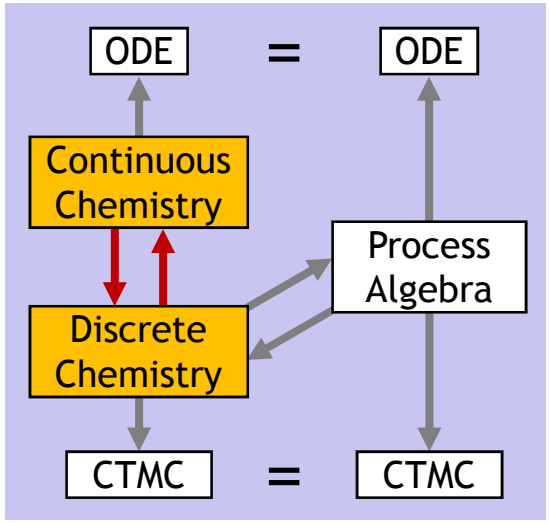
Discrete vs Continuous Chemistry



The "Type System" of Chemistry

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

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

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

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

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

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

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

Relating Concentration to Number of Molecules

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

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

#X / γ : M = concentration of X molecules

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

The Gillespie Conversion

Discrete Chemistry	Continuous Chemistry	$\gamma = N_A V$	$:M^{-1}$
initial quantities $\#A_0$	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

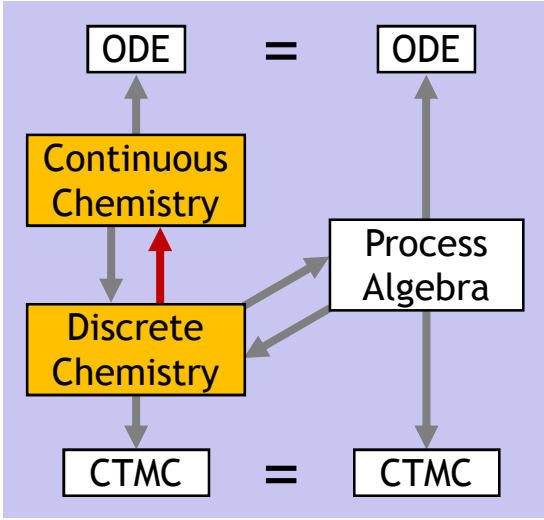
N_A = Avogadro's number

Think $\gamma = 1$

i.e. $V = 1/N_A$

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

molarity (concentration)



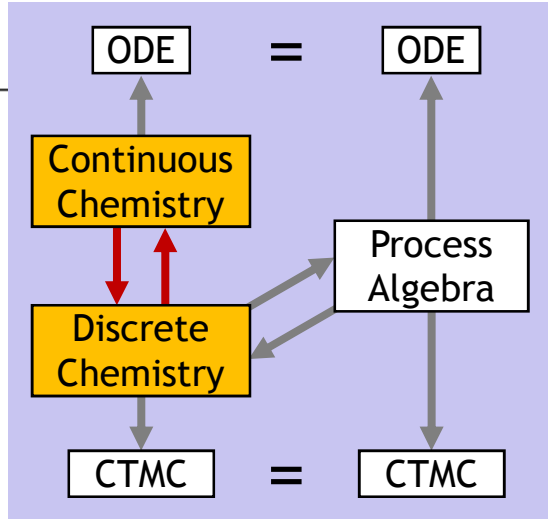
$Cont_\gamma$ and $Disc_\gamma$

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

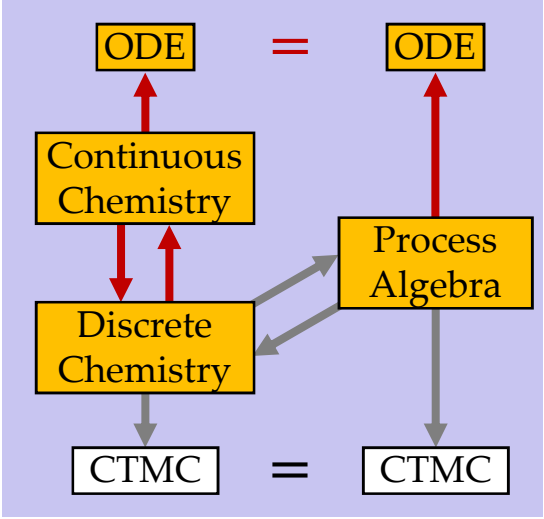
For a volumetric factor $\gamma:M^{-1}$, we define a translation $Cont_\gamma$ from a discrete chemical systems (C,P), with species X and initial molecule count $\#X_0 = \#X(P)$, to a continuous chemical systems (C,V) with initial concentration $[X]_0 = V_X$. The translation $Disc_\gamma$ is its inverse,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

$Cont_\gamma(X \to^r P)$	$= X \to^k P$	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 $\#X_0 = \lceil \gamma[X]_0 \rceil$	$[X]_0:M$	$X_0:mol$

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



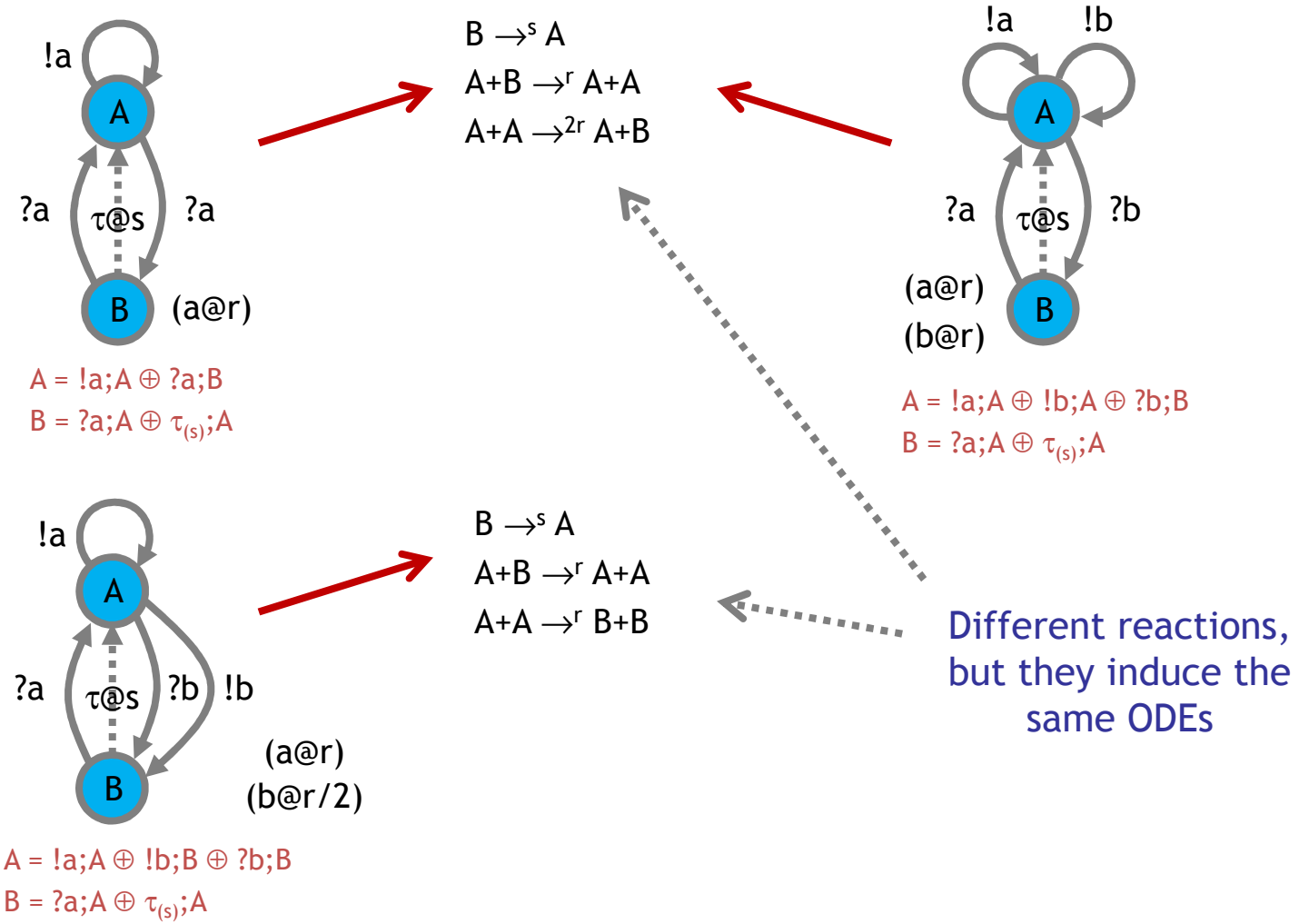
Continuous-State Semantics



Same Semantics

Could chemistry itself be that semantics?

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



From Reactions to ODEs (Law of Mass Action)

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

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

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

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

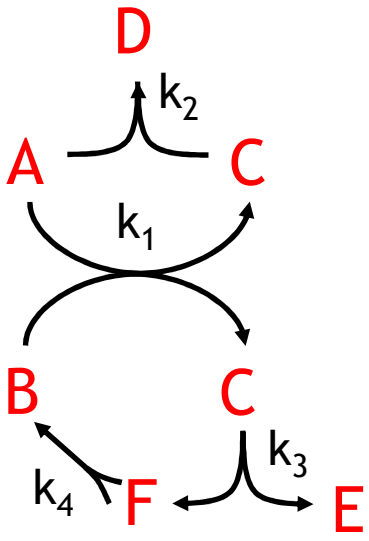
Write the coefficients by columns

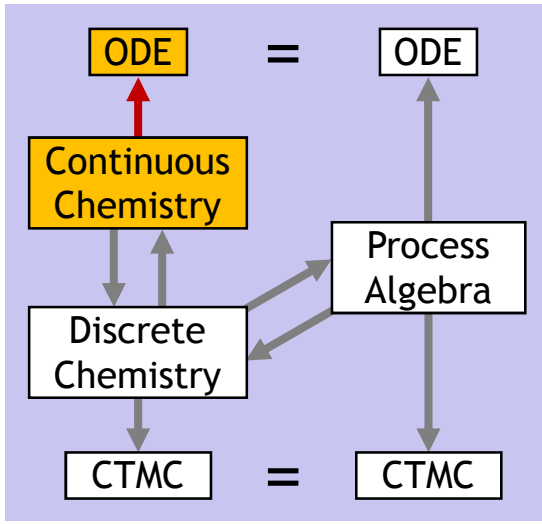
Stoichiometric Matrix

reactions

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

X





Quantity changes

Stoichiometric matrix

Rate laws

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

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

Read the concentration changes from the rows

$d[A]/dt = -l_1 - l_2$

$d[B]/dt = -l_1 + l_4$

$d[C]/dt = 2l_1 - l_2 - l_3$

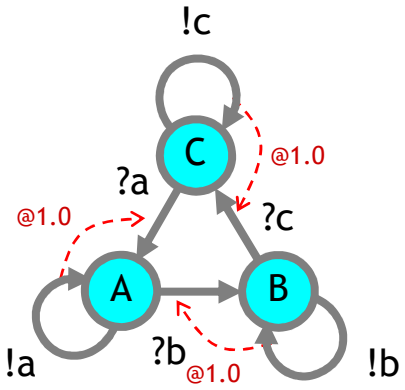
$d[D]/dt = l_2$

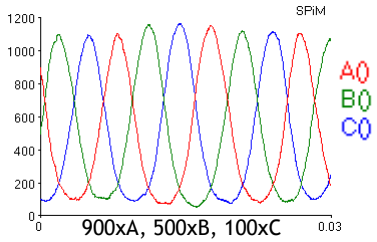
$d[E]/dt = l_3$

$d[F]/dt = l_3 - 2l_4$

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

From Processes to ODEs via Chemistry!





