On Process Rate Semantics

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Semantics of Collective Behavior

"Micromodels": Continuous Time Markov Chains

- The underlying semantics of stochastic process algebras.
  - Transition graphs with rates (*not* probabilities) on transitions.
- The molecular-level semantics of chemistry.
  - Executable: Gillespie stochastic simulation algorithm.
- But do not give a good sense of "collective" properties.
  - Yes it is "mechanistic".
  - Yes it supports classical Markov (e.g. steady-state) analysis.
  - Yes one can do simulation.
  - Yes one can do some program analysis/modelchecking.
  - But somewhat lacking in "predictive power" for collective dynamics, particularly for process algebras.

"Macromodels": Ordinary Differential Equations

- The classical semantics of collective behavior.
  - E.g. kinetic theory of gasses.

- Not standard for studying process algebras.
  - They always ask: "How is you process model related to the ODE models in the literature?"

- Going from processes algebras to ODEs <u>directly</u>:
  - *In principle*: just write down the Rate Equation: [Calder, Hillston]
    - Let [S] be the "number of processes in state S" as a function of time.
    - Define for each state S:

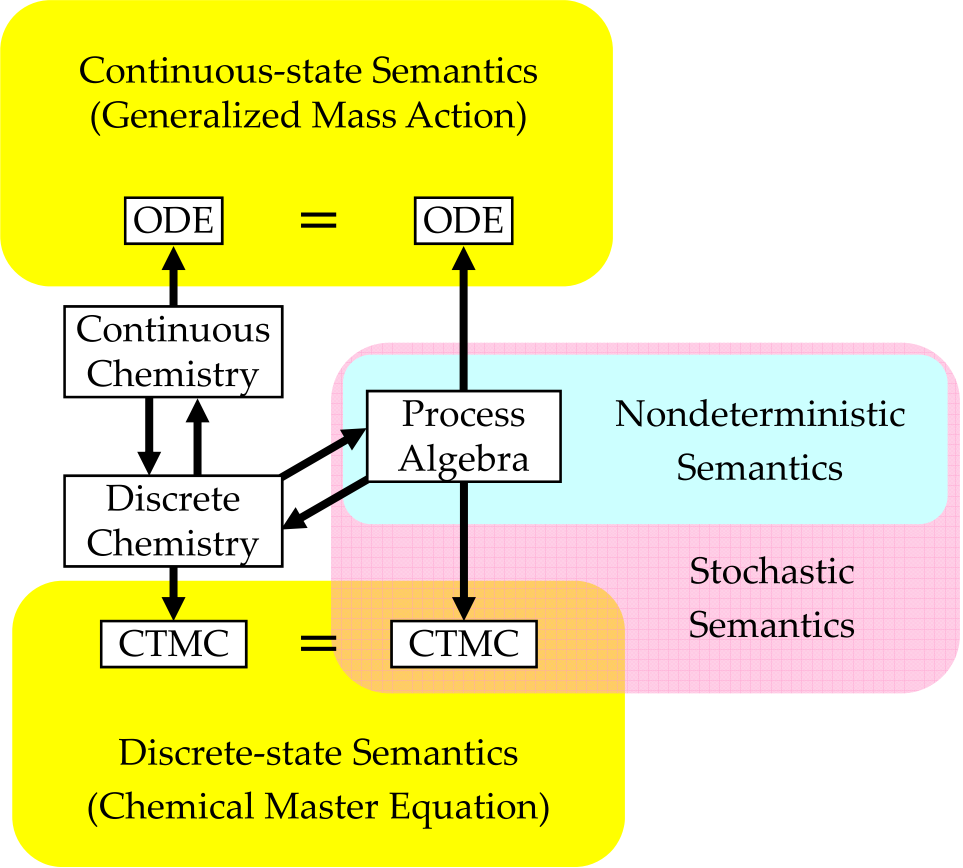
      $[S]^\bullet$ = (rate of change of the number of processes in state S)

      Cumulative rate of transitions from any state S' to state S, times [S'], minus cumulative rate of transitions from S to any state S", times [S].
  - I.e. rate = inflow minus outflow.

- Another way: going to ODEs <u>indirectly</u> through chemistry

  !
  - If we first convert processes to chemical reactions, then we can pass to ODEs by standard means!
  - This can be done "by hand".

Outline



Continuous-state Semantics
(Generalized Mass Action)

ODE = ODE

Continuous Chemistry

Discrete Chemistry

Process Algebra

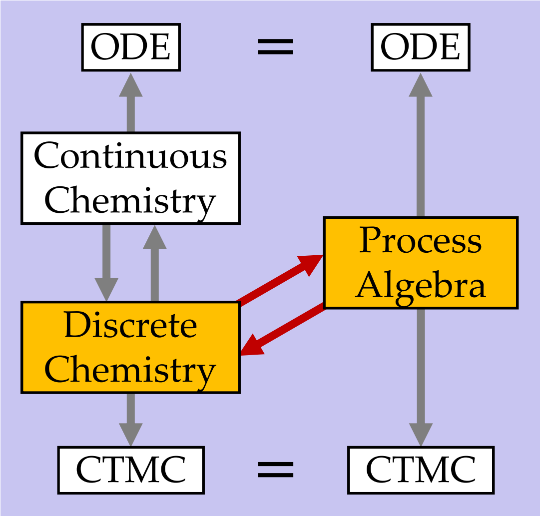
Nondeterministic Semantics

Stochastic Semantics

CTMC = CTMC

Discrete-state Semantics
(Chemical Master Equation)

Stochastic Processes & Discrete Chemistry



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

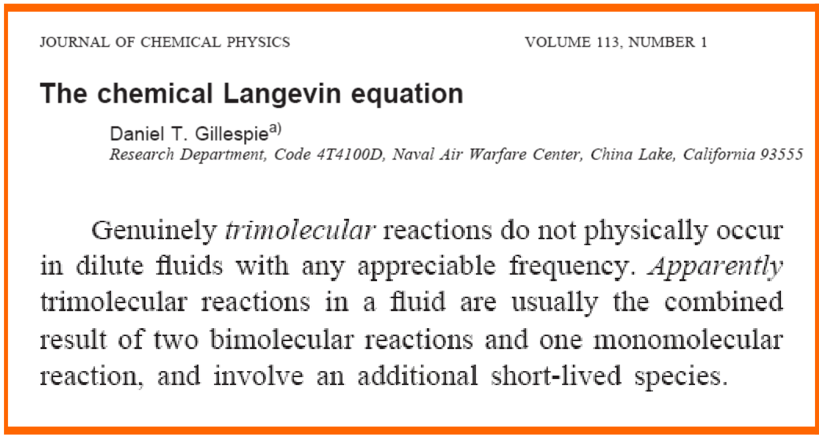
CTMC = CTMC

Chemical Reactions

$A \to^{r} B_1 + \ldots + B_n$	$(n \geq 0)$	Unary Reaction	$[A]^\bullet = -r[A]$	Exponential Decay
$A_1 + A_2 \to^{r} B_1 + \ldots + B_n$	$(n \geq 0)$	Hetero Reaction	$[A_i]^\bullet = -r[A_1][A_2]$	Mass Action Law
$A + A \to^{r} B_1 + \ldots + B_n$	$(n \geq 0)$	Homeo Reaction	$[A]^\bullet = -2r[A]^2$	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:

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

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)

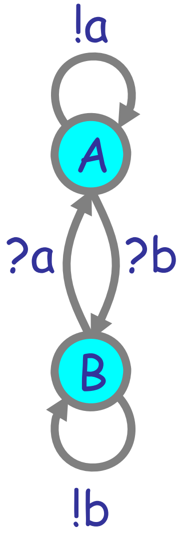
$E ::= 0 \;⁝\; X{=}M, E$	Reagents
$M ::= 0 \;⁝\; \pi;P \oplus M$	Molecules
$P ::= 0 \;⁝\; X \mid P$	Solutions
$\pi ::= \tau_{(r)} \;⁝\; ?a_{(r)} \;⁝\; !a_{(r)}$	Interactions (delay, input, output)
$CGF ::= E,P$	Reagents plus Initial Conditions

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.)

