Stochastic Collectives
Stochastic Collectives

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

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

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

Epidermal Growth Factor Receptor Pathway Map

LEGEND

- Pathway
- Protein
- Interaction
- Compartment

---

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Compositionality (NOT!)

http://www.expasy.ch/cgi-bin/show_thumbnails.pl
Interacting Automata

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

The stochastic version has rates on communications, and delays.

“Finite state” means: no composition or restriction inside recursion.

Analyzable by standard Markovian techniques, by first computing the “product automaton” to obtain the underlying finite Markov transition system. [Buchholz]
Interacting Automata Transition Rules

Delay

(a@r) → r → (a@r)

Current State
Delay
Transition

Interaction

(a@r) → ?a !a @r → r → ?a !a

Interactions have rates. Actions DO NOT have rates.

Q: What kind of mass behavior can this produce?
(We need to understand that if want to understand biochemical systems.)
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
Suppose this is the next interaction
Interactions in a Population (2)

All-B stable population

Nondeterministic population behavior ("multistability")
Groupies and Celebrities

Groupie (wants to be like somebody different)

Celebrity (does not want to be like somebody else)

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

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

let A() = do !a; A() or ?b; B()
and B() = do !b; B() or ?a; A()
run 100 of (A() | B())

A stochastic collective of celebrities:

A stochastic collective of groupies:

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

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

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

```
directive sample 10.0
directive plot Ag(); Bg(); Ac(); Bc()
new a@1.0:chan()
new b@1.0:chan()
let Ac() = do !a; Ac() or ?a; Bc()
and Bc() = do !b; Bc() or ?b; Ac()
let Ag() = do !a; Ag() or ?b; Bg()
and Bg() = do !b; Bg() or ?a; Ag()
run 1 of Ac()
run 100 of (Ag() | Bg())
```

A tiny bit of “noise” can make a huge difference

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Regularity can arise not far from chaos

Hysteric Groupies

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

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

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

“regular” oscillation

(With doping to break deadlocks)
Semantics of Collective Behavior
These diagrams commute via appropriate maps.

L. Cardelli: “On Process Rate Semantics”
From Processes to Chemistry
**Chemical Ground Form (CGF)**

\[ E ::= X_1=M_1, \ldots, X_n=M_n \]

\[ M ::= \pi_1;P_1 \oplus \ldots \oplus \pi_n;P_n \]

\[ P ::= X_1 | \ldots | X_n \]

\[ \pi ::= \tau_r \ ?n_{(r)} !n_{(r)} \]

\[ CGF ::= E,P \]

Reagents \((n \geq 0)\)

Molecules \((n \geq 0)\)

Solutions \((n \geq 0)\)

Interactions (delay, input, output)

Reagents plus 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 \(E\)

Each name \(n\) is assigned a fixed rate \(r\): \(n_{(r)}\)

(To translate chemistry to processes we need a bit more than interacting automata: we may have “\(+\)” on the right of \(\rightarrow\), that is we may need “\(|\)” after \(\pi\).)

---

**Ex: interacting automata**

(which are finite-control CGFs: use “\(|\)” only in initial conditions):

\[ A = !a;A \oplus ?b;B \]

\[ B = !b;B \oplus ?a;A \]

\[ A|A|B|B \]

Automaton in state \(A\)

Automaton in state \(B\)

Initial conditions: 2\(A\) and 2\(B\)
Processes to Chemistry

<table>
<thead>
<tr>
<th>Automata</th>
<th>Discrete Chemistry</th>
<th>Continuous Chemistry</th>
<th>( \gamma = N_A V )</th>
</tr>
</thead>
<tbody>
<tr>
<td>initial states</td>
<td>initial quantities</td>
<td>initial concentrations</td>
<td>( \gamma = 1 )</td>
</tr>
<tr>
<td>( A \mid A \mid ... \mid A )</td>
<td>#A_0</td>
<td>([A]_0) with ([A]_0 = #A_0/\gamma)</td>
<td>i.e. ( V = 1/N_A )</td>
</tr>
</tbody>
</table>

\[
A \xrightarrow{r} A' \quad A \xrightarrow{k} A' \quad \text{with } k = r
\]

\[
A + B \xrightarrow{r} A' + B' \quad A + B \xrightarrow{k} A' + B' \quad \text{with } k = r\gamma
\]

\[
A + A \xrightarrow{2r} A' + A'' \quad A + A \xrightarrow{2k} A' + A'' \quad \text{with } k = r\gamma/2
\]

Think \( \gamma = 1 \)
Processes to GMA Directly

Process Rate Equation for Reagents $E$

$$[X]^{*} = \left( \sum (Y \in E) \text{Accr}_{E}(Y, X) \cdot [Y] \right) - \text{Depl}_{E}(X) \cdot [X] \quad \text{for all } X \in E$$

Depl$_{E}$(X) =

$$\sum (i: E.X.i=\tau(r);P) \ r +
\sum (i: E.X.i=?a(r);P) \ r \gamma \cdot \text{OutsOn}_{E}(a) +
\sum (i: E.X.i=!a(r);P) \ r \gamma \cdot \text{InsOn}_{E}(a)$$