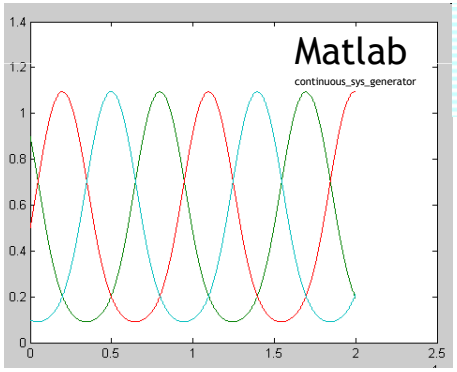

```
directive sample 0.03 1000
directive plot A(); B(); C()

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())
```

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

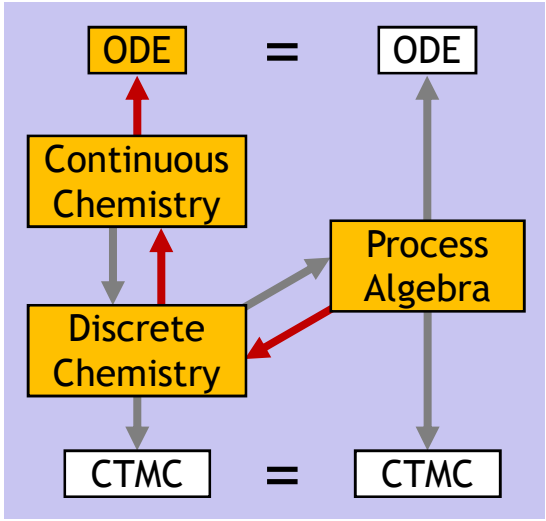
$$A+B \rightarrow^{s} B+B$$
$$B+C \rightarrow^{s} C+C$$
$$C+A \rightarrow^{s} A+A$$

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

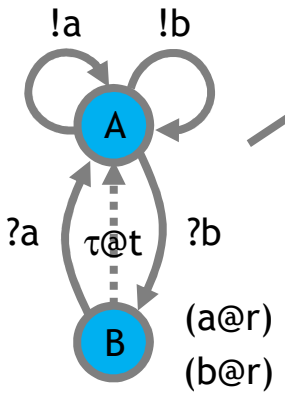
$(\gamma = 1)$




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



From Processes to ODEs via Chemistry!

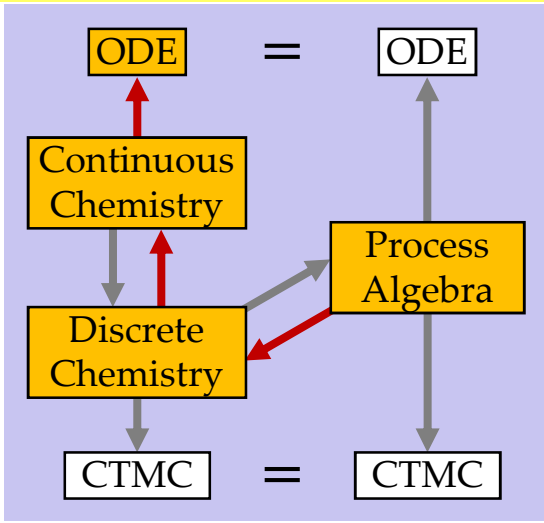


τ: $B \rightarrow^{t} A$
a: $A+B \rightarrow^{r} A+A$
b: $A+A \rightarrow^{2r} A+B$
(discrete reactions)

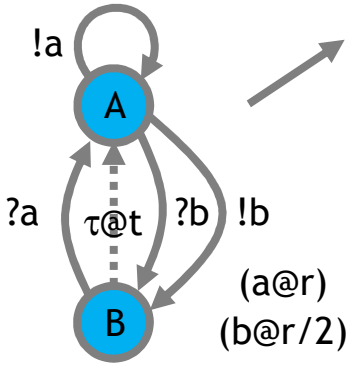
$B \rightarrow^{t} A$
$A+B \rightarrow^{r\gamma} A+A$
$A+A \rightarrow^{r\gamma} A+B$
(continuous reactions)

lose 1A at rate $r\gamma$

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



Different chemistry but same ODEs, hence equivalent automata



τ: $B \rightarrow^{t} A$
a: $A+B \rightarrow^{r} A+A$
b: $A+A \rightarrow^{r} B+B$
(discrete reactions)

$B \rightarrow^{t} A$
$A+B \rightarrow^{r\gamma} A+A$
$A+A \rightarrow^{r\gamma/2} B+B$
(continuous reactions)

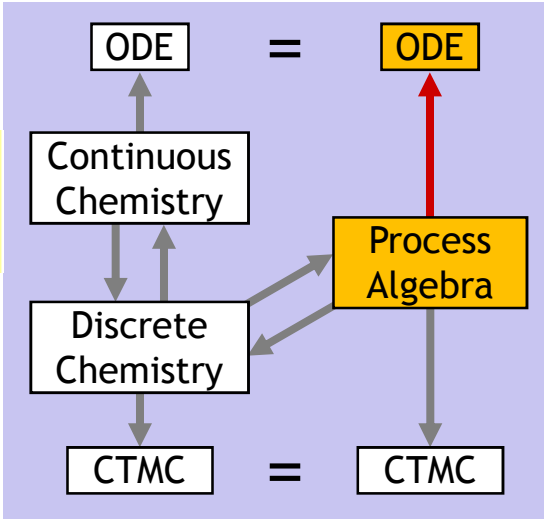
lose 2A at rate $r\gamma/2$

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

Processes Rate Equation

Process Rate Equation for Reagents E in volume 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"

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

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

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

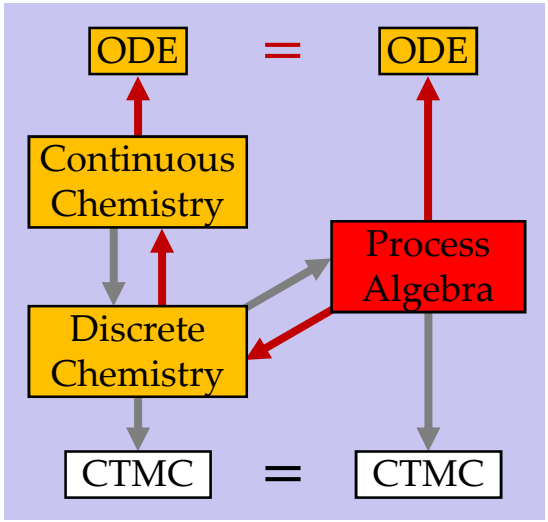
$X = \tau_{(r)};0 \rightarrow d[X]/dt = -r[X]$

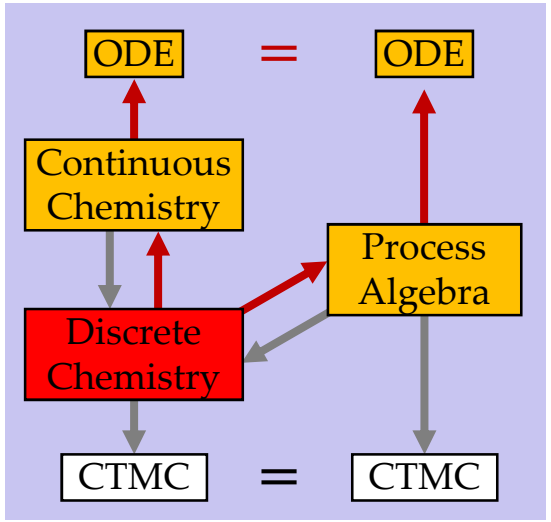
$X = ?a_{(r)};0 \rightarrow d[X]/dt = -r\gamma[X][Y]$
$Y = !a_{(r)};0 \rightarrow d[Y]/dt = -r\gamma[X][Y]$

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

Continuous State Equivalence

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

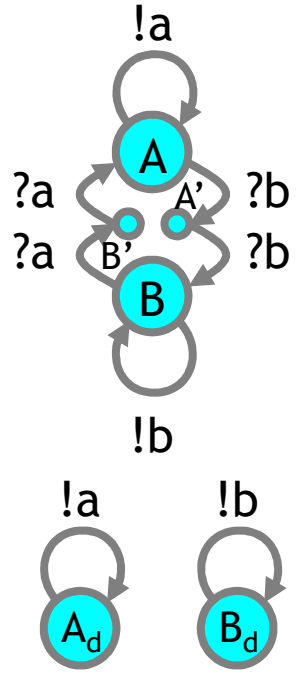


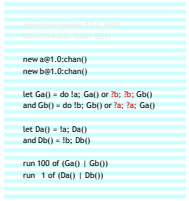


- For each E there is an E' ≈ E that is detangled (E' = Pi(Ch(E)))
- For each E in automata form there is an an E' ≈ E that is detangled and in automata form (E' = Detangle(E)).

Exercise 2

Q: What does this do?





