Molecules as Automata

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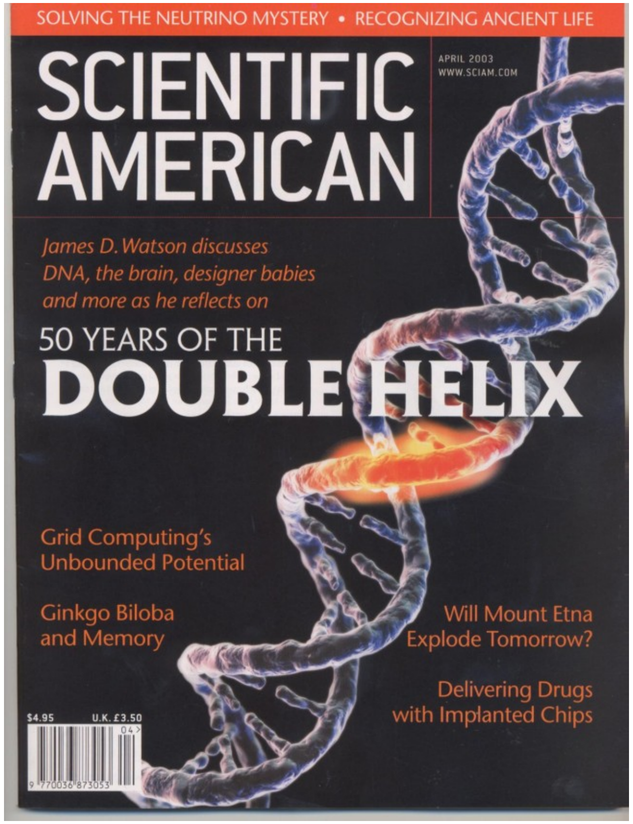
50 Years of Molecular Cell Biology

- The genome (human: 3 GBases = 750MB) is made of DNA
  - Stores digital information as sequences of 4 different nucleotides
  - Directs protein assembly through RNA and the Genetic Code
- Proteins (~1M coded from ~30K genes) are made of amino acids strings
  - Catalyze all biochemical reactions
  - Control metabolism (energy & materials)
  - Process signals, activate genes
- Bootstrapping still a mystery
  - DNA, RNA, proteins, membranes are today interdependent. Not clear who came first
  - Not understood, not essential for us



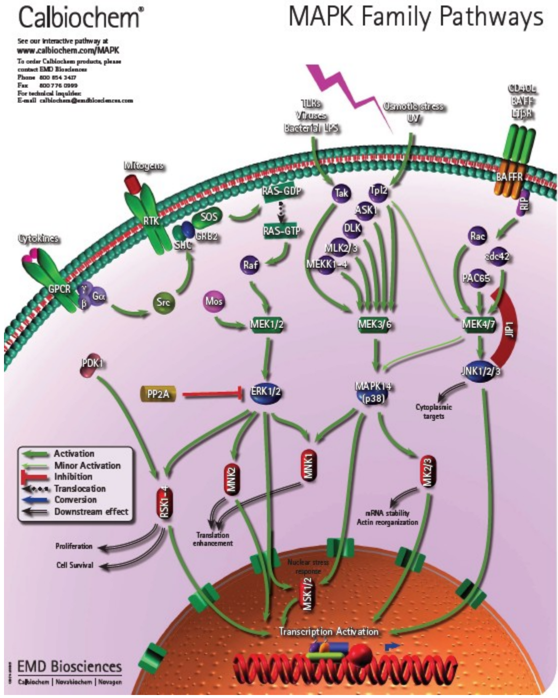
Cells Compute

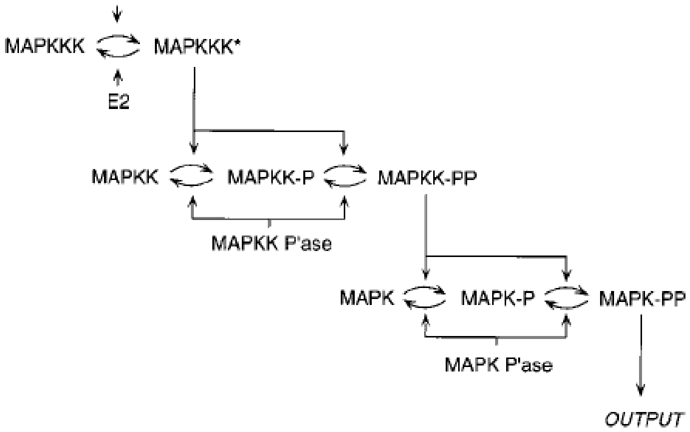
- No survival without computation!
  - Finding food
  - Avoiding predators

- How do they compute?
  - Unusual computational paradigms.
  - Proteins: do they work like electronic circuits? or process algebra?
  - Genes: what kind of software is that?

- Signaling networks
  - Clearly “information processing”
  - They are “just chemistry”: molecule interactions
  - But what are their principles and algorithms?

- Complex, higher-order interactions
  - MAPKKK = MAP Kinase Kinase Kinase: that which operates on that which operates on that which operates on protein.

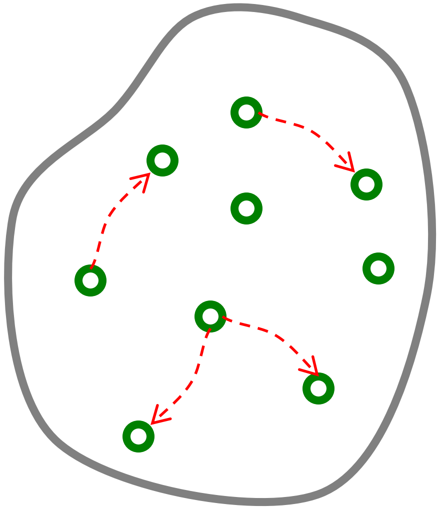




Ultrasensitivity in the mitogen-activated protein **cascade**, Chi-Ying F. Huang and James E. Ferrell, Jr., 1996, *Proc. Natl. Acad. Sci. USA*, 93, 10078-10083.

Stochastic Collectives

Stochastic Collectives

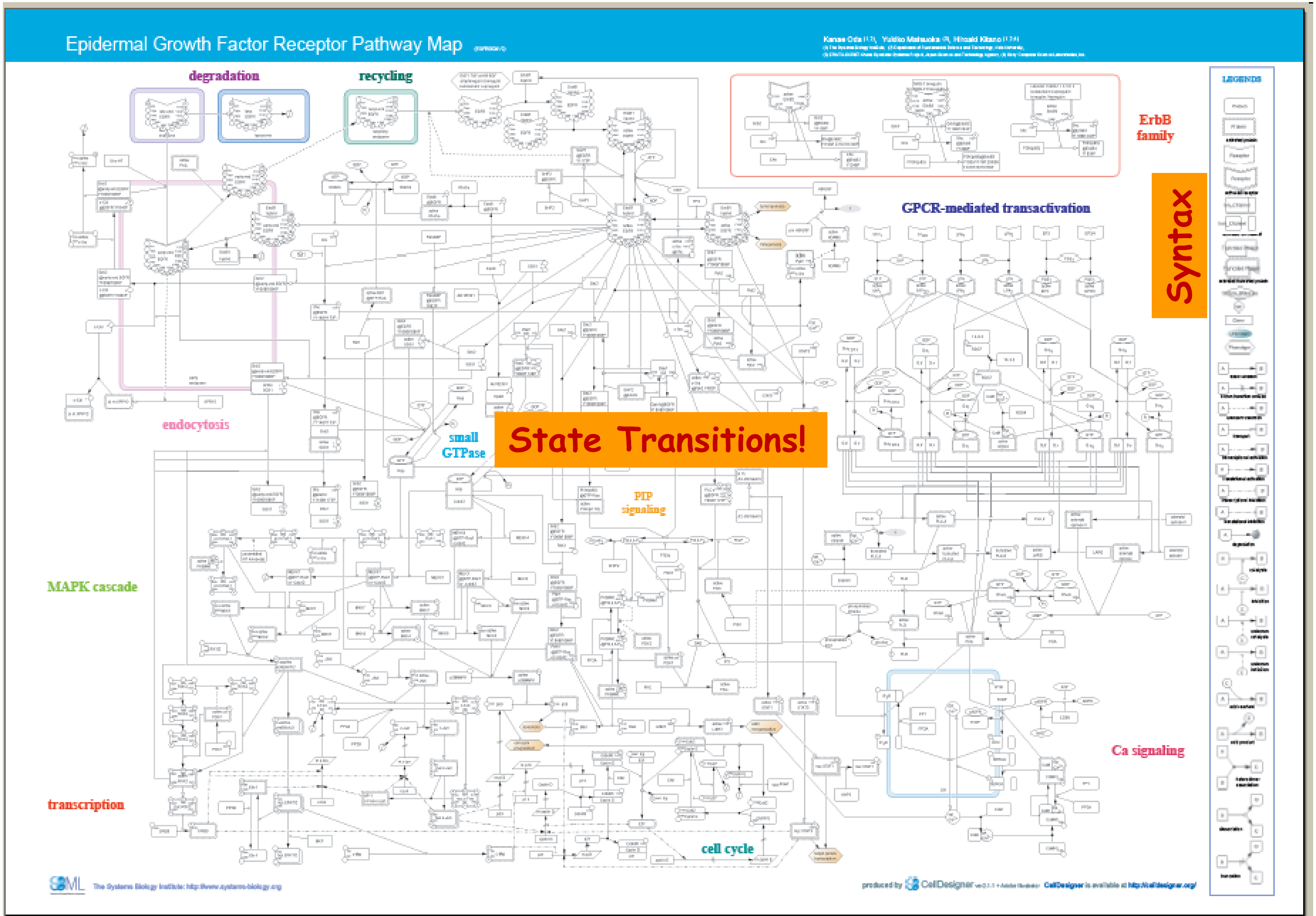


- "Collective":
  - A large set of interacting finite state automata:
    - Not quite language automata ("large set")
    - Not quite cellular automata ("interacting" but not on a grid)
    - Not quite process algebra ("collective behavior")
    - Cf. multi-agent systems and swarm intelligence

- "Stochastic":
  - Interactions have *rates*
    - Not quite discrete (hundreds or thousands of components)
    - Not quite continuous (non-trivial stochastic effects)
    - Not quite hybrid (no "switching" between regimes)

- Very much like biochemistry
  - Which is a large set of stochastically interacting molecules/proteins
  - Are proteins finite state and subject to automata-like transitions?
    - Let's say they are, at least because:
    - Much of the knowledge being accumulated in Systems Biology is described as state transition diagrams [Kitano].

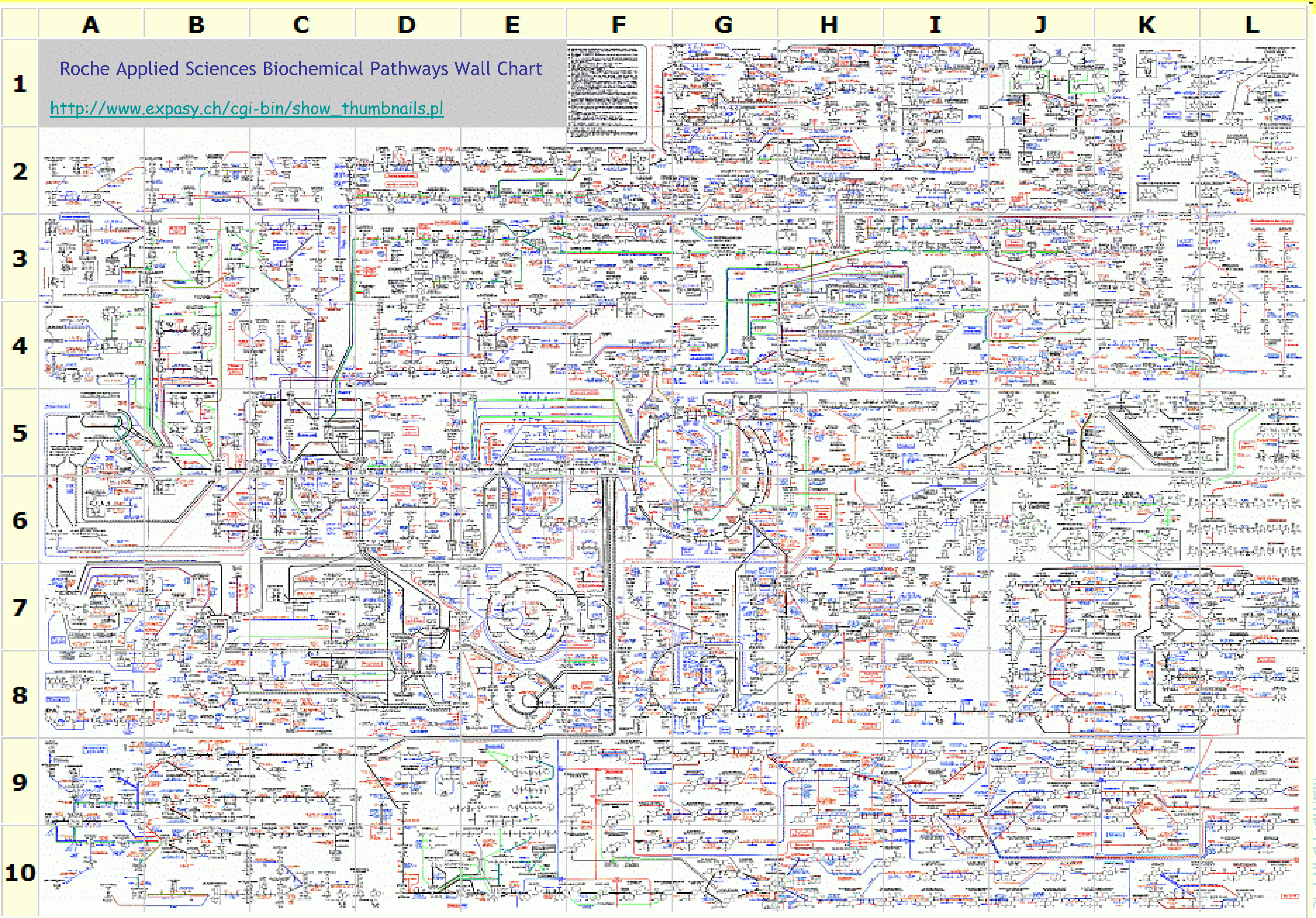
Towards Systems Biology



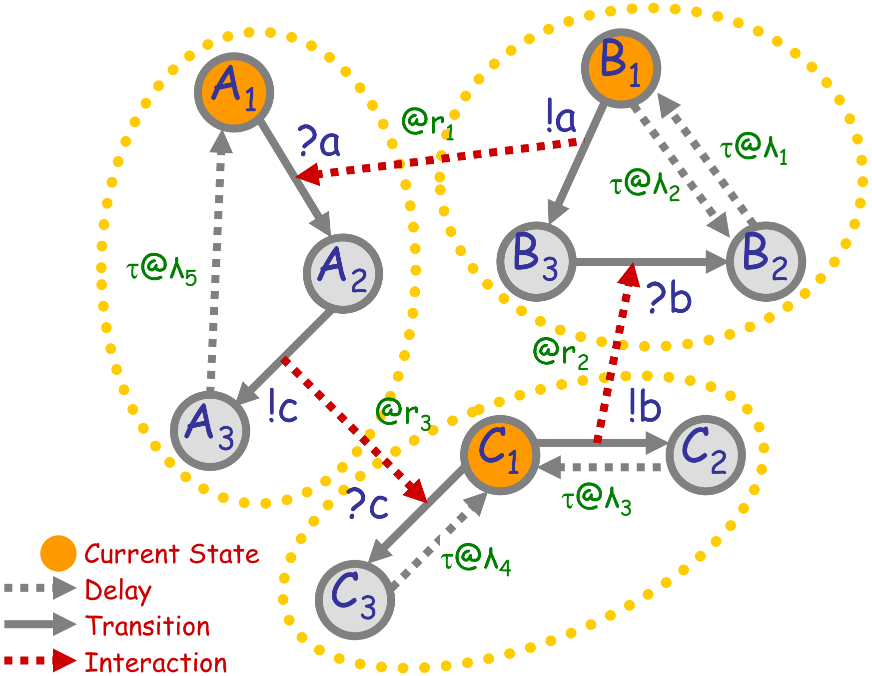
State Transitions!

Syntax

Compositionality (NOT!)



Interacting Automata



Communicating automata: a graphical FSA-like notation for "finite state restriction-free π-calculus processes". *Interacting* automata do not even exchange values on communication.