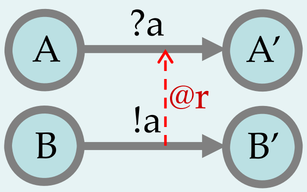
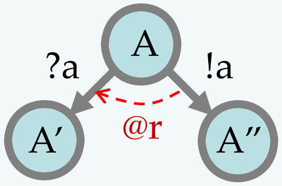
⊕ is stochastic choice (vs. + for chemical reactions)
0 is the null solution ($P|0 = 0|P = P$)
and null molecule ($M\oplus 0 = 0\oplus M = M$)
Each X in E is a distinct *species*
Each name a is assigned a fixed rate r: $a_{(r)}$

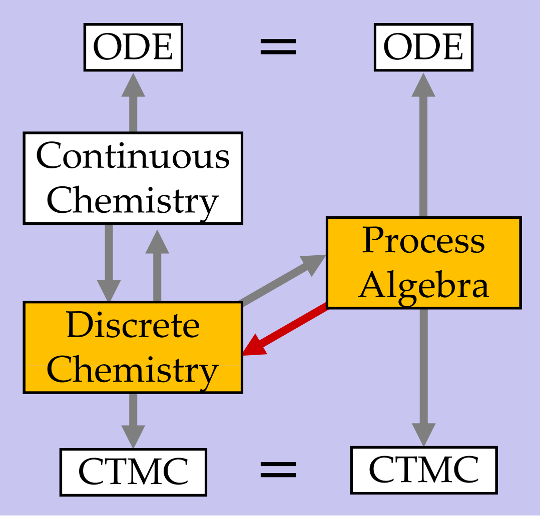


Ex: Interacting Automata
(= finite-control CGFs: they use "|" only in initial conditions):

$A = !a;A \oplus ?b;B$ — 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 ǀ A ǀ ... ǀ A	initial quantities $\#A_0$
	$A \xrightarrow{r} A'$
	$A+B \xrightarrow{r} A'+B'$
	$A+A \xrightarrow{2r} A'+A''$
	↓ CTMC



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

From Reagents to Reactions: Ch(E)

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

E.X.i $\stackrel{\text{def}}{=}$ the i-th $\oplus$-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) :=

$$\{(\langle X.i\rangle: X \rightarrow^{r} P)\ \mathit{s.t.}\ E.X.i = \tau_{(r)};P\} \cup$$

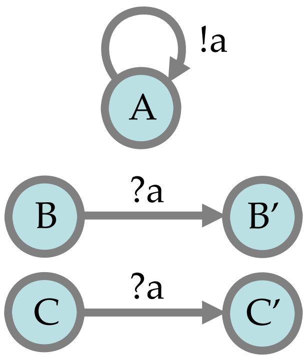
$$\{(\langle X.i,Y.j\rangle: X + Y \rightarrow^{r} P + Q)\ \mathit{s.t.}\ X \neq Y,\ E.X.i = ?a_{(r)};P,\ E.Y.j = !a_{(r)};Q\} \cup$$

$$\{(\langle X.i,X.j\rangle: X + X \rightarrow^{2r} P + Q)\ \mathit{s.t.}\ E.X.i = ?a_{(r)};P,\ E.X.j = !a_{(r)};Q)\rangle \in E\}$$

Initial conditions for P:

Ch(P) := P

Entangled vs Detangled



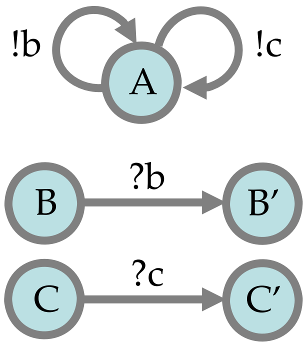
a: A+B $\to^{r}$ A+B′

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′

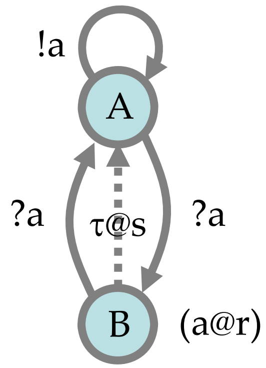
(b@r)
(c@r)

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



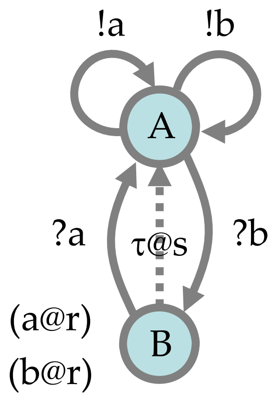
$A = !a;A \oplus ?a;B$

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

$B \to^{s} A$

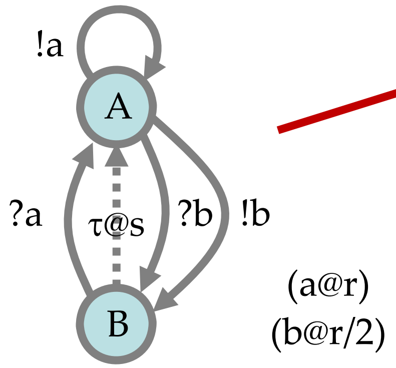
$A+B \to^{r} A+A$

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



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

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



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

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

$B \to^{s} A$

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

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

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

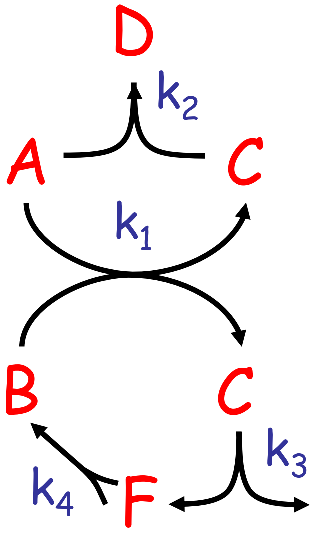
Interaction Matrix

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|C)	?;D		
B	!;0			
C		!;0	τ;(E|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 $\langle X, v_i \rangle$.

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:

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

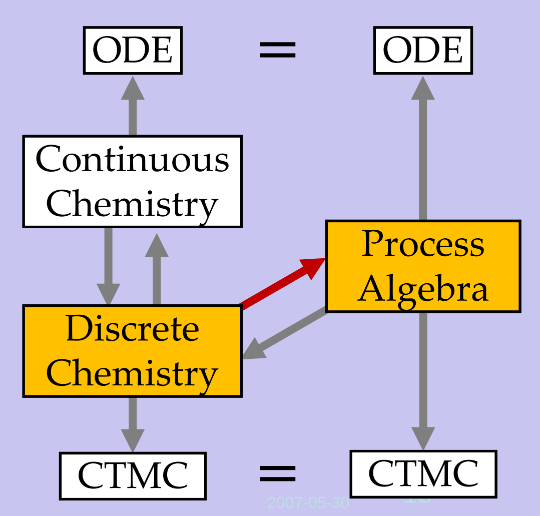
$B = !v_{1(k1)};0$

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

$D = 0$

$E = 0$

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



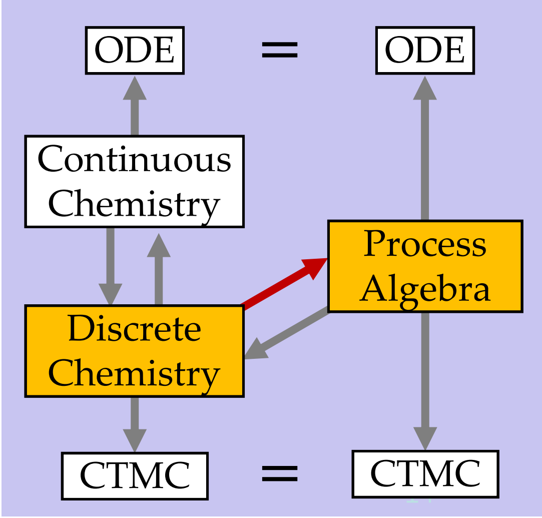
From Reactions to Reagents: Pi(C)

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

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

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

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



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

Some Syntactic Properties

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

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

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

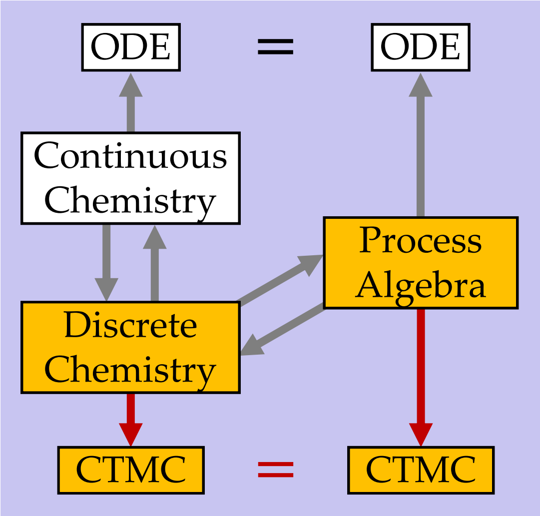
- Hence for any E, we have that Pi(Ch(E)) is detangled.
  - (E and Pi(Ch(E)) are "equivalent" CGFs, but that has to be shown later)

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

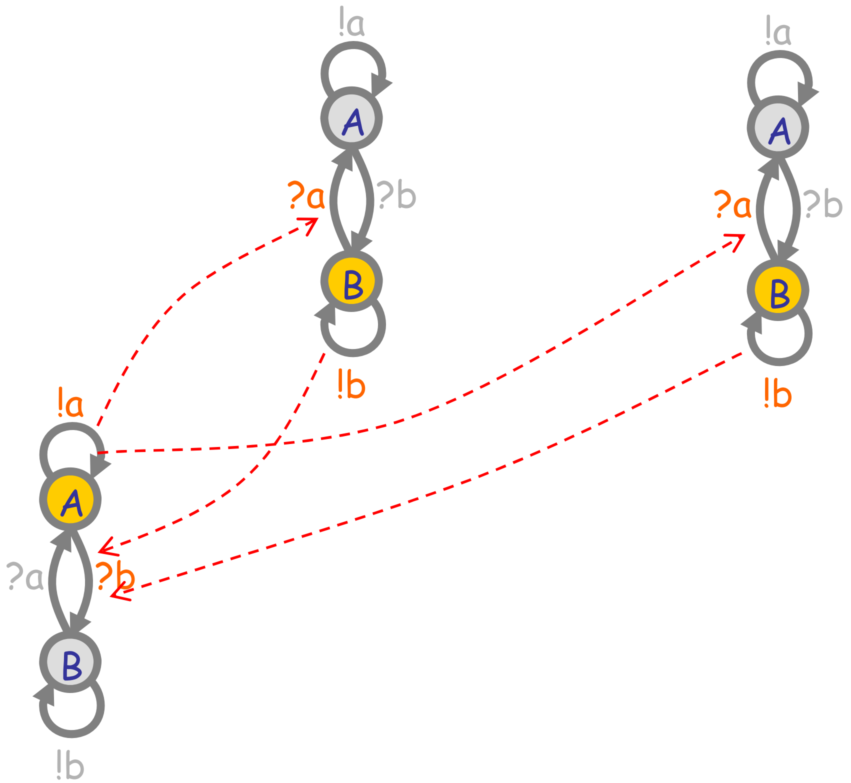
- Def: Detangle(E) is defined from Pi(Ch(E)) by replacing any occurrence pairs $?a_{(r)};(X|Y|0)$ and $!a_{(r)};0$ with $?a_{(r)};(X|0)$ and $!a_{(r)};(Y|0)$.