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

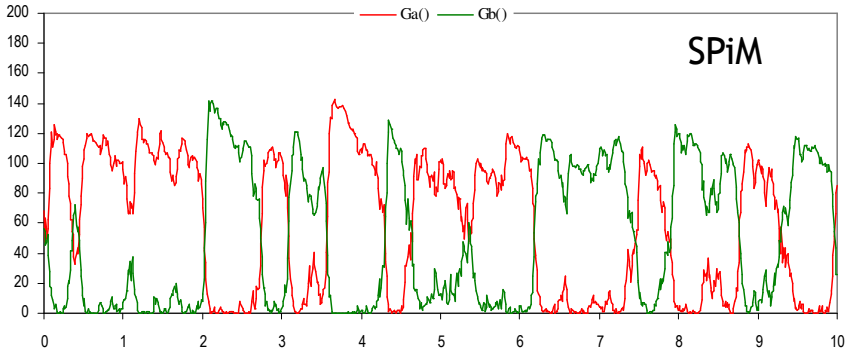
$B = !b_{(r)};B \oplus ?a;B'$ $B' = ?a;A$

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

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

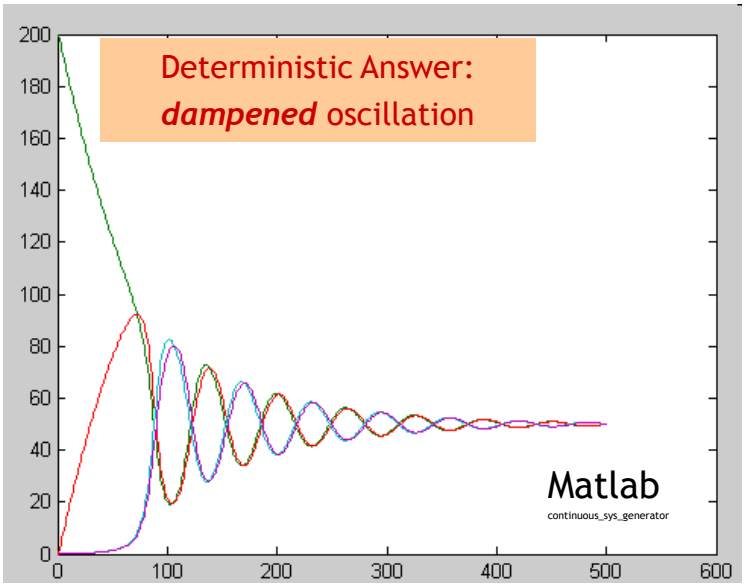
Derive the ODEs from these "Hysteric Groupies" automata. Either by going through the chemical reactions and the Law of Mass Action (easier), or directly from the Process Rate Equation.

Stochastic Answer:
robust quasi-oscillation



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

Deterministic Answer:
dampened oscillation



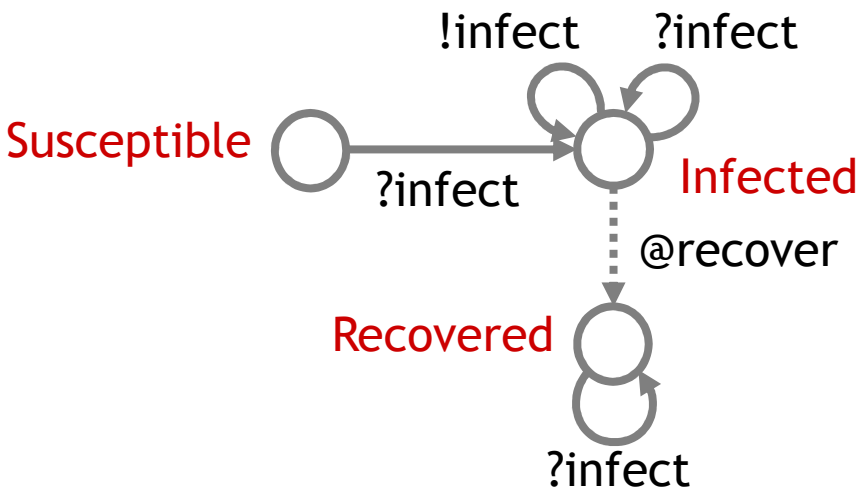
Epidemics

Non-Chemical Mass Action

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

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

Epidemics




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

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

let Recovered() =
  ?infect; Recovered()

and Susceptible() =
  ?infect; Infected()

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

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

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

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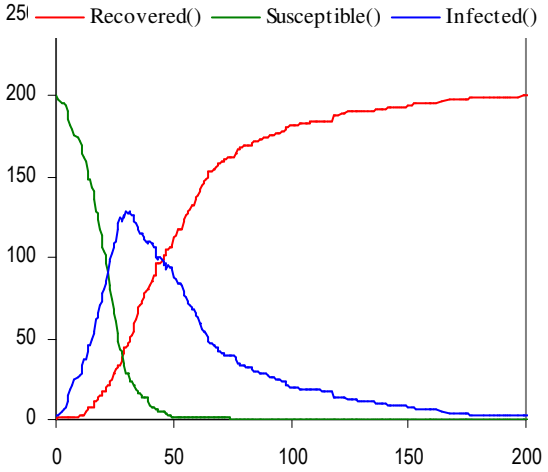
Abstract. We introduce a series of descriptions of disease spread using the process algebra WSCCS and compare the derived mean field equations with the traditional ordinary differential equation model. Even the preliminary work presented here brings to light interesting theoretical questions about the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



ODEs

$S = ?i_{(t)};I$

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

$R = ?i_{(t)};R$

Differentiating Processes!

$S + I \rightarrow^{t\gamma} I + I$

$I + I \rightarrow^{t\gamma} I + I$

$I \rightarrow^{r} R$

$R + I \rightarrow^{t\gamma} R + I$

"useless" reactions

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

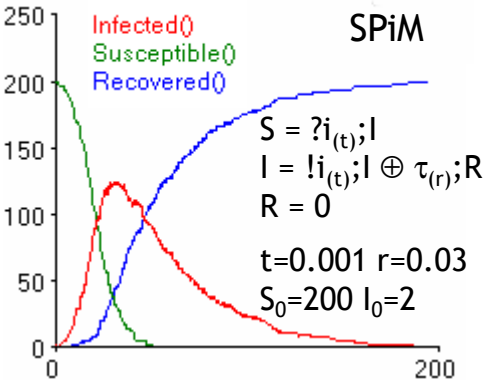
$d[I]/dt = t\gamma[S][I]-r[I]$

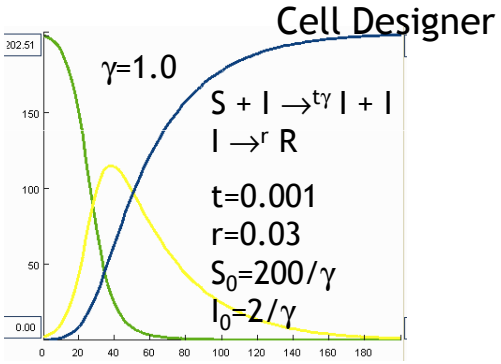
$d[R]/dt = r[I]$

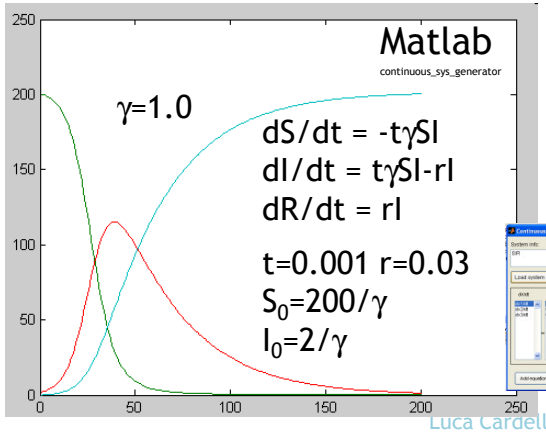
Automata produce the standard ODEs!

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

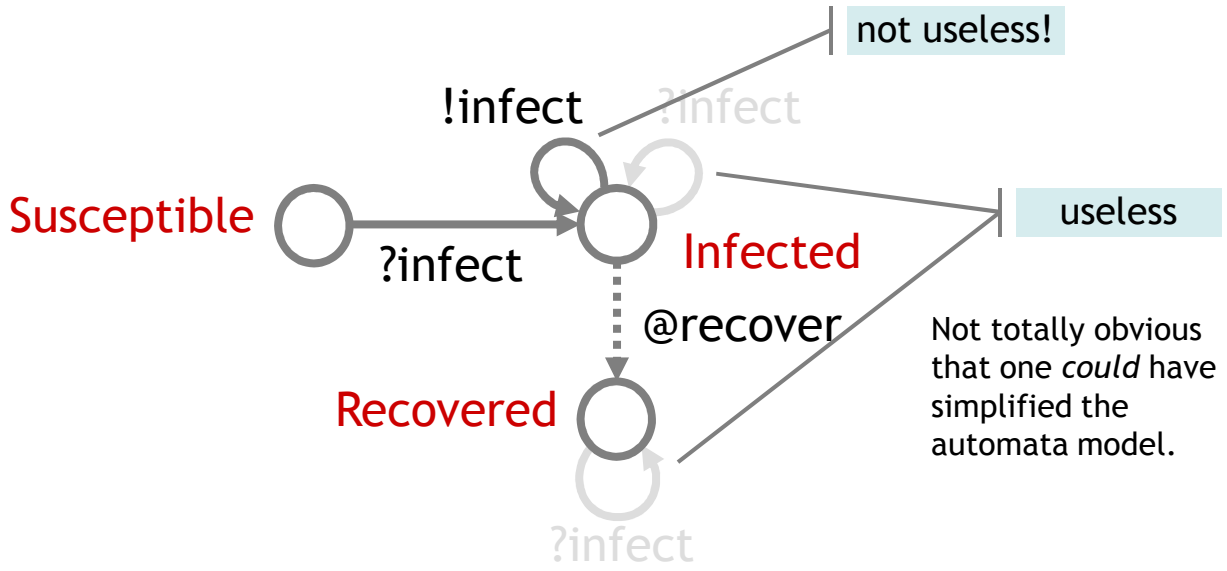
(the Kermack-McKendrick, or SIR model)







Simplified Model



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

$S = ?i_{(t)};I$

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

$R = 0$

$S + I \rightarrow^{t\gamma} I + I$

$I \rightarrow^{r} R$

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

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

$d[R]/dt = r[I]$

Same ODE, hence equivalent automata models.