The stochastic version has *rates* on communications, and delays.

new $a@r_1$
new $b@r_2$
new $c@r_3$

Communication channels

$A_1 = ?a;\ A_2$
$A_2 = !c;\ A_3$
$A_3 = \tau@\lambda_5;\ A_1$

$B_1 = \tau@\lambda_2;\ B_2 + !a;\ B_3$
$B_2 = \tau@\lambda_1;\ B_1$
$B_3 = ?b;\ B_2$

$C_1 = !b;\ C_2 + ?c;\ C_3$
$C_2 = \tau@\lambda_3;\ C_1$
$C_3 = \tau@\lambda_4;\ C_2$

Automata

$A_1 \mid B_1 \mid C_1$

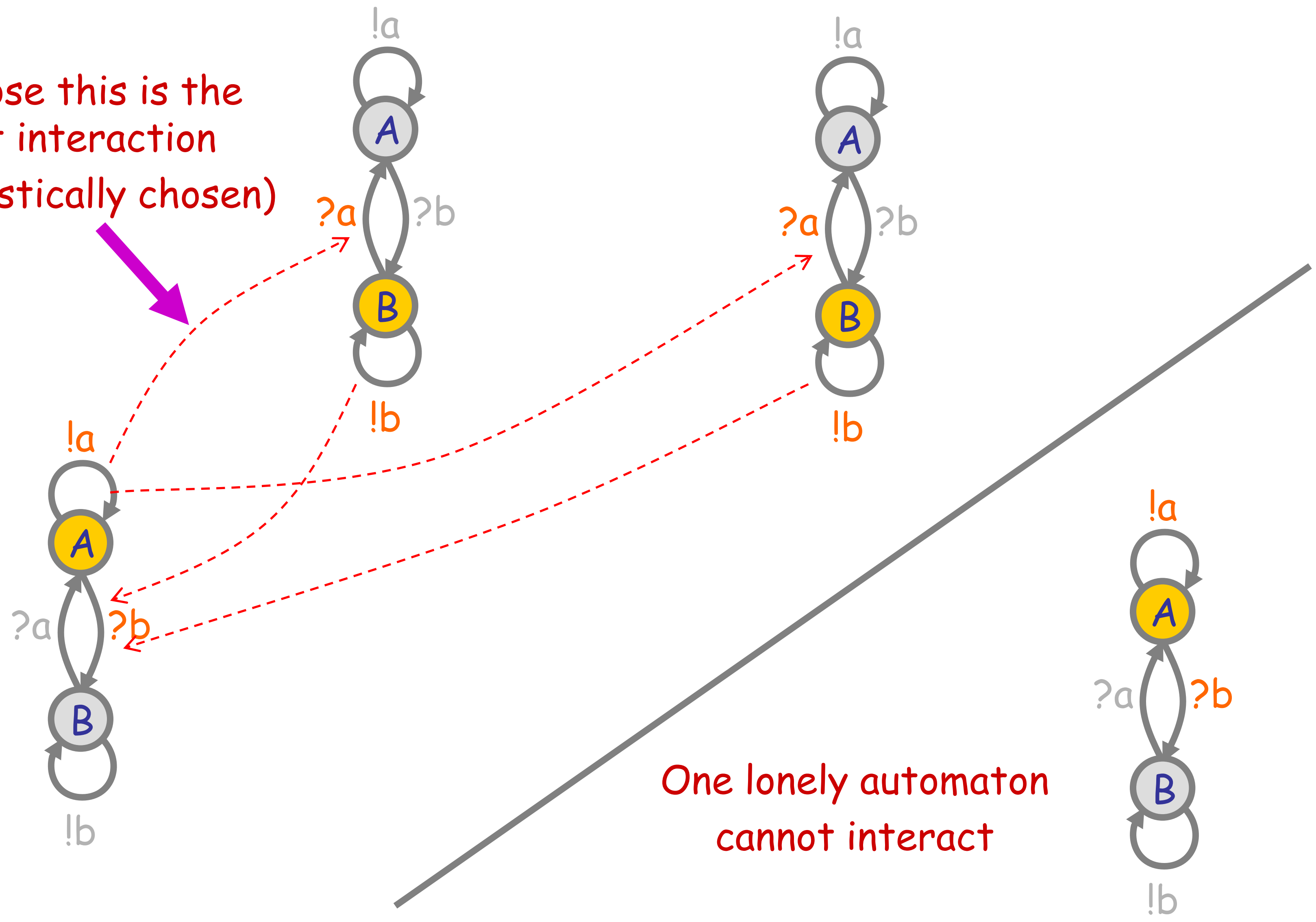
The system and initial state

"Finite state" means: no composition or restriction inside recursion.

Analyzable by standard Markovian techniques, by first computing the "product automaton" to obtain the underlying finite Markov transition system. [Buchholz]

Interactions have rates. Actions DO NOT have rates.

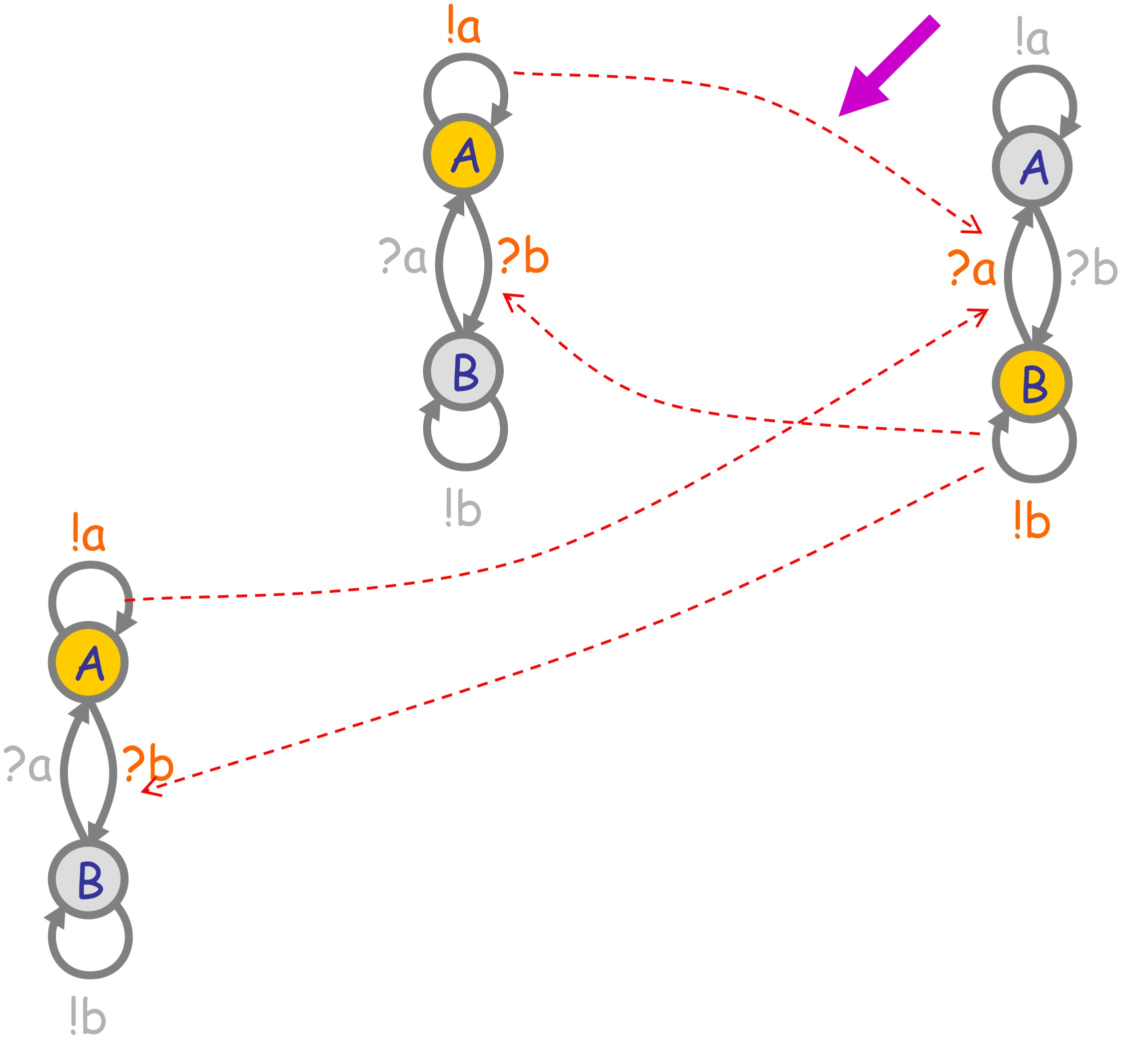
Interactions in a Population



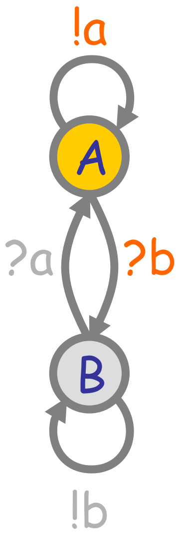
Suppose this is the next interaction (stochastically chosen)

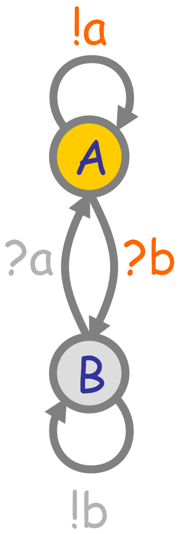
One lonely automaton cannot interact

Interactions in a Population



Interactions in a Population





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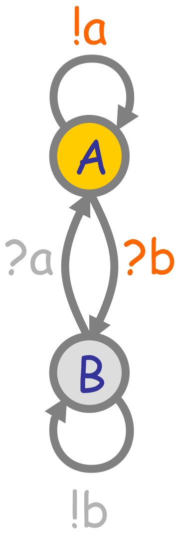
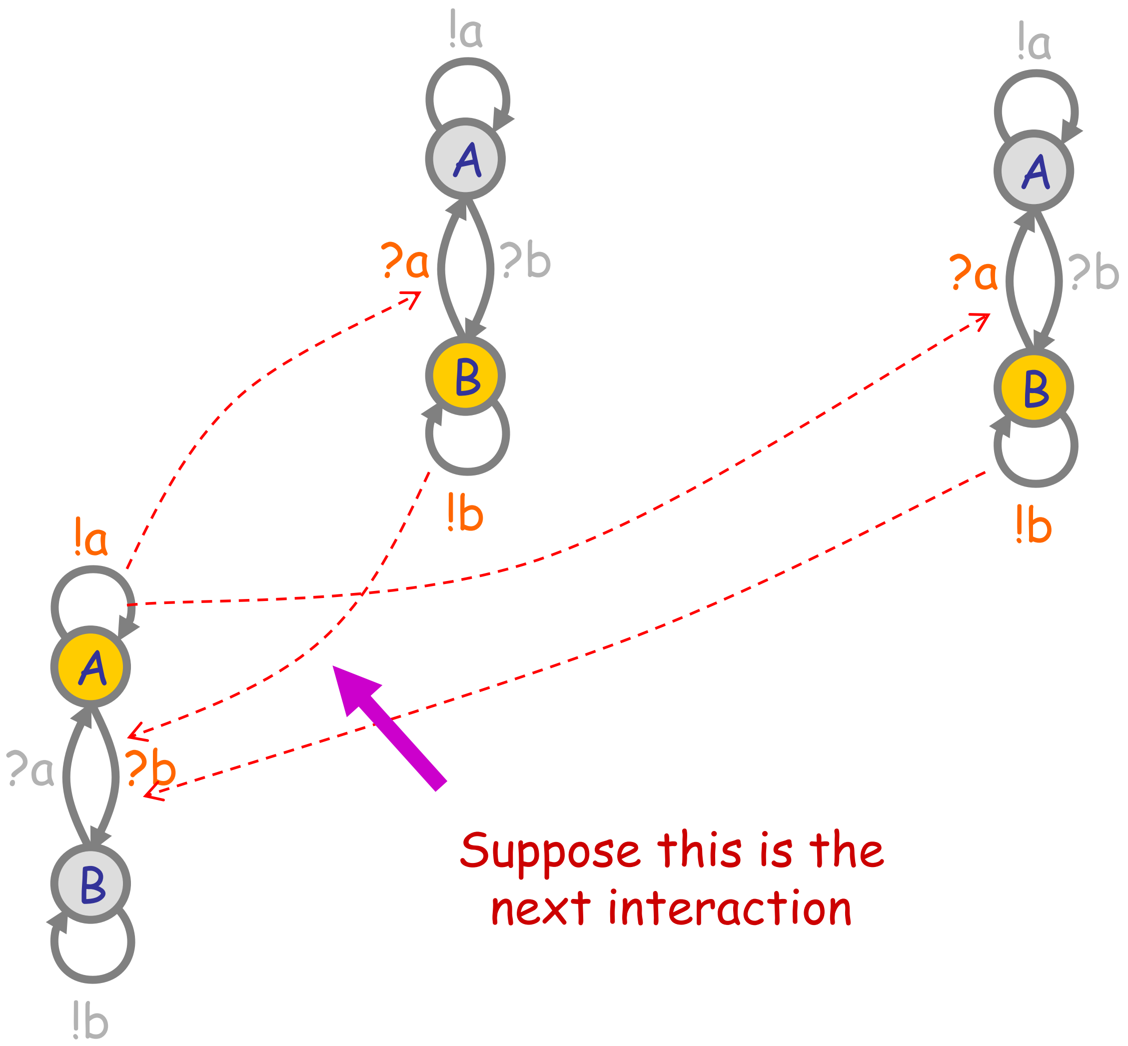


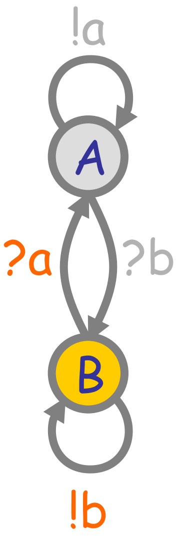
All-A stable
population

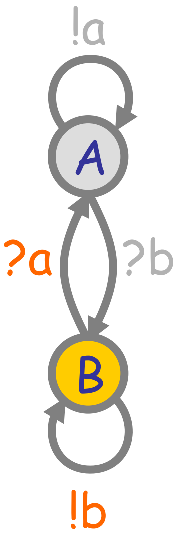
Interactions in a Population (2)



Suppose this is the next interaction

Interactions in a Population (2)





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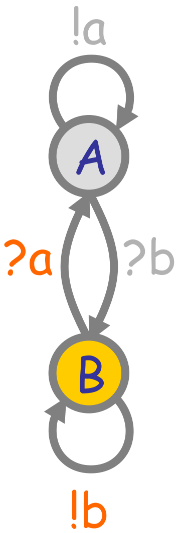
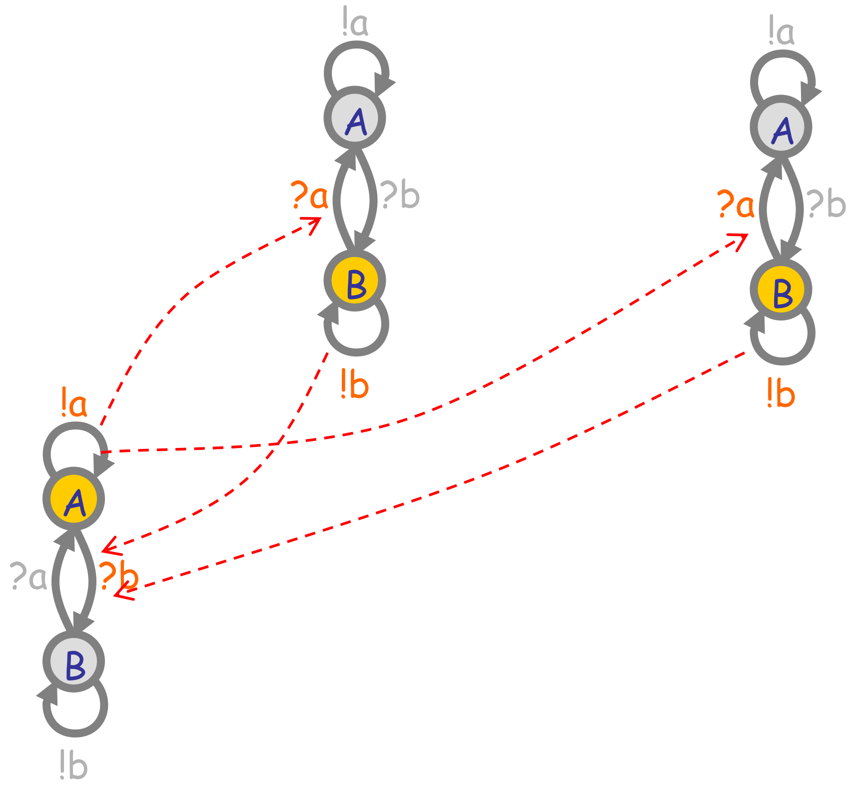
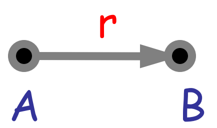


All-B stable
population

Nondeterministic
population behavior
("multistability")

CTMC Semantics



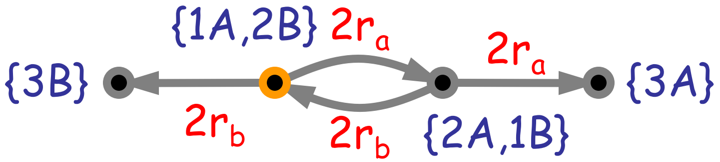


CTMC
(homogeneous) Continuous Time
Markov Chain
- directed graph with no self loops
- nodes are system states
- arcs have transition rates