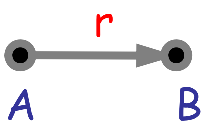
- If E is in automata form then Detangle(E) is (detangled and) in automata form
  - (but Pi(Ch(E)) may not be)

Discrete-State Semantics



CTMC Semantics



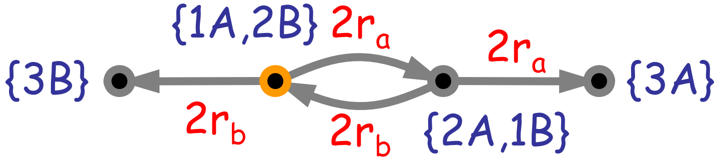


Probability of holding in state A:

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

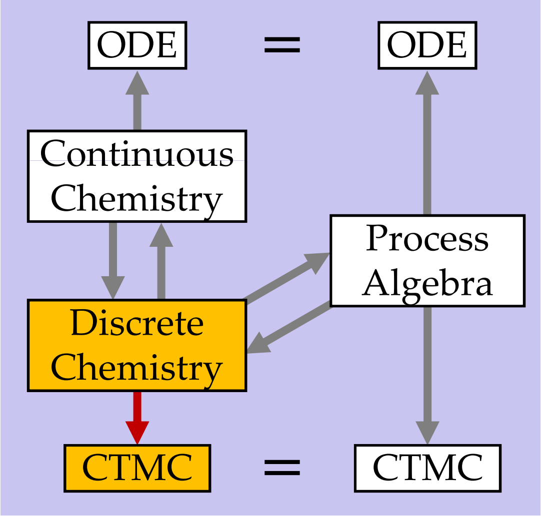
in general, $Pr(H_A>t) = e^{-Rt}$ where R is the sum of all the exit rates from A

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

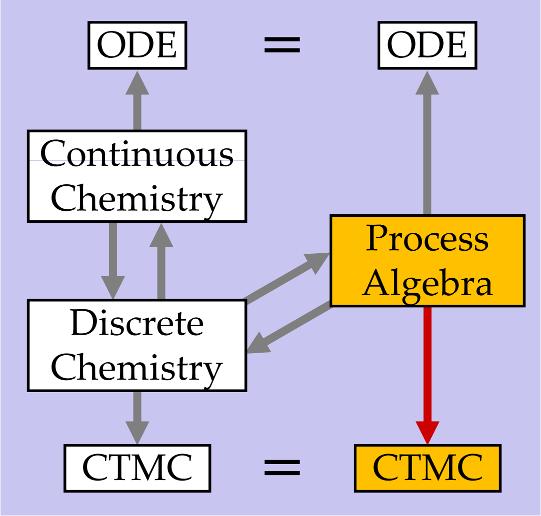


CTMC

Discrete Semantics of Reactions

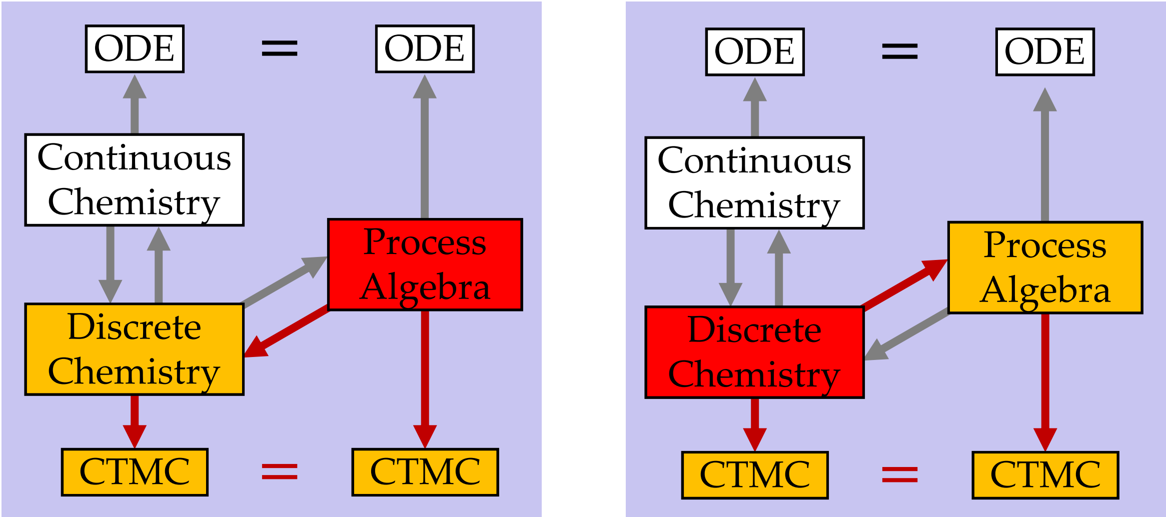


Discrete Semantics of Reagents



Discrete State Equivalence

- Def: ♒ is equivalent CTMC's (isomorphic graphs with same rates).
- Thm: E ♒ Ch(E)
- Thm: C ♒ Pi(C)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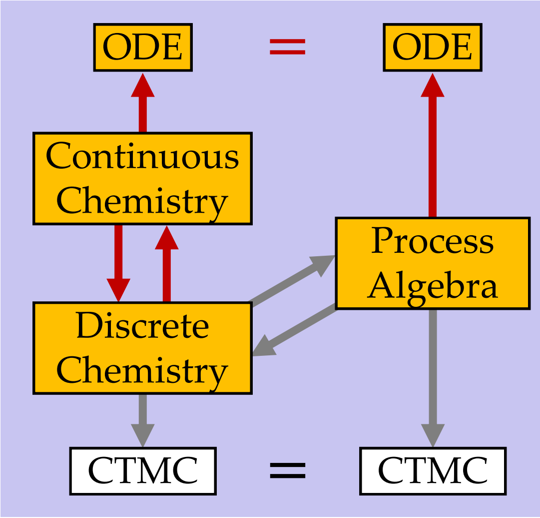
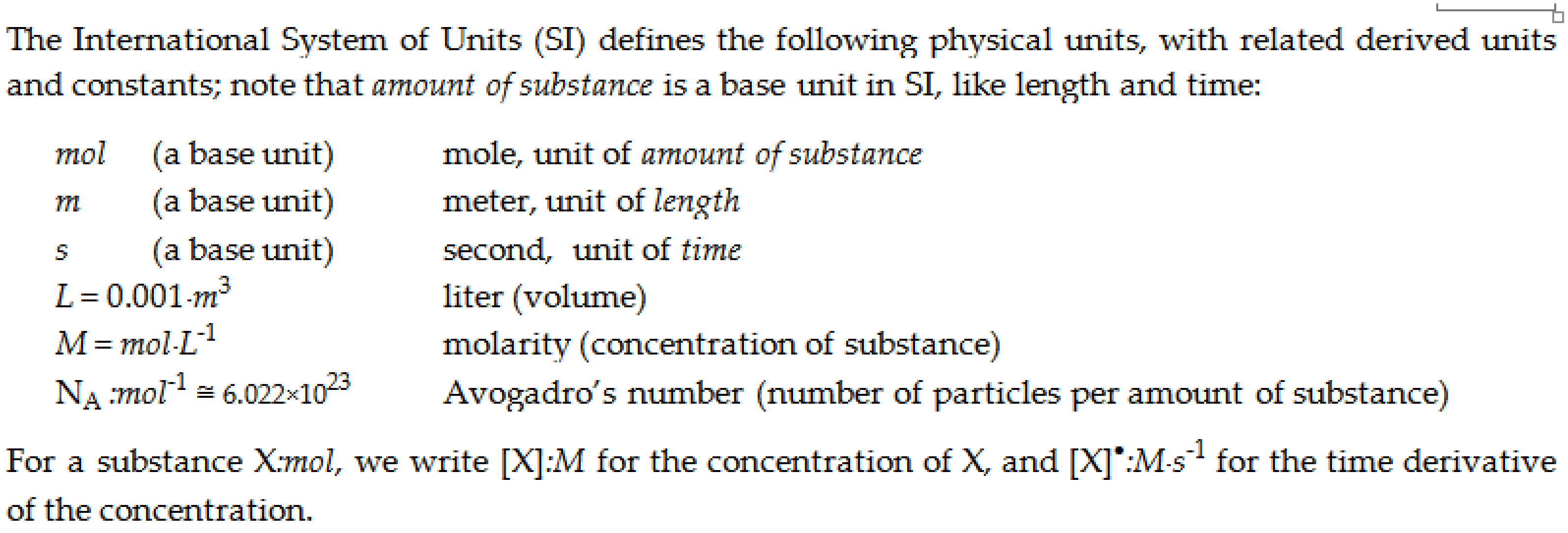
- For each E there is an E' ♒ E that is detangled (E' = Pi(Ch(E)))
- For each E in automata form there is an an E' ♒ E that is detangled and in automata form (E' = Detangle(E)).