Accr$_{E}$(Y, X) =

$$\sum (i: E.Y.i=\tau(r);P) \ #X(P) \cdot r +
\sum (i: E.Y.i=?a(r);P) \ #X(P) \cdot r \gamma \cdot \text{OutsOn}_{E}(a) +
\sum (i: E.Y.i=!a(r);P) \ #X(P) \cdot r \gamma \cdot \text{InsOn}_{E}(a)$$

InsOn$_{E}$(a) = $\sum (Y \in E) \ #\{Y.i | E.Y.i=?a(r);P\} \cdot [Y]$

OutsOn$_{E}$(a) = $\sum (Y \in E) \ #\{Y.i | E.Y.i=!a(r);P\} \cdot [Y]$

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

$$X = ?a_{(r)};0 \quad \rightarrow \quad [X]^{*} = -r \gamma [X][Y]$$

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

$$X = ?a_{(r)};0 \oplus !a_{(r)};0 \quad \rightarrow \quad [X]^{*} = -2r \gamma [X]^2$$
Processes to CME Directly

Process Master Equation for Reagents $E$

\[
\frac{\partial pr(p,t)}{\partial t} = \sum_{\iota \in \mathcal{I}} a_\iota (p-v_\iota) \cdot pr(p-v_\iota,t) - a_\iota (p) \cdot pr(p,t) \quad \text{for all } p \in \text{States}(E)
\]

\[pr(p,t) = \Pr\{S(t)=p \mid S(0)=p_0\}\] 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.

\[\mathcal{I} = \{(X.i) \text{ s.t. } E.X.i = \tau(r);Q\} \cup \{(X.i, Y.j) \text{ s.t. } E.X.i = ?n(r);Q \text{ and } E.Y.j = !n(r);R\}\]

is the set of possible interactions in $E$.

$v_\iota$ is the state change caused by an interaction $\iota \in \mathcal{I}$.

\[
\begin{align*}
  v_\iota &= -X+Q & \text{if } & \iota = \{X.i\} \text{ s.t. } E.X.i = \tau(r);Q \\
  v_\iota &= -X-Y+Q_R & \text{if } & \iota = \{X.i, Y.j\} \text{ s.t. } E.X.i = ?n(r);Q \text{ and } E.Y.j = !n(r);R
\end{align*}
\]

$a_\iota$ is the propensity of interaction $\iota$ in state $p$. Here $p^{#X}$ is the number of $X$ in $p$.

\[
\begin{align*}
a_\iota (p) &= r \cdot p^{#X} & \text{if } & \iota = \{X.i\} \text{ s.t. } E.X.i = \tau(r);Q \\
a_\iota (p) &= r \cdot p^{#X}.p^{#Y} & \text{if } & \iota = \{X.i, Y.j\} \text{ s.t. } X \neq Y \text{ and } E.X.i = ?a(r);Q \text{ and } E.Y.j = !a(r);R \\
a_\iota (p) &= r \cdot p^{#X}.(p^{#X}-1) & \text{if } & \iota = \{X.i, X.j\} \text{ s.t. } E.X.i = ?a(r);Q \text{ and } E.X.j = !a(r);R
\end{align*}
\]
Examples of stochastic collectives where:

(1) Simulation is puzzling and ODE analysis is more useful.

(2) ODE analysis is puzzling and simulation is more useful.
Zero-Order Regime
Second-order and Zero-order Regime

**Second-Order Regime**

\[ [S]^* = -r [E][S] \]

```plaintext
directive sample 1000.0
directive plot S(): P(): E()
new a@1.0: chan()
let E() = !a; E()
and S() = ?a; P()
and P() = ()
run (1 of E() | 1000 of S())
```

**Zero-Order Regime**

\[ [S]^* \approx -1 \quad \text{(by assuming } [ES]^* = 0) \]

```plaintext
directive sample 1000.0
directive plot S(): P(): E()
new a@1.0: chan()
let E() = !a; delay@1.0: E()
and S() = ?a; P()
and P() = ()
run (1 of E() | 1000 of S())
```

**Notation**
Ultrasensitivity

Zero-Order Regime
A small E-F inbalance causes a much larger S-P switch.