Probability of holding in state A:

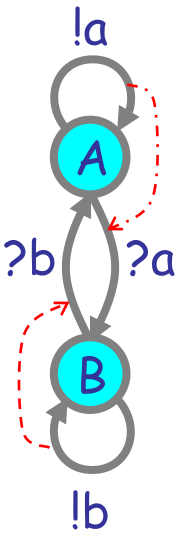
$\Pr(H_A>t) = e^{-rt}$

in general, $\Pr(H_A>t) = e^{-Rt}$ where R is the sum of all the exit rates from A



CTMC

Groupies and Celebrities



Celebrity

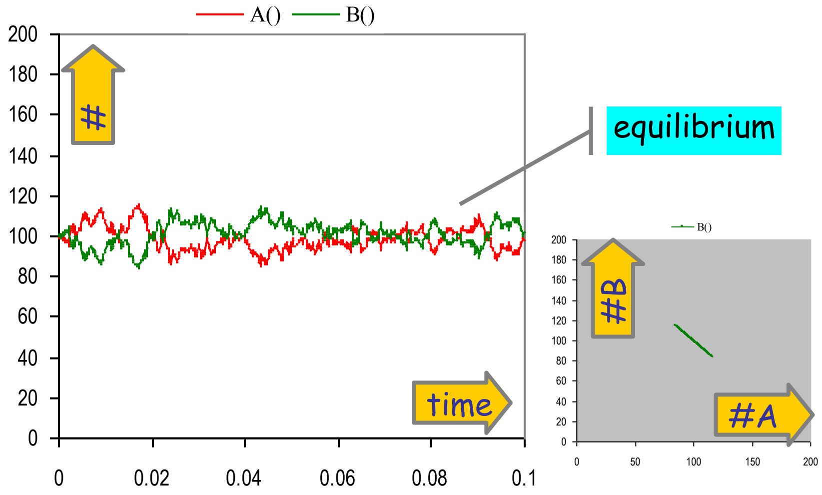
(does not want to be like somebody else)

```
directive sample 0.1 200
directive plot A(); B()

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

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

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

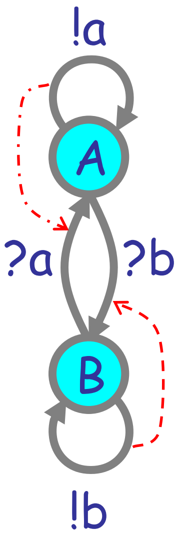
a@1.0

b@1.0

A stochastic collective of celebrities:



Stable because as soon as a A finds itself in the majority, it is more likely to find somebody in the same state, and hence change, so the majority is weakened.



Groupie

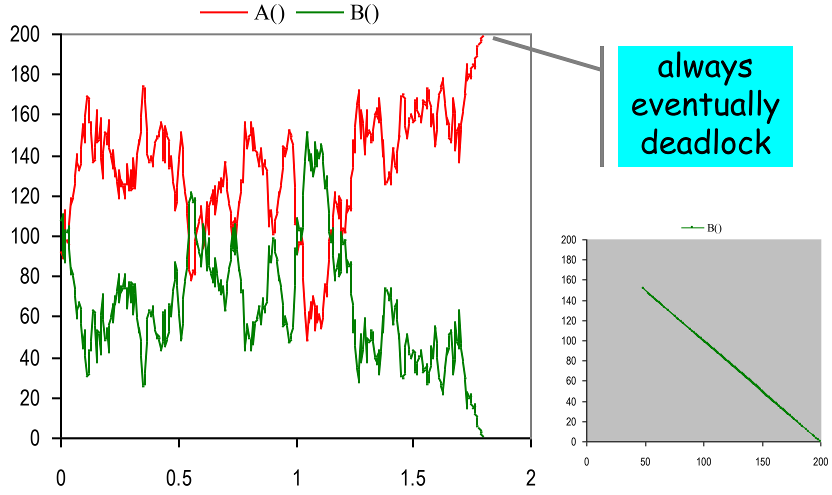
(wants to be like somebody different)

```
directive sample 0.1 200
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())
```

a@1.0

b@1.0

A stochastic collective of groupies:

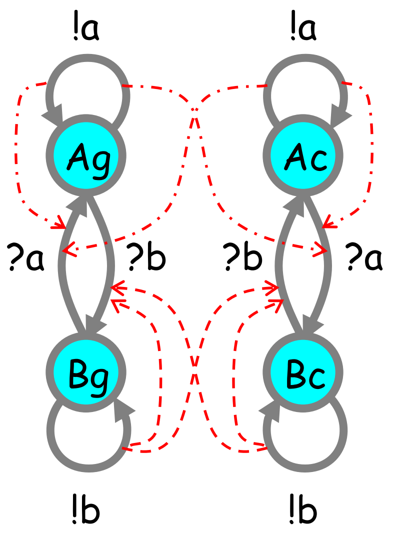


Unstable because within an A majority, an A has difficulty finding a B to emulate, but the few B's have plenty of A's to emulate, so the majority may switch to B. Leads to deadlock when everybody is in the same state and there is nobody different to emulate.

Both Together

A way to break the deadlocks: Groupies with just a few Celebrities

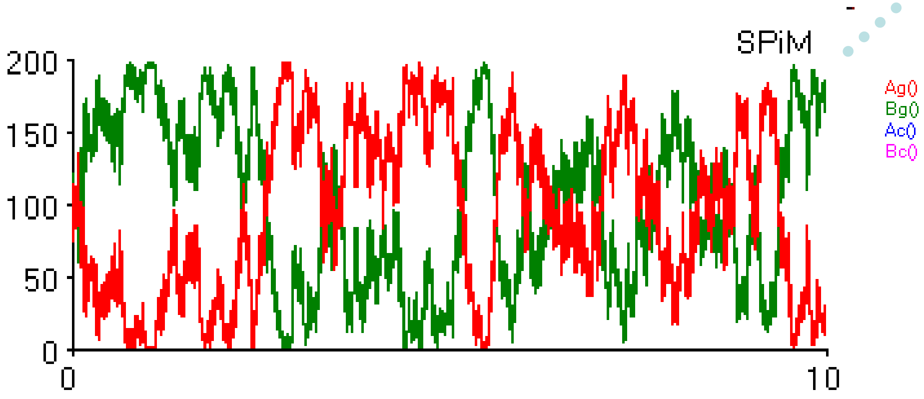
Many Groupies



A few Celebrities

```
directive sample 10.0
directive plot Ag(); Bg(); Ac(); Bc()

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

let Ac() = do !a; Ac() or ?a; Bc()
and Bc() = do !b; Bc() or ?b; Ac()

let Ag() = do !a; Ag() or ?b; Bg()
and Bg() = do !b; Bg() or ?a; Ag()

run 1 of Ac()
run 100 of (Ag() | Bg())
```

never deadlock

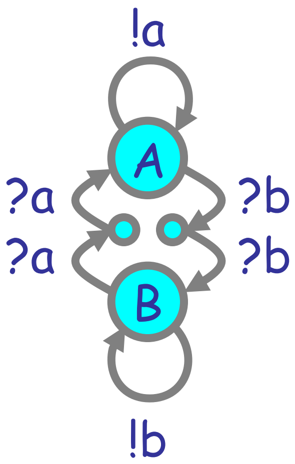


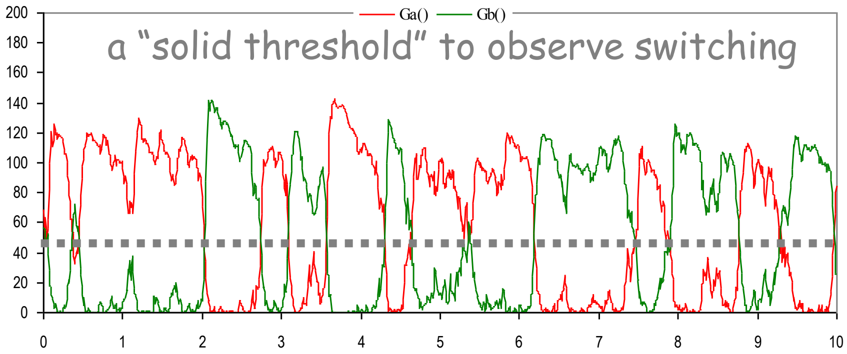
A tiny bit of "noise" can make a huge difference

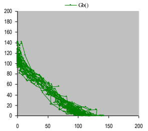
Regularity can arise not far from chaos

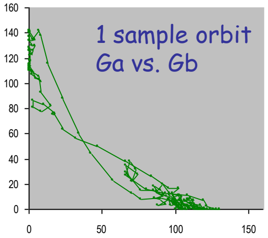
Hysteric Groupies

We can get more regular behavior from groupies if they “need more convincing”, or “hysteresis” (history-dependence), to switch states.

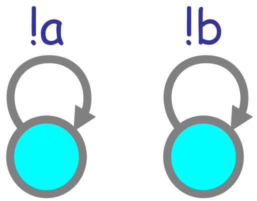



a “solid threshold” to observe switching




1 sample orbit
Ga vs. Gb

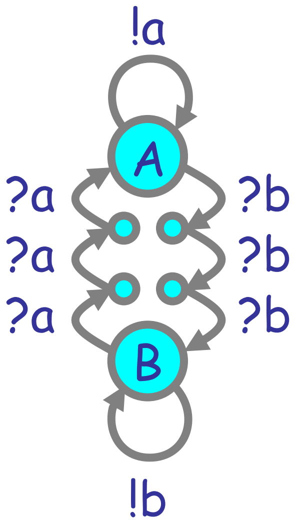
```
directive sample 10.0 1000
directive plot Ga(); Gb()
new a@1.0:chan()
new b@1.0:chan()
let Ga() = do !a; Ga() or ?b; ?b; Gb()
and Gb() = do !b; Gb() or ?a; ?a; Ga()
let Da() = !a; Da()
and Db() = !b; Db()
run 100 of (Ga() | Gb())
run   1 of (Da() | Db())
```

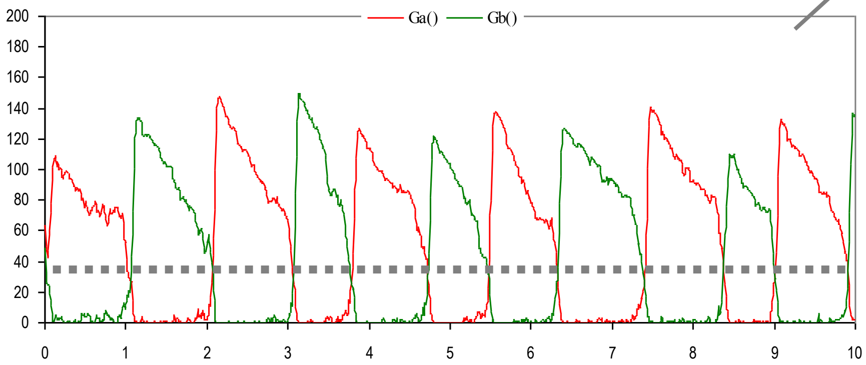


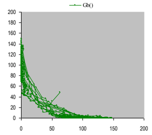
(With doping to break deadlocks)

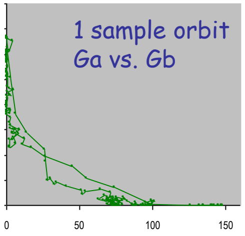
N.B.: It will not oscillate without doping (noise)

“regular” oscillation








1 sample orbit
Ga vs. Gb