Continuous-State Semantics



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

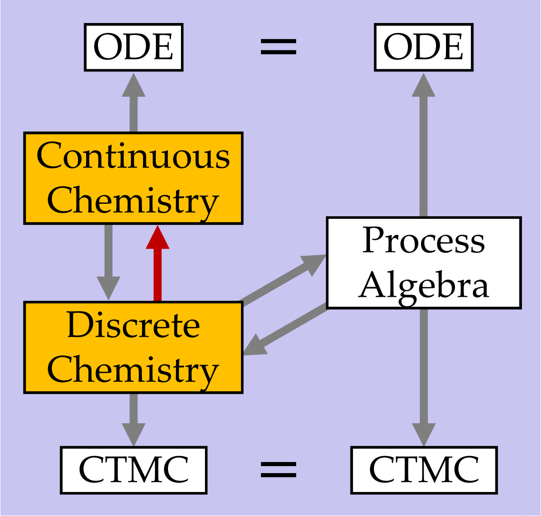
Discrete Chemistry	Continuous Chemistry	$\gamma = N_A V$	$:M^{-1}$
initial quantities $\#A_0$	initial concentrations $[A]_0$	with $[A]_0 = \#A_0/\gamma$	
$A \overset{r}{\dashrightarrow} A'$	$A \xrightarrow{k} A'$	with $k = r$	$:s^{-1}$
$A+B \overset{r}{\dashrightarrow} A'+B'$	$A+B \xrightarrow{k} A'+B'$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

V = interaction volume

N_A = Avogadro's number

Think $\gamma = 1$

i.e. $V = 1/N_A$



ODE = ODE

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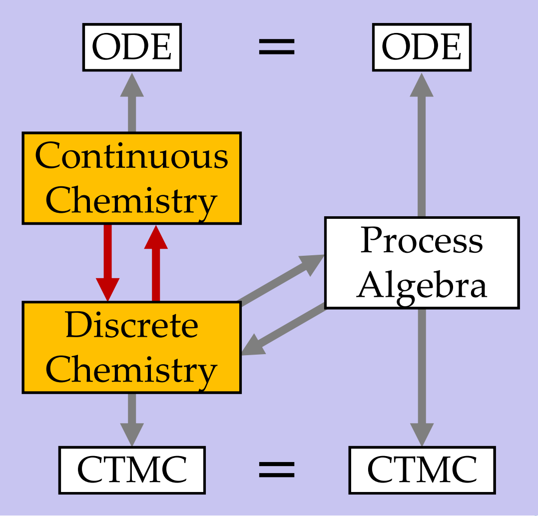
$Cont_\gamma$ and $Disc_\gamma$

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.

$Cont_\gamma(X \xrightarrow{r} P)$	$= X \xrightarrow{k} P$	with $k = r$,	$r{:}s^{-1}$	$k{:}s^{-1}$
$Cont_\gamma(X+Y \xrightarrow{r} P)$	$= X+Y \xrightarrow{k} P$	with $k = r\gamma$	$r{:}s^{-1}$	$k{:}M^{-1}s^{-1}$
$Cont_\gamma(X+X \xrightarrow{r} P)$	$= X+X \xrightarrow{k} P$	with $k = r\gamma/2$	$r{:}s^{-1}$	$k{:}M^{-1}s^{-1}$
$Cont_\gamma(\#X_0)$	$= [X]_0$	with $[X]_0 = \#X_0/\gamma$	$X_0{:}mol$	$[X]_0{:}M$
$Disc_\gamma(X \xrightarrow{k} P)$	$= X \xrightarrow{r} P$	with $r = k$,	$k{:}s^{-1}$	$r{:}s^{-1}$
$Disc_\gamma(X+Y \xrightarrow{k} P)$	$= X+Y \xrightarrow{r} P$	with $r = k/\gamma$	$k{:}M^{-1}s^{-1}$	$r{:}s^{-1}$
$Disc_\gamma(X+X \xrightarrow{k} P)$	$= X+X \xrightarrow{r} P$	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: $A+B \xrightarrow{k_1} C+C$

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

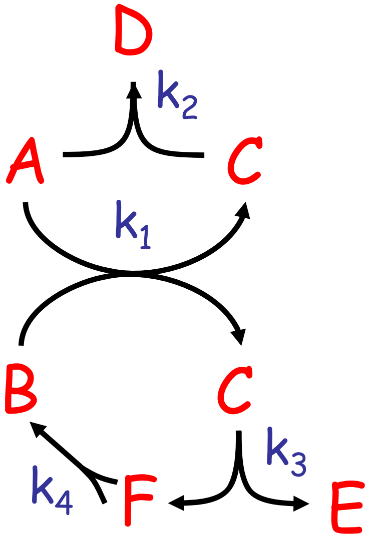
Stoichiometric Matrix

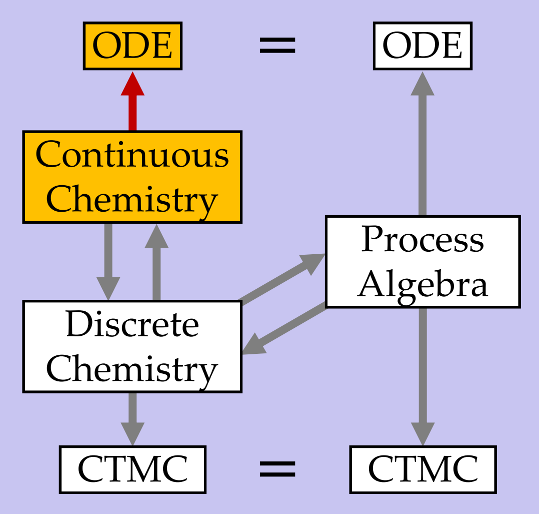
reactions

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




ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

Quantity changes

Stoichiometric matrix

Rate laws

$$[X]^\bullet = N \cdot l$$

$[A]^\bullet = -l_1 - l_2$

$[B]^\bullet = -l_1 + l_4$

$[C]^\bullet = 2l_1 - l_2 - l_3$

$[D]^\bullet = l_2$

$[E]^\bullet = l_3$

$[F]^\bullet = l_3 - 2l_4$

Read the concentration changes from the rows

E.g. $[A]^\bullet = -k_1[A][B] - k_2[A][C]$

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

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

X: chemical species

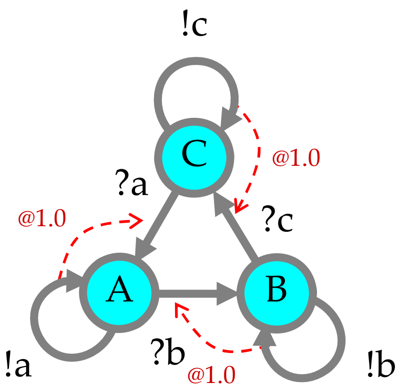
[-]: quantity of molecules

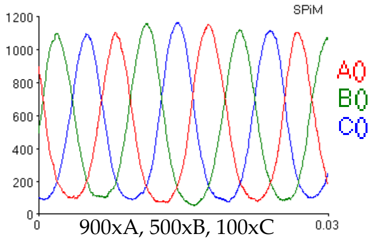
l: rate laws

k: kinetic parameters

N: stoichiometric matrix

From Processes to ODEs via Chemistry!