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

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

let Recovered() =
  ()

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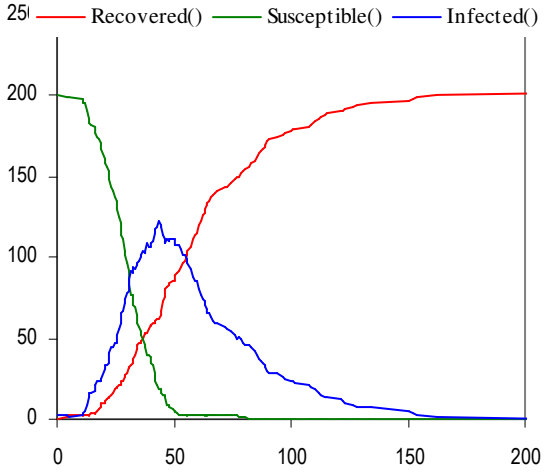
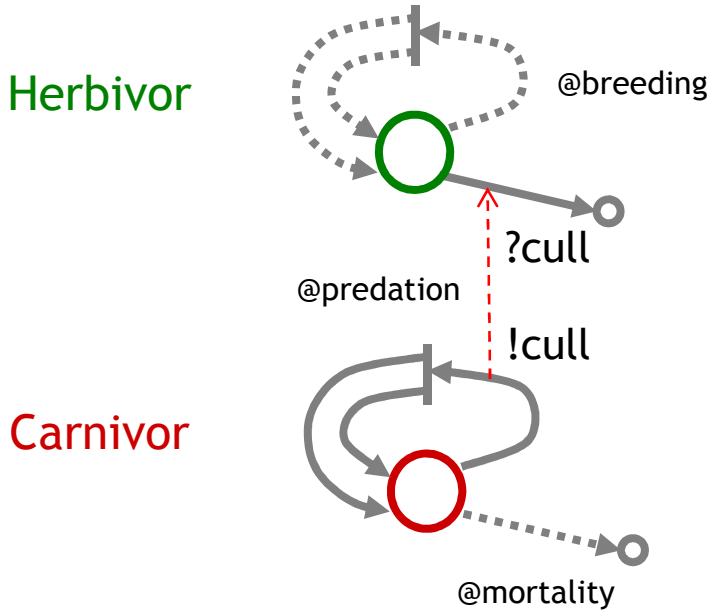



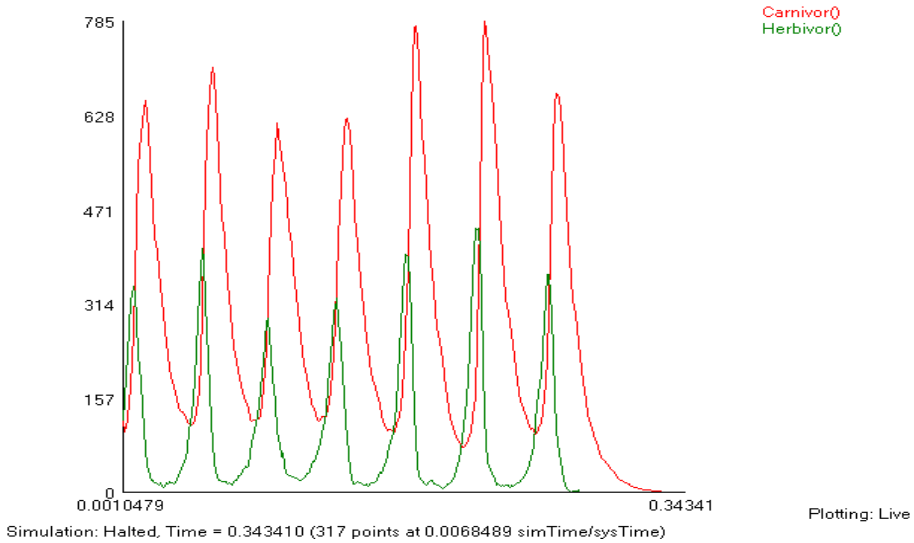
Lotka-Volterra

Unbounded Systems

Predator-Prey




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

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

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

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

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



An *unbounded state* system!

Lotka-Volterra in Matlab

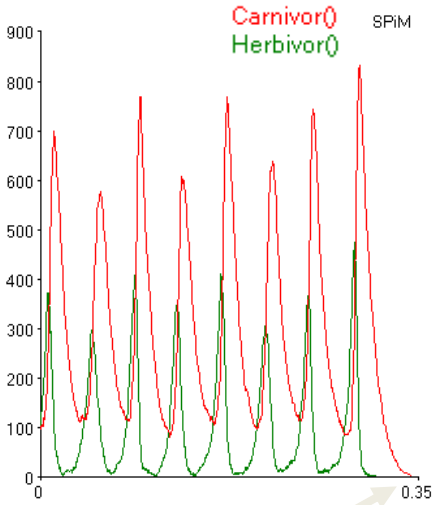
$H = \tau_b;(H|H) \oplus ?c_{(p)};0$
$C = \tau_m;0 \oplus !c_{(p)};(C|C)$
$\#H_0, \#C_0$

$H \rightarrow^b H + H$
$C \rightarrow^m 0$
$H + C \rightarrow^{p\gamma} C + C$
$[H]_0 = \#H_0/\gamma$
$[C]_0 = \#C_0/\gamma$

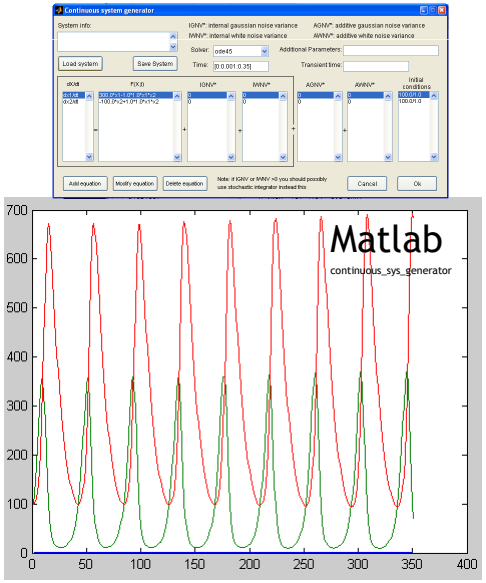
$d[H]/dt = b[H]-p\gamma[H][C]$
$d[C]/dt = -m[C]+p\gamma[H][C]$
$[H]_0 = \#H_0/\gamma$
$[C]_0 = \#C_0/\gamma$

$m=100.0$
$b=300.0$
$p=1.0$
$\gamma=1.0$
$\#H_0 = 100$
$\#C_0 = 100$

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

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

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

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

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



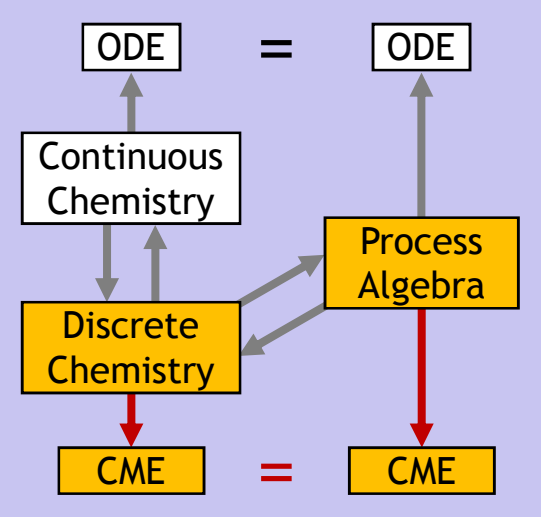
Extinction



No extinction

Which one is the “right prediction”?

Master Equation Semantics



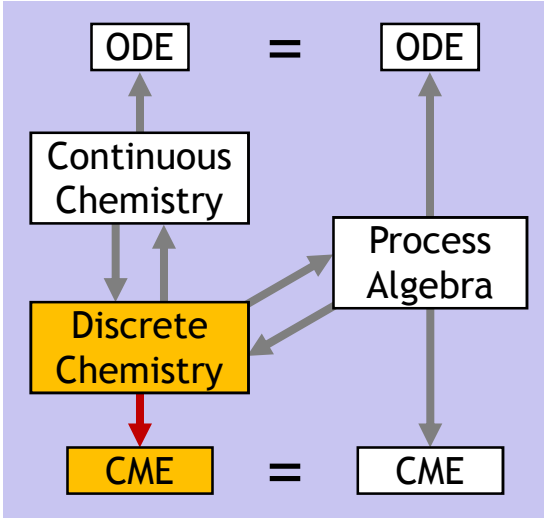
Chemical Master Equation

Chemical Master Equation for a chemical system C

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

Reactions — Propensity

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



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

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

There are 1..M chemical reactions.

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

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

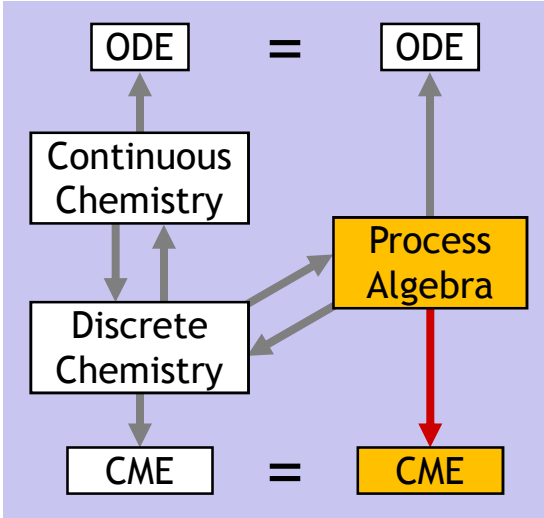
Process Algebra Master Equation

Process Master Equation for a system of reagents E

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

Interactions — Propensity

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



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

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

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

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

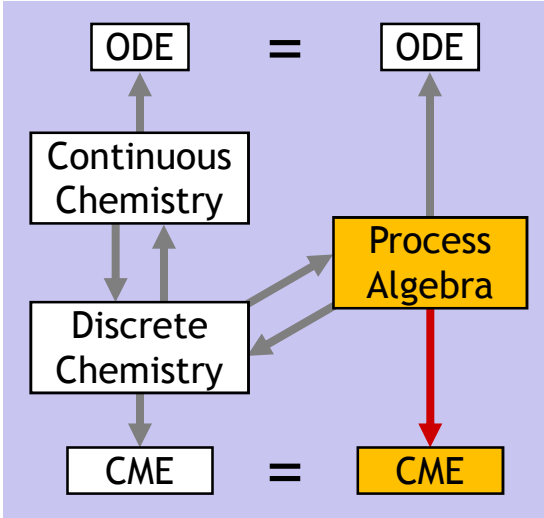
$a_i(r) = r_i\cdot h_i(r)$ is the *propensity* of interaction i in state r, defined by a base rate of interaction and a state-dependent count of the distinct combinations of reagents. (It depends on the kind of interaction.)