```
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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())
```
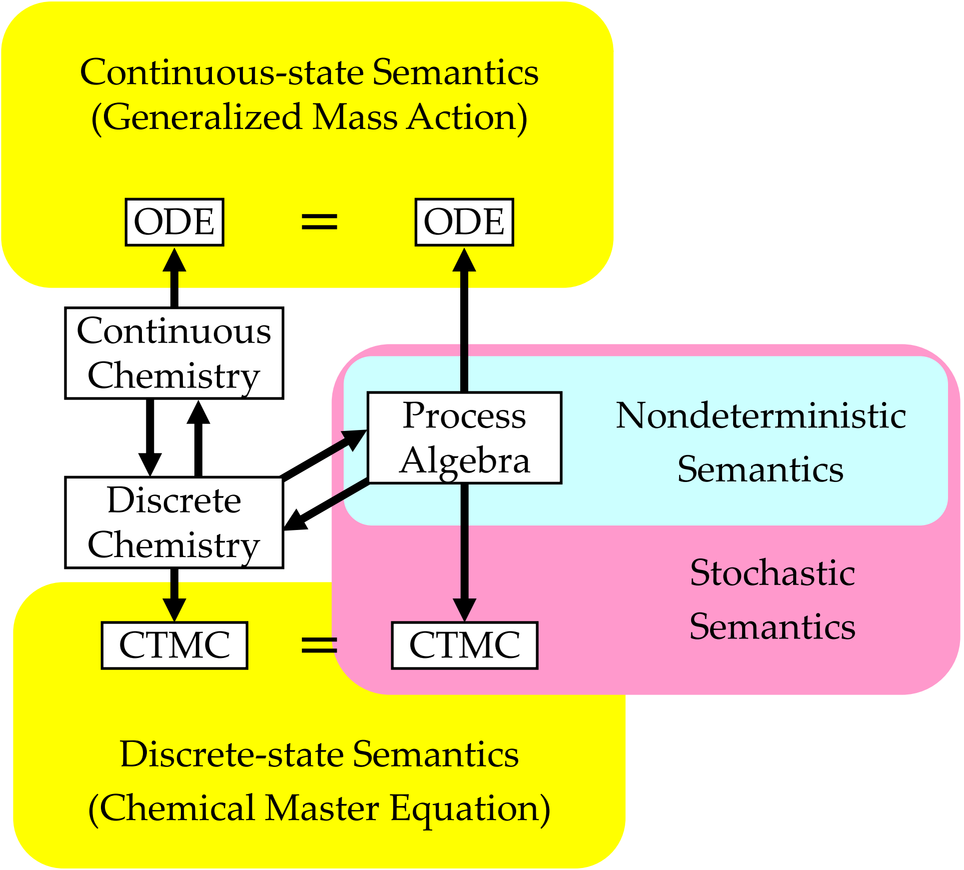

Semantics of Collective Behavior

The Two Semantic Sides of Chemistry


Continuous-state Semantics
(Generalized Mass Action)

ODE = ODE

Continuous Chemistry

Discrete Chemistry

Process Algebra

Nondeterministic Semantics

Stochastic Semantics

CTMC = CTMC

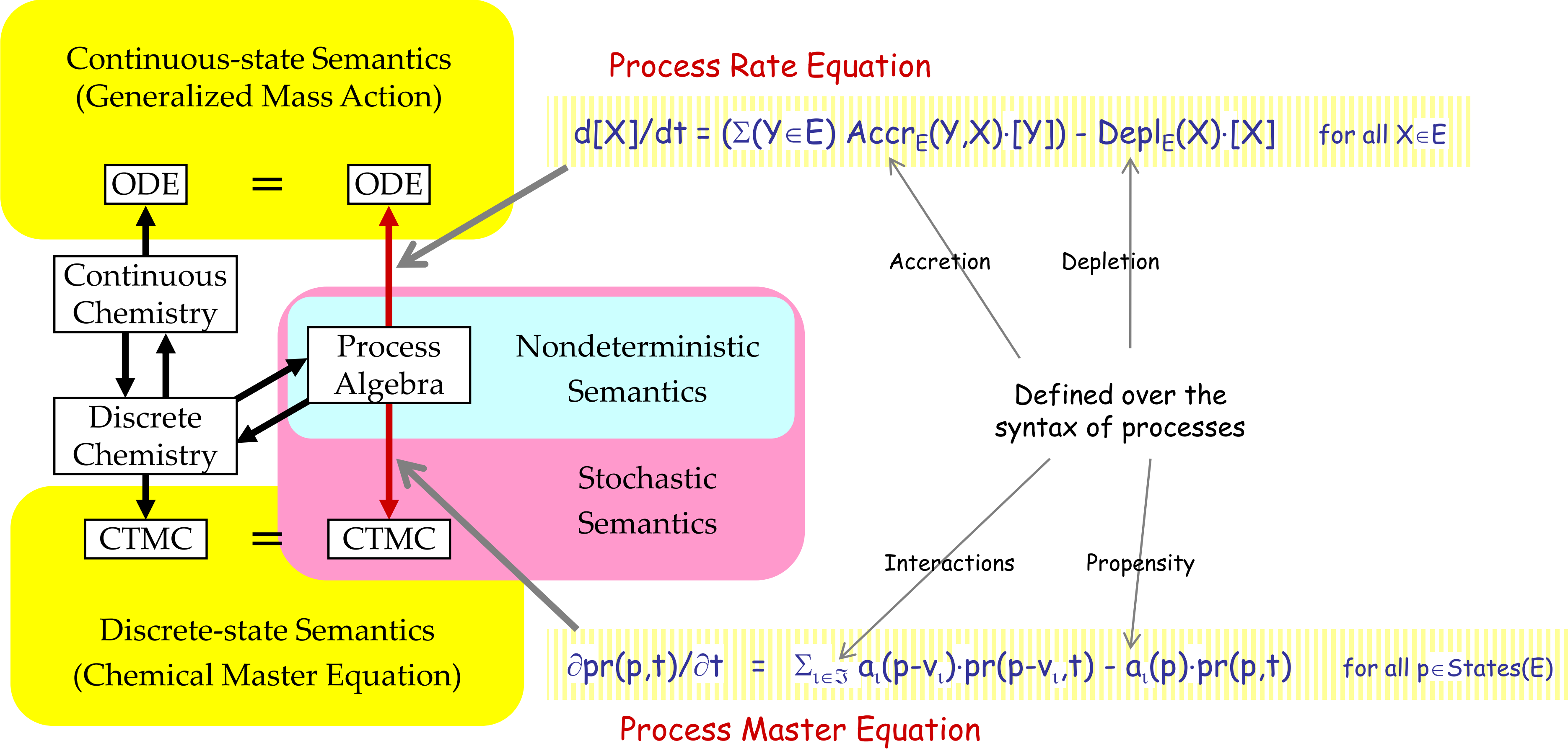
Discrete-state Semantics
(Chemical Master Equation)

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
(Generalized Mass Action)

ODE = ODE

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Process Algebra

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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

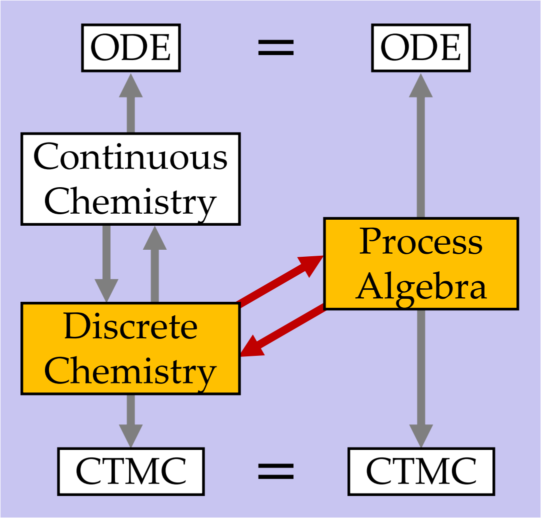
Interactions

Propensity

$\partial pr(p,t)/\partial t = \Sigma_{\iota \in \mathfrak{I}}\ a_\iota(p-v_\iota)\cdot pr(p-v_\iota,t) - a_\iota(p)\cdot pr(p,t)$ for all $p \in States(E)$

Process Master Equation

Stochastic Processes & Discrete Chemistry

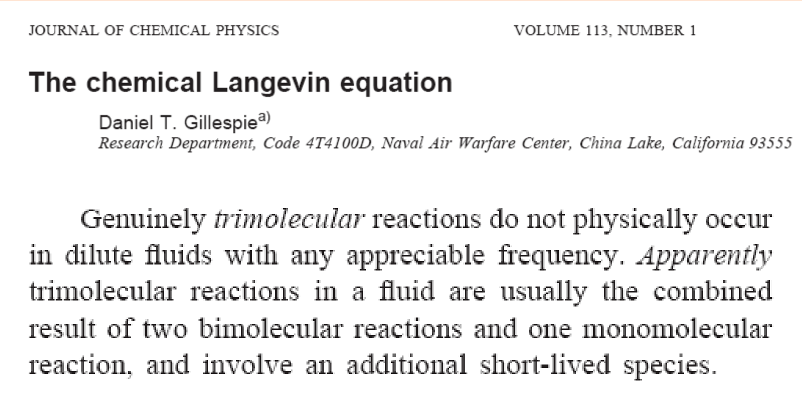


Chemical Reactions

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



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The chemical Langevin equation

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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!

Reactions have rates. Molecules *do not* have rates.

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)

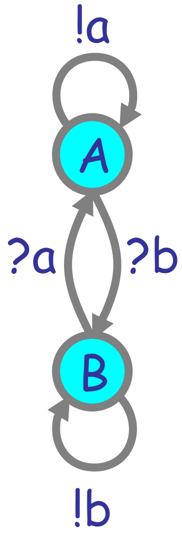
$E ::= 0 \;\vdots\; X{=}M, E$ Reagents
$M ::= 0 \;\vdots\; \pi;P \oplus M$ Molecules
$P ::= 0 \;\vdots\; X \mid P$ Solutions
$\pi ::= \tau_{(r)} \;\vdots\; ?a_{(r)} \;\vdots\; !a_{(r)}$ Actions (delay, input, output)
$CGF ::= E,P$ Reagents plus Initial Conditions

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

Interacting Automata
+ dynamic forking

(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.)

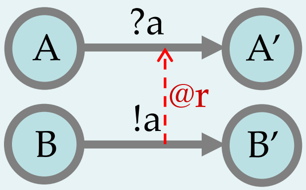
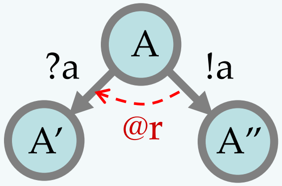
$\oplus$ is stochastic choice (vs. + for chemical reactions)
0 is the null solution ($P|0 = 0|P = P$)
and null molecule ($M\oplus 0 = 0\oplus M = M$)
Each X in E is a distinct *species*
Each name a is assigned a fixed rate r: $a_{(r)}$

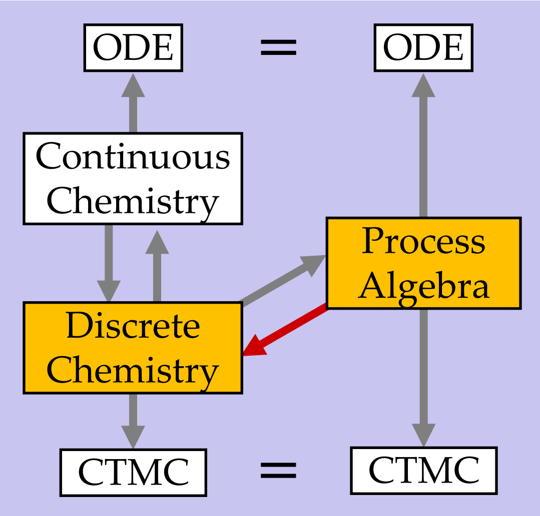


Ex: Interacting Automata
(= finite-control CGFs: they use "|" only in initial conditions):

$A = !a;A \oplus ?b;B$ Automaton in state A
$B = !b;B \oplus ?a;A$ Automaton in state B
$A|A|B|B$ Initial conditions: 2A and 2B

From Reagents to Reactions (by example)

Interacting Automata →	Discrete Chemistry
initial states A | A | … | A	initial quantities $\#A_0$
	$A \xrightarrow{r} A'$
	$A+B \xrightarrow{r} A'+B'$
	$A+A \xrightarrow{2r} A'+A''$



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

From Reagents to Reactions: 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 ⊕-summand of the molecule M associated with the X reagent of E

Chemical reactions for E,P:

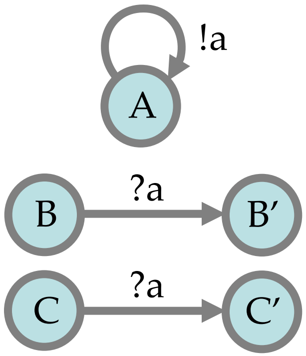
(N.B.: <...> are reaction tags to obtain multiplicity of reactions,
and P is P with all the | changed to +)

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

Initial conditions for P:

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

Entangled vs Detangled



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

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

(a@r)

A = !a;A

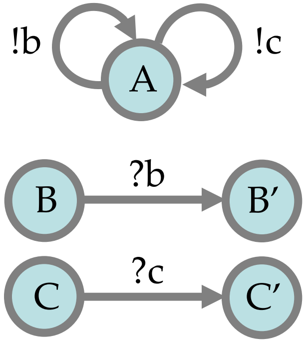
B = ?a;B′

C = ?a;C′

B′ = 0

C′ = 0

Two reactions on one channel



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

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

(b@r)

(c@r)

A = !b;A ⊕ !c;A

B = ?b;B′

C = ?c;C′

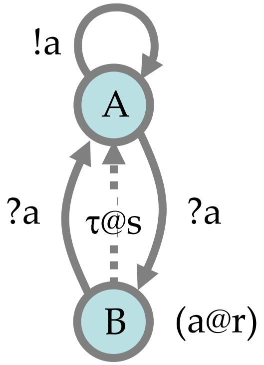
B′ = 0

C′ = 0

Two reactions on two separate channels

Detangled processes are in simple correspondence with chemistry.

Same Semantics



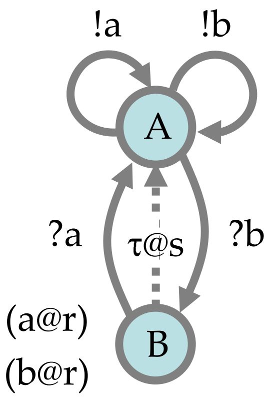
A = !a;A ⊕ ?a;B

B = ?a;A ⊕ $\tau_{(s)}$;A

$B \rightarrow^{s} A$

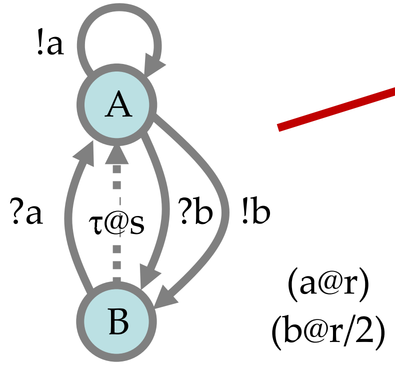
$A+B \rightarrow^{r} A+A$

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



A = !a;A ⊕ !b;A ⊕ ?b;B

B = ?a;A ⊕ $\tau_{(s)}$;A



A = !a;A ⊕ !b;B ⊕ ?b;B

B = ?a;A ⊕ $\tau_{(s)}$;A

$B \rightarrow^{s} A$

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

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

Different reactions,
but they induce the
same ODEs

From Reactions to Reagents (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: $F+F \rightarrow_{k_4} B$

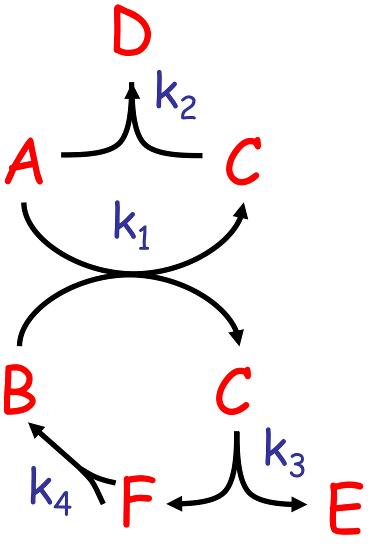
Interaction Matrix

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				$?;B$ $!;0$



1: Fill the matrix by columns:

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

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

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:

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

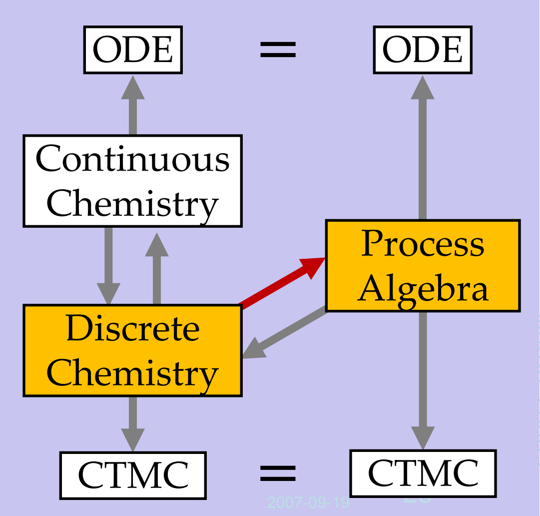