900xA, 500xB, 100xC

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

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

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

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

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

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

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

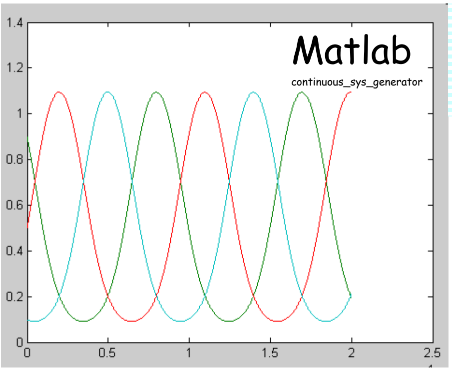
$B+C \rightarrow^{s} C+C$

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

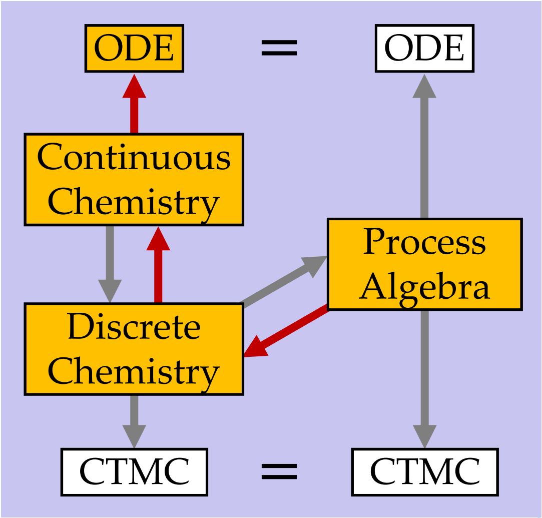
$[A]^{\bullet} = -s[A][B]+s[C][A]$

$[B]^{\bullet} = -s[B][C]+s[A][B]$

$[C]^{\bullet} = -s[C][A]+s[B][C]$



```
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

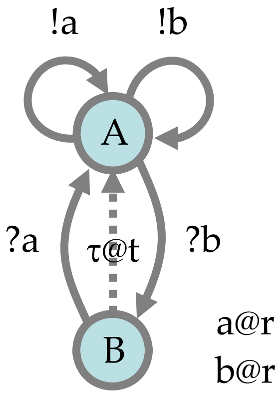
Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

From Processes to ODEs via Chemistry!



$\tau: B \to^{t} A$

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

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

(discrete reactions)

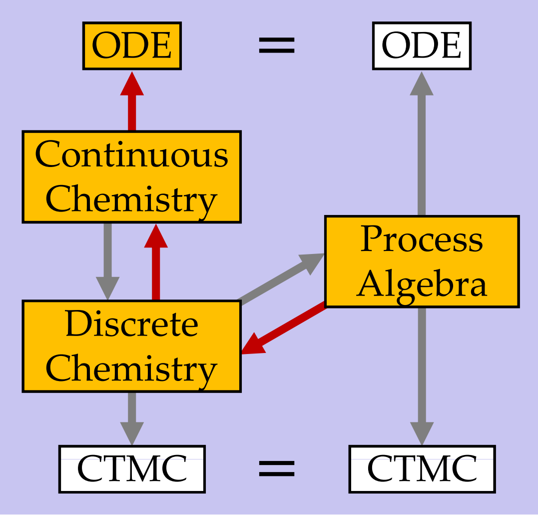
$B \to^{s} A$

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

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

(continuous reactions)

$$[A]^\bullet = t[B] + r\gamma[A][B] - r\gamma[A]^2$$
$$[B]^\bullet = -t[B] - r\gamma[A][B] + r\gamma[A]^2$$



ODE = ODE

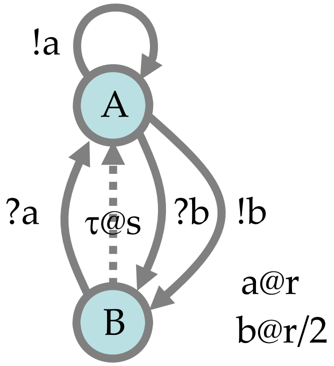
Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

Different chemistry but same ODEs, hence equivalent automata



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

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

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

(discrete reactions)

$B \to^{s} A$

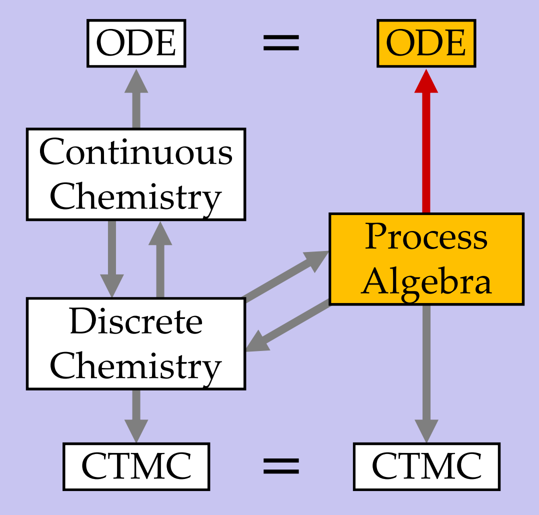
$A+B \to^{r\gamma} A+A$

$A+A \to^{r\gamma/2} B+B$

(continuous reactions)

$$[A]^\bullet = t[B] + r\gamma[A][B] - r\gamma[A]^2$$
$$[B]^\bullet = -t[B] - r\gamma[A][B] + r\gamma[A]^2$$

Processes Rate Equation



ODE = ODE

Continuous Chemistry

Process Algebra

Discrete Chemistry

CTMC = CTMC

Process Rate Equation for Reagents E

$$[X]^\bullet = (\Sigma(Y\in E)\ Accr_E(Y,X)\cdot[Y]) - Depl_E(X)\cdot[X] \qquad \text{for all } X\in E$$

$Depl_E(X) =$

$\quad \Sigma(i:\ E.X.i=\tau_{(r)};P)\ r\ +$

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

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

$Accr_E(Y, X) =$

$\quad \Sigma(i:\ E.Y.i=\tau_{(r)};P)\ \#X(P)\cdot r\ +$

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

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

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

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

$X = \tau_{(r)};0 \quad \longrightarrow \quad [X]^\bullet = -r[X]$

$X = ?a_{(r)};0$

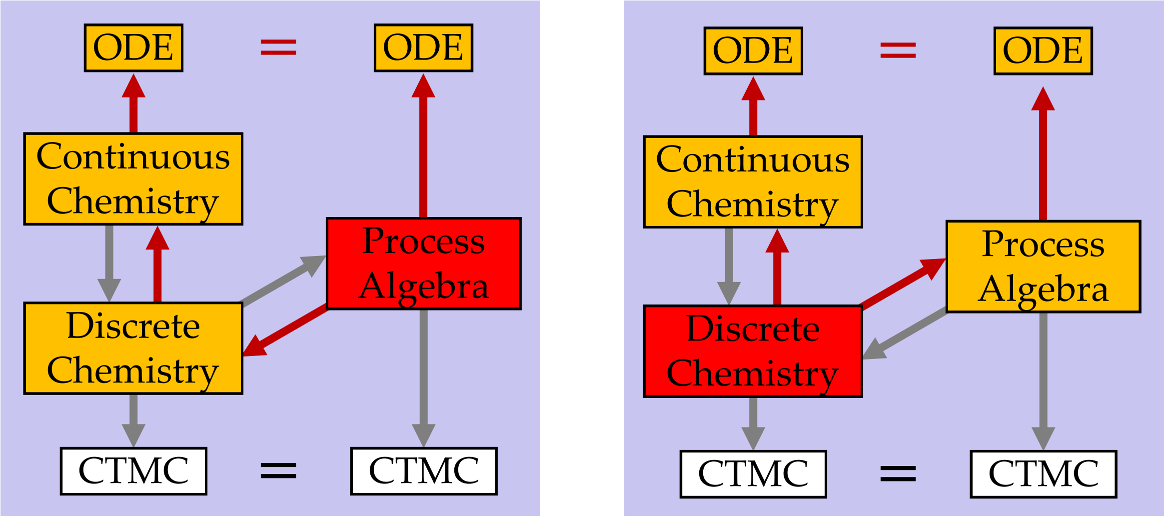
$Y = !a_{(r)};0 \quad \longrightarrow \quad [X]^\bullet = -r\gamma[X][Y]$

$[Y]^\bullet = -r\gamma[X][Y]$

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

Continuous State Equivalence

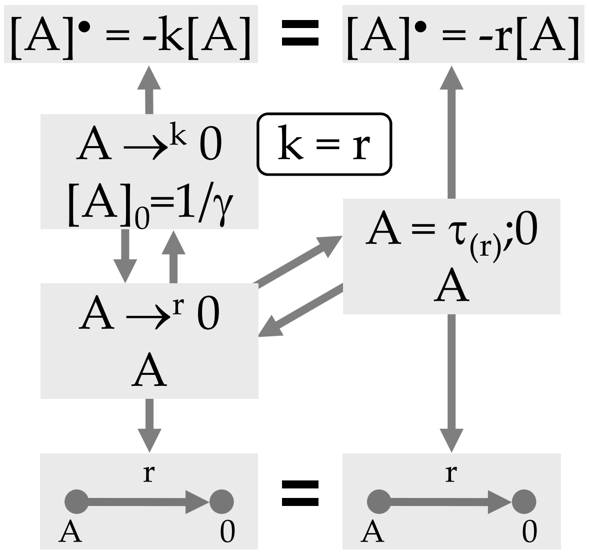
- Def: ≈ is equivalence of polynomials over the field of reals.
- Thm: E ≈ Cont(Ch(E))
- Thm: Cont(C) ≈ Pi(C)


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)).

Basic Examples: Unary Reactions



$[A]^\bullet = -k[A]$ = $[A]^\bullet = -r[A]$

$A \to^{k} 0$

$[A]_0 = 1/\gamma$

$\boxed{k = r}$

