Molecules as Automata

Representing Biochemical Systems as Collectives of Interacting Automata

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Dagstuhl 2009-02-24

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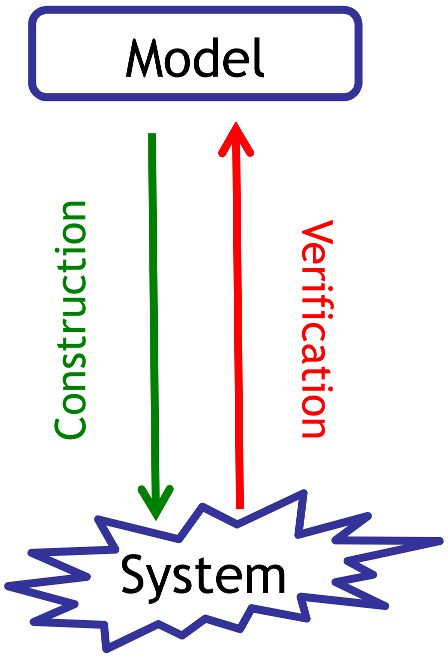
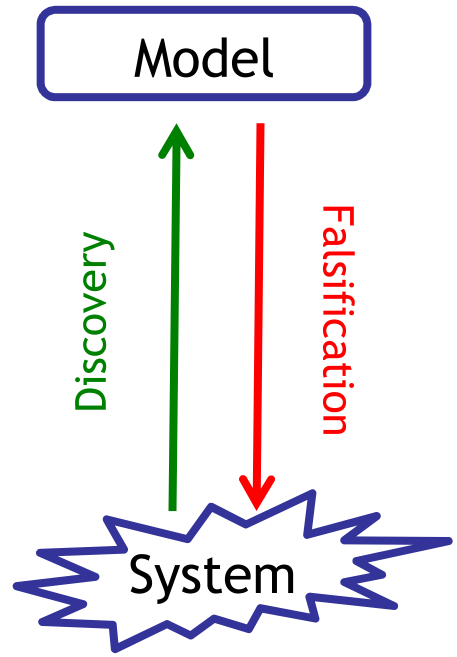
Scientific Method vs. Engineering Method

Engineering Method



Direct Engineering
(Synthetic Biology)

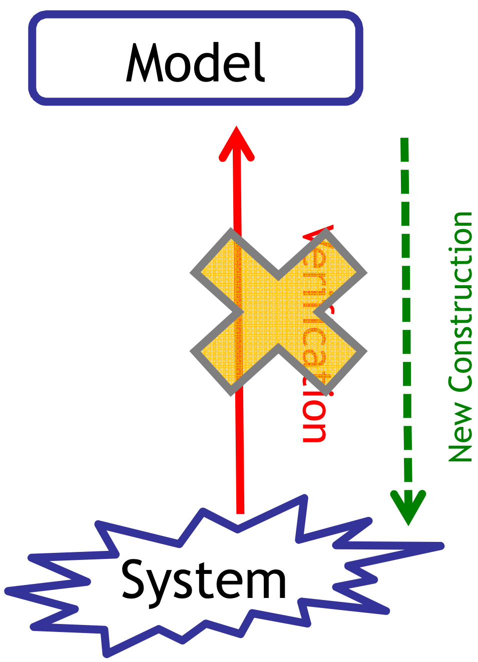
Scientific Method



Reverse Engineering
(Systems Biology)

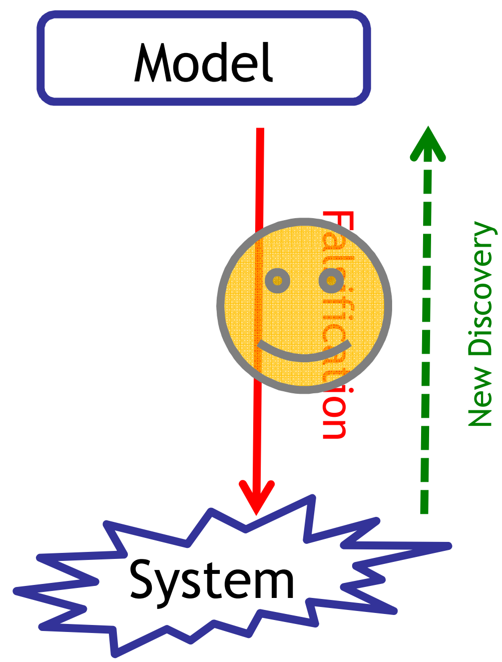
Scientific Method vs. Engineering Method

Engineering Method



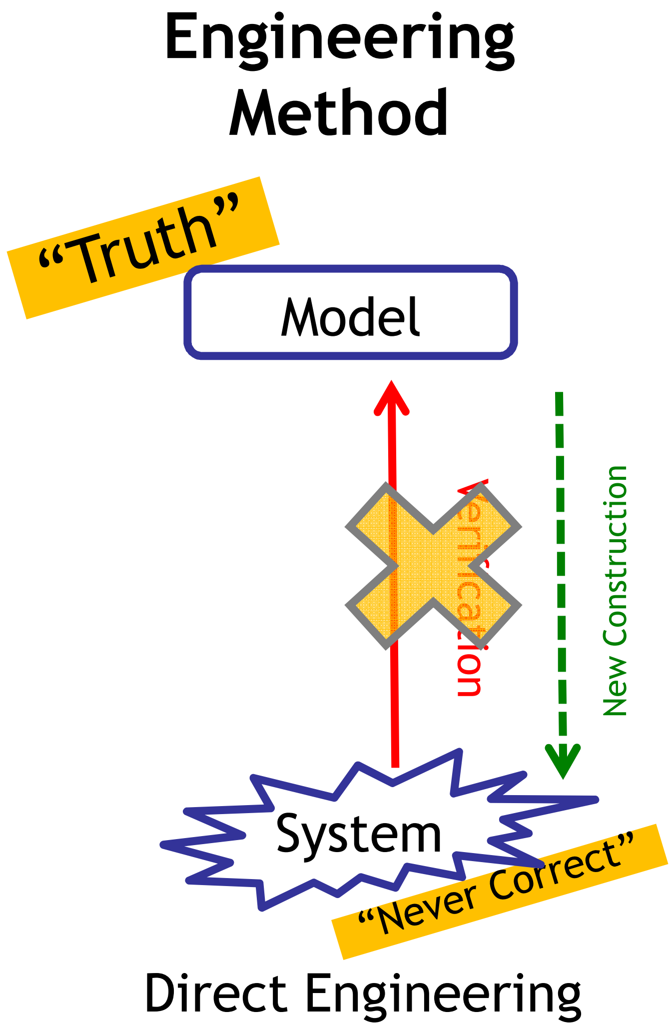
Direct Engineering

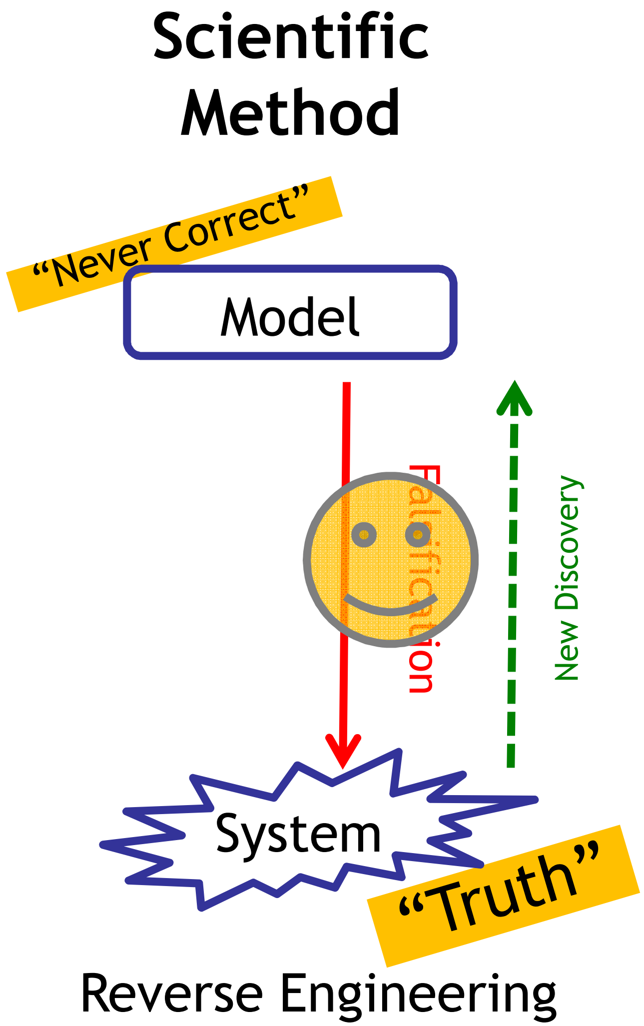
Scientific Method



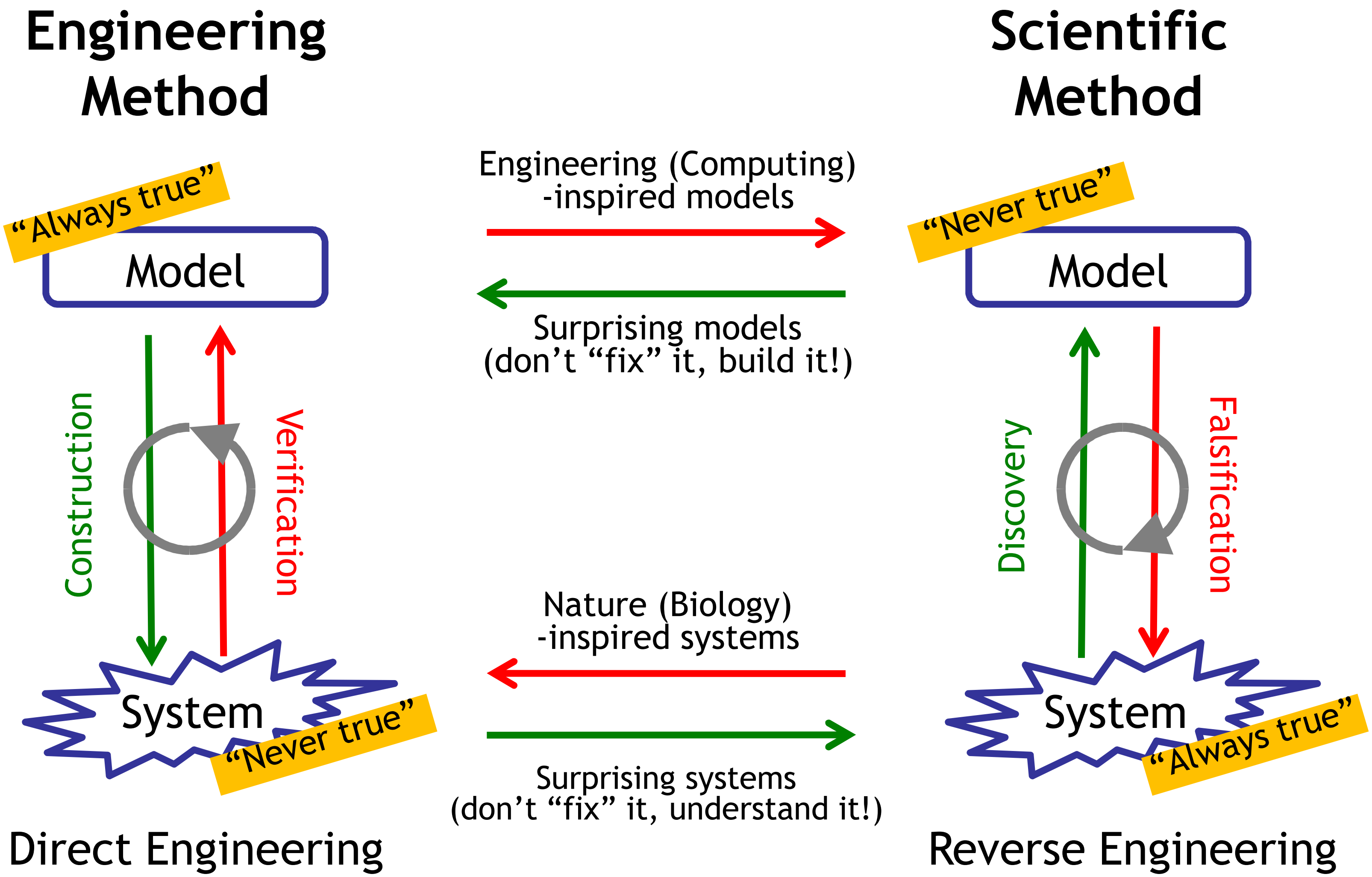
Reverse Engineering

Scientific Method vs. Engineering Method





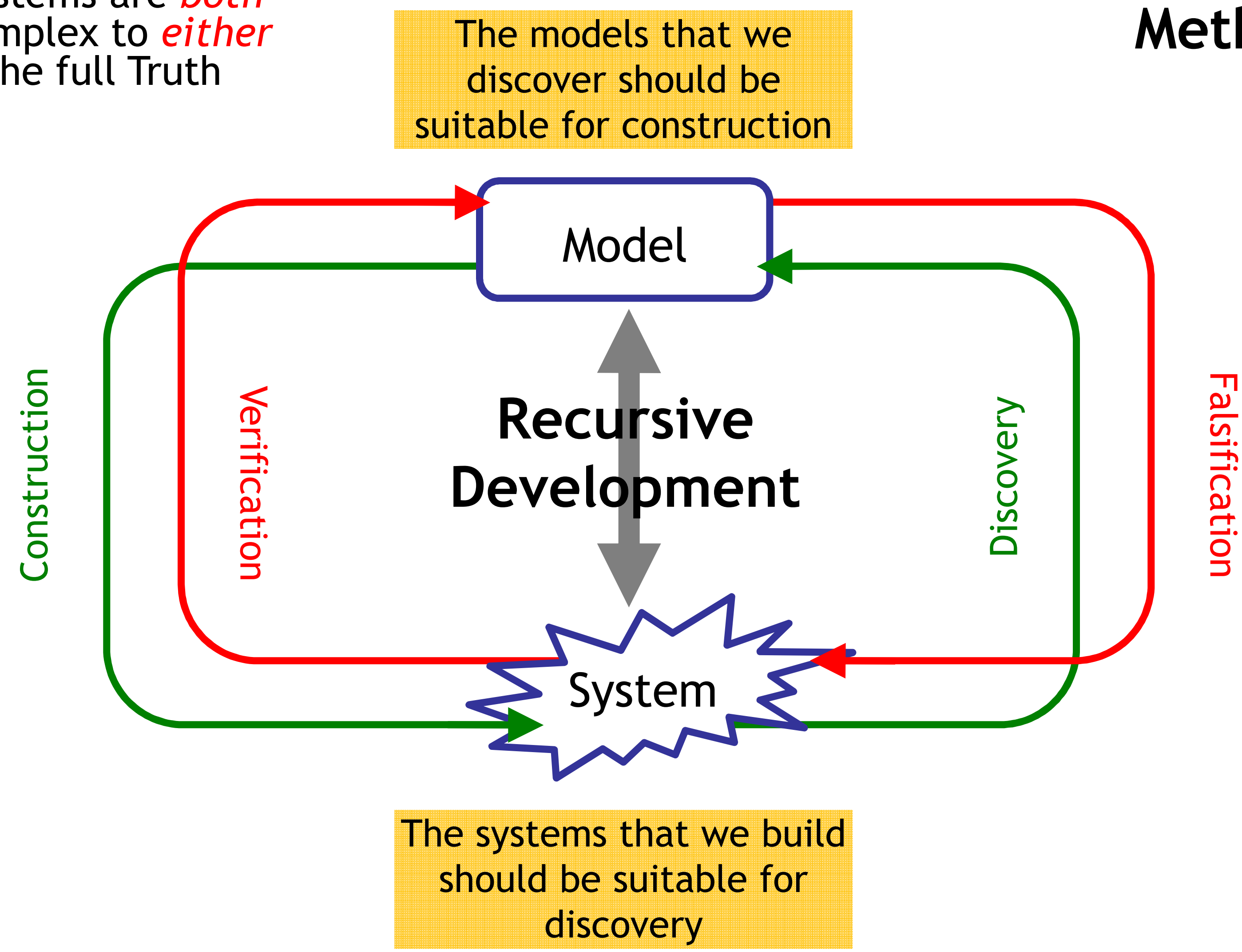
Scientific Method vs. Engineering Method