$B = !v_{1(k1)};0$

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

$D = 0$

$E = 0$

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



ODE = ODE

Continuous Chemistry

Discrete Chemistry

Process Algebra

CTMC = CTMC

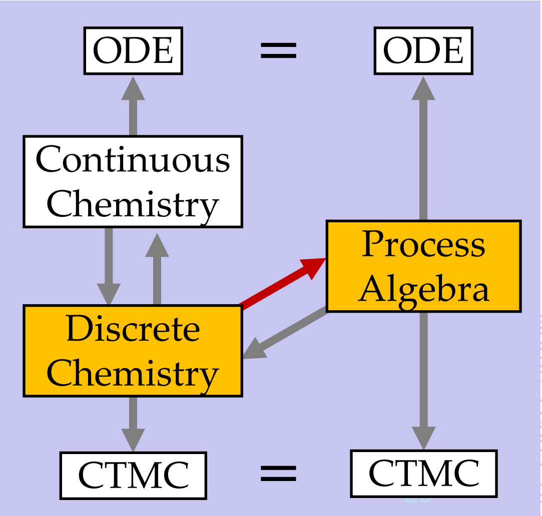
From Reactions to Reagents: Pi(*C*)

$v\colon\ X \xrightarrow{r} Y_1 + \ldots + Y_n + 0$ Unary Reaction

$v\colon\ X_1 + X_2 \xrightarrow{r} Y_1 + \ldots + Y_n + 0$ Binary Reaction

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

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



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)

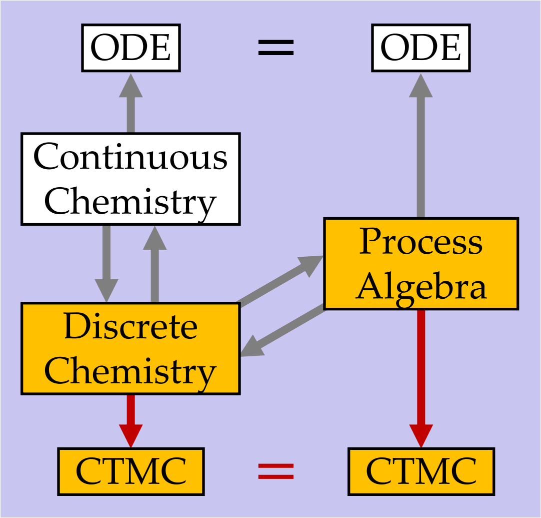
- Hence for any E, we have that Pi(Ch(E)) is detangled.
  - (E and Pi(Ch(E)) are “equivalent” CGFs, but that has to be shown later)

- 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


ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

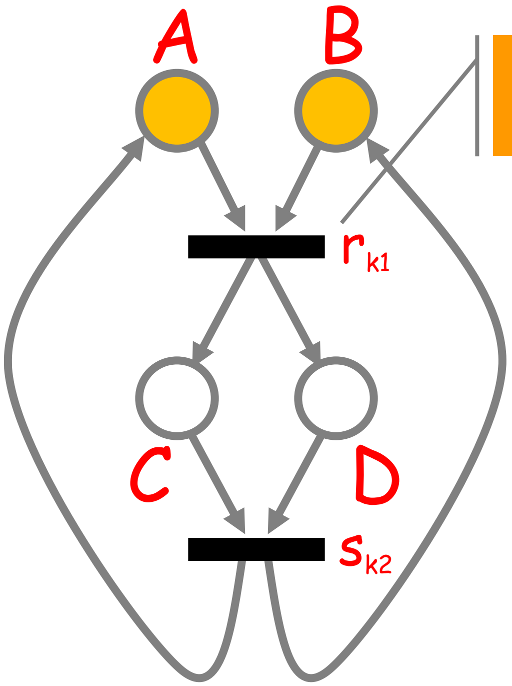
Chemistry vs. Automata

A process calculus (chemistry)

$r: A + B \rightarrow_{k1} C + D$

$s: C + D \rightarrow_{k2} A + B$

Does A become C or D?

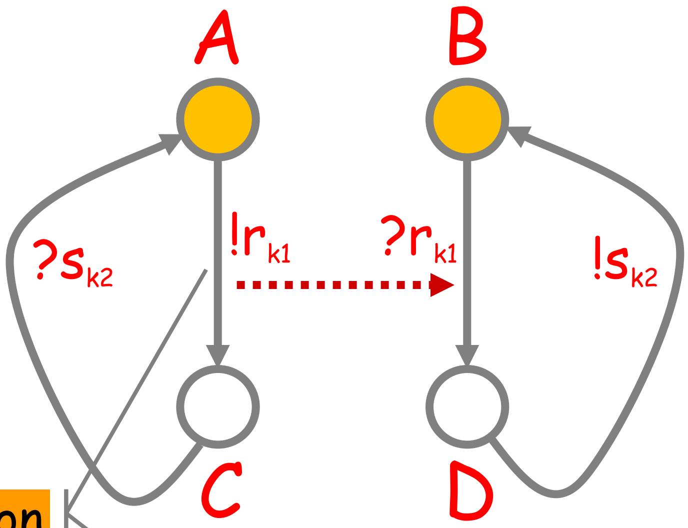


Reaction oriented

1 line per reaction

A Petri-Net-like representation. Precise and dynamic, but not modular, scalable, or maintainable.

A different process calculus (automata)



Interaction oriented

1 line per component

$A = !r_{k1}; C$

$C = ?s_{k2}; A$

$B = ?r_{k1}; D$

$D = !s_{k2}; B$

A becomes C not D!

The same "model"

Maps to a CTMC	Maps to a CTMC

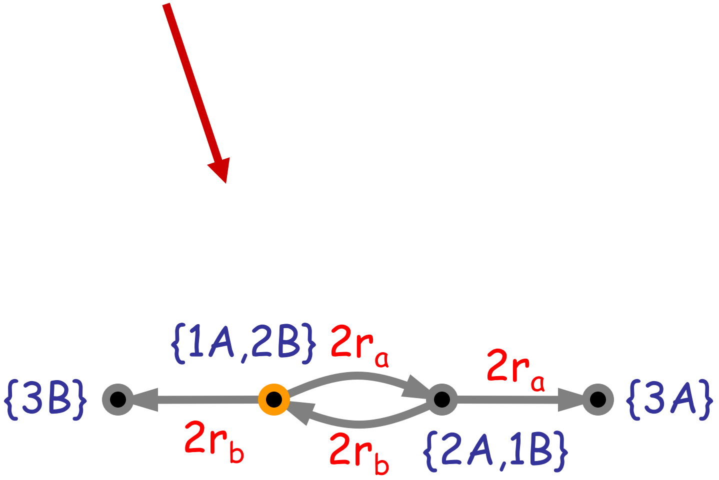
A compositional graphical representation (precise, dynamic *and* modular) and the corresponding calculus.

Discrete Semantics of Reactions

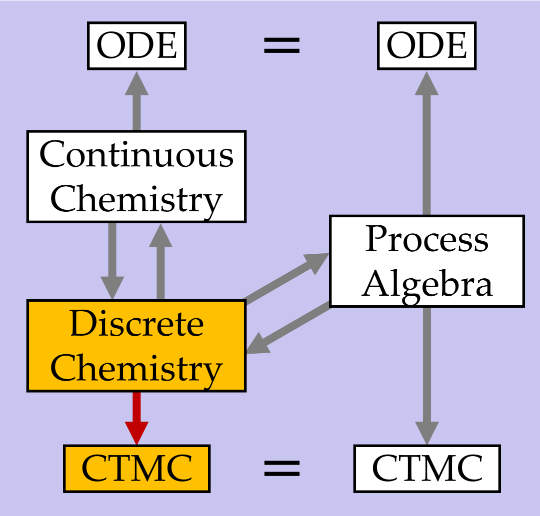
$A+B \to^{r} A+A$

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

$A+B+B$



CTMC



ODE = ODE

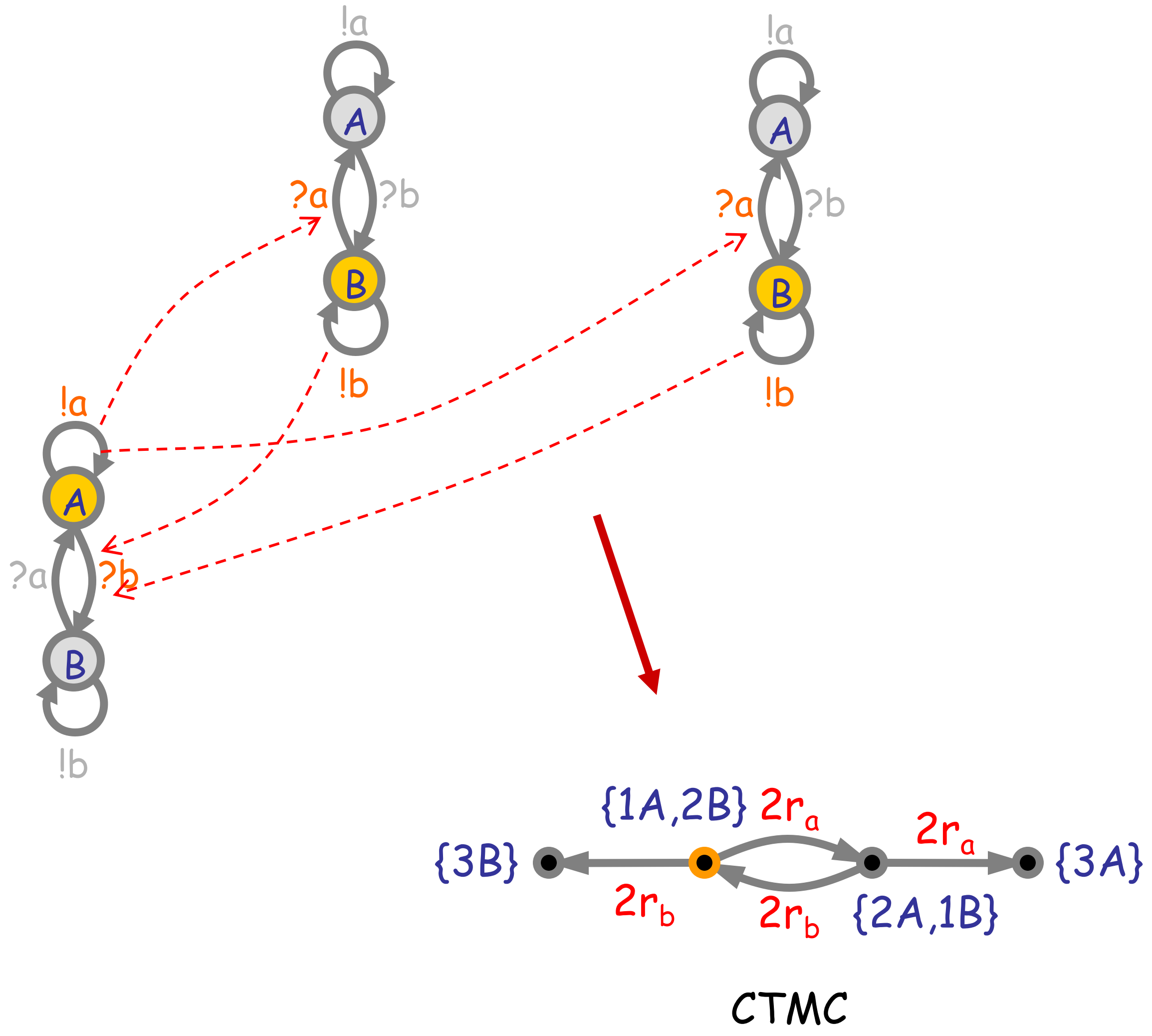
Continuous Chemistry

Process Algebra

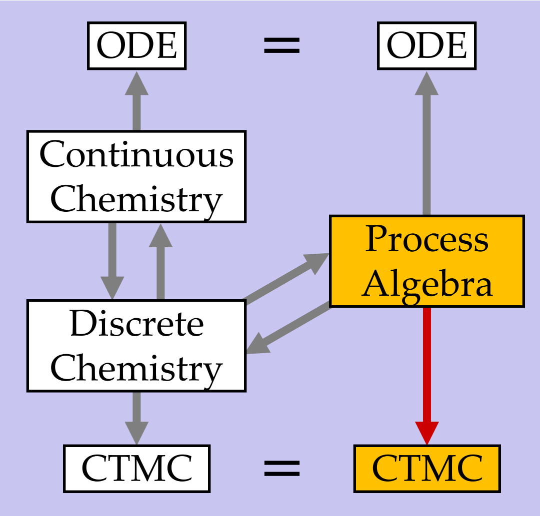
Discrete Chemistry

CTMC = CTMC

Discrete Semantics of Reagents

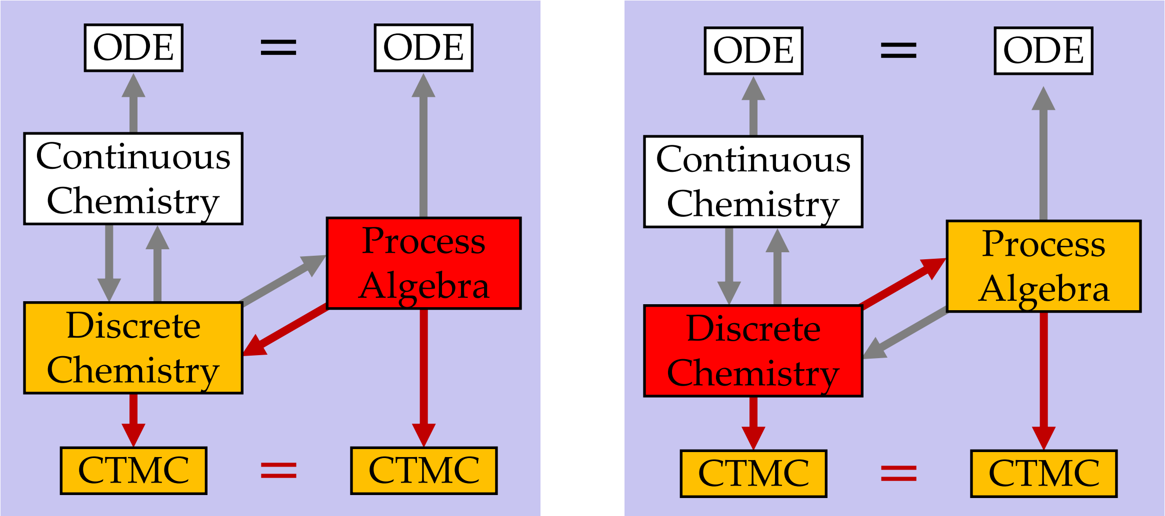


CTMC



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

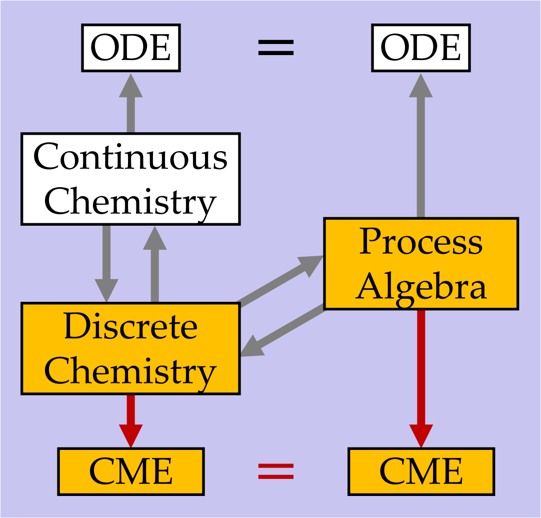
Process Algebra

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)).

Master Equation Semantics



Chemical Master Equation

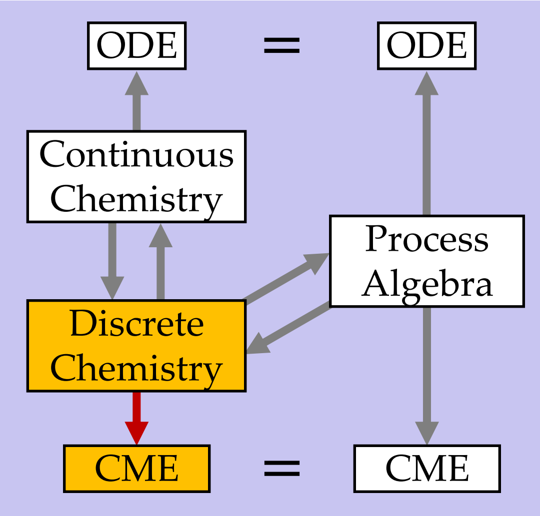
Chemical Master Equation for a chemical system *C*

$$\partial pr(\sigma,t)/\partial t \quad = \quad \Sigma_{\iota\in 1..M}\ a_\iota(\sigma-v_\iota)\cdot pr(\sigma-v_\iota,t) - a_\iota(\sigma)\cdot pr(\sigma,t) \qquad \text{for all } \sigma\in States(C)$$

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"



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CME = CME

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

$pr(\sigma,t) = Pr\{\chi(t)=\sigma\ |\chi(0)=\sigma_0\}$ is the conditional probability of the system χ being in state σ at time t given that it was in state σ_0 at time 0.

There are 1..M chemical reactions.

v_ι is the state change caused by reaction ι (as a difference)

$a_\iota(\sigma) = c_\iota\cdot h_\iota(\rho)$ is the *propensity* of reaction ι in state σ, defined by a base reaction rate and a state-dependent count of the distinct combinations of reagents. (It depends on the kind of reactions.)

Process Algebra Master Equation

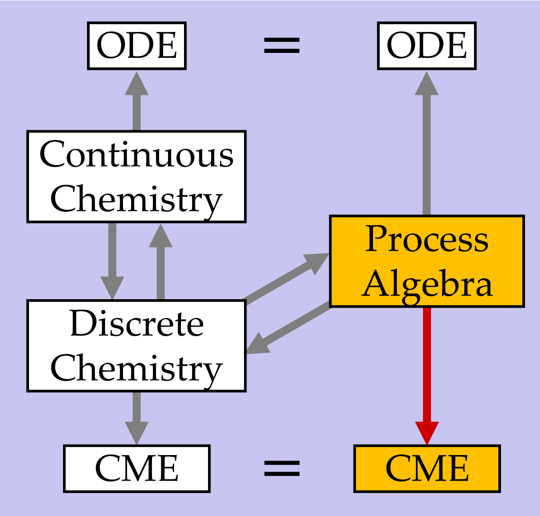
Process Master Equation for a system of reagents E

$$\partial pr(\rho,t)/\partial t \;=\; \Sigma_{\iota\in\Im}\; a_\iota(\rho-v_\iota)\cdot pr(\rho-v_\iota,t) - a_\iota(\rho)\cdot pr(\rho,t) \qquad \text{for all } \rho\in States(E)$$

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"



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CME = CME

$\rho\in$ *species*(E)$\to$Nat is a *state* of the system

$pr(\rho,t) = Pr\{\chi(t)=\rho\ |\chi(0)=\rho_0\}$ is the conditional probability of the system χ being in state ρ at time t given that it was in state ρ_0 at time 0.

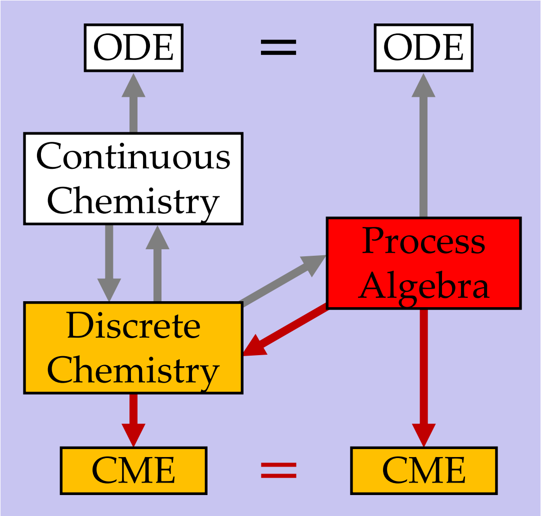
$\Im$ is the finite set of *possible interactions* arising from a set of reagents E. (All τ and all ?a/!a pairs in E)

v_ι is the state change caused by interaction ι (as a difference)

$a_\iota(\rho) = r_\iota\cdot h_\iota(\rho)$ is the *propensity* of interaction ι in state ρ, 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.)

Equivalence of Master Equations

- Def: ≈ is equivalence of derived Master Equations (they are identical).
- Thm: E ≈ Ch(E)
- Thm: C ≈ Pi(C)



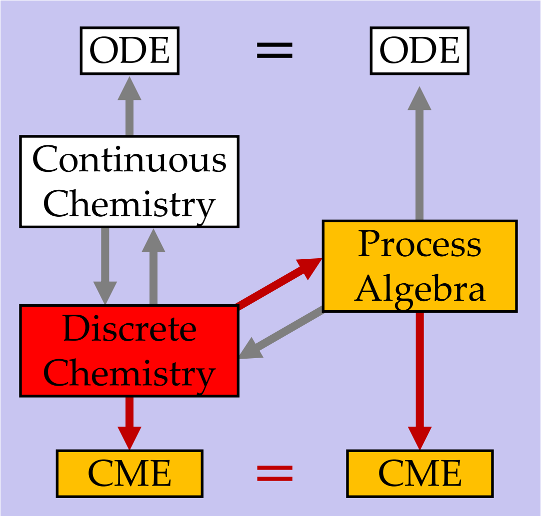
ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CME = CME



ODE = ODE

Continuous Chemistry

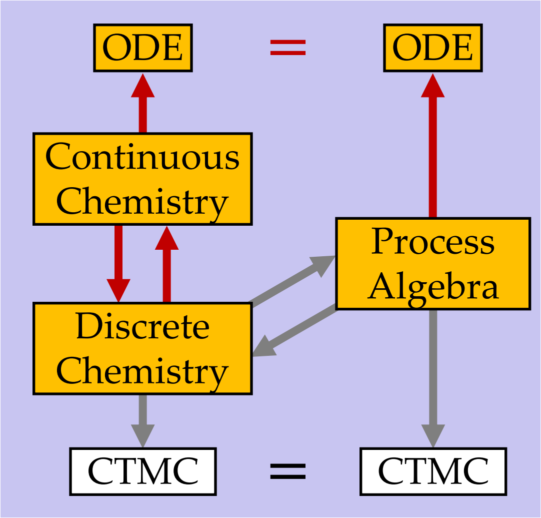
Process Algebra

Discrete Chemistry

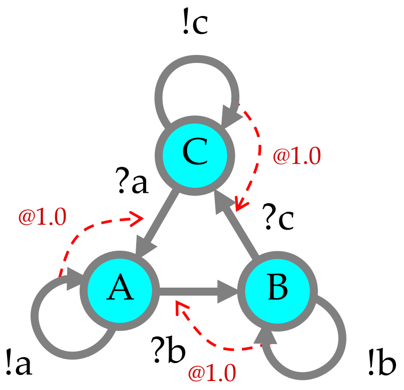
CME = CME

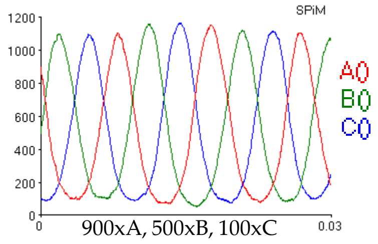
Continuous-State Semantics

(short version)



From Processes to ODEs via Chemistry!





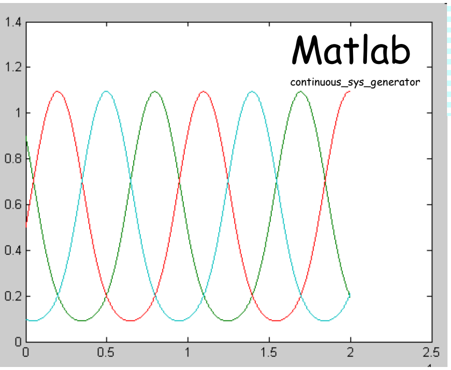
900xA, 500xB, 100xC