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

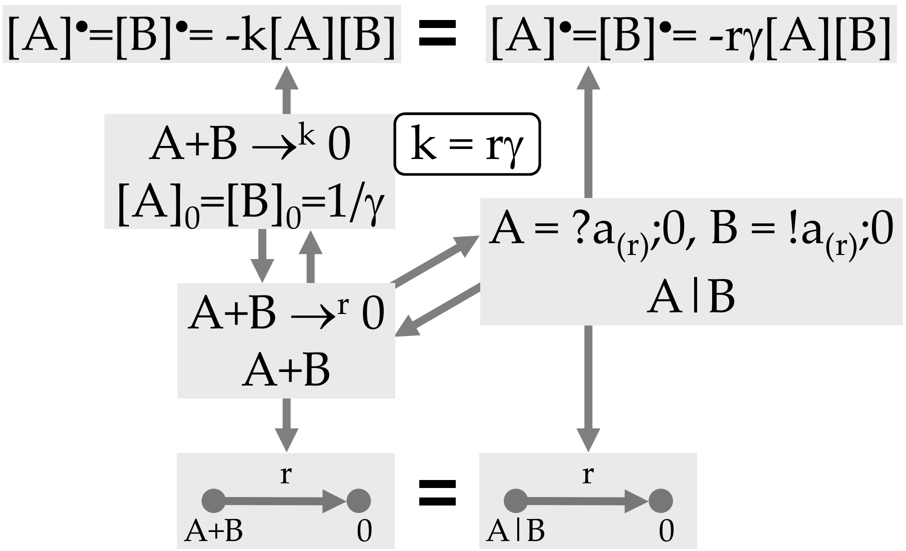
A

$A \to^{r} 0$

A

○┈┈▸∘ Unary Reaction

Basic Examples: Binary Reactions



$[A]^\bullet=[B]^\bullet= -k[A][B]$ **=** $[A]^\bullet=[B]^\bullet= -r\gamma[A][B]$

$A+B \xrightarrow{k} 0$

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

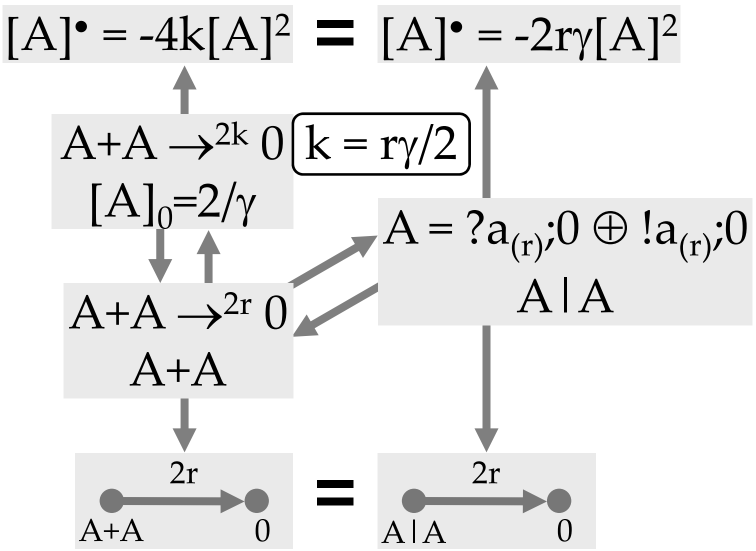
$\boxed{k = r\gamma}$

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

A|B

$A+B \xrightarrow{r} 0$

A+B



$[A]^\bullet = -4k[A]^2$ **=** $[A]^\bullet = -2r\gamma[A]^2$

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

$[A]_0=2/\gamma$

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

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

A|A

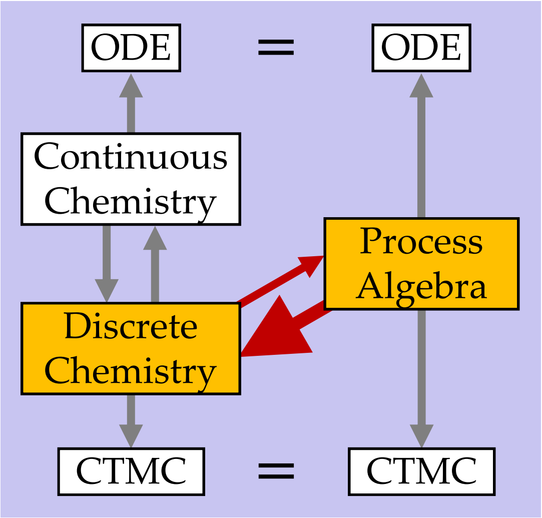
$A+A \xrightarrow{2r} 0$

A+A

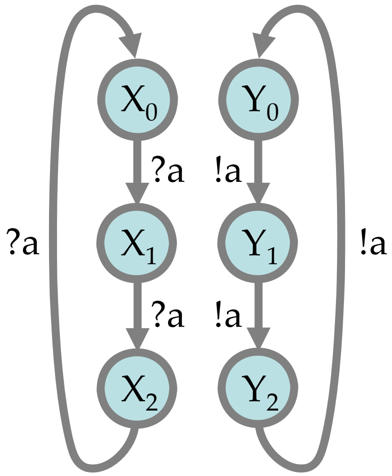
Hetero Reaction

Homeo Reaction

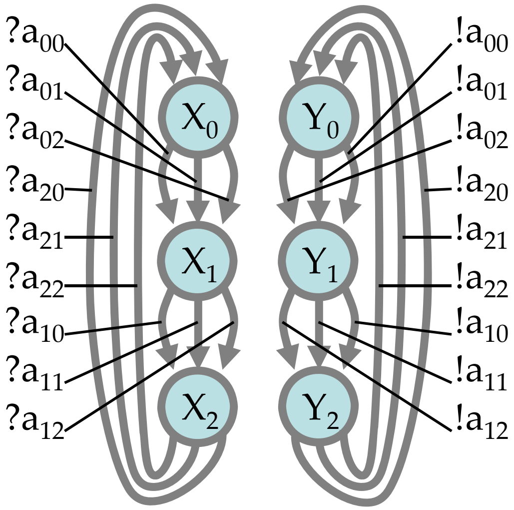
Model Compactness



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

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

$Ch(E_3)$

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

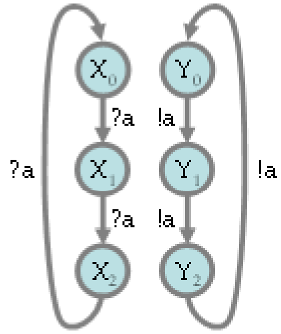
StoichiometricMatrix($Ch(E_3)$)

	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

$ODE(E_3)$

$[X_0]^\bullet = -r[X_0][Y_0] - r[X_0][Y_1] - r[X_0][Y_2] + r[X_2][Y_0] + r[X_2][Y_1] + r[X_2][Y_2]$
$[X_1]^\bullet = -r[X_1][Y_0] - r[X_1][Y_1] - r[X_1][Y_2] + r[X_0][Y_0] + r[X_0][Y_1] + r[X_0][Y_2]$
$[X_2]^\bullet = -r[X2_1][Y_0] - r[X_2][Y_1] - r[X_2][Y_2] + r[X_1][Y_0] + r[X_1][Y_1] + r[X_1][Y_2]$
$[Y_0]^\bullet = -r[X_0][Y_0] - r[X_1][Y_0] - r[X_2][Y_0] + r[X_0][Y_2] + r[X_1][Y_2] + r[X_2][Y_2]$
$[Y_1]^\bullet = -r[X_0][Y_1] - r[X_1][Y_1] - r[X_2][Y_1] + r[X_0][Y_0] + r[X_1][Y_0] + r[X_2][Y_0]$
$[Y_2]^\bullet = -r[X_0][Y_2] - r[X_1][Y_2] - r[X_2][Y_2] + r[X_0][Y_1] + r[X_1][Y_1] + r[X_2][Y_1]$

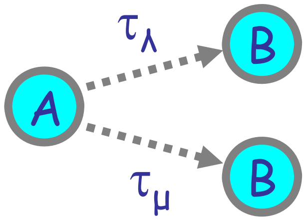
=?!



Laws by ODEs

Choice Law by ODEs

$$\tau_\lambda;B \oplus \tau_\mu;B = \tau_{\lambda+\mu};B$$



$$A = \tau_\lambda;B \oplus \tau_\mu;B$$

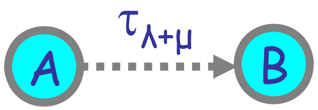
$\downarrow$

$$A \xrightarrow{\lambda} B$$
$$A \xrightarrow{\mu} B$$

$\downarrow$

$$[A]^\bullet = -\lambda[A] - \mu[A]$$
$$[B]^\bullet = \lambda[A] + \mu[A]$$

=



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

$\downarrow$

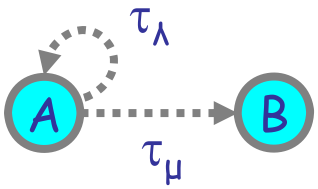
$$A \xrightarrow{\lambda+\mu} B$$

$\downarrow$

$$[A]^\bullet = -(\lambda+\mu)[A]$$
$$[B]^\bullet = (\lambda+\mu)[A]$$

Idle Delay Law by ODEs

$A = \tau_\lambda;A \oplus \tau_\mu;B \quad = \quad A = \tau_\mu;B$



$A = \tau_\lambda;A \oplus \tau_\mu;B$

↓

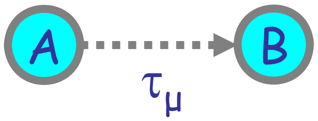
useless→

$A \xrightarrow{\lambda} A$
$A \xrightarrow{\mu} B$

↓

$[A]^\bullet = -\mu[A]$
$[B]^\bullet = \mu[A]$

=



$A = \tau_\mu;B$

↓

$A \xrightarrow{\mu} B$

↓

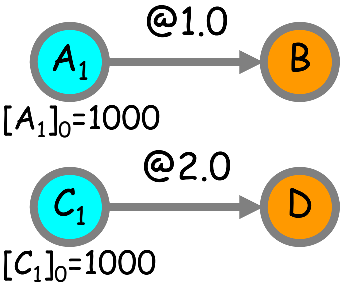
$[A]^\bullet = -\mu[A]$
$[B]^\bullet = \mu[A]$

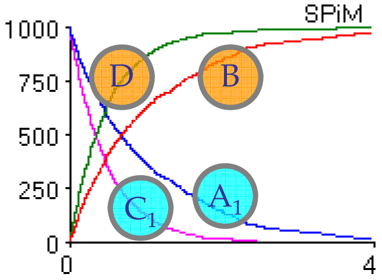
Stochastic Interleaving

Hermanns: Interactive Markov Chains. Sec 4.1.2

$$\tau_\lambda;B \mid \tau_\mu;D \; = \; \tau_\lambda;(B \mid \tau_\mu;D) \oplus \tau_\mu;(\tau_\lambda;B \mid D)$$

Ex: λ=1.0, μ=2.0



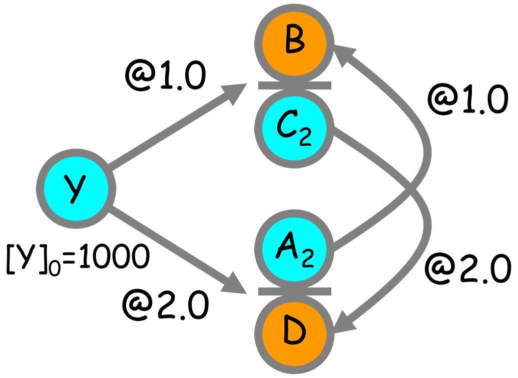


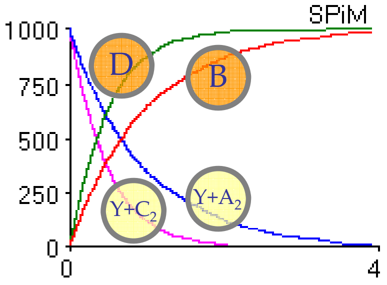
```
directive sample 4.0 10000
directive plot A(); B(); C(); D()