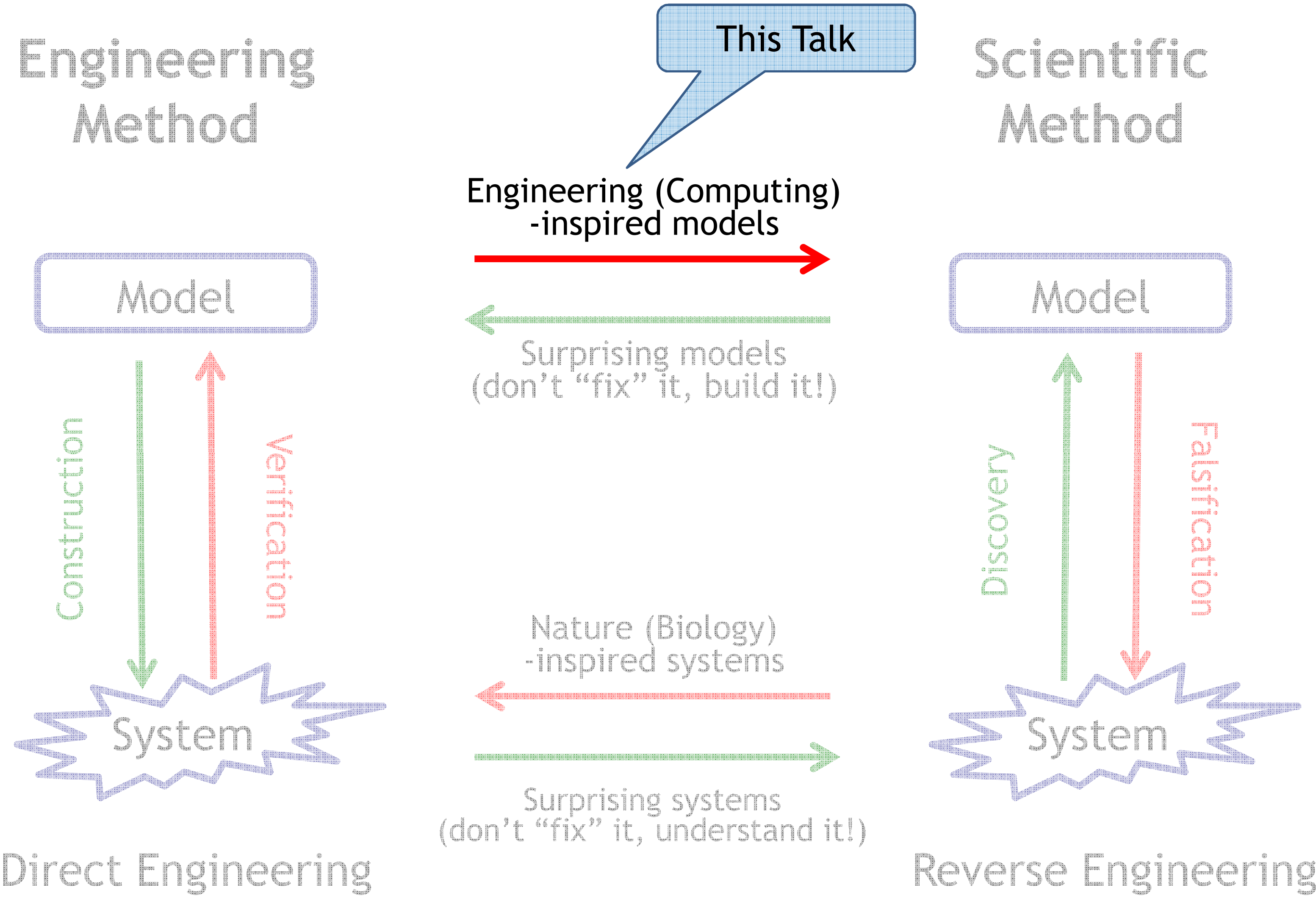
Scientific Method vs. Engineering Method

When the models and the systems are *both* too complex to *either* be the full Truth

Combined Method



Scientific Method vs. Engineering Method



Modeling Approach

- We believe that {petri nets, process algebra, term rewriting, multiagent systems} are {better, complementary} for modeling biological systems than {SBML, Kohn charts, chemical reactions, ODEs}.
- We take a paper from the literature (usually ODEs or chemical reactions) and "code it up" in e.g. Petri nets.
- How do we know that's the "same system" ? How do we convince mathematical biologists that we are doing the "right thing"?

(Macro-) Molecules as (Interacting) Automata

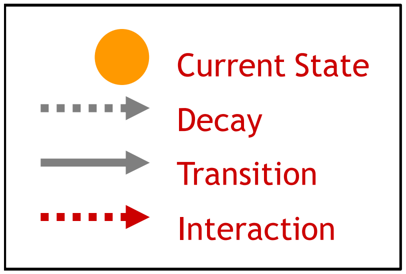
Process Algebra

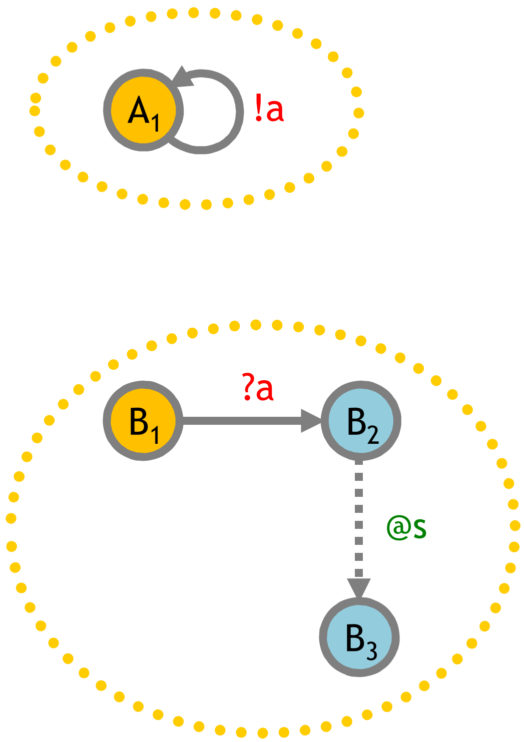
[Hoare, Milner, Pnueli, etc.]

- Reactive systems (living organisms, computer networks, operating systems, …)
  - Math is based on *entities that react/interact with their environment* (“*processes*”), not on functions from domains to codomains.
- Concurrent
  - Events (reactions/interactions) happen concurrently and asynchronously, not sequentially like in function composition.
- Stochastic
  - Or probabilistic, or nondeterministic, but is never about deterministic system evolution.
- Stateful
  - Each concurrent activity (“process”) maintains its own local state, as opposed to stateless functions from inputs to outputs.
- Discrete
  - Evolution through discrete transitions between discrete states, not incremental changes of continuous quantities.
- Kinetics of interaction
  - An “interaction” is anything that moves a system from one state to another.

Interacting Automata

Legend





A_1 is a *state*

a is a *channel* i.e. a named *interaction interface* (e.g. a surface patch)

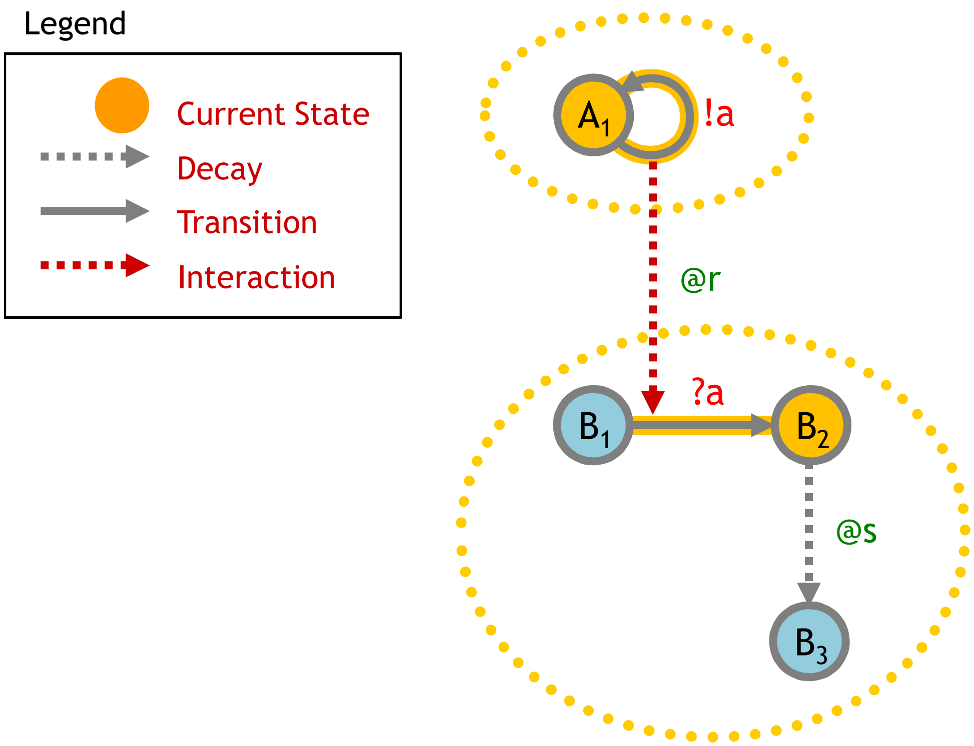
?,! indicate any *complementarity* of interaction (e.g. charge)

?a, !a indicate *complementary actions*,

@r, @s are rates

Kinetic laws:

Interacting Automata

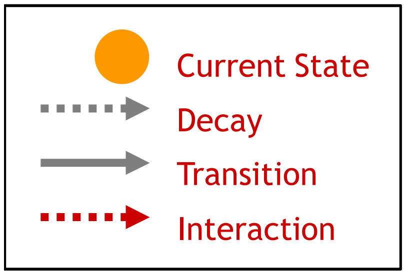


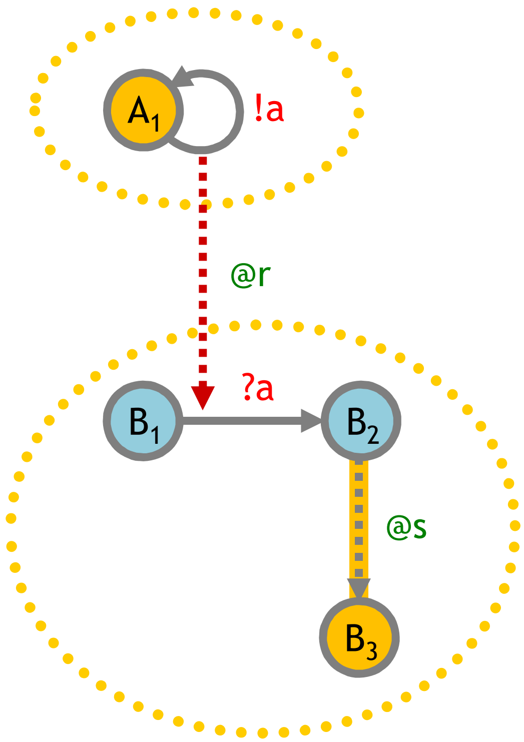
A_1	is a *state*
a	is a *channel* i.e. a named *interaction interface* (e.g. a surface patch)
?,!	indicate any *complementarity* of interaction (e.g. charge, shape)
?a, !a	indicate *complementary actions*, joined by an interaction arrow
@r, @s	are rates

Kinetic laws: ***Two complementary actions may result in an interaction.***

Interacting Automata

Legend





A_1	is a *state*
a	is a *channel* i.e. a named *interaction interface* (e.g. a surface patch)
?,!	indicate any *complementarity* of interaction (e.g. charge)
?a, !a	indicate *complementary actions*, joined by an interaction arrow
@r, @s	are rates