… details

Process Master Equation for Reagents E

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

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



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

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

$v_i = -X+Q$ if $i = \{X.i\}\ s.t.\ E.X.i = \tau_{(r)};Q$

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

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

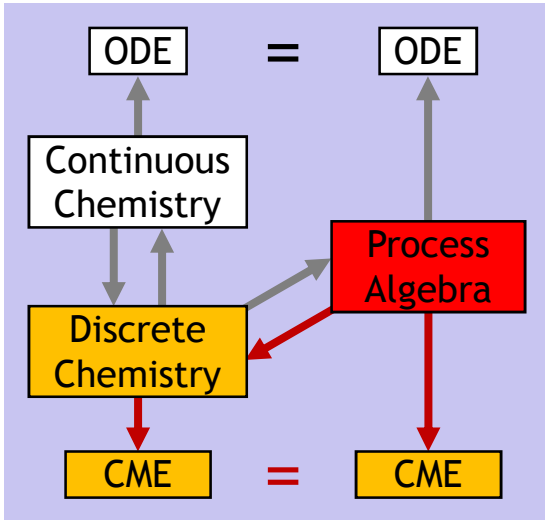
$a_i(p) = r\cdot p^{\#X}$ if $i = \{X.i\}\ s.t.\ E.X.i = \tau_{(r)};Q$

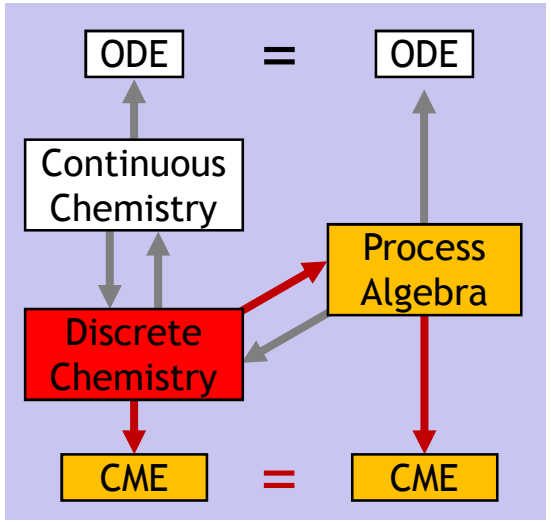
$a_i(p) = r\cdot p^{\#X}\cdot p^{\#Y}$ if $i = \{X.i, Y.j\}\ s.t.\ X\neq Y$ and $E.X.i = ?a_{(r)};Q$ and $E.Y.j = !a_{(r)};R$

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

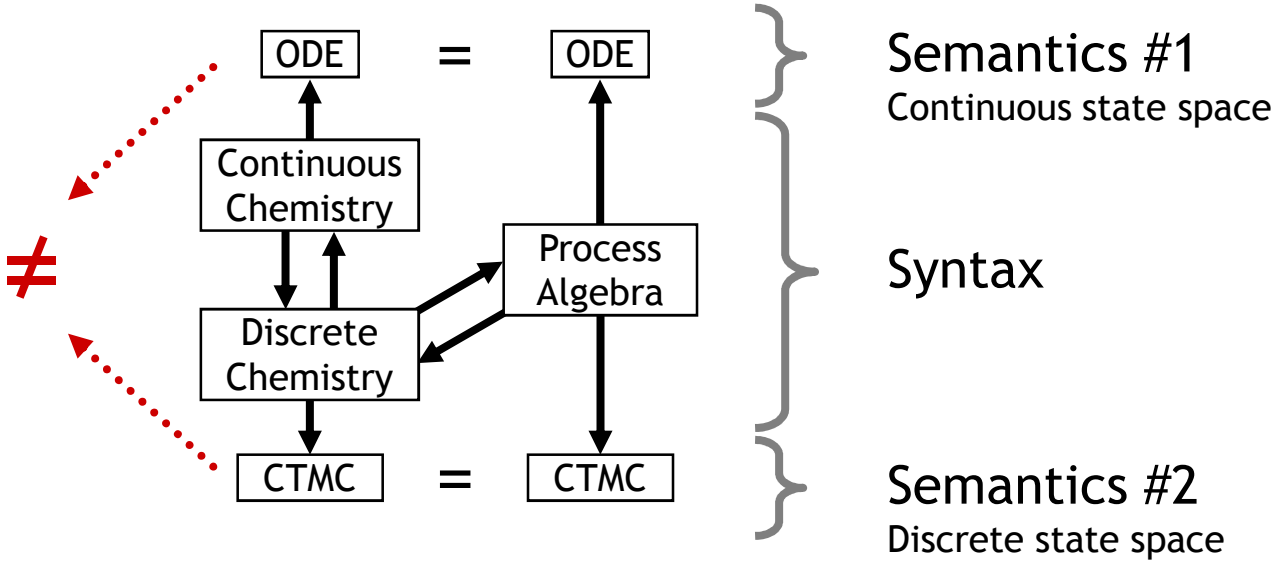
Equivalence of Master Equations

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





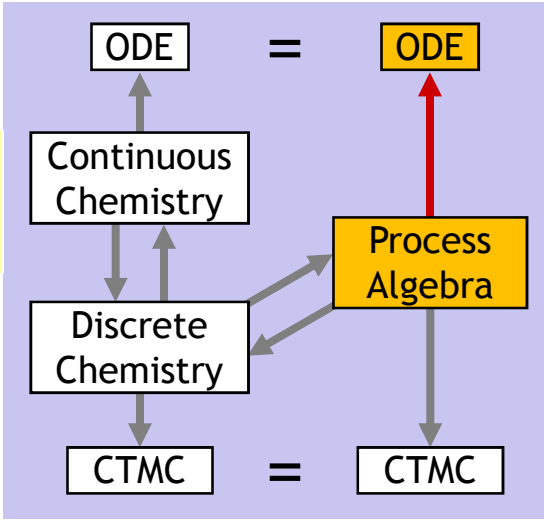
GMA ≠ CME


ODE
=
ODE
Continuous Chemistry
≠
Process Algebra
Discrete Chemistry
CTMC
=
CTMC
Semantics #1
Continuous state space
Syntax
Semantics #2
Discrete state space

Processes to GMA Directly

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"

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

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

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

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

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

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

Process Algebra Master Equation

Process Master Equation for a system of reagents E

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

Interactions — Propensity

"The change of probability at time t of a state is:
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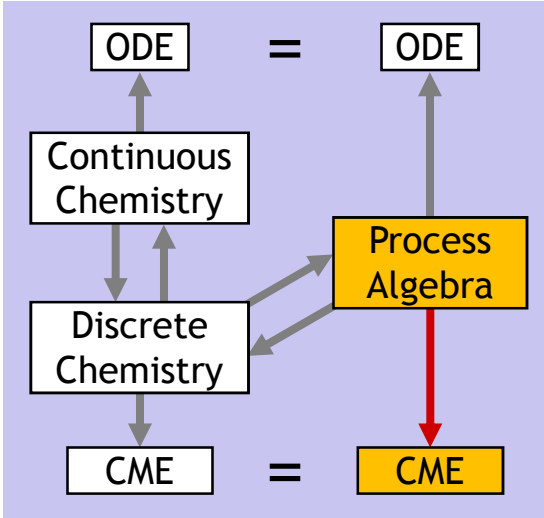
minus the probability at time t of the current state
times the propensity of each interaction in the current state"



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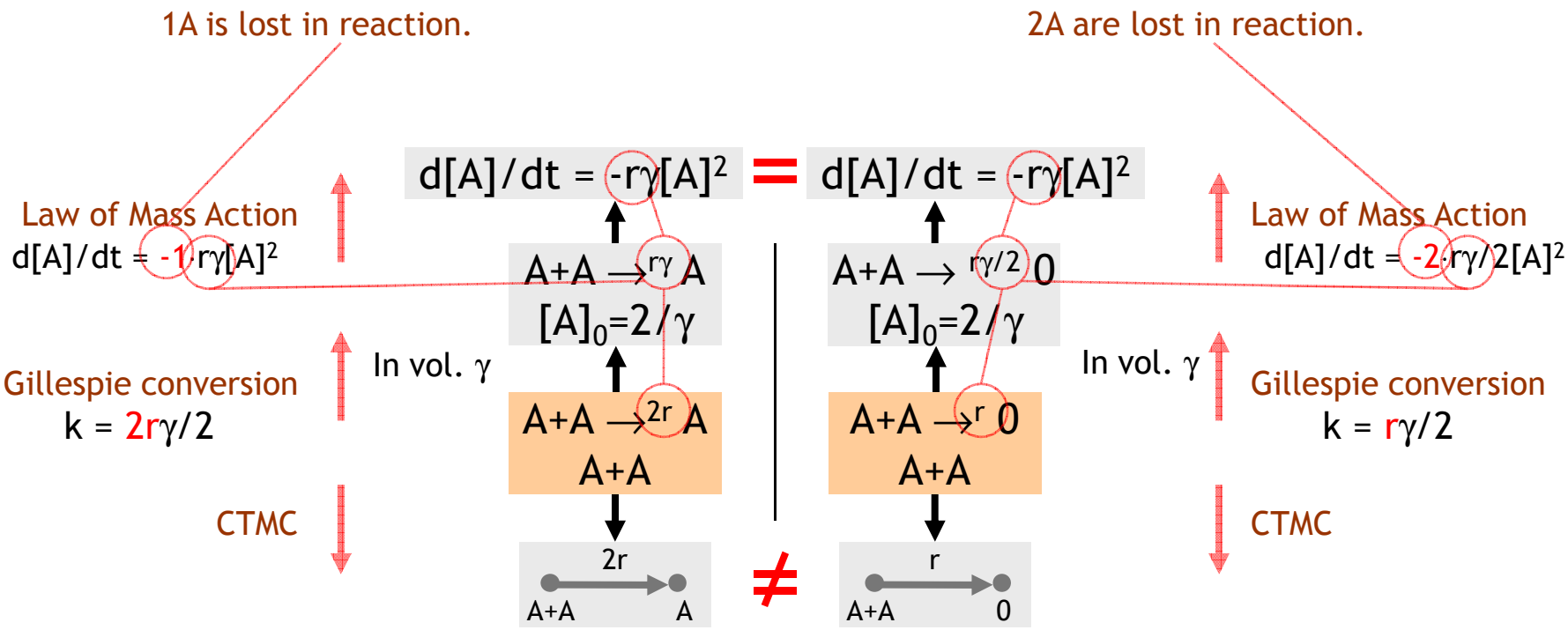
$\Im$ is the finite set of *possible interactions* arising from a set of reagents E. (All τ and all ?a/!a pairs in E)

