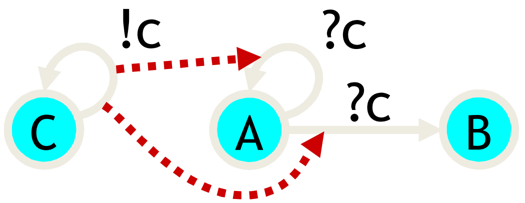
[A]$^\cdot$ = -r[A][C]
[B]$^\cdot$ = r[A][C]
[C]$^\cdot$ = 0

directive sample 6.0 1000
directive plot A()

ne
c@

le
B()
and B() = ()





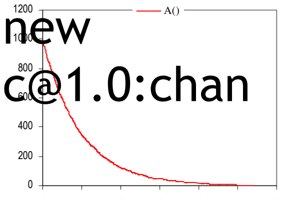
It may seem like A should decrease half as fast,
but NO! Two ways to explain:
- State A is *memoryless* of any past idling.
- Activity on c is double

A = ?c;A Å ?c;B
C = !c;C

A+C ®$^r$ A+C
A+C ®$^r$ B+C

[A]$^\cdot$ = -r[A][C]
[B]$^\cdot$ = r[A][C]
[C]$^\cdot$ = 0

directive sample 6.0 1000
directive plot A()

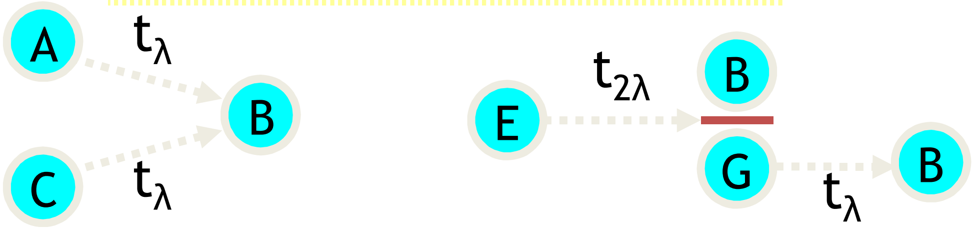


new c@1.0:chan
let A() = do ?c; B() or ?c; A()

2013-09-08

# Equiconfluence Law by ODEs

$t_{\lambda};B \mid t_{\lambda};B = t_{2\lambda};(B \mid t_{\lambda};B)$



Want to show that B on both sides has the “same behavior” (equal quantities of B produced at all times)

$A = t_{\lambda};B$
$C = t_{\lambda};B$
$A \mid C$

=?

$E = t_{2\lambda};(B \mid G)$
$G = t_{\lambda};B$
$E$

$A\ \text{®}^{\lambda}B$
$C\ \text{®}^{\lambda}B$
$A + C$

=?

$E\ \text{®}^{2\lambda}\ B + G$
$G\ \text{®}^{\lambda}B$
$E$

$[E]^{\cdot} = -2\lambda[E]$
$[G]^{\cdot} = 2\lambda[E] - \lambda[G]$
$[B]^{\cdot} = 2\lambda[E] + \lambda[G]$

$[A]^{\cdot} = -\lambda[A]$
$[C]^{\cdot} = -\lambda[C]$
$[B]^{\cdot} = \lambda[A] + \lambda[C]$

=?

$[A']^{\cdot} = -\lambda[A']$
$[C']^{\cdot} = -\lambda[C']$
$[B]^{\cdot} = \lambda[A'] + \lambda[C']$

let $A' = C' = E+G/2$

$\lambda[A'] + \lambda[C']$
$= \lambda[E+G/2] + \lambda[E+G/2]$
$= 2\lambda[E] + \lambda[G] = [B]^{\cdot}$

$[A']^{\cdot} = [E+G/2]^{\cdot} = [E]^{\cdot}+[G]^{\cdot}/2$
$= -2\lambda[E]+(2\lambda[E]-\lambda[G])/2$
$= -\lambda[E]-\lambda[G]/2$
$= -\lambda[E+G/2] = -\lambda[A']$

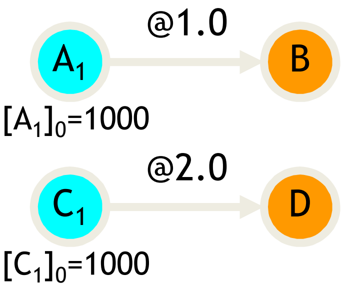
[B] has equal time evolutions on the two sides provided that [A]=[E+G/2] and [C]=[E+G/2]. This imposes the constraint, in particular, that $[A]_0=[E+G/2]_0$ and $[C]_0=[E+G/2]_0$ (at time zero). The initial conditions of the right hand system specify that $[G/2]_0=0$ (since only E is present). Therefore, we obtain that $[A]_0=[C]_0=[E]_0$.