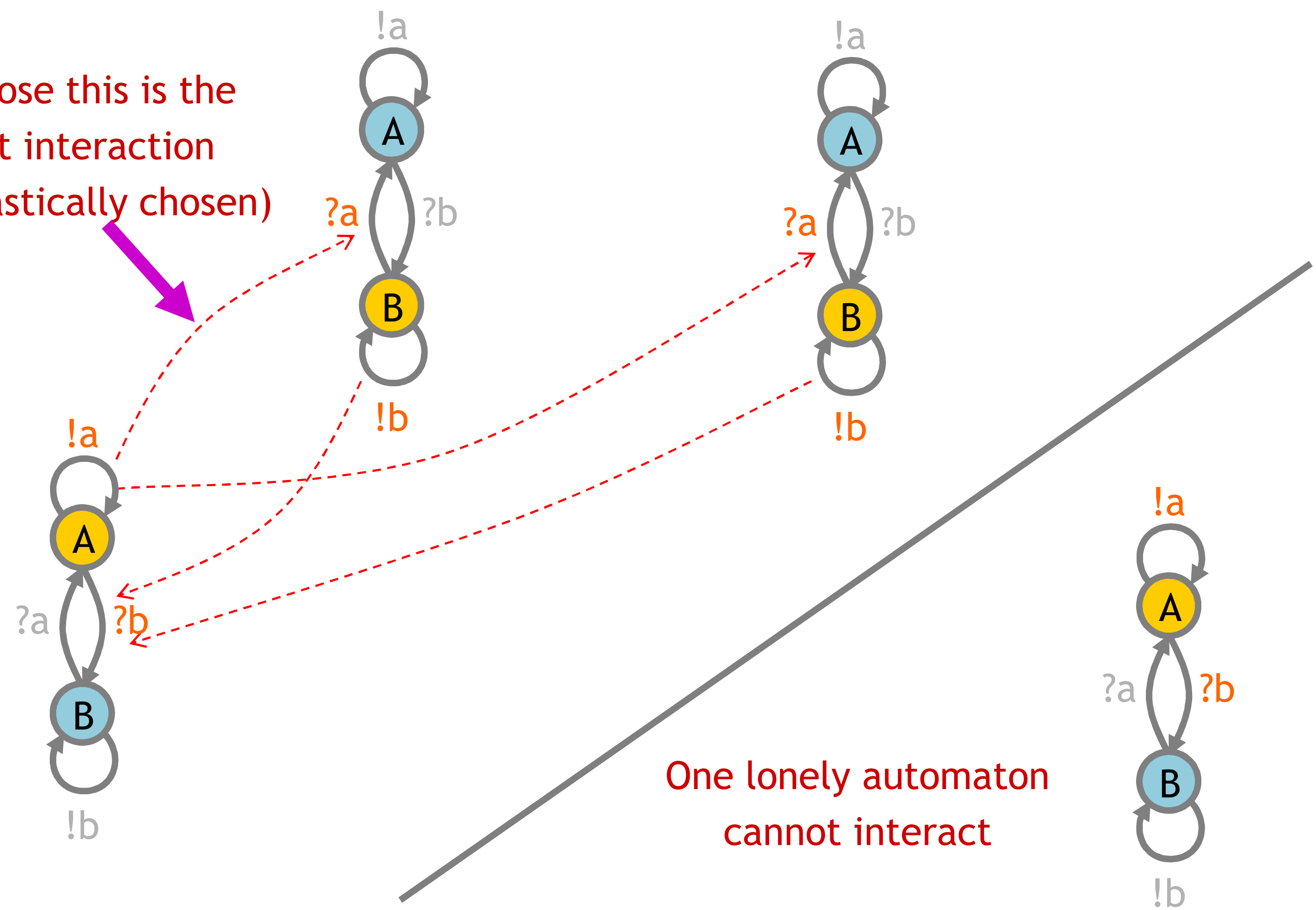
Kinetic laws:

Two complementary actions may result in an interaction.

A decay may happen spontaneously.

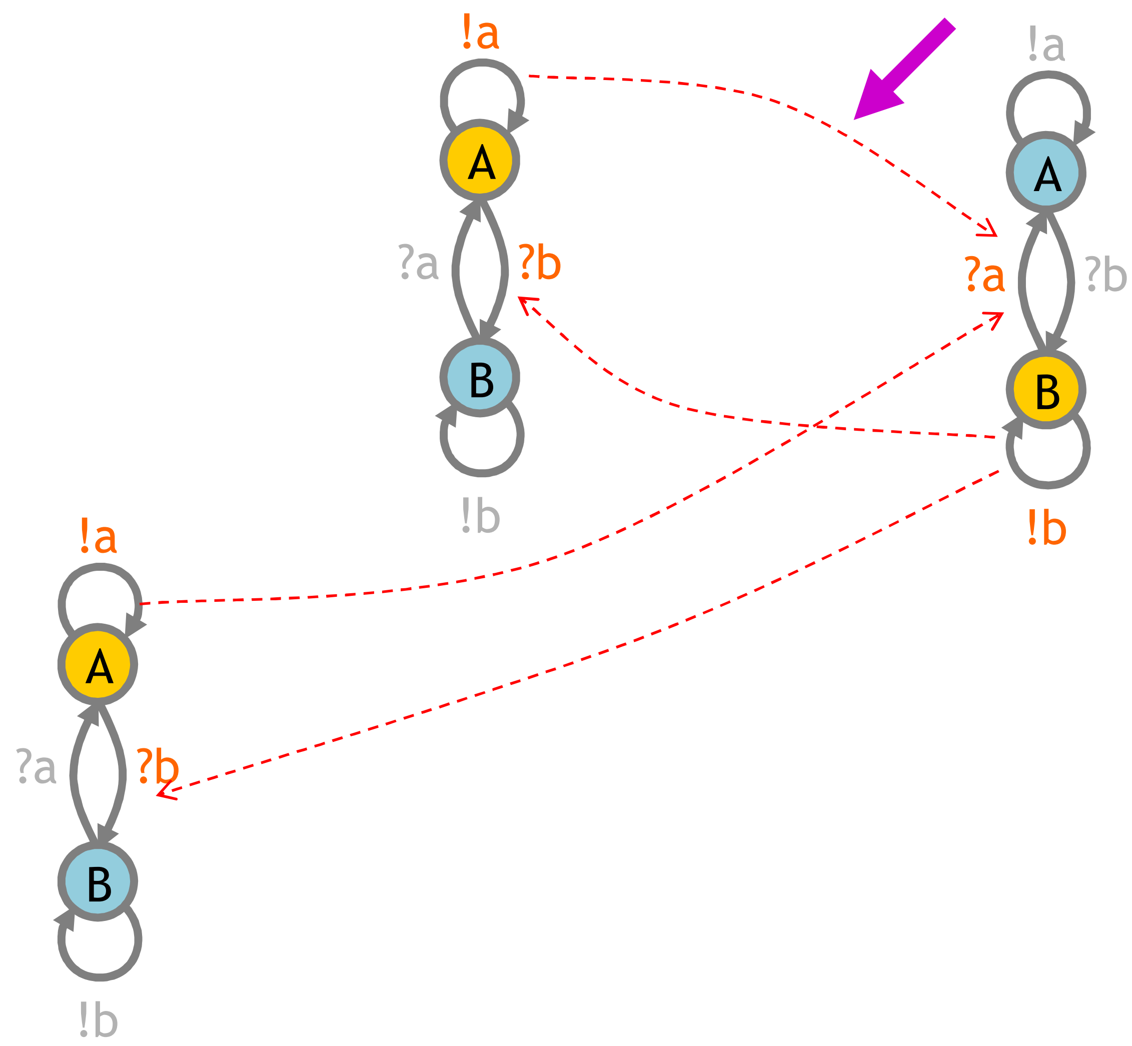
Interactions in a Population

Suppose this is the next interaction (stochastically chosen)

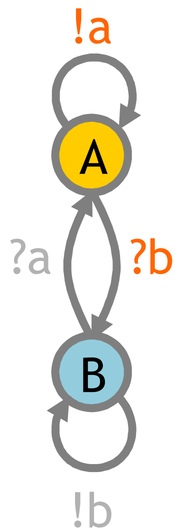


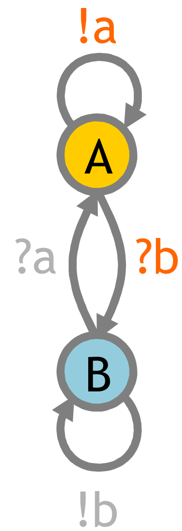
One lonely automaton cannot interact

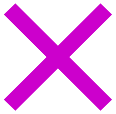
Interactions in a Population

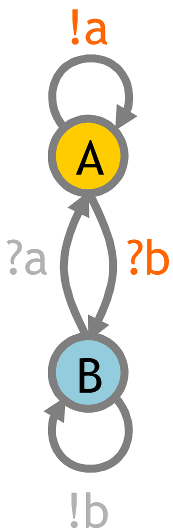


Interactions in a Population



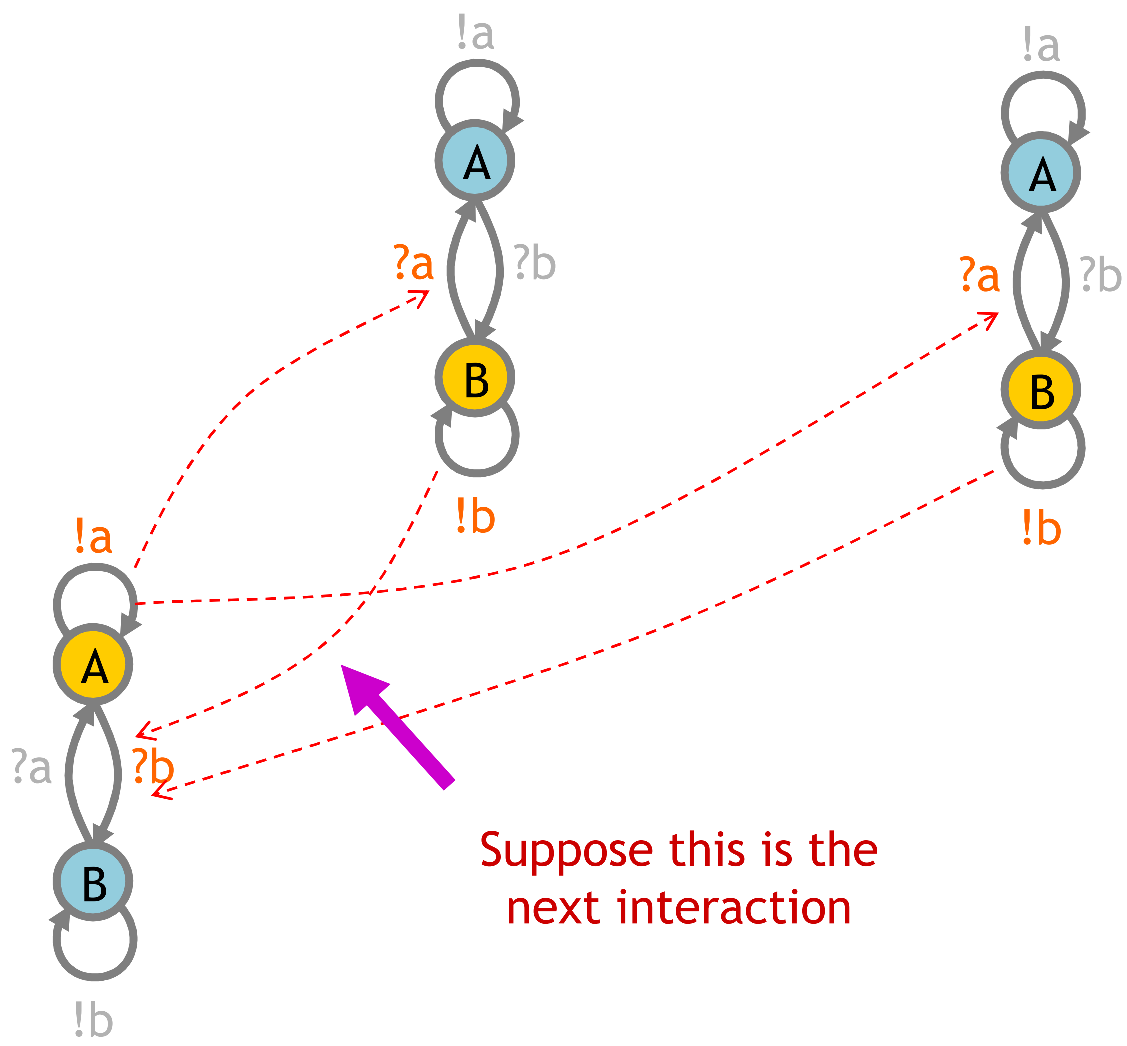






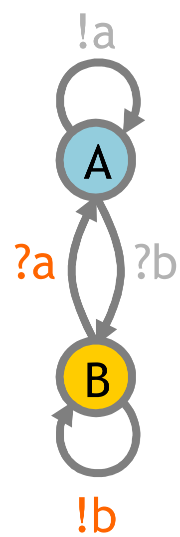
All-A stable population

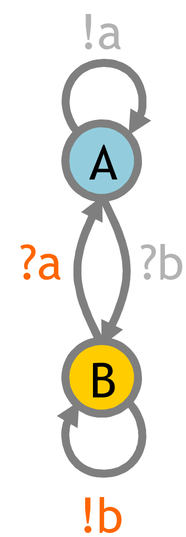
Interactions in a Population (2)

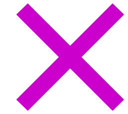


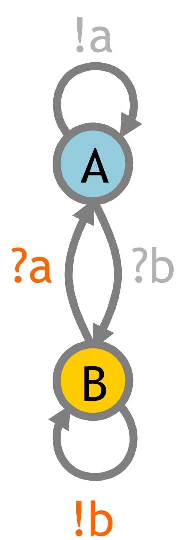
Suppose this is the next interaction

Interactions in a Population (2)





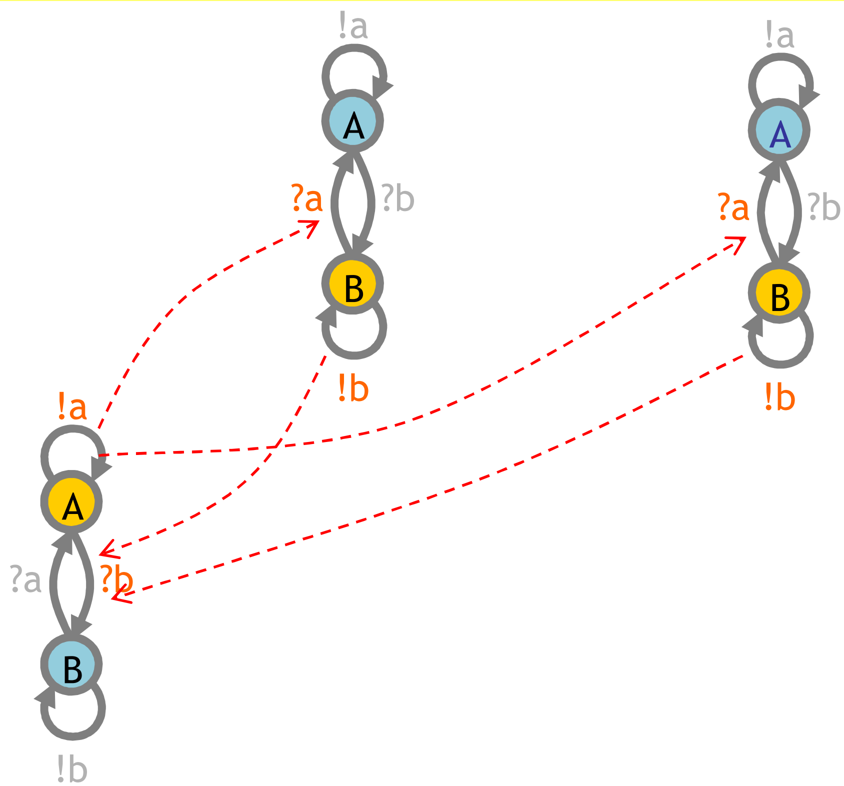


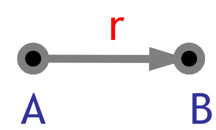


All-B stable population

Nondeterministic population behavior ("multistability")

CTMC Semantics



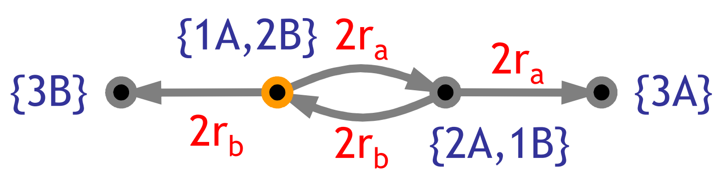


CTMC
(homogeneous) Continuous Time Markov Chain
- directed graph with no self loops
- nodes are system states
- arcs have transition rates

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

Reactions vs. Components

Says what "A" *does*.