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

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

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





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

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

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

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

run 1000 of Y()
```

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

Stochastic Interleaving Law by ODEs

$$\tau_\lambda;B \mid \tau_\mu;D \;=\; \tau_\lambda;(B \mid \tau_\mu;D) \oplus \tau_\mu;(\tau_\lambda;B \mid D)$$

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

$A_1 = \tau_\lambda;B$
$C_1 = \tau_\mu;D$
$n\times A_1 \mid n\times C_1$

$Y = \tau_\lambda;(B \mid C_2) \oplus \tau_\mu;(A_2 \mid D)$
$C_2 = \tau_\mu;D$
$A_2 = \tau_\lambda;B$
$n\times Y$

$A_1 \xrightarrow{\lambda} B$
$C_1 \xrightarrow{\mu} D$
$[A_1]_0 = n/\gamma$
$[C_1]_0 = n/\gamma$

$Y \xrightarrow{\lambda} B + C_2$
$Y \xrightarrow{\mu} A_2 + D$
$C_2 \xrightarrow{\mu} D$
$A_2 \xrightarrow{\lambda} B$
$[Y]_0 = n/\gamma$

$[Y]^\bullet = -\lambda[Y]-\mu[Y]$
$[A_2]^\bullet = \mu[Y]-\lambda[A_2]$
$[B]^\bullet = \lambda[Y]+\lambda[A_2]$
$[C_2]^\bullet = \lambda[Y]-\mu[C_2]$
$[D]^\bullet = \mu[Y]+\mu[C_2]$

$[A_1]^\bullet = -\lambda[A_1]$
$[B]^\bullet = \lambda[A_1]$
$[C_1]^\bullet = -\mu[C_1]$
$[D]^\bullet = \mu[C_1]$

=?

$[Y+A_2]^\bullet = -\lambda[Y+A_2]$
$[B]^\bullet = \lambda[Y+A_2]$
$[Y+C_2]^\bullet = -\mu[Y+C_2]$
$[D]^\bullet = \mu[Y+C_2]$

$[Y+A_2]^\bullet = [Y]^\bullet+[A_2]^\bullet$
$= -\lambda[Y]-\mu[Y]+\mu[Y]-\lambda[A_2]$
$= -\lambda[Y]-\lambda[A_2]$
$= -\lambda[Y+A_2]$

$[Y+A_2]$ decays exponentially!

[B] and [D] have equal time evolutions on the two sides provided that $[A_1]=[Y+A_2]$ and $[C_1]=[Y+C_2]$. Moreover $[A_1]_0=[C_1]_0=[Y]_0=n/\gamma$, and the initial conditions of the right hand system specify that $[A_2]_0=[C_2]_0=0$ (since only Y is present), hence $[A_1]_0=[Y+A_2]_0$ and $[C_1]_0=[Y+C_2]_0$. Similarly $[B]_0=[D]_0=0$. Therefore the final ODEs have the same initial conditions for all variables, and hence have the same time evolution.

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

Parametric Processes

Chemical Parametric Form (CPF)

E	$::= X_1(\mathbf{p}_1)=M_1, \ldots, X_n(\mathbf{p}_n)=M_n$	Reagents	$(n \geq 0)$
M	$::= \pi_1;P_1 \oplus \ldots \oplus \pi_n;P_n$	Molecules	$(n \geq 0)$
P	$::= X_1(\mathbf{p}_1) \mid \ldots \mid X_n(\mathbf{p}_n)$	Solutions	$(n \geq 0)$
π	$::= \tau_r \quad ?n(\mathbf{p}) \quad !n(\mathbf{p})$	Interactions	
CPF	$::=$ E,P	with initial conditions	

$\oplus$ is stochastic choice (vs. + for chemical reactions)
0 is the null solution ($P|0 = 0|P = P$)
and null molecule ($M\oplus 0 = 0\oplus M = M$) ($\tau_0;P = 0$)
X_i are distinct in E, **p** are vectors of names
p are vectors of distinct names when in binding position
Each free name n in E is assigned a fixed rate r:
written either $n_{(r)}$, or $\rho_{CPF}(n)=r$.

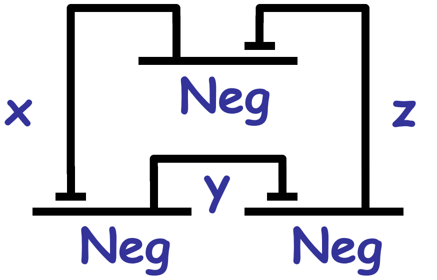
Not bounded-state systems.
Not finite-control systems.
But still finite-species systems.

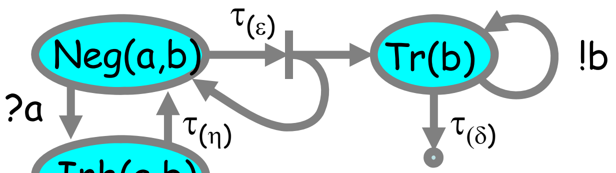
A translation from CPF to CGF exists
(expanding all possible instantiation of parameters from the initial conditions)

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

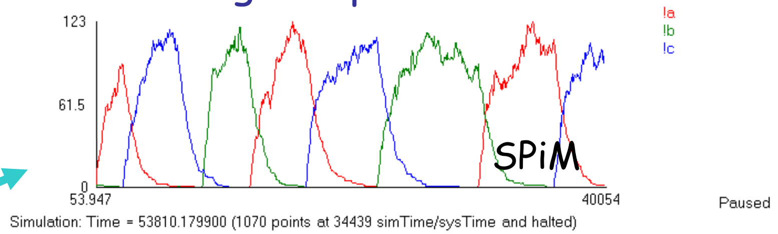
And Yet It Moves

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

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

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

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

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

$\mathrm{Neg}/x,y \xrightarrow{\varepsilon} \mathrm{Tr}/y + \mathrm{Neg}/x,y$

$\mathrm{Neg}/y,z \xrightarrow{\varepsilon} \mathrm{Tr}/z + \mathrm{Neg}/y,z$