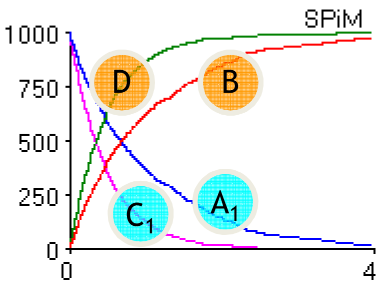
# Stochastic Interleaving

Hermanns: Interactive Markov Chains. Sec 4.1.2

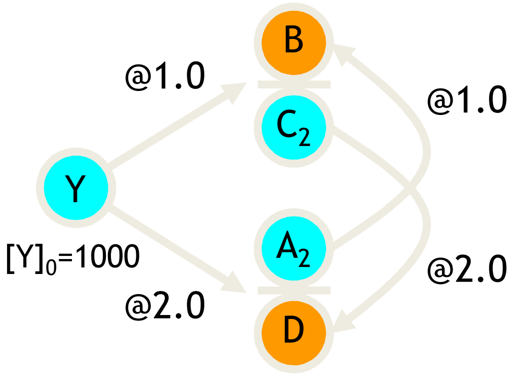
$$t_{\lambda};B \mid t_{\mu};D \;=\; t_{\lambda};(B \mid t_{\mu};D) \text{ Å } t_{\mu};(t_{\lambda};B \mid D)$$

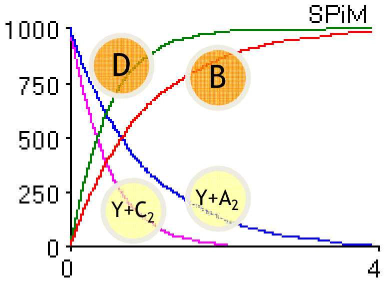
Ex: $\lambda=1.0$, $\mu=2.0$





```
directive sample 4.0 10000
directive plot A(); B(); C(); D()

let A() = delay@1.0; B()
and B() = ()

let C() = delay@2.0; D()
and D() = ()

run 1000 of (A() | C())
```





```
directive sample 4.0 10000
directive plot
  ?YA; B(); ?YC; D(); Y(); A(); C()
new YA@1.0:chan new YC@1.0:chan

let A() = do delay@1.0; B() or ?YA
and B() = ()

let C() = do delay@2.0; D() or ?YC
and D() = ()

let Y() =
  do delay@1.0; (B() | C())
  or delay@2.0; (A() | D())
  or ?YA or ?YC

run 1000 of Y()
```

Amazingly, the B's and the D's from the two branches sum up to exponential distributions

# Stochastic Interleaving Law by ODEs

$t_\lambda$;B | $t_\mu$;D = $t_\lambda$;(B | $t_\mu$;D) Å $t_\mu$;($t_\lambda$;B | D)

Want to show that B and D on both sides have the “same behavior” (equal quantities of B and D produced at all times)

$A_1$ = $t_\lambda$;B
$C_1$ = $t_\mu$;D
$A_1$ | $C_1$

$A_1$ ®$^\lambda$ B
$C_1$ ®$^\mu$ D
$A_1$ + $C_1$

$$[A_1]^{\cdot} = -\lambda[A_1]$$
$$[B]^{\cdot} = \lambda[A_1]$$
$$[C_1]^{\cdot} = -\mu[C_1]$$
$$[D]^{\cdot} = \mu[C_1]$$

=?

Y = $t_\lambda$;(B | $C_2$) Å $t_\mu$;($A_2$ | D)
$C_2$ = $t_\mu$;D
$A_2$ = $t_\lambda$;B
Y

Y ®$^\lambda$ B + $C_2$
Y ®$^\mu$ $A_2$ + D
$C_2$ ®$^\mu$ D
$A_2$ ®$^\lambda$ B
Y

$$[Y]^{\cdot} = -\lambda[Y]-\mu[Y]$$
$$[A_2]^{\cdot} = \mu[Y]-\lambda[A_2]$$
$$[B]^{\cdot} = \lambda[Y]+\lambda[A_2]$$
$$[C_2]^{\cdot} = \lambda[Y]-\mu[C_2]$$
$$[D]^{\cdot} = \mu[Y]+\mu[C_2]$$

$$[Y+A_2]^{\cdot} = [Y]^{\cdot}+[A_2]^{\cdot}$$
$$= -\lambda[Y]-\mu[Y]+\mu[Y]-\lambda[A_2]$$
$$= -\lambda[Y]-\lambda[A_2]$$
$$= -\lambda[Y+A_2]$$

$[Y+A_2]$ decays exponentially!

$$[Y+A_2]^{\cdot} = -\lambda[Y+A_2]$$
$$[B]^{\cdot} = \lambda[Y+A_2]$$
$$[Y+C_2]^{\cdot} = -\mu[Y+C_2]$$
$$[D]^{\cdot} = \mu[Y+C_2]$$

[B] and [D] have equal time evolutions on the two sides provided that $[A_1]=[Y+A_2]$ and $[C_1]=[Y+C_2]$.
This imposes the constraint, in particular, that $[A_1]_0=[Y+A_2]_0$ and $[C_1]_0=[Y+C_2]_0$ (at time zero).
The initial conditions of the right hand system specify that $[A_2]_0=[C_2]_0=0$ (since only Y is present).
Therefore, we obtain that $[A_1]_0=[C_1]_0=[Y]_0$.

So, for example, if we run a stochastic simulation of the left hand side with 1000*A1 and 1000*C1, we obtain the same curves for B and D than a stochastic simulation of the right hand side with 1000*Y.