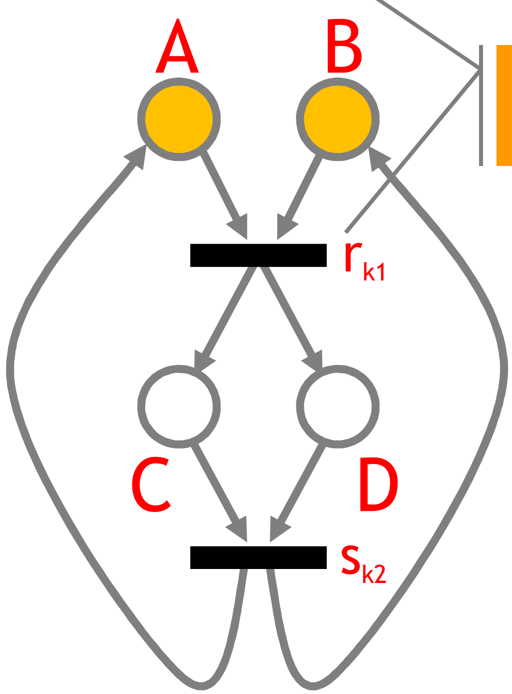
Says what "A" *is*.

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

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

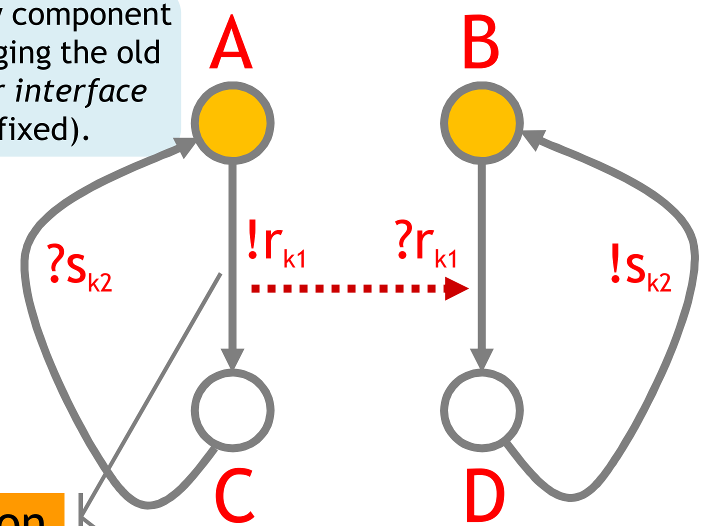
Does A become C or D?

Can add a new component without changing the old ones (if their *interface* remains fixed).



Reaction oriented

1 line per reaction



Interaction oriented

1 line per component

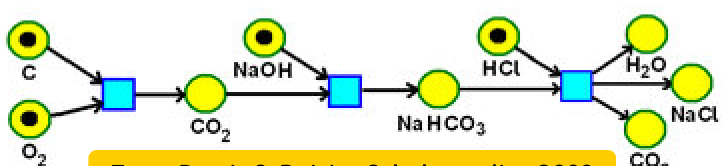
$A = !r_{k1}; C$

$C = ?s_{k2}; A$

$B = ?r_{k1}; D$

$D = !s_{k2}; B$

A becomes C not D!



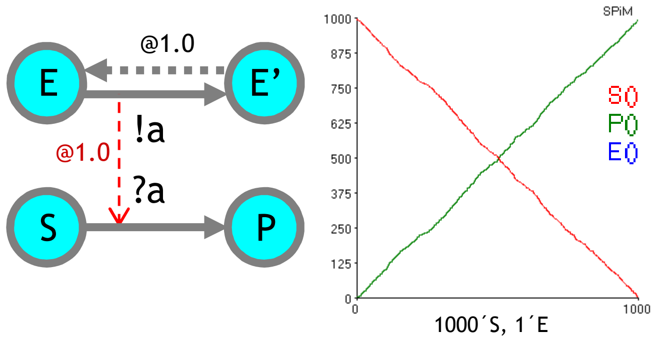
From Petri & Reisig, Scholarpedia, 2009

The same "state space"

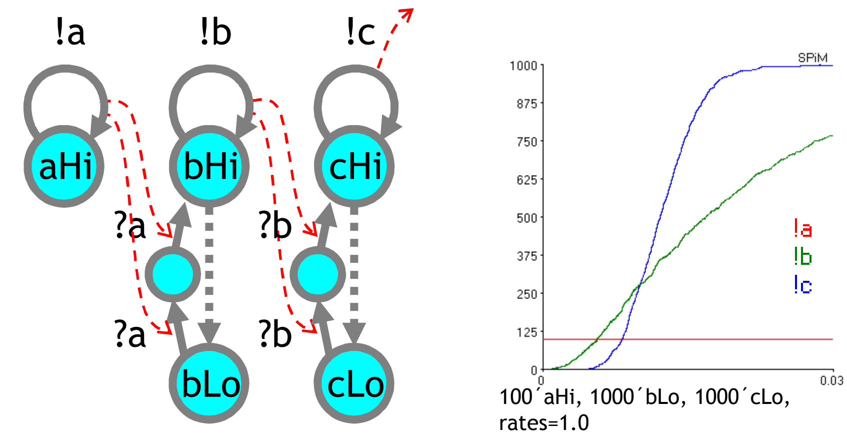
CTMC

Some Devices

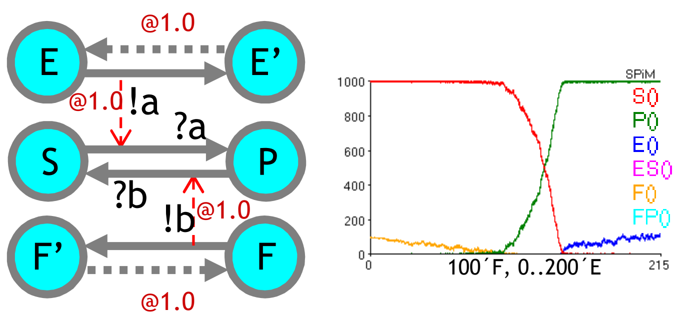
Linear Pump



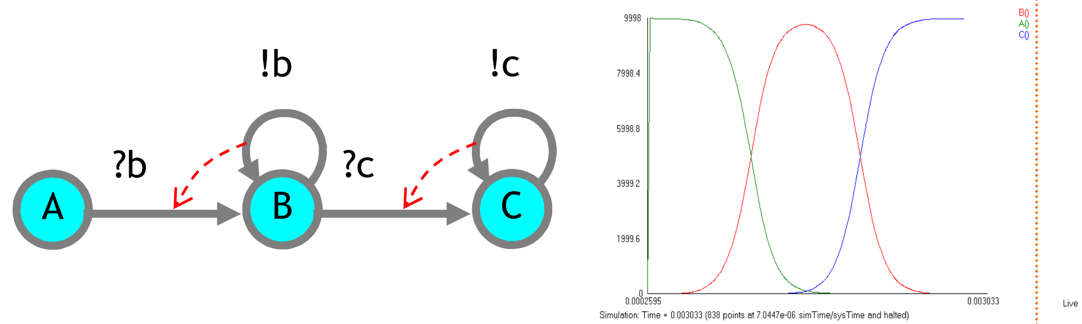
Cascade Amplifier



Ultrasensitive Switch

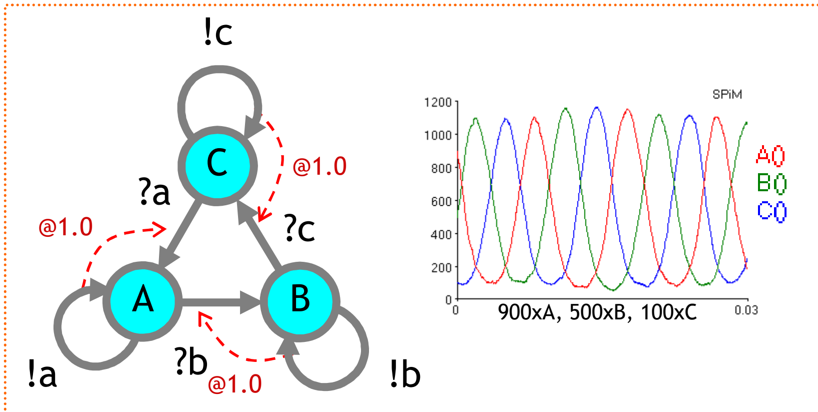


Symmetric Wave Generator

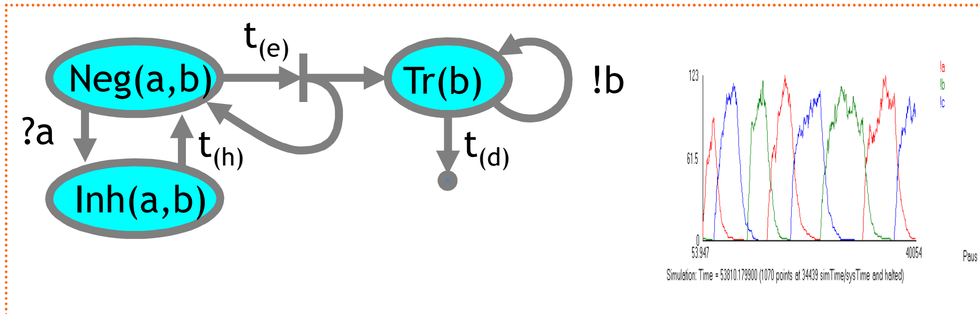


More Devices

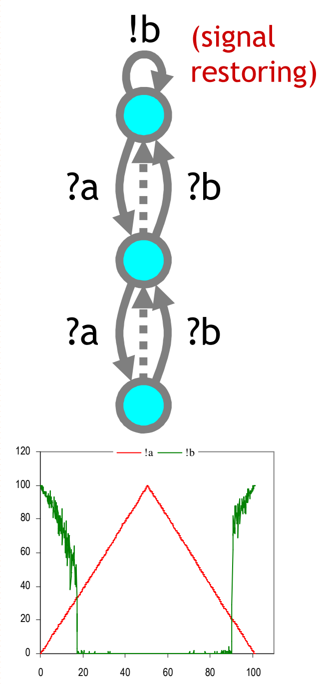
Oscillator



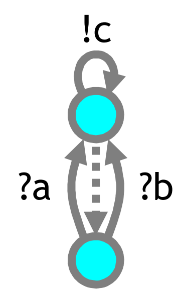
Repressilator (1 of 3 similar gates)