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

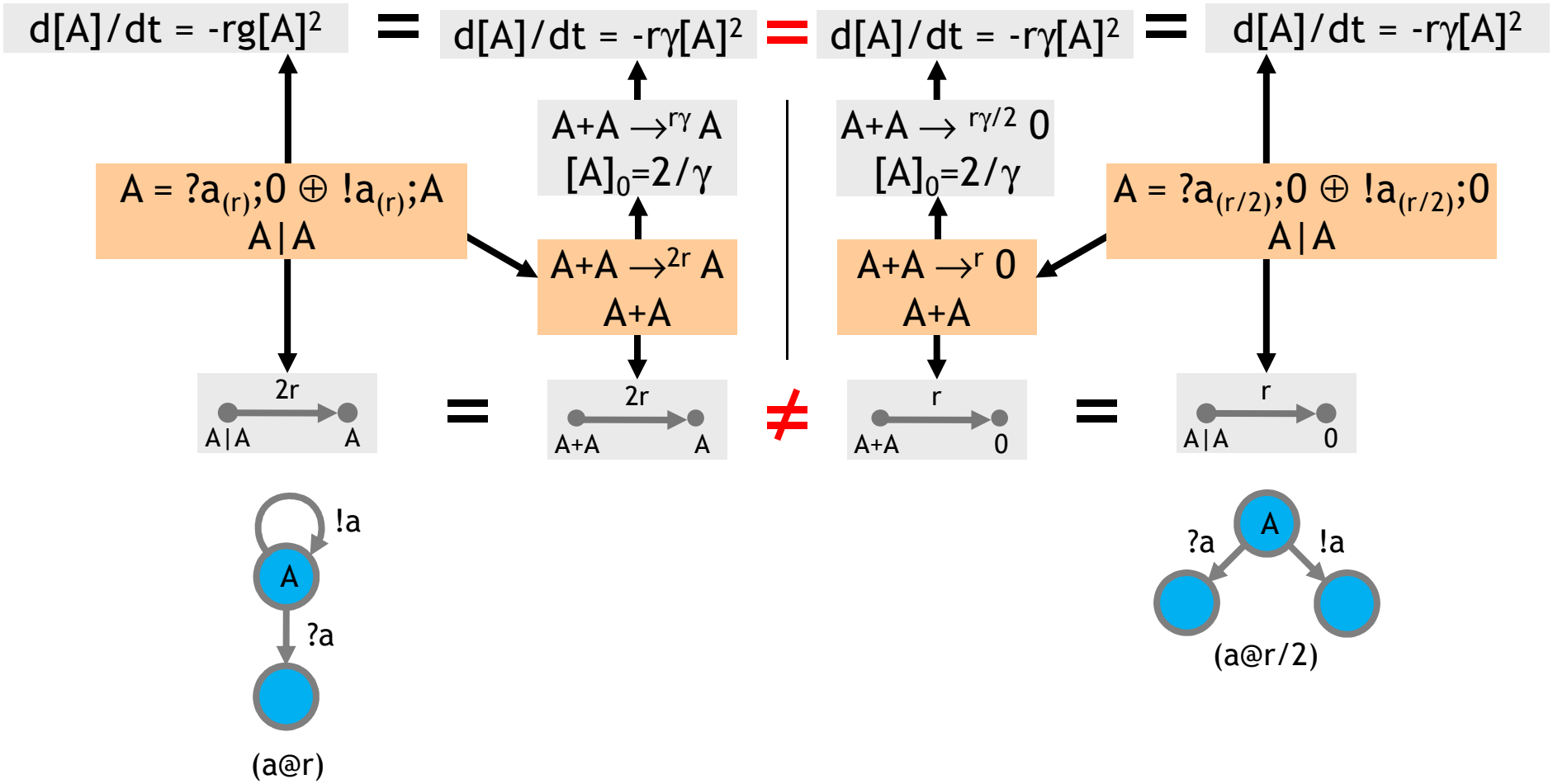
$a_i(r) = r_i\cdot h_i(r)$ is the *propensity* of interaction i in state r, defined by a base rate of interaction and a state-dependent count of the distinct combinations of reagents. (It depends on the kind of interaction.)

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

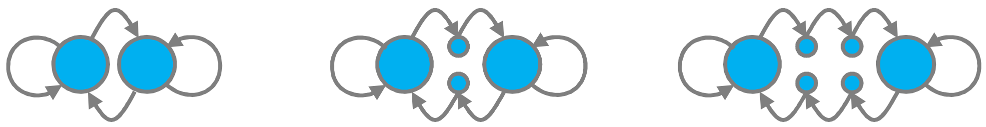


(For conservation of mass, consider instead $A+A \rightarrow^{2r} A+B$ vs. $A+A \rightarrow^{r} B+B$)

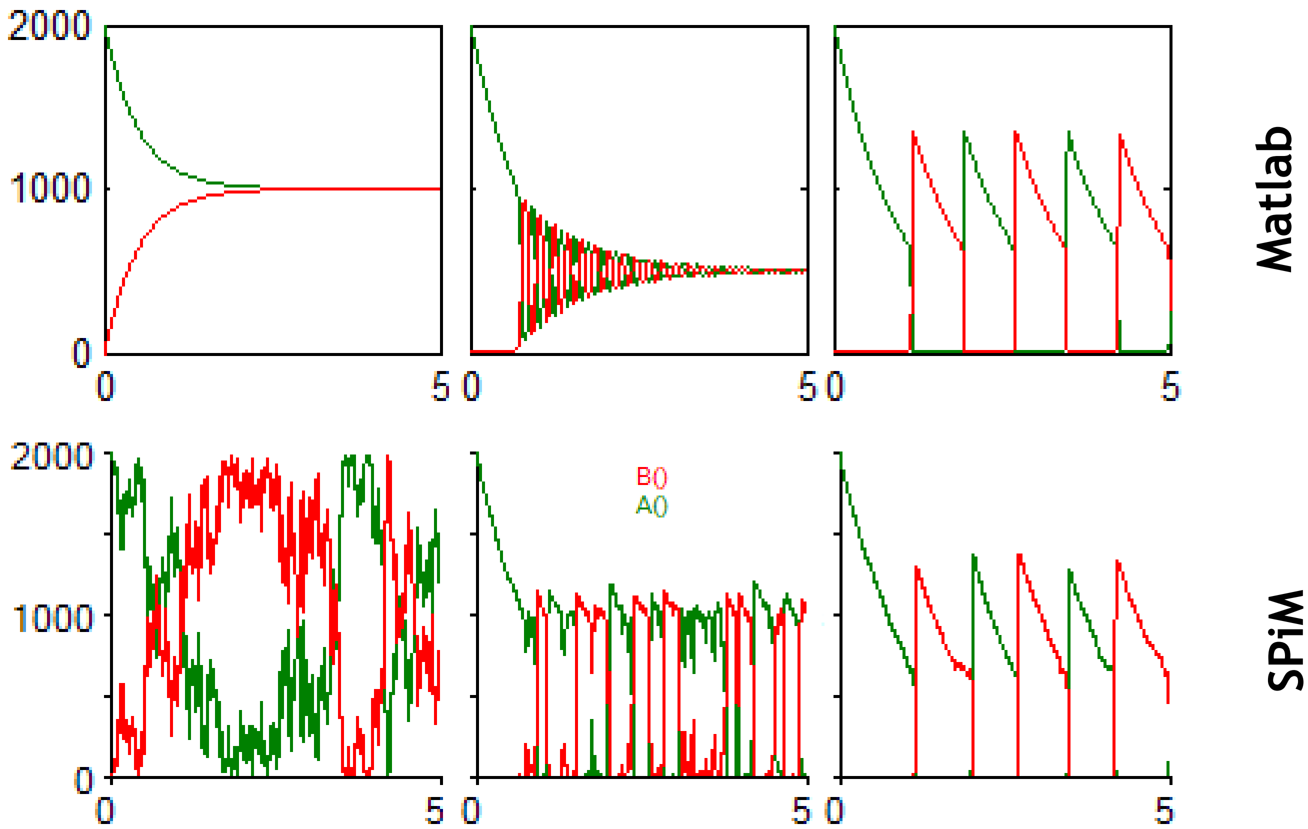
$A+A \rightarrow^{2r} A$ =? $A+A \rightarrow^{r} 0$



Continuous vs. Discrete Groupies



(all with doping)



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

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

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

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

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

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

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

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

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

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

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

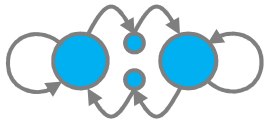
```
directive sample 5.0 1000
directive plot B(); A()

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

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

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

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

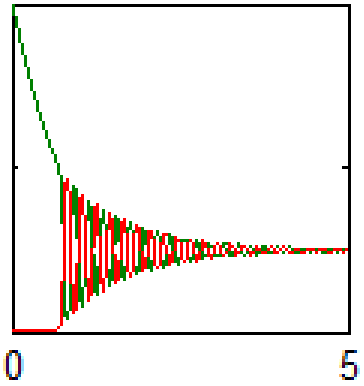
```
Groupe ODEs - Groupies.mat

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

```
Groupe ODEs - Groupies Hysteric 1.mat

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

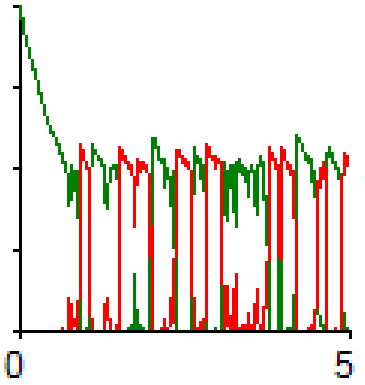
```
Groupe ODEs - Groupies Hysteric 2.mat

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

Scientific Predictions





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

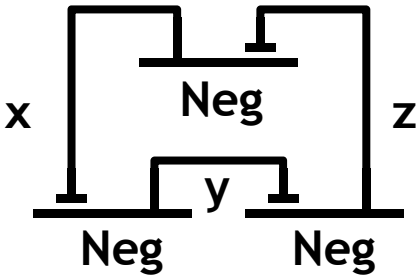


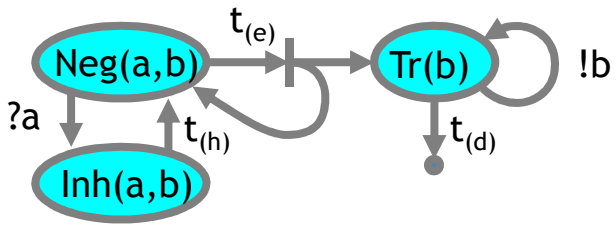
The 4 states are almost never equally occupied.