```
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())
```

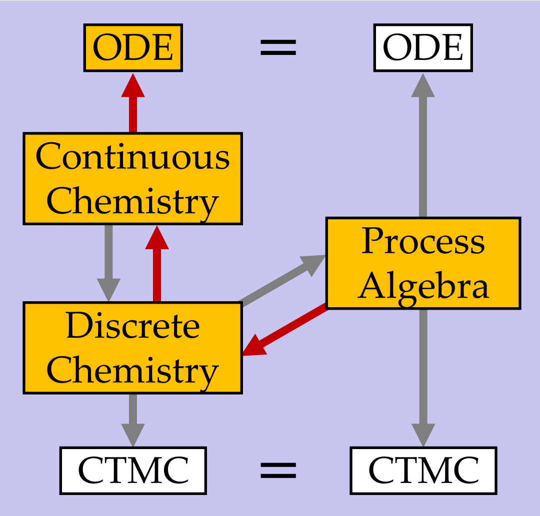
$$A = !a_{(s)};A \oplus ?b_{(s)};B$$
$$B = !b_{(s)};B \oplus ?c_{(s)};C$$
$$C = !c_{(s)};C \oplus ?a_{(s)};A$$

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

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



```
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

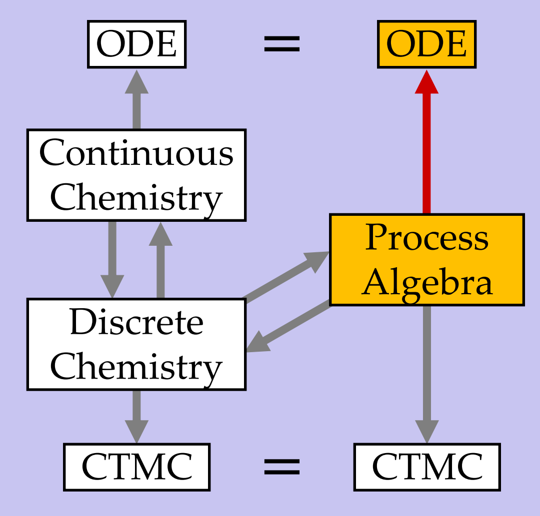
Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

Processes Rate Equation



Process Rate Equation for Reagents E in volume γ

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

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"

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

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

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

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

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

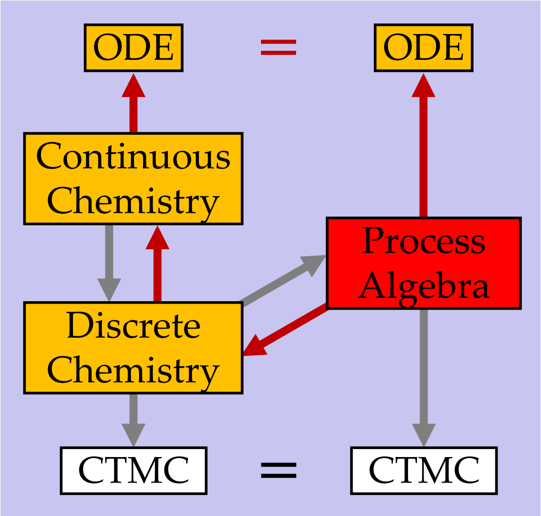
$X = ?a_{(r)};0 \oplus !a_{(r)};0 \quad \rightarrow \quad d[X]/dt = -2r\gamma[X]^2$

Continuous State Equivalence

- Def: ≈ is equivalence of polynomials over the field of reals.

- Thm: E ≈ Cont(Ch(E))

- Thm: Cont(C) ≈ Pi(C)



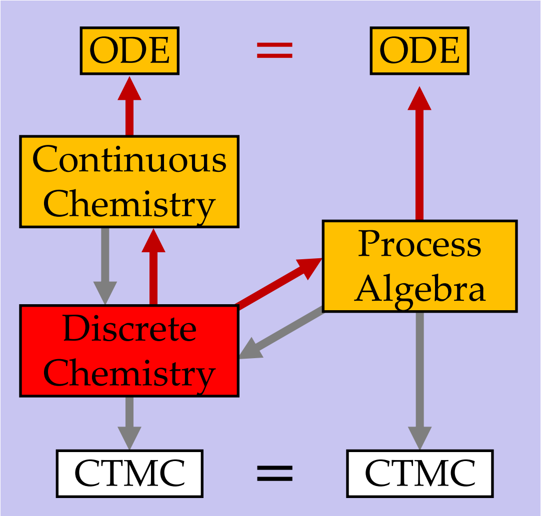
ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC



ODE = ODE

Continuous Chemistry

Process Algebra

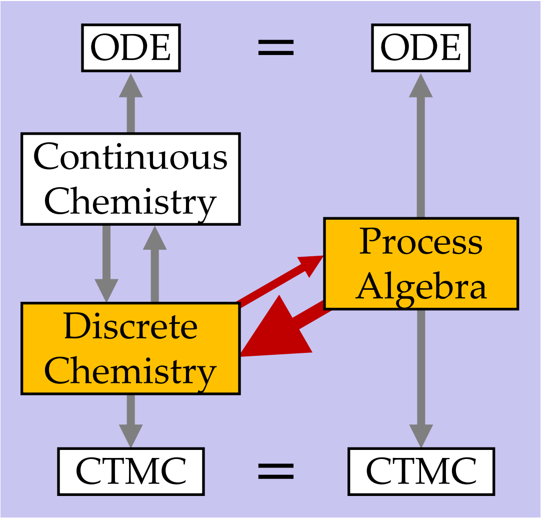
Discrete Chemistry

CTMC = CTMC

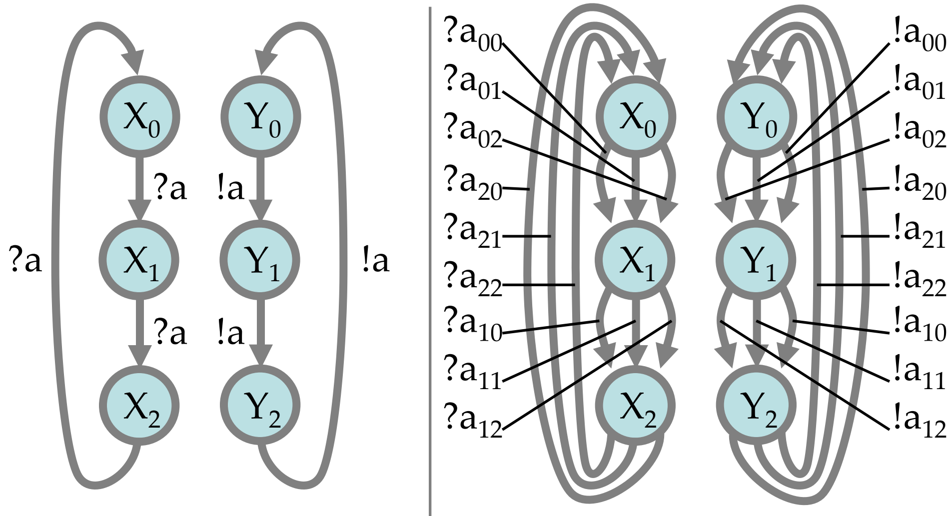
- For each E there is an E′ ≈ E that is detangled (E′ = Pi(Ch(E)))

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

Model Compactness



Entangled vs detangled



E_3 Detangle(E_3)

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

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

$Ch(E_3)$

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

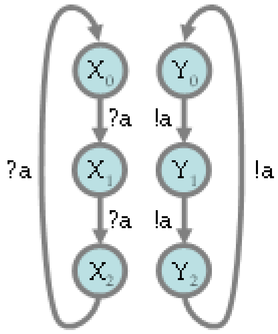
StoichiometricMatrix($Ch(E_3)$)

	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

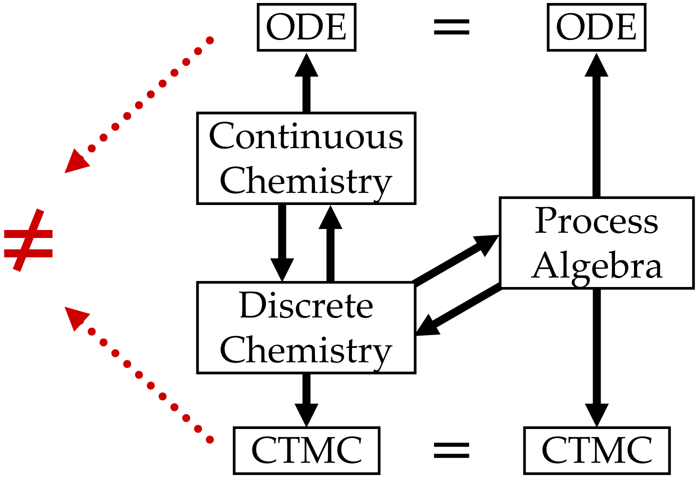
ODE(E_3)

$d[X_0]/dt = -r[X_0][Y_0] - r[X_0][Y_1] - r[X_0][Y_2] + r[X_2][Y_0] + r[X_2][Y_1] + r[X_2][Y_2]$
$d[X_1]/dt = -r[X_1][Y_0] - r[X_1][Y_1] - r[X_1][Y_2] + r[X_0][Y_0] + r[X_0][Y_1] + r[X_0][Y_2]$
$d[X_2]/dt = -r[X2_1][Y_0] - r[X_2][Y_1] - r[X_2][Y_2] + r[X_1][Y_0] + r[X_1][Y_1] + r[X_1][Y_2]$
$d[Y_0]/dt = -r[X_0][Y_0] - r[X_1][Y_0] - r[X_2][Y_0] + r[X_0][Y_2] + r[X_1][Y_2] + r[X_2][Y_2]$
$d[Y_1]/dt = -r[X_0][Y_1] - r[X_1][Y_1] - r[X_2][Y_1] + r[X_0][Y_0] + r[X_1][Y_0] + r[X_2][Y_0]$
$d[Y_2]/dt = -r[X_0][Y_2] - r[X_1][Y_2] - r[X_2][Y_2] + r[X_0][Y_1] + r[X_1][Y_1] + r[X_2][Y_1]$

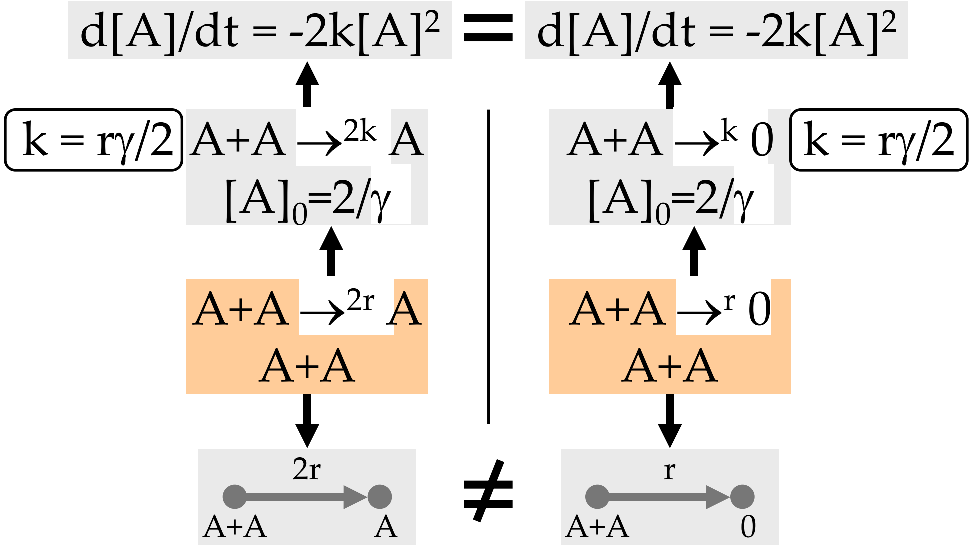
=



GMA ≠ CME


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

$A+A \xrightarrow{2r} A$ =? $A+A \xrightarrow{r} 0$



$d[A]/dt = -2k[A]^2$ = $d[A]/dt = -2k[A]^2$

$\boxed{k = r\gamma/2}$ $A+A \xrightarrow{2k} A$, $[A]_0=2/\gamma$

$A+A \xrightarrow{k} 0$, $[A]_0=2/\gamma$ $\boxed{k = r\gamma/2}$

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

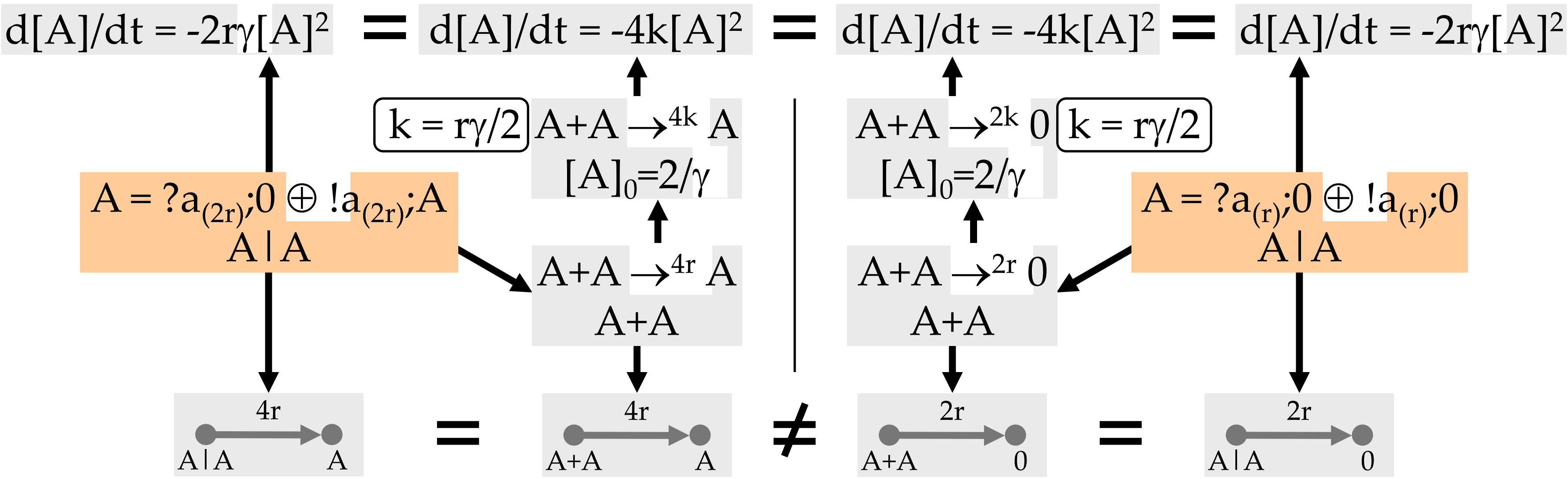
A+A

$A+A \xrightarrow{r} 0$

A+A

≠

... as Automata



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

$\boxed{k = r\gamma/2}$ $A+A \to^{4k} A$

$[A]_0=2/\gamma$

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

$A | A$

$A+A \to^{4r} A$

$A+A$

$A+A \to^{2k} 0$ $\boxed{k = r\gamma/2}$

$[A]_0=2/\gamma$

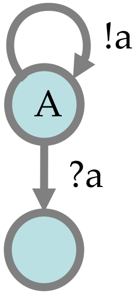
$A = ?a_{(r)};0 \oplus !a_{(r)};0$

$A | A$

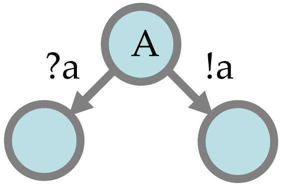
$A+A \to^{2r} 0$

$A+A$

$A|A \xrightarrow{4r} A$ = $A+A \xrightarrow{4r} A$ ≠ $A+A \xrightarrow{2r} 0$ = $A|A \xrightarrow{2r} 0$