$\mathrm{Neg}/z,x \xrightarrow{\varepsilon} \mathrm{Tr}/x + \mathrm{Neg}/z,x$

$\mathrm{Tr}/x + \mathrm{Neg}/x,y \xrightarrow{r} \mathrm{Tr}/x + \mathrm{Inh}/x,y$

$\mathrm{Tr}/y + \mathrm{Neg}/y,z \xrightarrow{r} \mathrm{Tr}/y + \mathrm{Inh}/y,z$

$\mathrm{Tr}/z + \mathrm{Neg}/z,x \xrightarrow{r} \mathrm{Tr}/z + \mathrm{Inh}/z,x$

$\mathrm{Inh}/x,y \xrightarrow{\eta} \mathrm{Neg}/x,y$

$\mathrm{Inh}/y,z \xrightarrow{\eta} \mathrm{Neg}/y,z$

$\mathrm{Inh}/z,x \xrightarrow{\eta} \mathrm{Neg}/z,x$

$\mathrm{Tr}/x \xrightarrow{\gamma} 0$

$\mathrm{Tr}/y \xrightarrow{\gamma} 0$

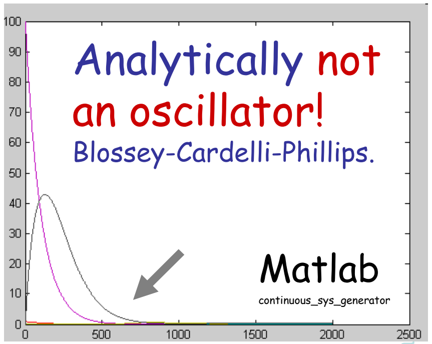
$\mathrm{Tr}/z \xrightarrow{\gamma} 0$

$\mathrm{Neg}/x,y + \mathrm{Neg}/y,z + \mathrm{Neg}/z,x$

$$
\begin{aligned}
&[\mathrm{Neg}/x,y]^\bullet = -r[\mathrm{Tr}/x][\mathrm{Neg}/x,y] + \eta[\mathrm{Inh}/x,y]\\
&[\mathrm{Neg}/y,z]^\bullet = -r[\mathrm{Tr}/y][\mathrm{Neg}/y,z] + \eta[\mathrm{Inh}/y,z]\\
&[\mathrm{Neg}/z,x]^\bullet = -r[\mathrm{Tr}/z][\mathrm{Neg}/z,x] + \eta[\mathrm{Inh}/z,x]\\
&[\mathrm{Inh}/x,y]^\bullet = r[\mathrm{Tr}/x][\mathrm{Neg}/x,y] - \eta[\mathrm{Inh}/x,y]\\
&[\mathrm{Inh}/y,z]^\bullet = r[\mathrm{Tr}/y][\mathrm{Neg}/y,z] - \eta[\mathrm{Inh}/y,z]\\
&[\mathrm{Inh}/z,x]^\bullet = r[\mathrm{Tr}/z][\mathrm{Neg}/z,x] - \eta[\mathrm{Inh}/z,x]\\
&[\mathrm{Tr}/x]^\bullet = \varepsilon[\mathrm{Neg}/z,x] - \gamma[\mathrm{Tr}/x]\\
&[\mathrm{Tr}/y]^\bullet = \varepsilon[\mathrm{Neg}/x,y] - \gamma[\mathrm{Tr}/y]\\
&[\mathrm{Tr}/z]^\bullet = \varepsilon[\mathrm{Neg}/y,z] - \gamma[\mathrm{Tr}/z]
\end{aligned}
$$

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

$$
\begin{aligned}
&[\mathrm{Neg}/x,y]^\bullet = \eta N - (\eta + r[\mathrm{Tr}/x])[\mathrm{Neg}/x,y]\\
&[\mathrm{Neg}/y,z]^\bullet = \eta N - (\eta + r[\mathrm{Tr}/y])[\mathrm{Neg}/y,z]\\
&[\mathrm{Neg}/z,x]^\bullet = \eta N - (\eta + r[\mathrm{Tr}/z])[\mathrm{Neg}/z,x]\\
&[\mathrm{Tr}/x]^\bullet = \varepsilon[\mathrm{Neg}/z,x] - \gamma[\mathrm{Tr}/x]\\
&[\mathrm{Tr}/y]^\bullet = \varepsilon[\mathrm{Neg}/x,y] - \gamma[\mathrm{Tr}/y]\\
&[\mathrm{Tr}/z]^\bullet = \varepsilon[\mathrm{Neg}/y,z] - \gamma[\mathrm{Tr}/z]
\end{aligned}
$$



Analytically not an oscillator!

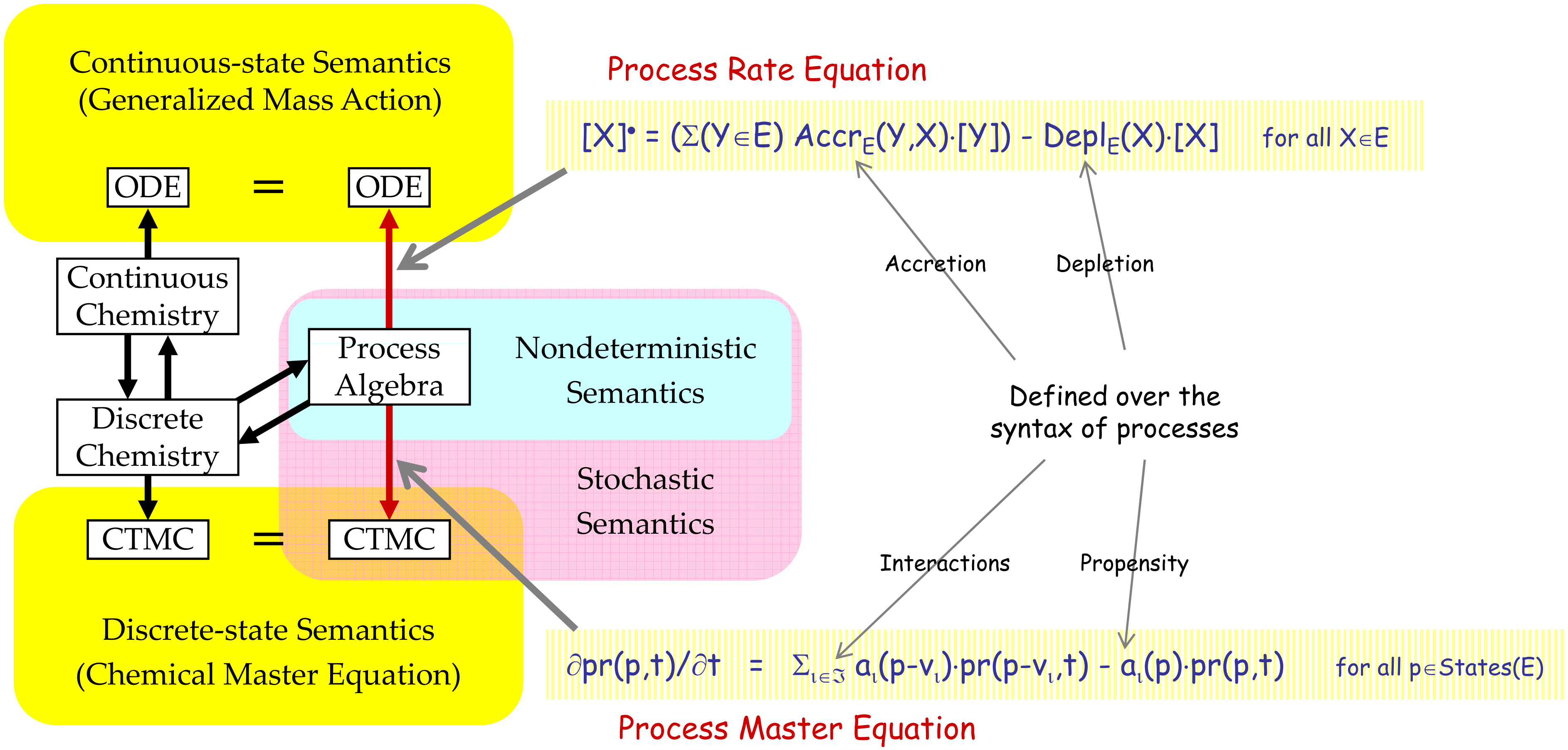
Blossey-Cardelli-Phillips.

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

Quantitative Process Semantics



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)

Process Rate Equation

$[X]^{\bullet} = (\Sigma(Y \in E)\ Accr_E(Y,X) \cdot [Y]) - Depl_E(X) \cdot [X]$ for all $X \in E$

Accretion

Depletion

Defined over the
syntax of processes

Interactions

Propensity

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

Process Master Equation

Some Consequences

- Process algebras are faithful to chemical semantics.
  - And hence can be used for biochemical modeling

    Pi(Ch(E)) ♒ E　　　　Pi(Ch(E)) ≈ E

    Ch(Pi(C)) ♒ C　　　　*Cont*(Ch(Pi(C))) ≈ *Cont*(C)

  - (N.B. although CTMC graphs were sufficient for our purposes, there is still the issue of when two CTMC graphs are stochastically equivalent. The "true" stochastic semantics is given by the Chapman-Kolmogorov equation for Markov processes, a.k.a. the Chemical Master Equation. Such equation can be extracted directly from process algebra as well, but it is notoriously difficult to use.)
- Process algebras lead to more compact models (representations), which in addition are compositional.
  - This is relevant to the current efforts in "scaling up" biological modeling.
- We also obtain a bulk (ODE) semantics for process algebras
  - Opens up the possibility of studying "bulk laws" of processes; classical analytical tools can be used.
  - One has to be careful (as in chemistry) about stochastic effects.

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Q?