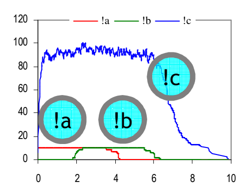
b = not a



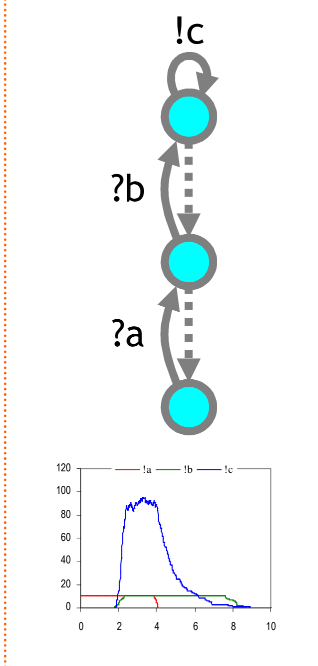
c = a or b



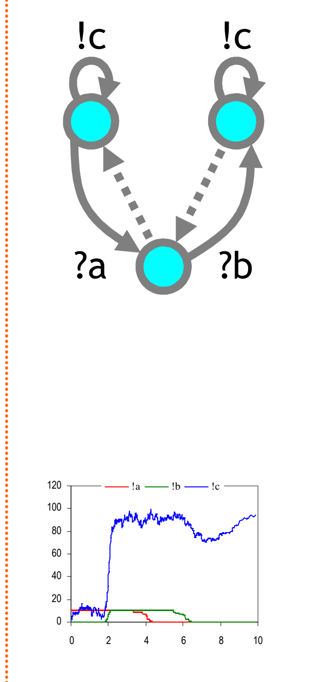
Inputs:
10 !a for 4t
2t; 10 !b for 4t



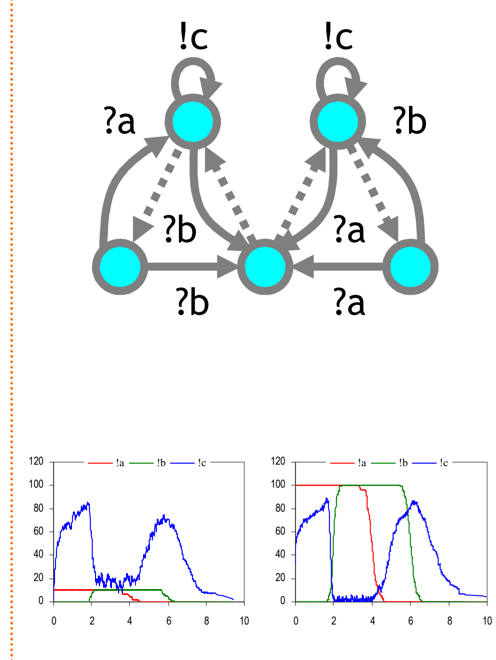
c = a and b



c = a imply b

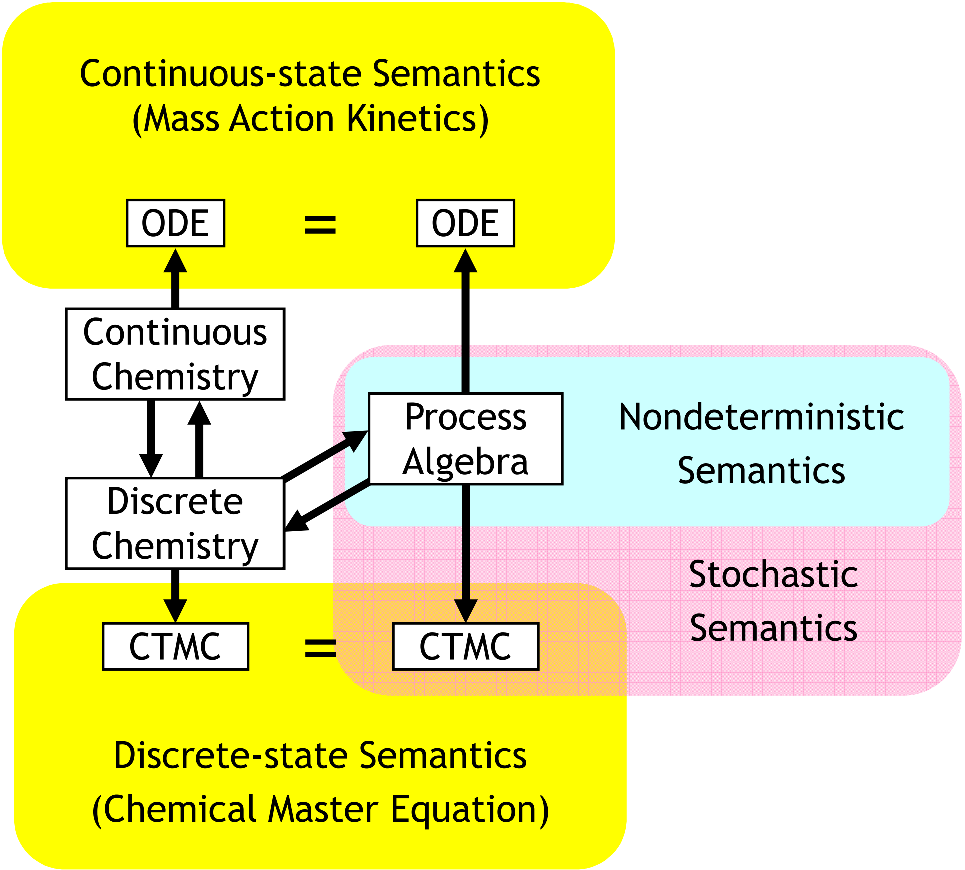


c = a xor b



Semantics of Collective Behavior

The Two Semantic Sides of Chemistry

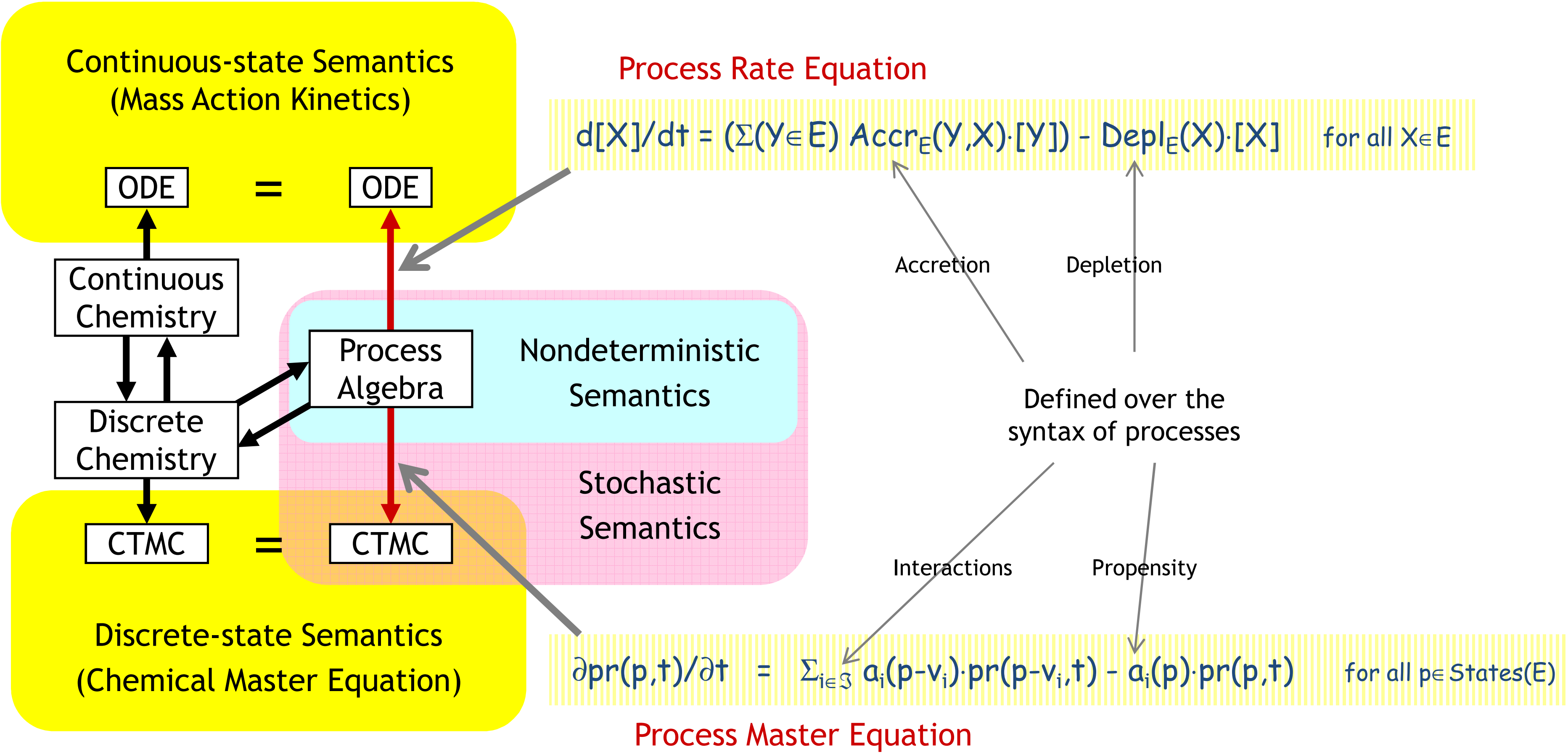


These diagrams commute via appropriate maps.

L. Cardelli: "On Process Rate Semantics" (TCS)

L. Cardelli: "A Process Algebra Master Equation" (QEST'07)

Quantitative Process Semantics



From CGF to Chemistry

Chemical Reactions

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

Trimolecular reactions:

$A + B + C \to^r D$

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

$A + B \leftrightarrow AB$

$AB + C \to D$

Enzymatic reactions:

$S \xrightarrow{E,r} P$

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

$E + S \leftrightarrow ES$

$ES \to P + E$

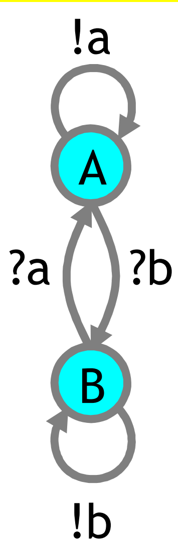
Chemical Ground Form (CGF)

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

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

(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.)

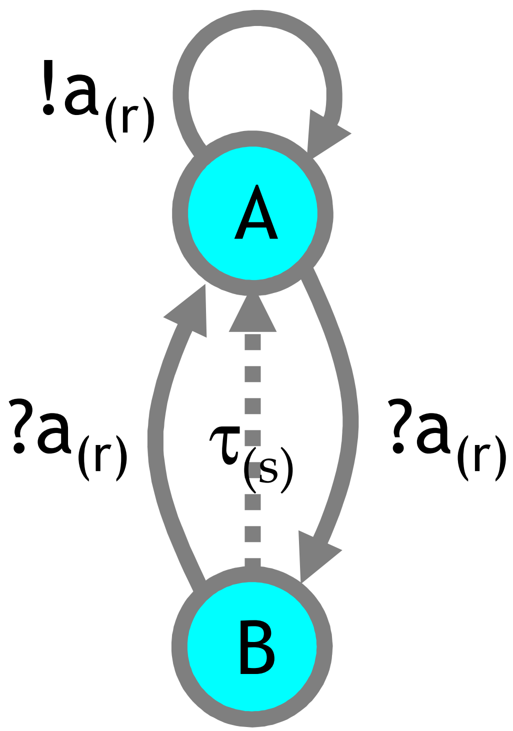
⊕ is stochastic choice (vs. + for chemical reactions)
0 is the null solution (P|0 = 0|P = P)
and null molecule (M⊕0 = 0⊕M = M)
Each X in E is a distinct *species*
Each name a is assigned a fixed rate r: $a_{(r)}$



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

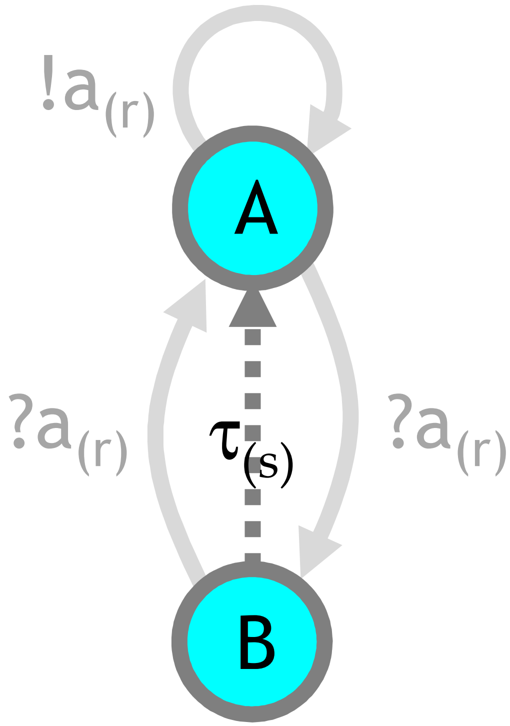
From CGF to Chemistry (by example)

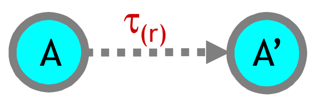


$A = !a_{(r)};A \oplus ?a_{(r)};B$

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

From CGF to Chemistry (by example)





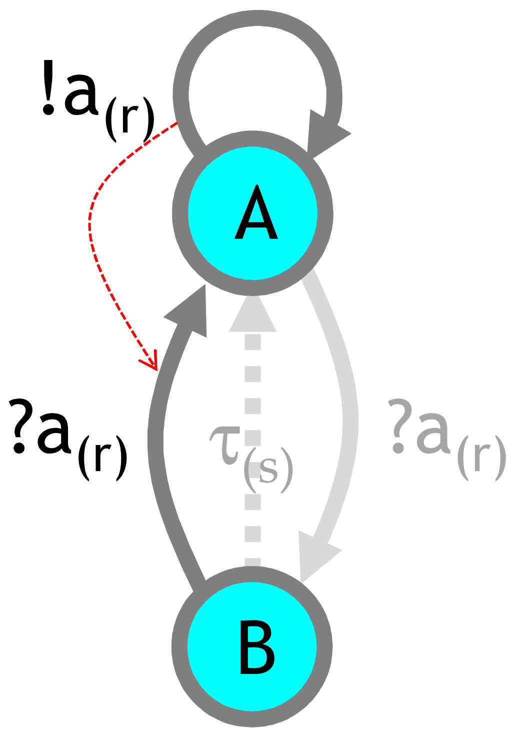
$A \rightarrow^{r} A'$

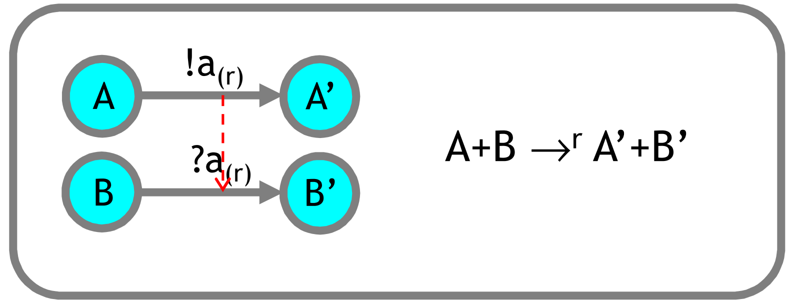
$B \rightarrow^{s} A$

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

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

From CGF to Chemistry (by example)





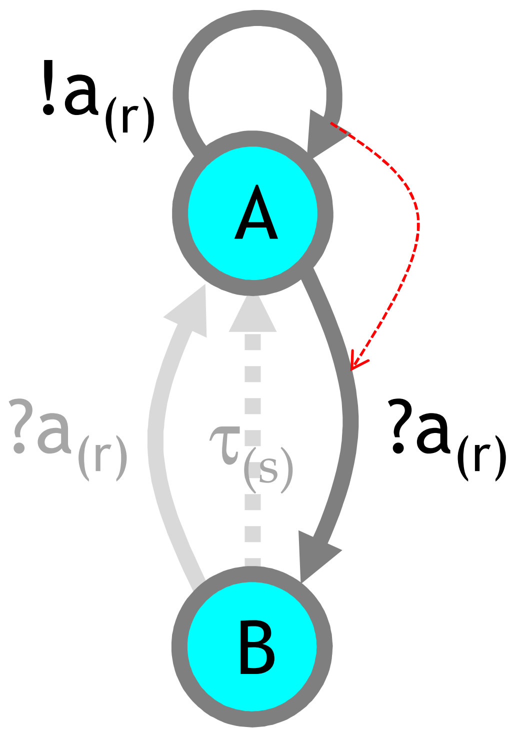
$B \rightarrow^{s} A$

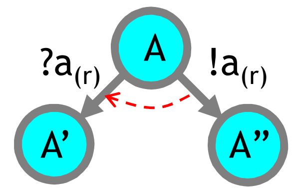
$A+B \rightarrow^{r} A+A$

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

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

From CGF to Chemistry (by example)