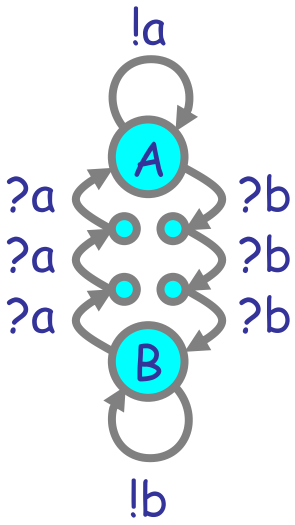


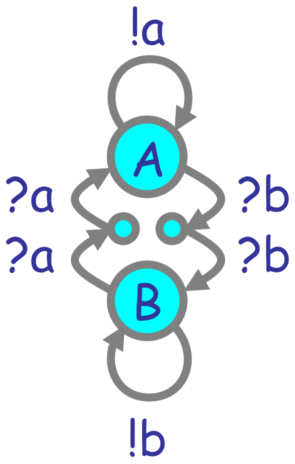
(a@2r)

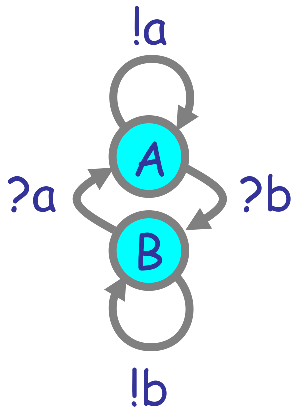


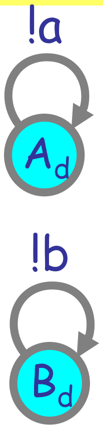
(a@r)

Continuous vs. Discrete Groupies

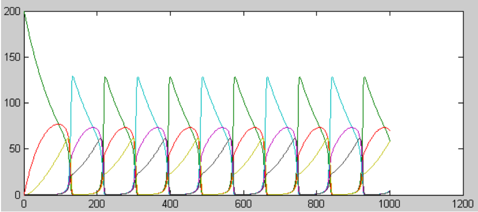


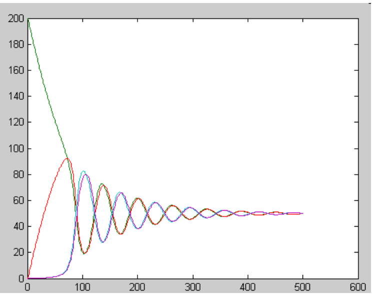


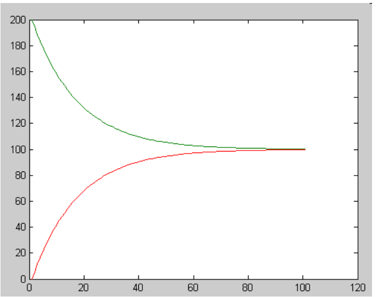




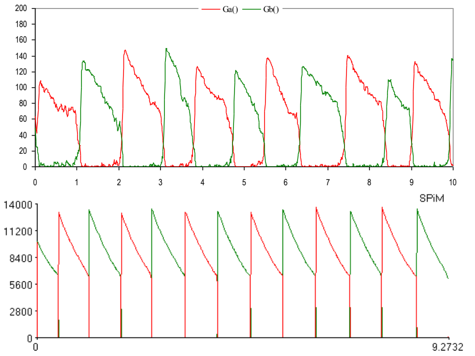
All with
1x Doping

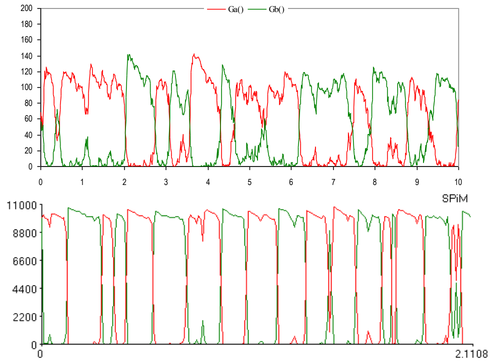


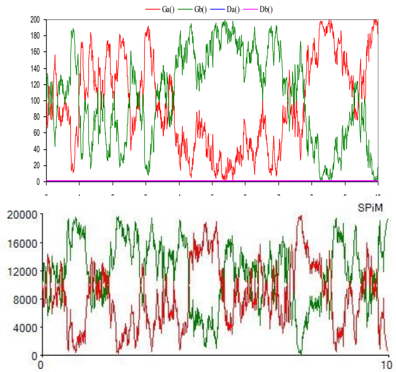




Matlab
continuous_sys_generator







SPiM

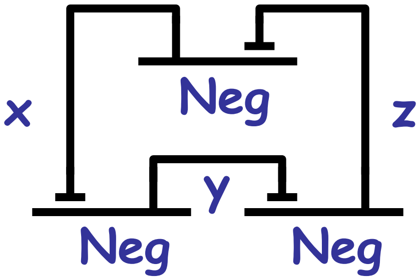
x200

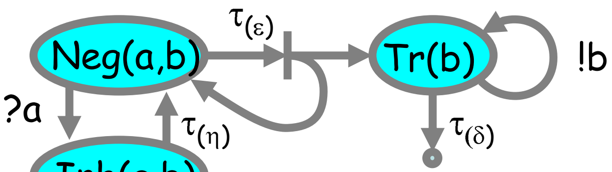
x20000

And Yet It Moves

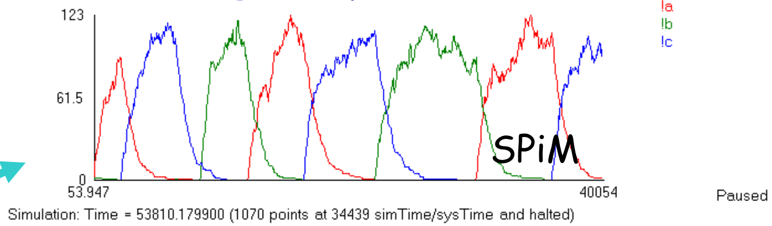
R.Blossey, L.Cardelli, A.Phillips: **Compositionality, Stochasticity and Cooperativity in Dynamic Models of Gene Regulation** (HFSP Journal)

The Repressilator





A fine stochastic oscillator over a wide range of parameters.



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

```
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))
```

Parametric representation

$Neg(a,b) = ?a;\ Inh(a,b) \oplus \tau_{\varepsilon};\ (Tr(b) \mid Neg(a,b))$

$Inh(a,b) = \tau_{\eta};\ Neg(a,b)$

$Tr(b) = !b;\ Tr(b) \oplus \tau_{\gamma};\ 0$

$Neg(x_{(r)},y_{(r)}) \mid Neg(y_{(r)},z_{(r)}) \mid Neg(z_{(r)},x_{(r)})$

$Neg/x,y \to^{\varepsilon} Tr/y + Neg/x,y$

$Neg/y,z \to^{\varepsilon} Tr/z + Neg/y,z$

$Neg/z,x \to^{\varepsilon} Tr/x + Neg/z,x$

$Tr/x + Neg/x,y \to^{r} Tr/x + Inh/x,y$

$Tr/y + Neg/y,z \to^{r} Tr/y + Inh/y,z$

$Tr/z + Neg/z,x \to^{r} Tr/z + Inh/z,x$

$Inh/x,y \to^{\eta} Neg/x,y$

$Inh/y,z \to^{\eta} Neg/y,z$

$Inh/z,x \to^{\eta} Neg/z,x$

$Tr/x \to^{\gamma} 0$

$Tr/y \to^{\gamma} 0$

$Tr/z \to^{\gamma} 0$

$Neg/x,y + Neg/y,z + Neg/z,x$

$d[Neg/x,y]/dt = -r[Tr/x][Neg/x,y] + \eta[Inh/x,y]$

$d[Neg/y,z]/dt = -r[Tr/y][Neg/y,z] + \eta[Inh/y,z]$

$d[Neg/z,x]/dt = -r[Tr/z][Neg/z,x] + \eta[Inh/z,x]$

$d[Inh/x,y]/dt = r[Tr/x][Neg/x,y] - \eta[Inh/x,y]$

$d[Inh/y,z]/dt = r[Tr/y][Neg/y,z] - \eta[Inh/y,z]$

$d[Inh/z,x]/dt = r[Tr/z][Neg/z,x] - \eta[Inh/z,x]$

$d[Tr/x]/dt = \varepsilon[Neg/z,x] - \gamma[Tr/x]$

$d[Tr/y]/dt = \varepsilon[Neg/x,y] - \gamma[Tr/y]$

$d[Tr/z]/dt = \varepsilon[Neg/y,z] - \gamma[Tr/z]$

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

$d[Neg/x,y]/dt = \eta N - (\eta + r[Tr/x])[Neg/x,y]$

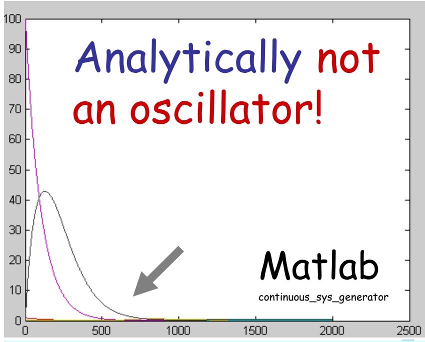
$d[Neg/y,z]/dt = \eta N - (\eta + r[Tr/y])[Neg/y,z]$

$d[Neg/z,x]/dt = \eta N - (\eta + r[Tr/z])[Neg/z,x]$

$d[Tr/x]/dt = \varepsilon[Neg/z,x] - \gamma[Tr/x]$

$d[Tr/y]/dt = \varepsilon[Neg/x,y] - \gamma[Tr/y]$

$d[Tr/z]/dt = \varepsilon[Neg/y,z] - \gamma[Tr/z]$



Analytically not an oscillator!

interval/step [0:10:20000]   N=1, r=1.0, ε=0.1, η=0.001, γ=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

Conclusions

Conclusions

- Compositional models
  - Accurate (at the "appropriate" abstraction level).
  - Manageable (so we can scale them up by composition).
  - Executable (stochastic simulation).

- Analysis techniques
  - Mathematical techniques: Markov theory, Chemical Master Equation, and Rate Equation
  - Computing techniques: Abstraction and Refinement, Model Checking, Causality Analysis.

- Many lines of extensions
  - Parametric processes for model factorization
  - *Poly*automata for ***Bio***-Chemistry: complexation and polymerization
  - Ultimately, rich process-algebra based modeling languages.

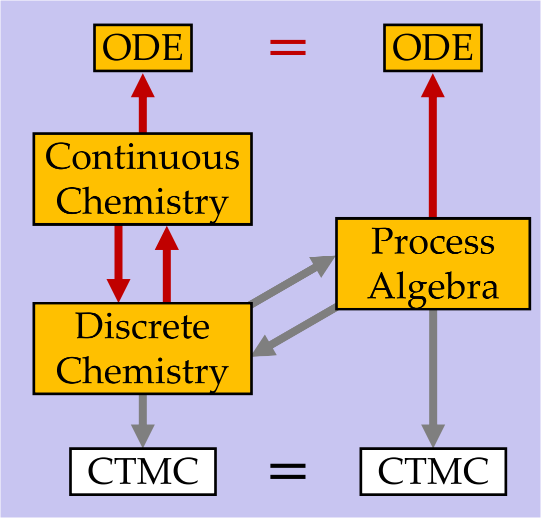
- Quantitative techniques
  - Important in the "real sciences".

http://LucaCardelli.name

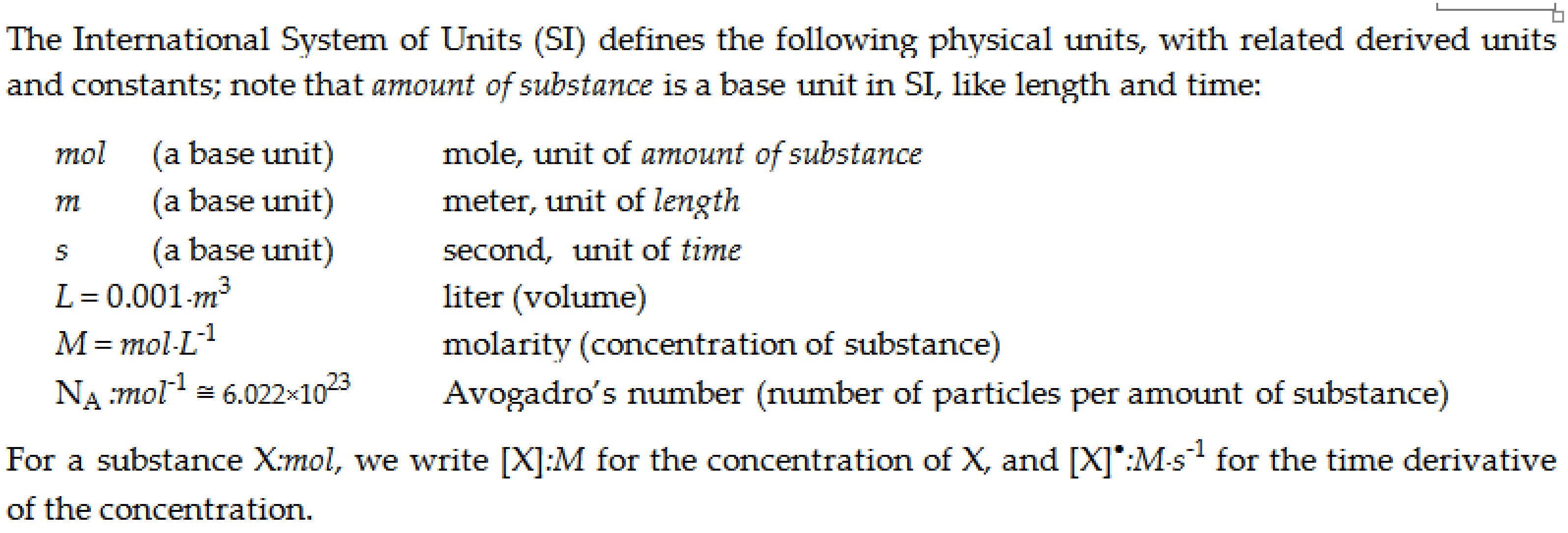
Q?

Continuous-State Semantics

(long version)



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 $M \cdot s^{-1}$).