And Yet It Moves

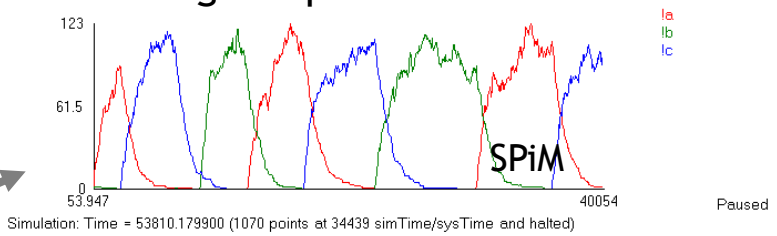
R.Blossey, L.Cardelli, A.Phillips: **Compositionality, Stochasticity and Cooperativity in Dynamic Models of Gene Regulation** (HFSP Journal)

The Repressilator





A fine stochastic oscillator over a wide range of parameters.



Parametric representation

$Neg(a,b) = ?a;\ Inh(a,b) \oplus \tau_e;\ (Tr(b) \mid Neg(a,b))$

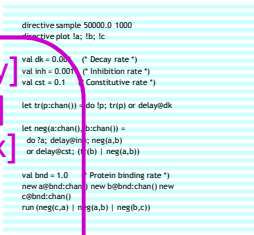
$Inh(a,b) = \tau_h;\ Neg(a,b)$

$Tr(b) = !b;\ Tr(b) \oplus \tau_g;\ 0$

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

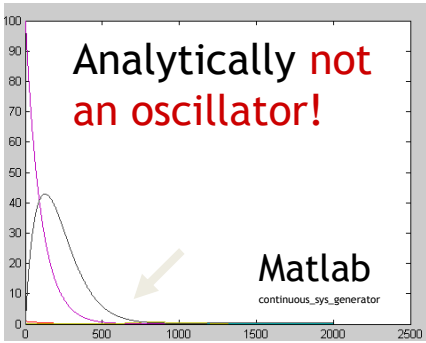
$Neg/x,y \to^{e} Tr/y + Neg/x,y$
$Neg/y,z \to^{e} Tr/z + Neg/y,z$
$Neg/z,x \to^{e} Tr/x + Neg/z,x$
$Tr/x + Neg/x,y \to^{r} Tr/x + Inh/x,y$
$Tr/y + Neg/y,z \to^{r} Tr/y + Inh/y,z$
$Tr/z + Neg/z,x \to^{r} Tr/z + Inh/z,x$
$Inh/x,y \to^{h} Neg/x,y$
$Inh/y,z \to^{h} Neg/y,z$
$Inh/z,x \to^{h} Neg/z,x$
$Tr/x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

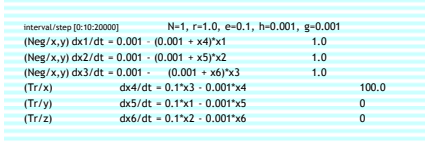
$d[Neg/x,y]/dt = -r[Tr/x][Neg/x,y] + h[Inh/x,y]$
$d[Neg/y,z]/dt = -r[Tr/y][Neg/y,z] + h[Inh/y,z]$
$d[Neg/z,x]/dt = -r[Tr/z][Neg/z,x] + h[Inh/z,x]$
$d[Inh/x,y]/dt = r[Tr/x][Neg/x,y] - h[Inh/x,y]$
$d[Inh/y,z]/dt = r[Tr/y][Neg/y,z] - h[Inh/y,z]$
$d[Inh/z,x]/dt = r[Tr/z][Neg/z,x] - h[Inh/z,x]$
$d[Tr/x]/dt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



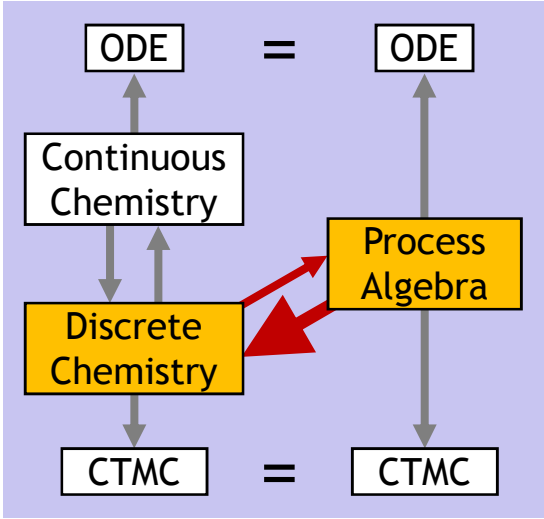
simplifying (N is the quantity of each of the 3 gates)

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





Model Compactness



n^2 Scaling Problems

- E_n has 2n variables (nodes) and 2n terms (arcs).
- $Ch(E_n)$ has 2n species and n^2 reactions.
- The stoichiometric matrix has size $2n \cdot n^2 = 2n^3$.
- The ODEs have 2n variables and $2n(n+n) = 4n^2$ terms
  (number of variables times number of accretions plus depletions when sums are distributed)

E_3

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

$Ch(E_3)$

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

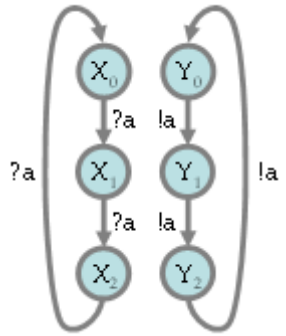
StoichiometricMatrix($Ch(E_3)$)

	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

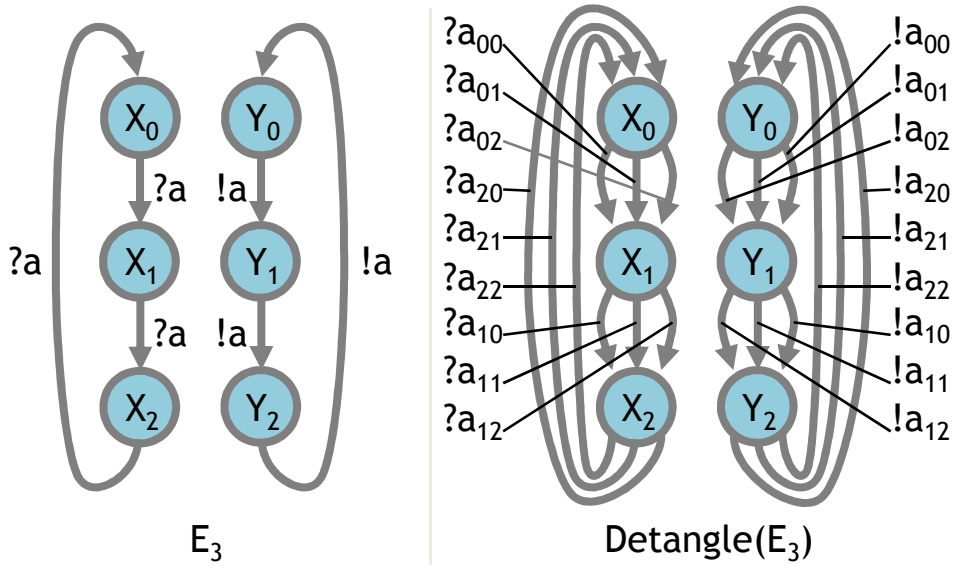
$ODE(E_3)$

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

E_3



Entangled vs detangled

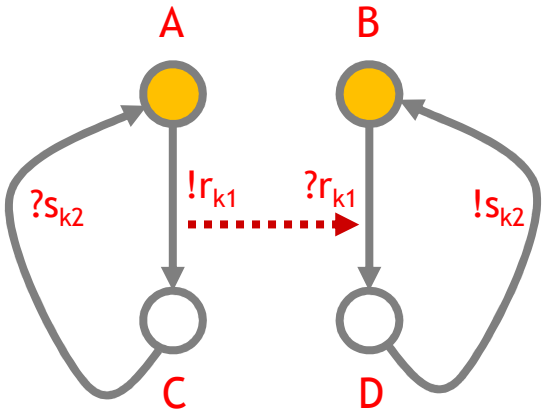


E_3 Detangle(E_3)