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

$B \rightarrow^{s} A$

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

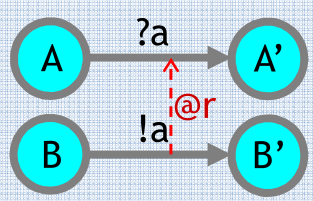
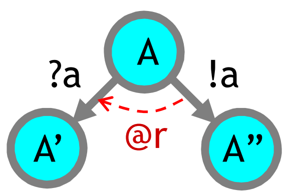
$A+A \rightarrow^{2r} A+B$

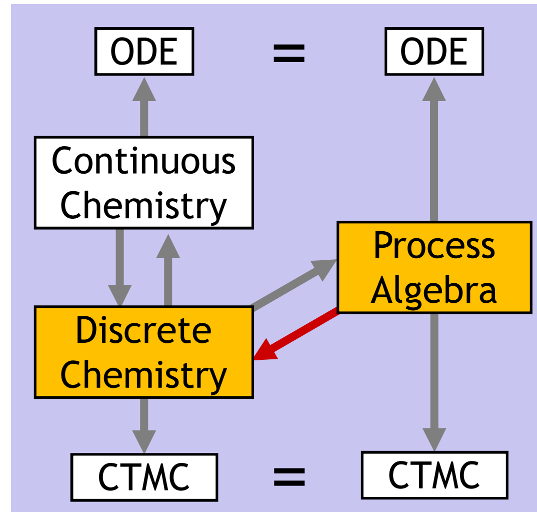
Double rate for homeo reactions

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

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

From CGF to Chemistry (by example)

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



From CGF to Chemistry: Ch(E)

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

E.X.i $\stackrel{def}{=}$ 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 +)

Ch(E) :=

{(<X.i>: X $\rightarrow^{r}$ P) *s.t.* E.X.i = $\tau_{(r)}$;P} ∪

{(<X.i,Y.j>: X + Y $\rightarrow^{r}$ P + Q) *s.t.* X≠Y, E.X.i = $?a_{(r)}$;P, E.Y.j = $!a_{(r)}$;Q} ∪

{(<X.i,X.j>: X + X $\rightarrow^{2r}$ P + Q) *s.t.* E.X.i = $?a_{(r)}$;P, E.X.j = $!a_{(r)}$;Q}

Initial conditions for P:

Ch(P) := P

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	τ;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 !;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 $<X,v_{ij}>$.

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 !;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 $<X,v_{ij}>$.

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

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

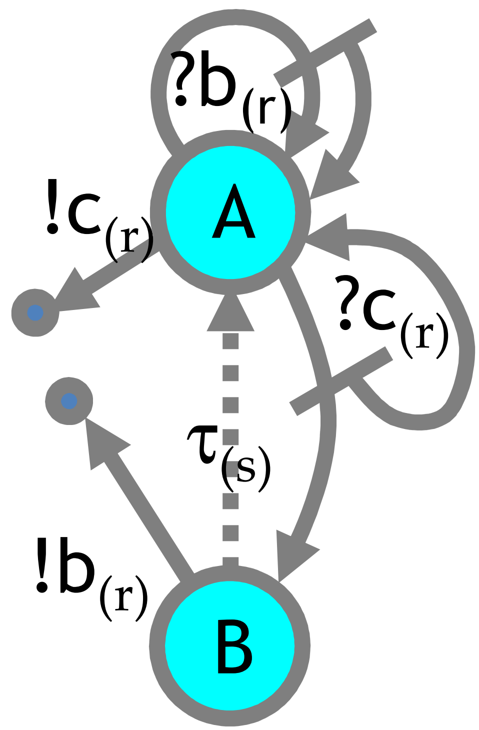
Homeo reaction v_i: $X+X \rightarrow k_i\ P_i$

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

2: Read the result by rows:

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

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



From FSRN to CGF (by example)

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

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

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

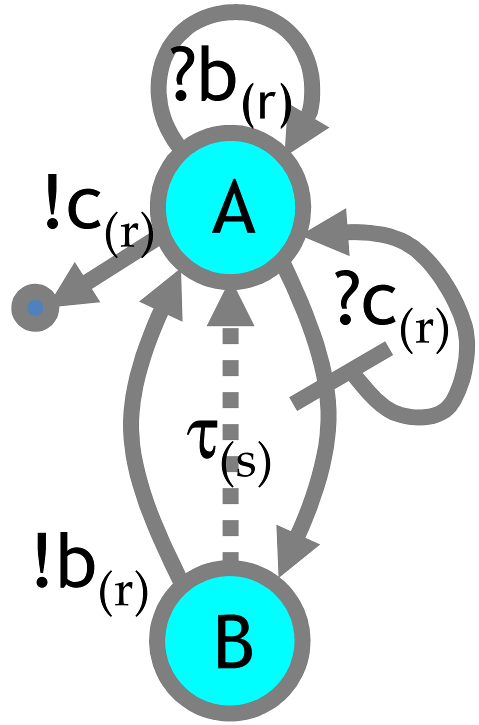
	$x_{(s)}$	$b_{(r)}$	$c_{(r)}$
A		?;A	?;A|B !;0
B	τ;A	!;A	

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:

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

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

From FSRN to CGF (by example)

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

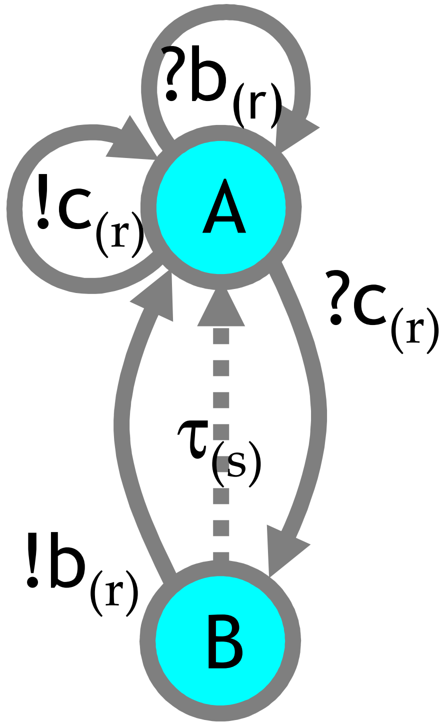
b: $A+B \to^{r} A+A$

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

	$x_{(s)}$	$b_{(r)}$	$c_{(r)}$
A		?;A	?;B !;A
B	τ;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:

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

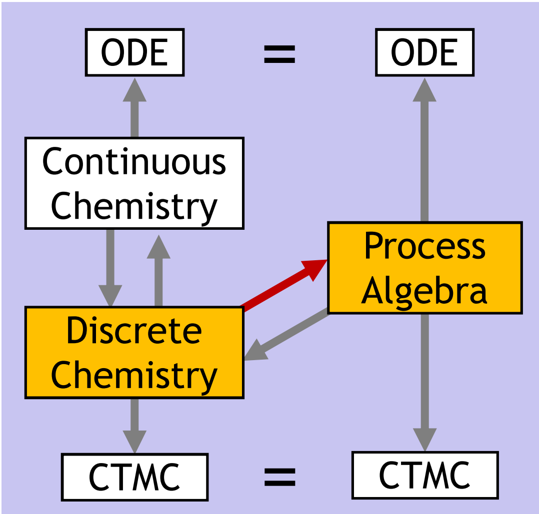
$B = \tau_{(s)};A \oplus !b_{(r)};A$

From Chemistry to CGF: Pi(C)

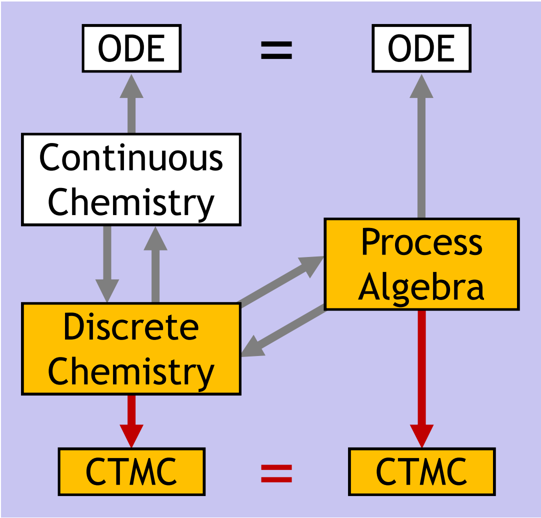
v:	$X \rightarrow^{r} Y_1 + \ldots + Y_n + 0$	Unary Reaction
v:	$X_1 + X_2 \rightarrow^{r} Y_1 + \ldots + Y_n + 0$	Binary Reaction

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

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

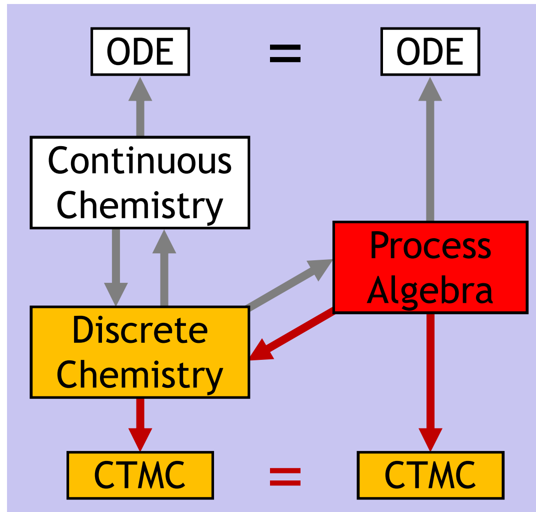


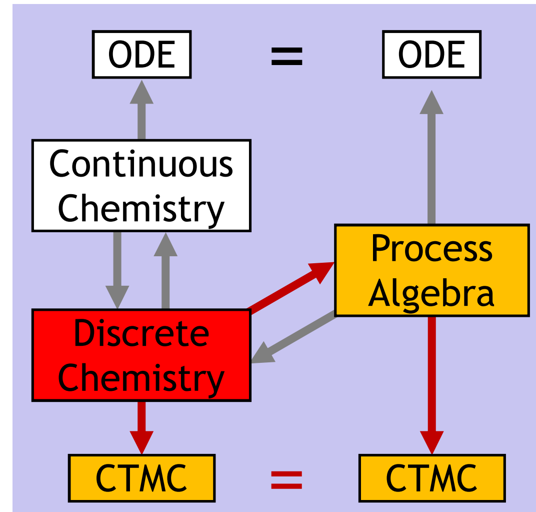
Discrete-State Semantics



Discrete State Equivalence

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





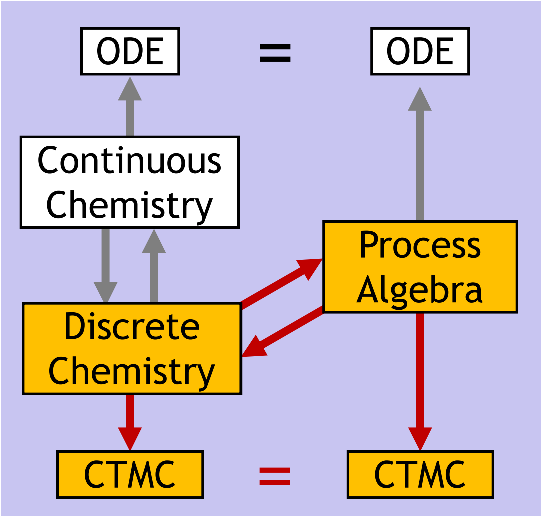
- For each E there is an E' ≈ E that is detangled (E' = Pi(Ch(E)))
- For each E in automata form there is an an E' ≈ E that is detangled and in automata form (E' = Detangle(E)).

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).



From Discrete to Continuous Chemistry

The Gillespie Conversion

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

V = interaction volume

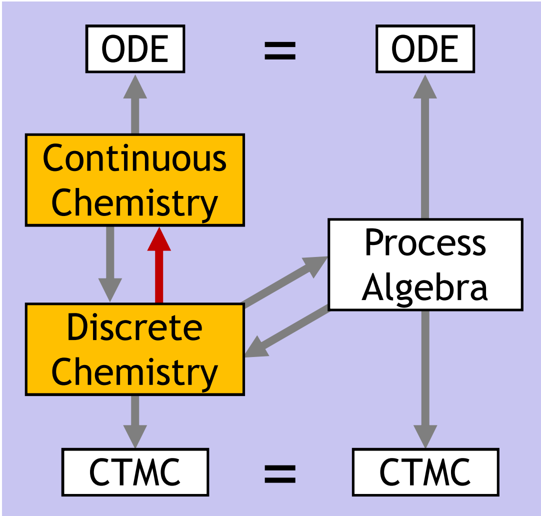
N_A = Avogadro's number

Think $\gamma = 1$

i.e. $V = 1/N_A$

$M = mol \cdot L^{-1}$

molarity (concentration)



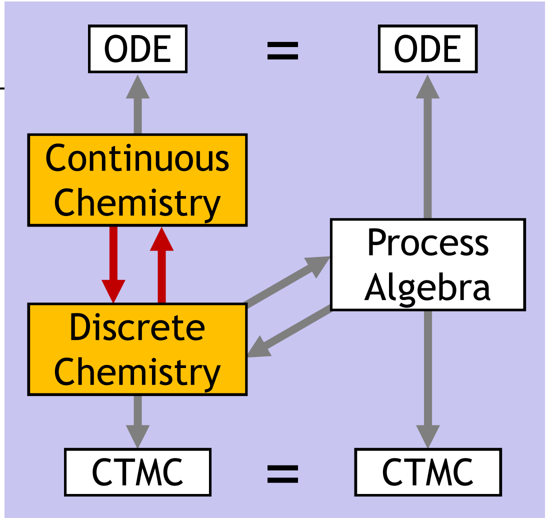
$Cont_\gamma$ and $Disc_\gamma$

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

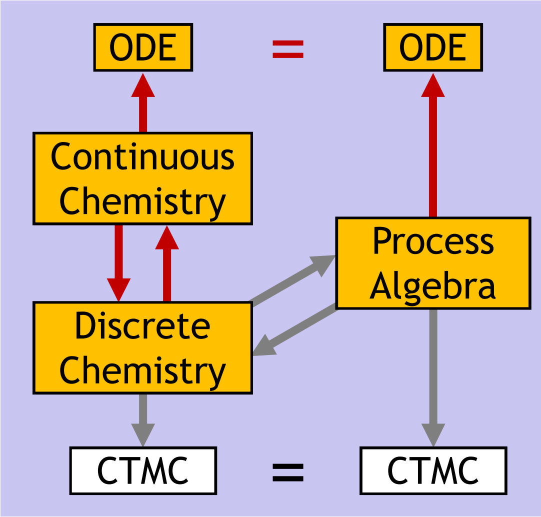
For a volumetric factor $\gamma{:}M^{-1}$, we define a translation $Cont_\gamma$ from a discrete chemical systems (C,P), with species X and initial molecule count $\#X_0 = \#X(P)$, to a continuous chemical systems (C,V) with initial concentration $[X]_0 = V_X$. The translation $Disc_\gamma$ is its inverse, 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.