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

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

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

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

The Gillespie$^{(?)}$ Conversion

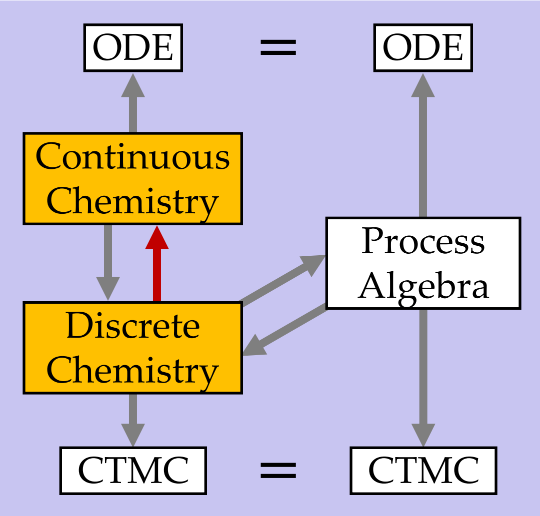
Discrete Chemistry	Continuous Chemistry	$\gamma = N_A V$	$:M^{-1}$
initial quantities $\#A_0$	initial concentrations $[A]_0$	with $[A]_0 = \#A_0/\gamma$	
$A \dashrightarrow^{r} A'$	$A \rightarrow^{k} A'$	with $k = r$	$:s^{-1}$
$A+B \dashrightarrow^{r} A'+B'$	$A+B \rightarrow^{k} A'+B'$	with $k = r\gamma$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

V = interaction volume

N_A = Avogadro's number

Think $\gamma = 1$

i.e. $V = 1/N_A$



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

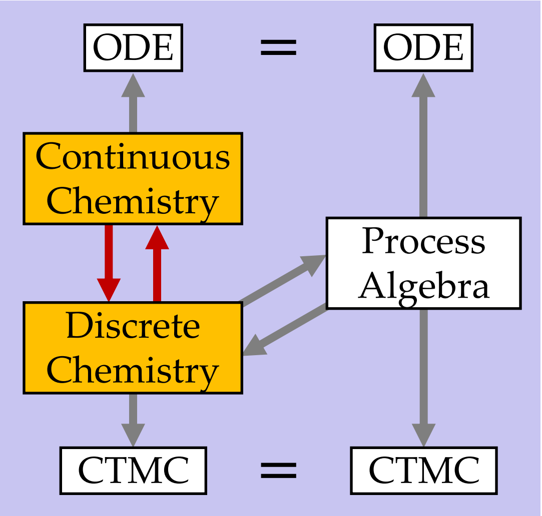
CTMC = CTMC

$Cont_\gamma$ and $Disc_\gamma$

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 γ 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 $\#X_0 = \lceil\gamma[X]_0\rceil$	$[X]_0{:}M$	$X_0{:}mol$



From Reactions to ODEs

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

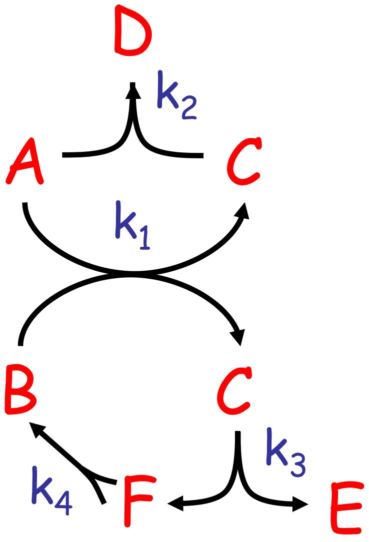
Stoichiometric Matrix

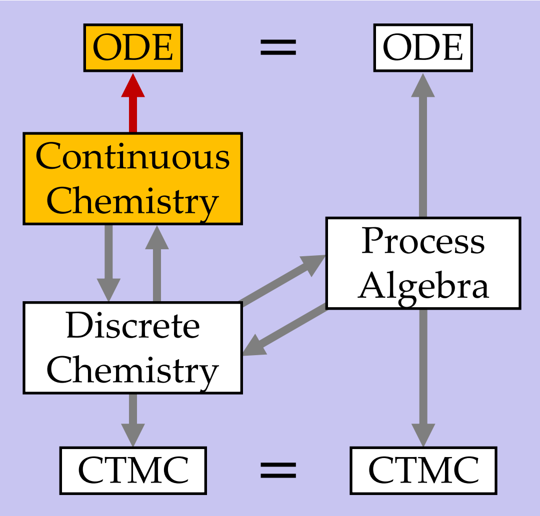
reactions

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




ODE = ODE

Continuous Chemistry

Discrete Chemistry

Process Algebra

CTMC = CTMC

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

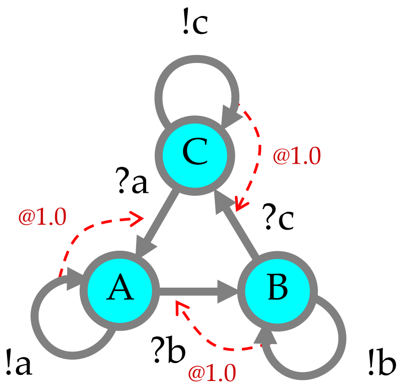
E.g. $d[A]/dt =$
$-k_1[A][B] - k_2[A][C]$

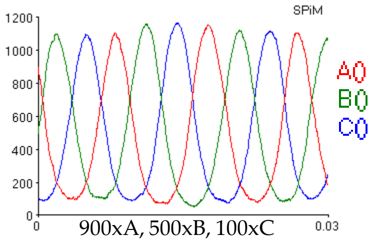
Set a rate law for each reaction
(Degradation/Hetero/Homeo)

	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!



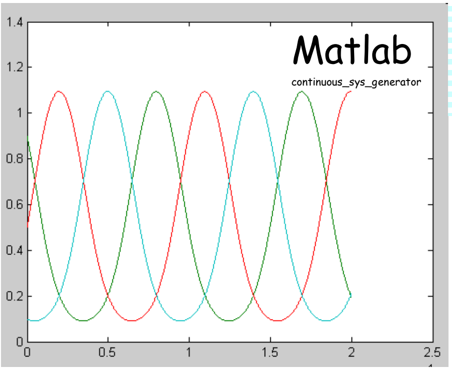


```
directive sample 0.03 1000
directive plot A(); B(); C()

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())
```

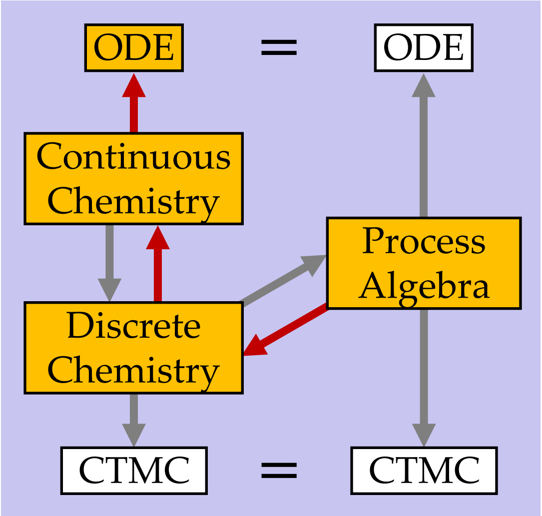
$$A = !a_{(s)};A \oplus ?b_{(s)};B$$
$$B = !b_{(s)};B \oplus ?c_{(s)};C$$
$$C = !c_{(s)};C \oplus ?a_{(s)};A$$

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

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



```
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

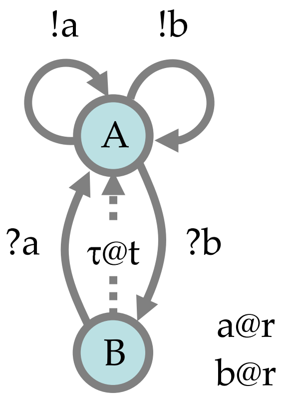
Continuous Chemistry

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)

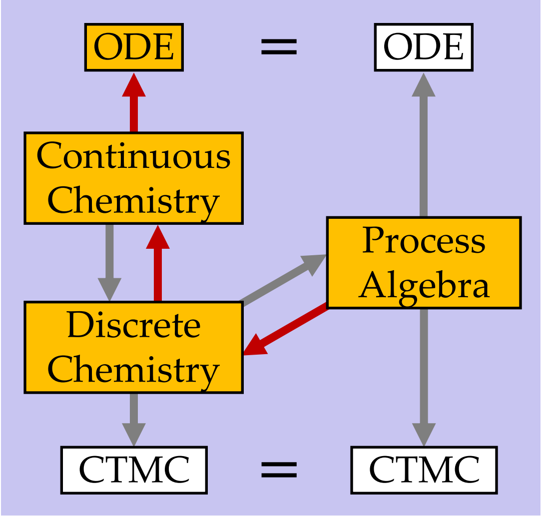
$B \xrightarrow{s} A$

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

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

(continuous reactions)

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


ODE = ODE

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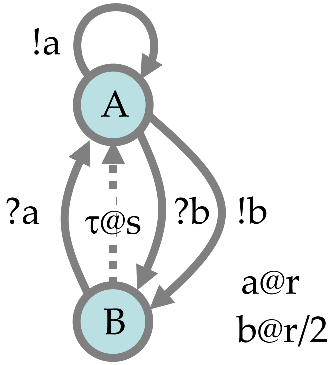
Different chemistry but same ODEs, hence equivalent automata



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

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

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

(discrete reactions)

$B \xrightarrow{s} A$

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

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

(continuous reactions)

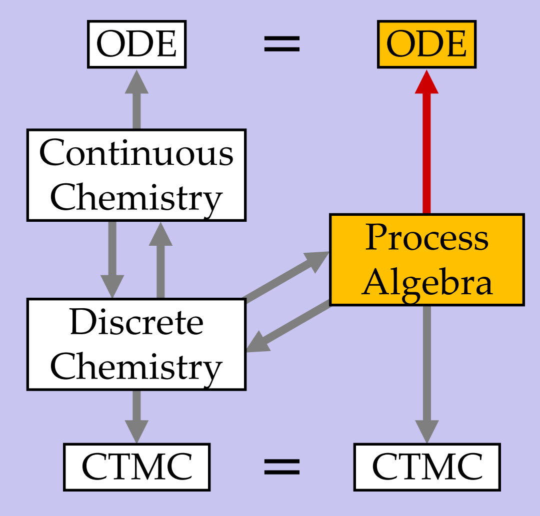
$$d[A]/dt = t[B] + r\gamma[A][B] - r\gamma[A]^2$$
$$d[B]/dt = -t[B] - r\gamma[A][B] + r\gamma[A]^2$$

Processes Rate Equation

Process Rate Equation for Reagents E in volume γ

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

for all $X\in E$



ODE = ODE

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"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"

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

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

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

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

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

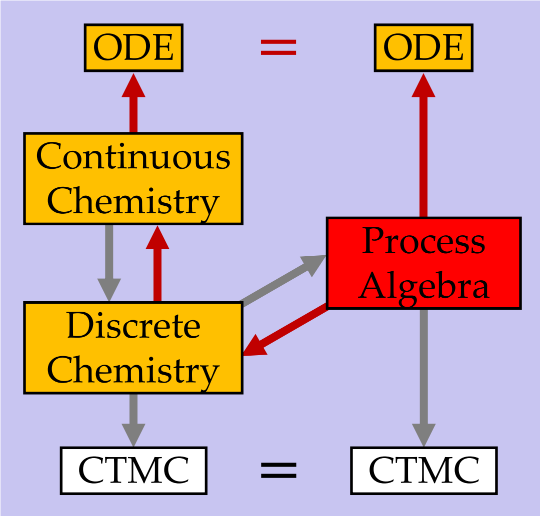
$X = ?a_{(r)};0 \quad\rightarrow\quad d[X]/dt = -2r\gamma[X]^2$
$\quad \oplus\ !a_{(r)};0$

Continuous State Equivalence

- Def: ≈ is equivalence of polynomials over the field of reals.

- Thm: E ≈ Cont(Ch(E))

- Thm: Cont(C) ≈ Pi(C)



ODE = ODE

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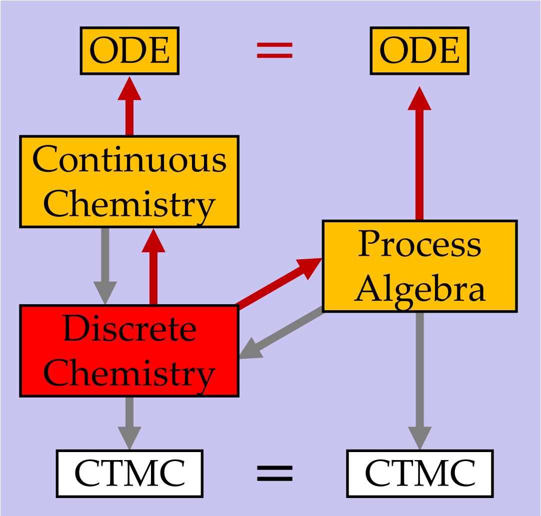

ODE = ODE

Continuous Chemistry

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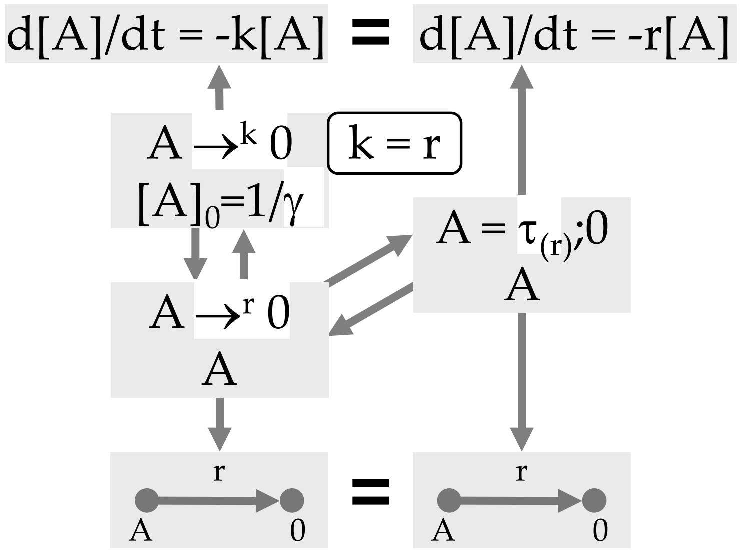
- For each E there is an E' ≈ E that is detangled (E' = Pi(Ch(E)))

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

Basic Examples: Unary Reactions



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

$A \rightarrow^{k} 0$

$[A]_0 = 1/\gamma$

$\boxed{k = r}$

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

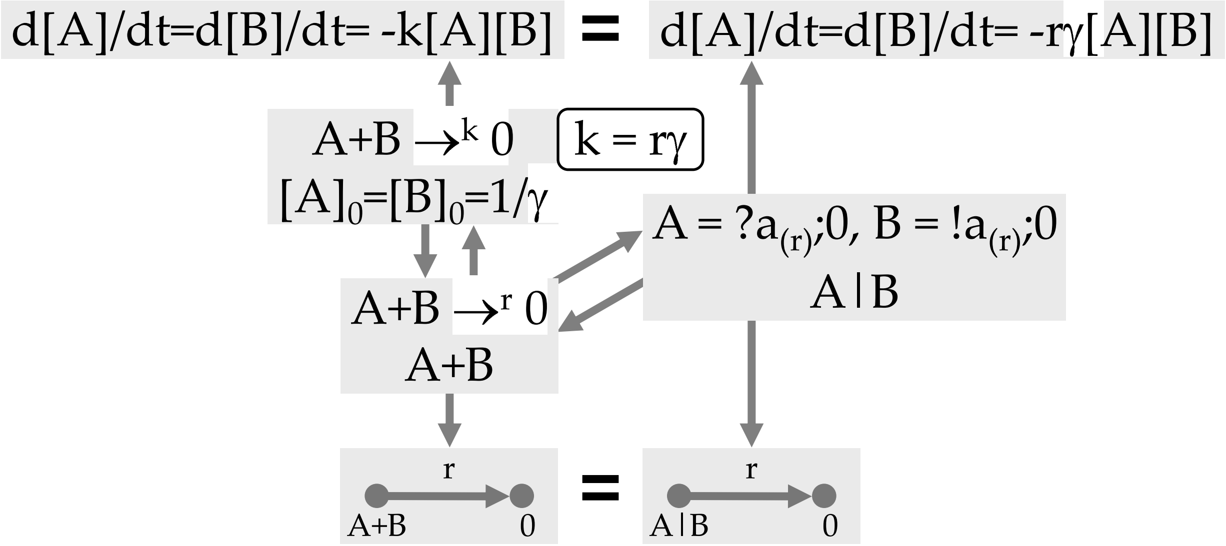
A

$A \rightarrow^{r} 0$

A

○·······▸∘ Unary Reaction

Basic Examples: Hetero Reactions



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

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

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

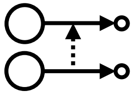
$\boxed{k = r\gamma}$

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

$A|B$

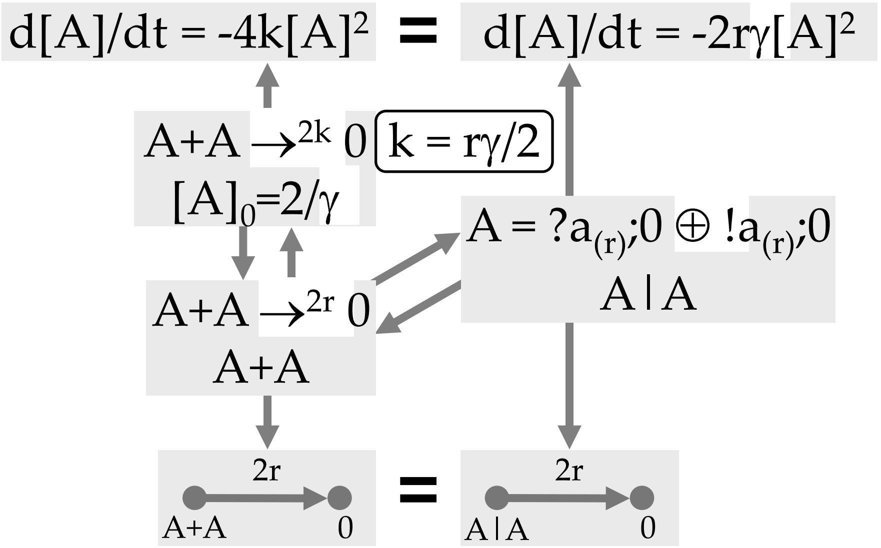
$A+B \rightarrow^{r} 0$

$A+B$



Hetero Reaction

Basic Examples: Homeo Reactions



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

$A+A \xrightarrow{2k} 0$

$[A]_0=2/\gamma$

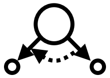
$\boxed{k = r\gamma/2}$

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

$A|A$

$A+A \xrightarrow{2r} 0$

$A+A$

 Homeo Reaction