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

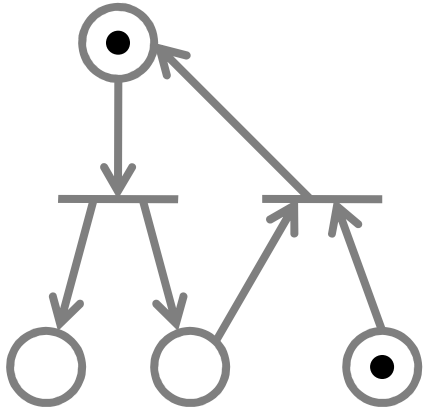
Model Maintenance

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



Or

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

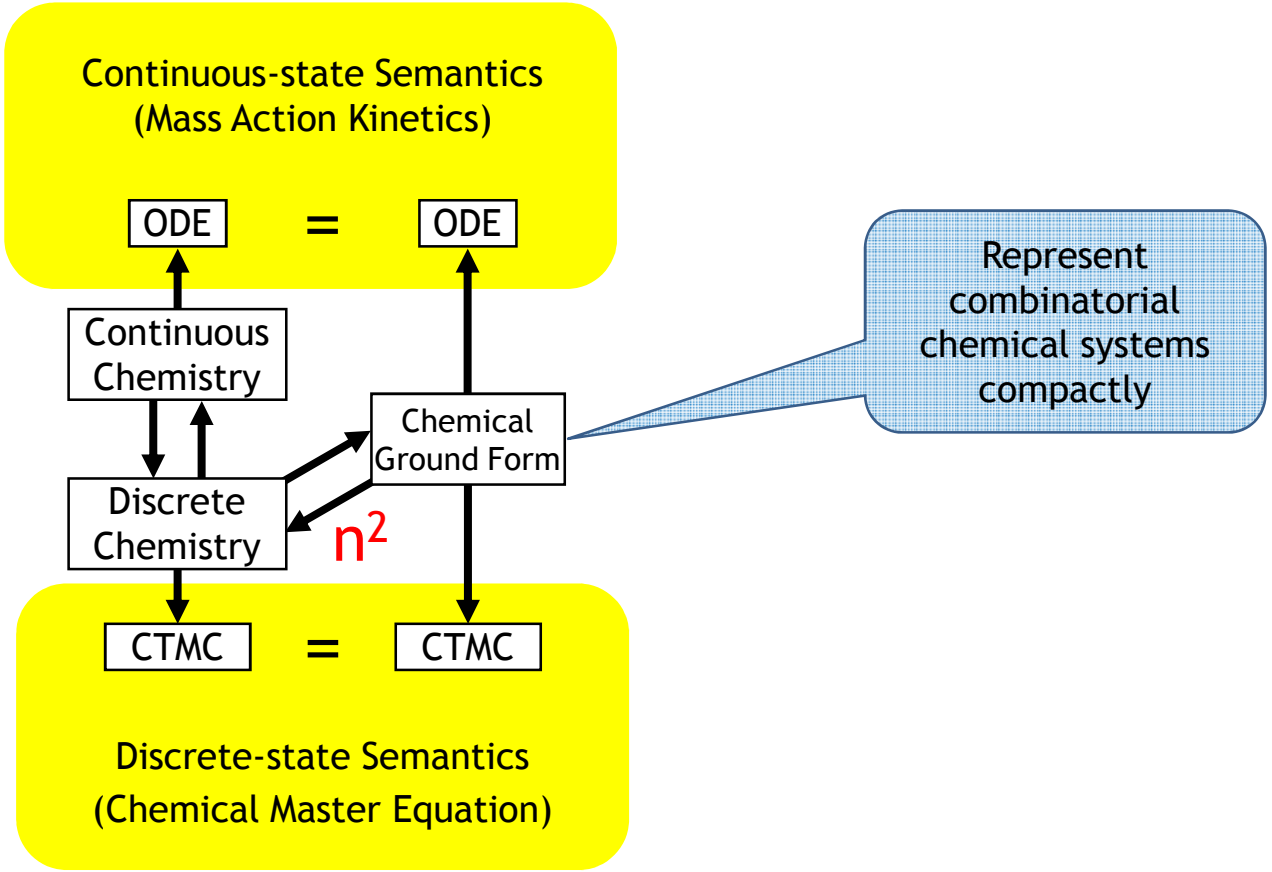


Or …

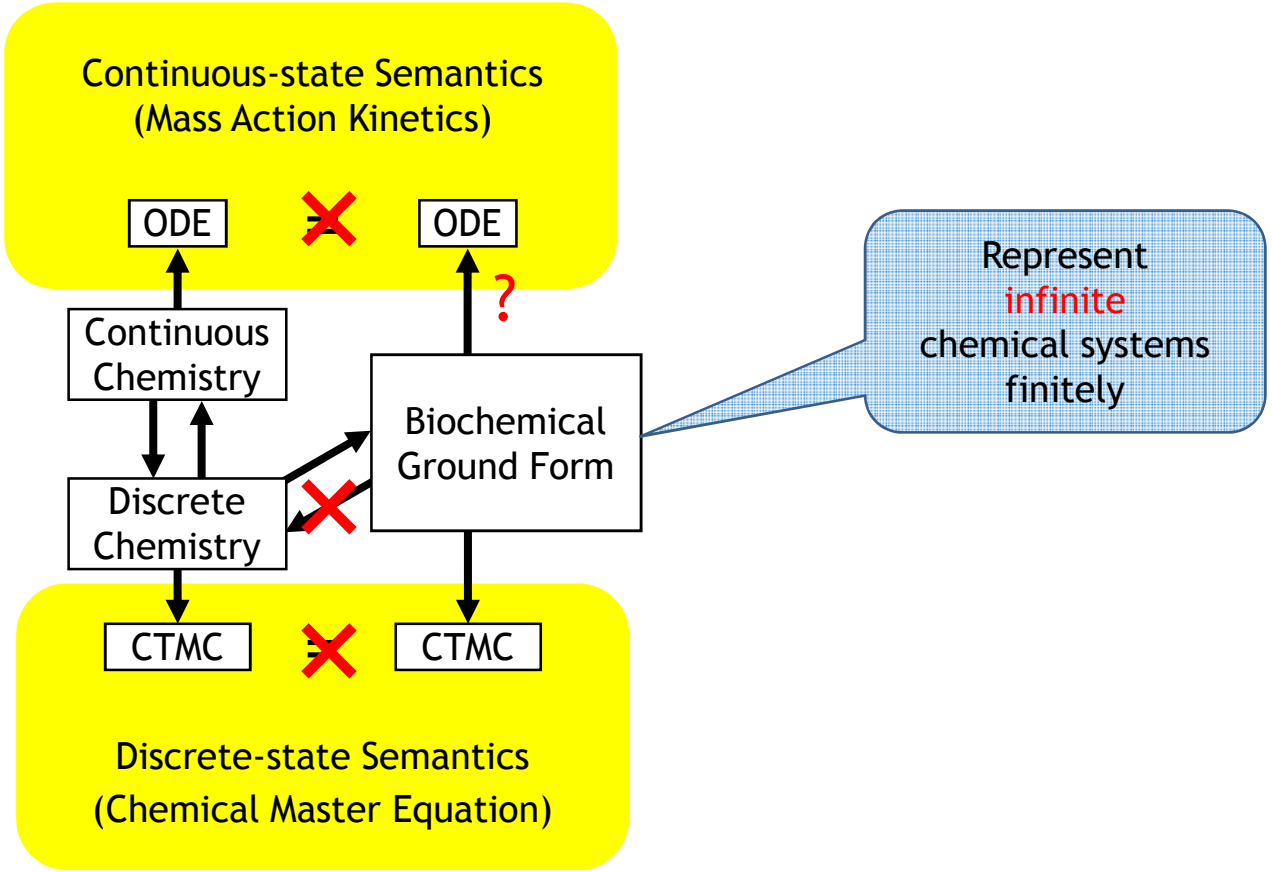
- There is a good way:
  - Describe biochemical systems compositionally
  - Each component with its own state and interactions
  - … as Nature intended…

Chemistry *and Beyond*

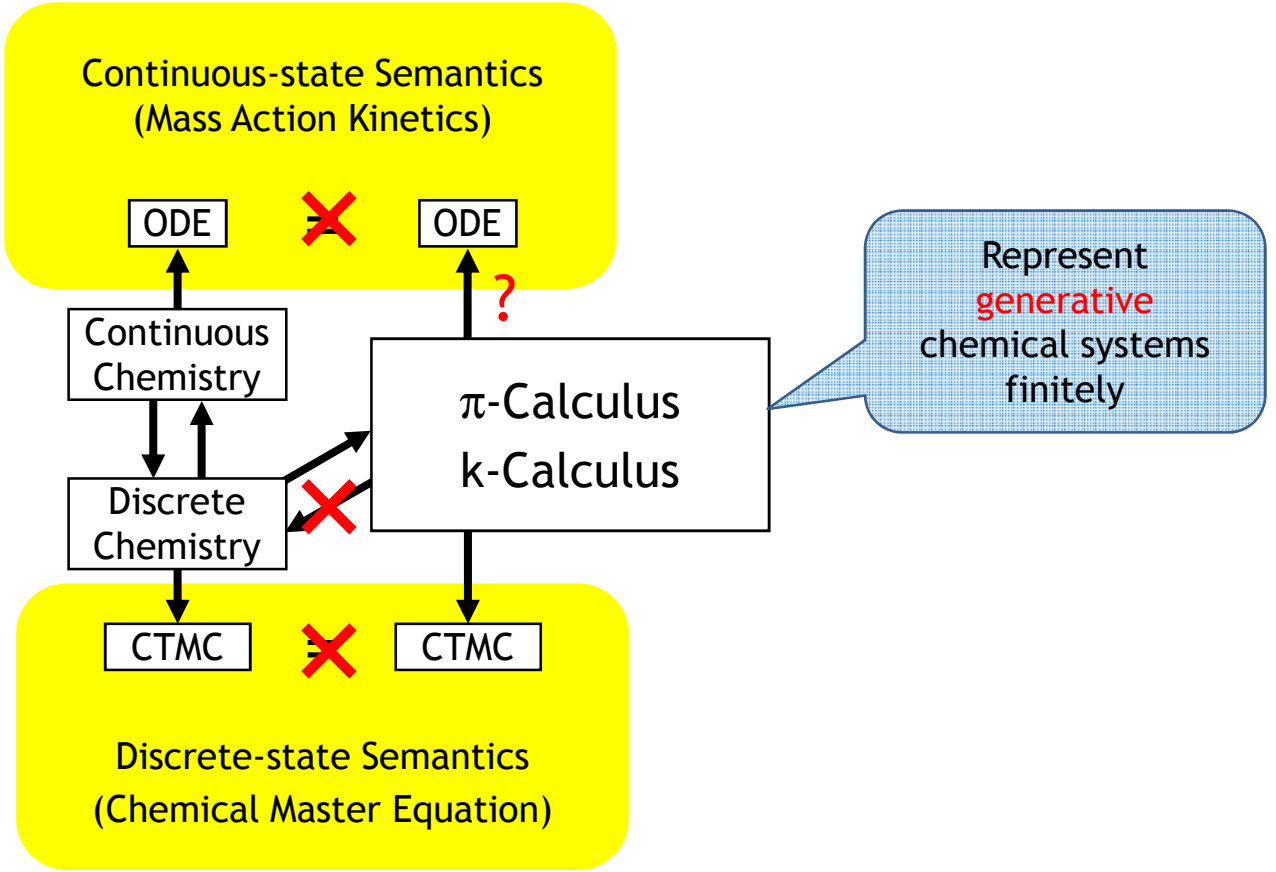
Process Algebra is 'Bigger' than Chemistry



Process Algebra is 'Bigger' than Chemistry

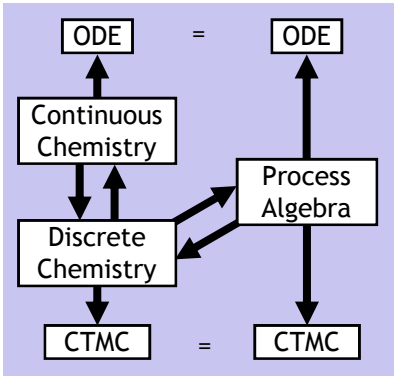


Process Algebra is 'Bigger' than Chemistry



Conclusions

Conclusions



- Process Algebra
  - An extension of automata theory to populations of interacting automata
  - Modeling the behavior of individuals in an arbitrary environment
  - Compositionality (combining models by juxtaposition)
- Connections between modeling approaches
  - Connecting the discrete/concurrent/stochastic/molecular approach
  - to the continuous/sequential/deterministic/population approach
- Connecting syntax with semantics
  - Syntax = model presentation (equations/programs/diagrams/blobs etc.)
  - Semantics = state space (generated by the syntax)
- Ultimately, connections between analysis techniques
  - We need (and sometimes have) good semantic techniques to analyze state spaces (e.g. calculus, but also increasingly modelchecking)
  - But we need equally good syntactic techniques to structure complex models (e.g. compositionality) and analyze them (e.g. process algebra)
- A bright future for Computer Science and Logic in modern Biology
  - Biology needs good analysis techniques for discrete systems analysis (modal logics, modelchecking, causality analysis, abstract interpretation, …)