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

$$Ch_\gamma \ := \ Cont_\gamma \circ Ch$$

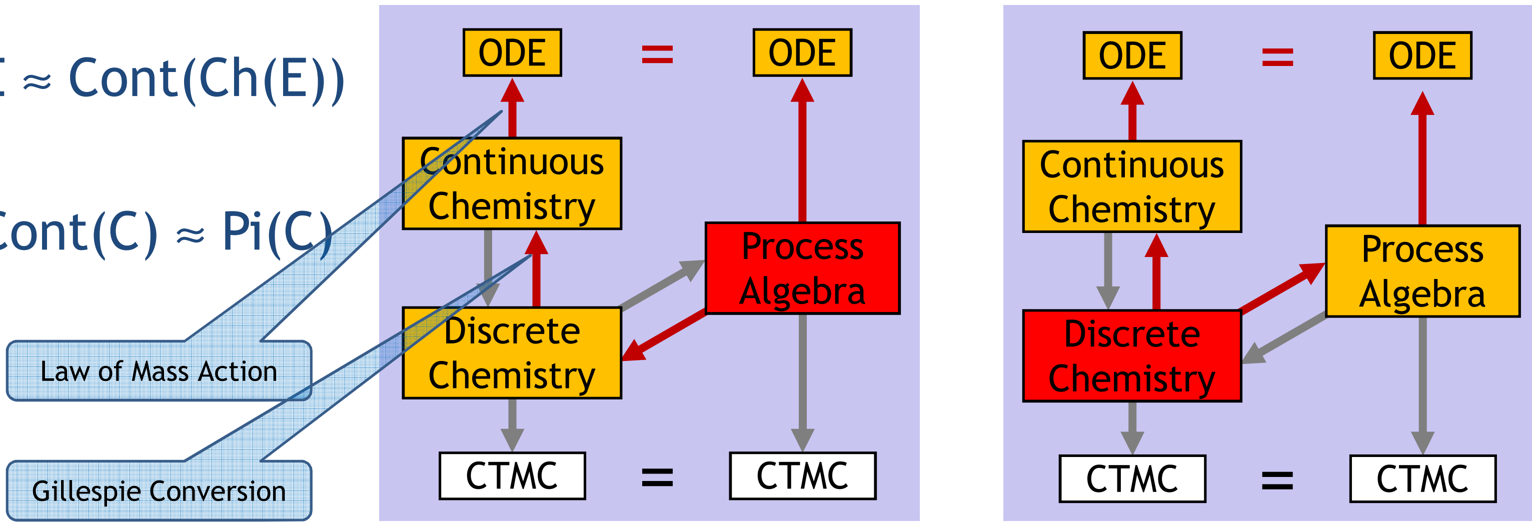


Continuous-State Semantics
(summary)



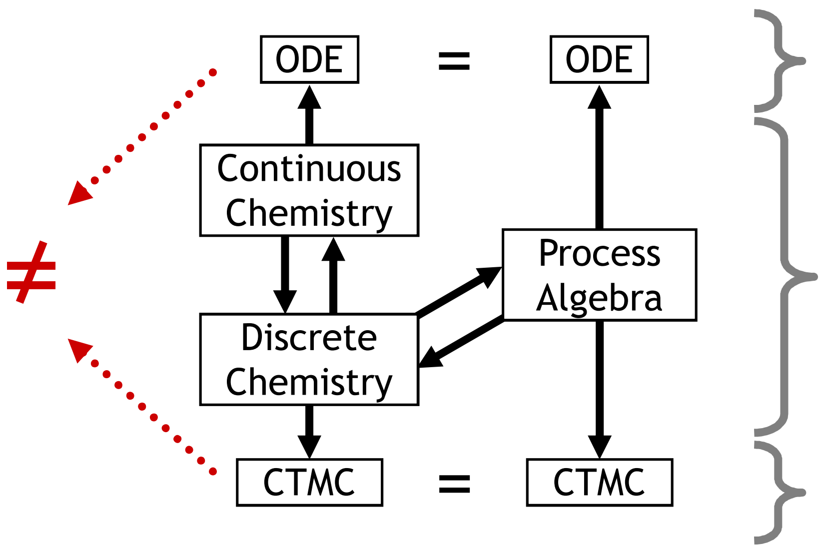
Continuous State Equivalence

- 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)).

GMA ≠ CME

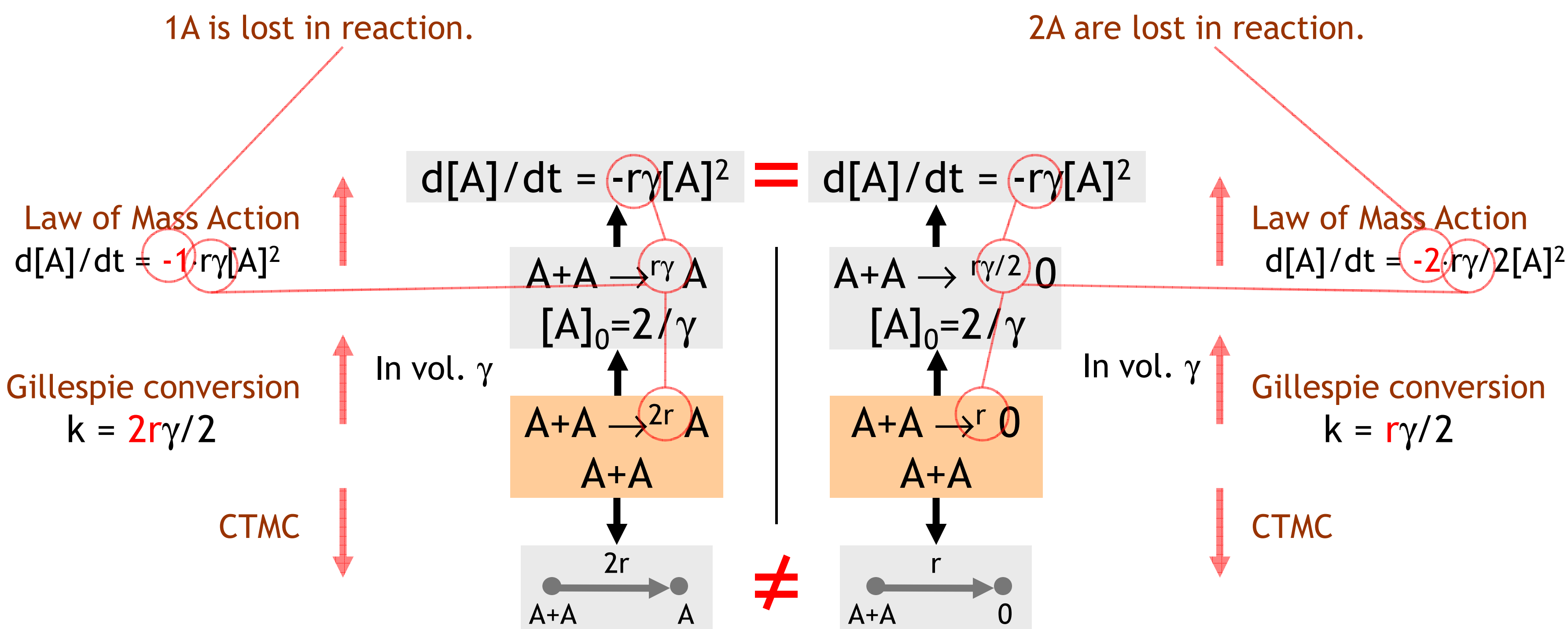


Semantics #1
Continuous state space

Syntax

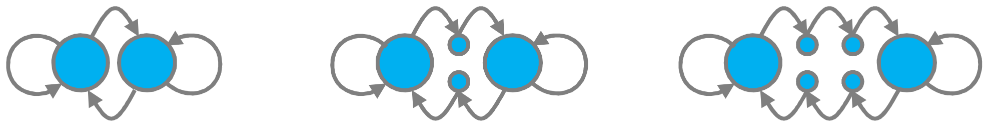
Semantics #2
Discrete state space

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

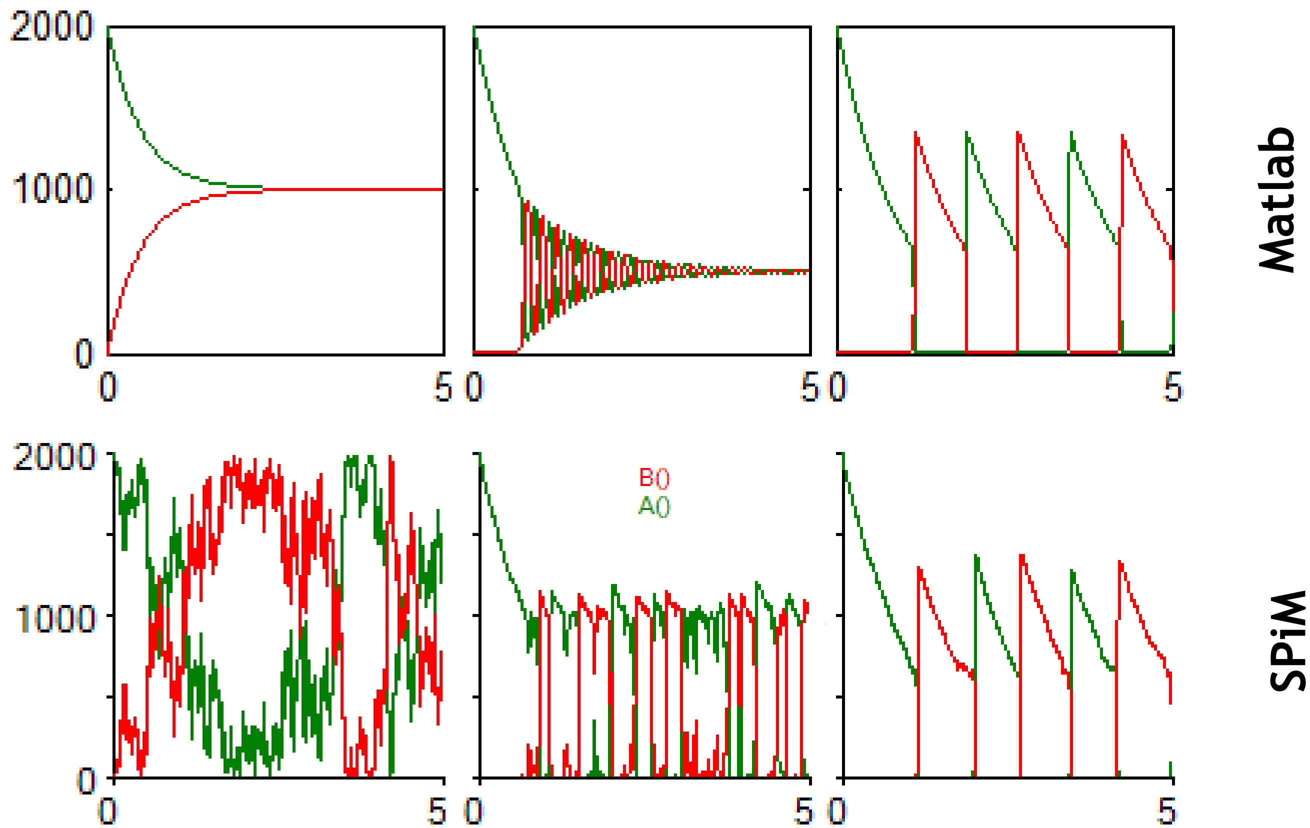


(For conservation of mass, consider instead $A+A \to^{2r} A+B$ vs. $A+A \to^{r} B+B$)

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())
```

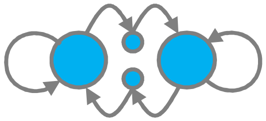
```
directive sample 5.0 1000
directive plot B(); A()

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())
```

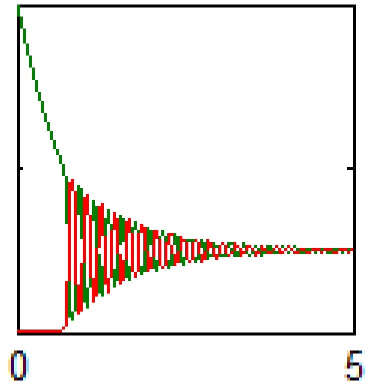
```
Groupe ODEs - Groupies.mat

[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
```

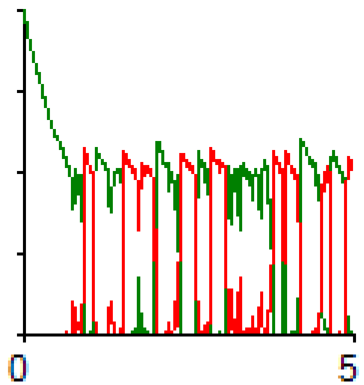
```
Groupe ODEs - Groupies Hysteric 2.mat

[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





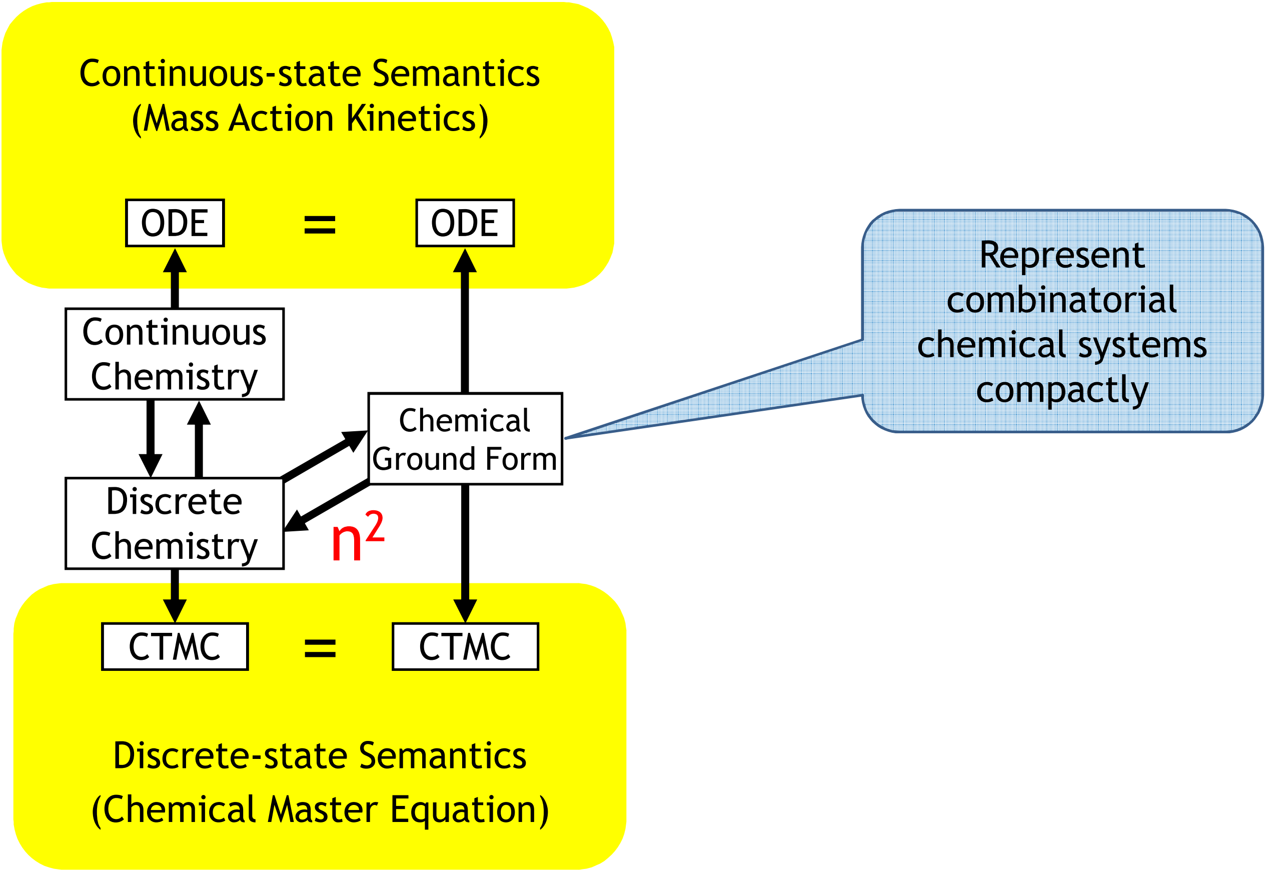
After a while, all 4 states are almost equally occupied.



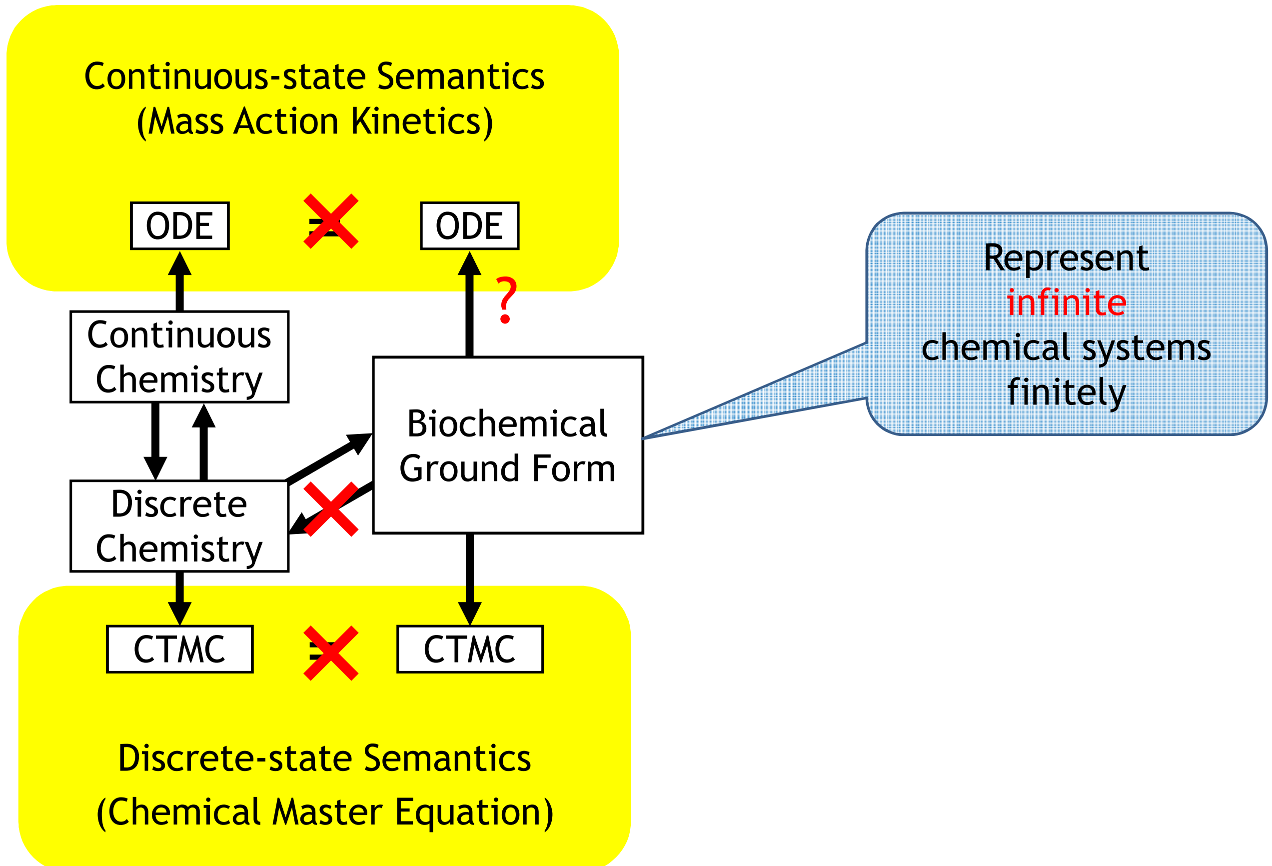
The 4 states are almost never equally occupied.

Chemistry and Beyond

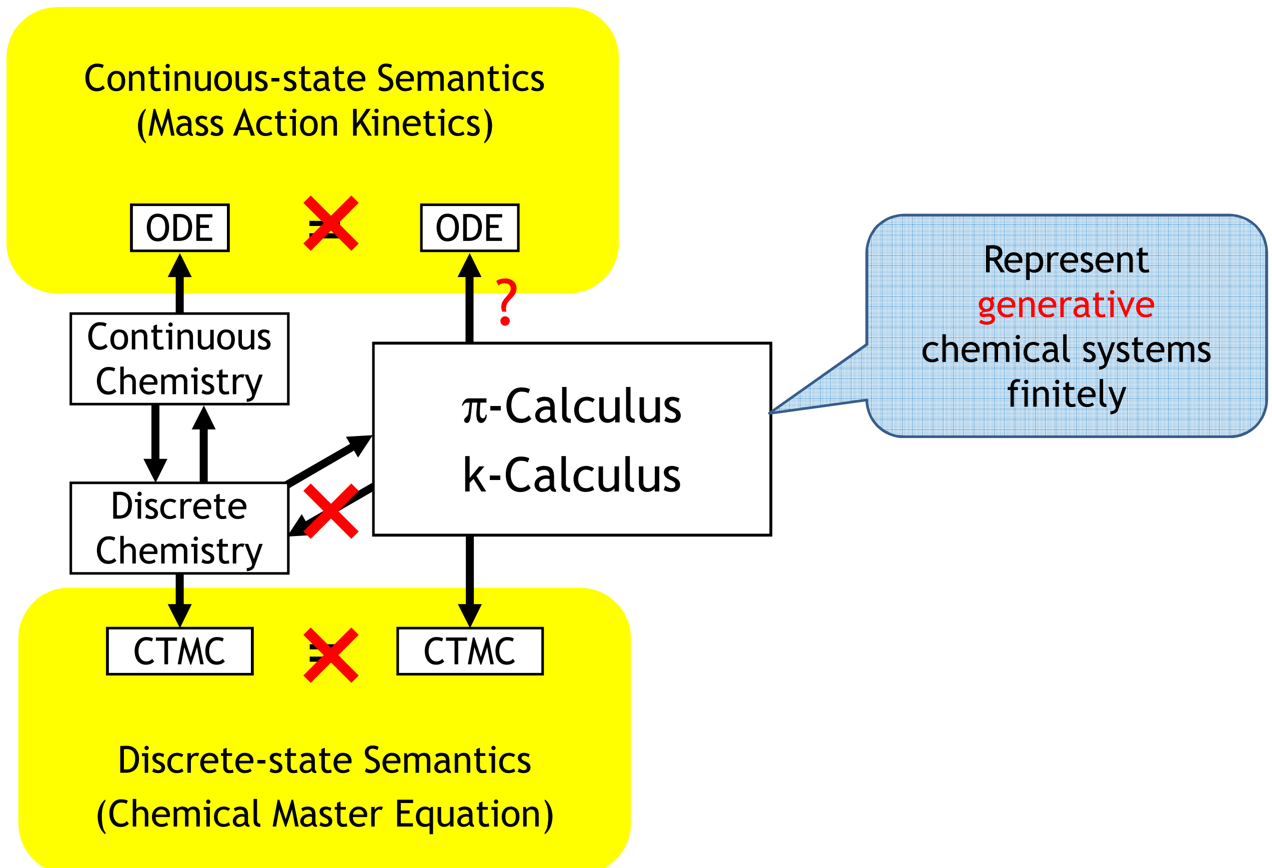
Process Algebra is ‘Bigger’ than Chemistry



Process Algebra is 'Bigger' than Chemistry



Process Algebra is 'Bigger' than Chemistry



On the Computational Power of Biochemistry

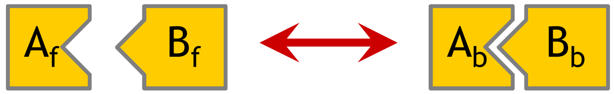
joint work with

Gianluigi Zavattaro

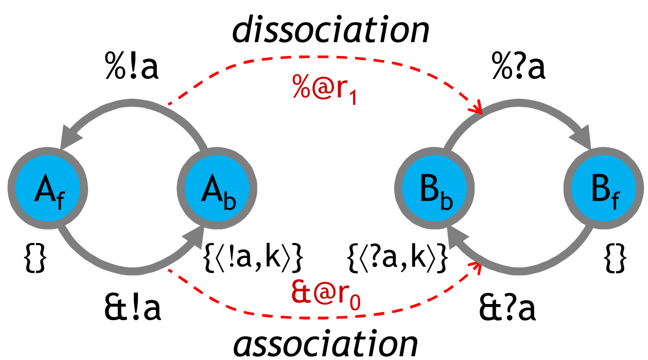
University of Bologna

in: Algebraic Biology '08

Biochemistry = Collision + Complexation



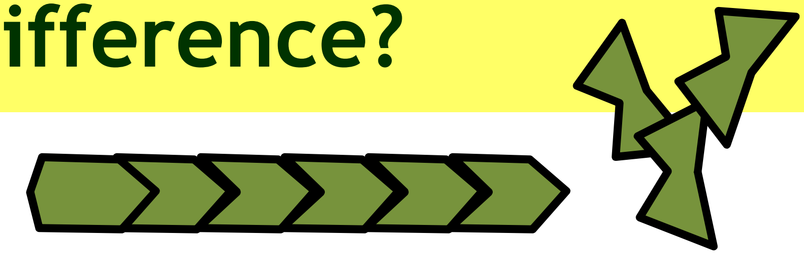
- Complexation is what proteins "do", in contrast to simpler chemicals.



- Leading to a process algebra that we call the Biochemical Ground Form (BGF).

What's the Difference?

Consider linear polymerization:



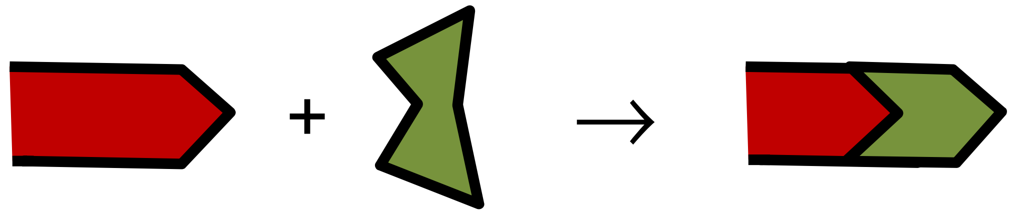
The "chemical program" for polymerization:

$P_0 + M \rightarrow P_1$
$P_1 + M \rightarrow P_2$
$P_2 + M \rightarrow P_3$
$P_3 + M \rightarrow P_4$
....

- an infinite (non-)program
- an infinite set of species
- an infinite set of ODEs

$P_{10757} + M \rightarrow P_{10758}$
Such specificity is unreal.

But "nature's program" for polymerization has to fit e.g. in the genome, so it cannot be infinite! Clearly, nature must be using a different "language" than basic chemistry:



molecule with convex patch +
molecule with concave patch →
molecule with convex patch

- a finite program
- a local rule

Expressiveness of Biochemistry

- Basic chemistry (FSRN, or CGF) is not Turing-complete
  - By reduction to Petri Net reachability [Soleveichik&al.].
- Biochemistry (FSRN + complexation, or BGF) is Turing-complete.
  - By an encoding of Random Access Machines, using polymers for registers.
- A relatively simple extension of our CGF automata
  - But it is not as easy to find a corresponding extension of chemistry!
- More powerful process algebras of course *are* Turing complete
  - They (e.g. π-calculus) include BGF, but they also have mechanisms that are not directly biologically justifiable.
  - In BGF we have in a sense the minimal biologically-inspired extension of FSRN, and it is already Turing-complete.
- Intrinsic to biochemistry (but not to simple chemistry) is a Turing-complete mechanism.

Conclusions

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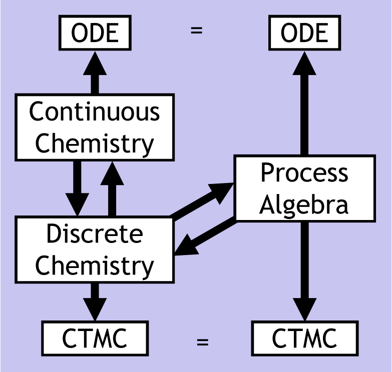

- Process Algebra
  - An extension of automata theory to populations of interacting automata
  - Modeling the behavior of individuals in an arbitrary environment
  - Compositionality (combining models by juxtaposition)

- 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, …)