Second-Order Regime
Cascades

Second-Order Regime cascade:
* a signal amplifier (MAPK)

\[ a_{Hi} > 0 \implies c_{Hi} = \max \]


Zero-Order Regime cascade:
* a signal divider!

\[ a_{Hi} = \max \implies c_{Hi} = \frac{1}{3} \max \]
Nonlinear Transitions
Nonlinear Transition (NLT)

\[ A = ?c(s) ; B \]
\[ B = !c(s) ; B \]

\[ A + B \rightarrow^s B + B \]

\[ [A]^* = -s[A][B] \]
\[ [B]^* = s[A][B] \]

N.B.: needs at least 1 B to "get started".
Two NLTs: Bell Shape

\[ [B]^* = [B][A]-[C] \]

A = ?b₁; B
B = !b₁; B ⊕ ?c₁; C
C = !c₁; C

A + B →¹ B + B
B + C →¹ C + C

\[ [A]^* = -[A][B] \]
\[ [B]^* = [A][B] - [B][C] \]
\[ [C]^* = [B][C] \]
NLTs in Series: Soliton Propagation

```
directive sample 0.1 1000

directive plot A0(); A2(); A3(); A4(); A5(); A6(); A7(); A8();
A9(); A10(); A12(); A13();
val r=1.0 val s=1.0
new a2@s:chan new a3@s:chan new a4@s:chan new a5@s:chan
new a6@s:chan new a7@s:chan new a8@s:chan

let A1() = do delay@r;A9() or ?a9;A9()
and A1() = do !a9;A9() or delay@r;A10() or ?a10;A10()
and A1() = do !a10;A10() or delay@r;A11() or ?a11;A11()
and A1() = do !a11;A11() or delay@r;A12() or ?a12;A12()
and A1() = do !a12;A12() or delay@r;A13() or ?a13;A13()
and A1() = do !a13;A13()
run 1000 of A1()
```

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NLT in a Cycle: Oscillator

A = !a(s); A ⊕ ?b(s); B
B = !b(s); B ⊕ ?c(s); C
C = !c(s); C ⊕ ?a(s); A

A+B → s B+B
B+C → s C+C
C+A → s A+A

\[
\begin{align*}
[A] & = -s[A][B]+s[C][A] \\
[B] & = -s[B][C]+s[A][B] \\
[C] & = -s[C][A]+s[B][C]
\end{align*}
\]

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.
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\[ S = \gamma(t)I \]
\[ I = t_0 \gamma(t)I + \gamma(t)I \]
\[ R = \gamma(t)R \]

Differentiating processes:

\[ S + I \rightarrow \gamma I + I \]
\[ I + I \rightarrow \gamma I + I \]
\[ I \rightarrow rR \]
\[ R + I \rightarrow \gamma R + I \]

\[ [S]^* = -\gamma[S][I] \]
\[ [I]^* = \gamma[S][I] - r[I] \]
\[ [R]^* = r[I] \]

"useless" reactions

Automata produce the standard ODEs!

\[
\begin{align*}
\frac{dS}{dt} &= -aIS \\
\frac{dI}{dt} &= aIS - bI \\
\frac{dR}{dt} &= bI
\end{align*}
\]

(the Kermack-McKendrick, or SIR model)!
A simplified model of disease spread is shown, with states for Susceptible, Infected, and Recovered individuals. The model equations are:

\[
S = i(t)I \\
I = i(t)I + rR \\
R = 0 \\
S + I \rightarrow^\gamma I + I \\
I \rightarrow^r R
\]

The transition rates are denoted by \(\gamma\). The simulation shows the evolution of the disease spread over time. The code snippet is:

```chef
directive sample 500.0 1000
directive plot Recovered(); Susceptible(); Infected()
new infect @0.001:chan()
val recover = 0.03
let Recovered() = ()
and Susceptible() = ?infect; Infected()
and Infected() = do !infect; Infected()
  or delay@recover; Recovered()
run (200 of Susceptible() | 2 of Infected())
```

The diagram illustrates the flow between these states and the transitions, with comments indicating that the model is not totally obvious, but one could have simplified the automata model. The ODEs represent the same model, hence equivalent automata models.
Lotka-Volterra
An unbounded state system!
Lotka-Volterra in Matlab

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

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

\[ [H]^* = b[H] - p\gamma[H][C] \]
\[ [C]^* = -m[C] + p\gamma[H][C] \]
\[ [H]_0 = \#H_0 / \gamma \]
\[ [C]_0 = \#C_0 / \gamma \]

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

```
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()
```
Parametric Processes
**Chemical Parametric Form (CPF)**

\[
E ::= X_1(p_1)=M_1, \ldots, X_n(p_n)=M_n
\]

**Reagents**  
\(n \geq 0\)

\[
M ::= \pi_1;P_1 \oplus \ldots \oplus \pi_n;P_n
\]

**Molecules**  
\(n \geq 0\)

\[
P ::= X_1(p_1) \mid \ldots \mid X_n(p_n)
\]

**Solutions**  
\(n \geq 0\)

\[
\pi ::= \tau_r \ ?n(p) \ !n(p)
\]

**Interactions**

With initial conditions

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

\(\oplus\) is stochastic choice (vs. + for chemical reactions)
0 is the null solution \((P|0 = 0|P = P)\)
and null molecule \((M\oplus0 = 0\oplus M = M)\) \((\tau_0;P = 0)\)
\(X_i\) 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 \(\rho_{CPF}(n)=r\).

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

Parametric representation

$\text{Neg}(a,b) = ?a; \text{Inh}(a,b) \oplus \tau_\epsilon; (\text{Tr}(b) \mid \text{Neg}(a,b))$
$\text{Inh}(a,b) = \tau_\eta; \text{Neg}(a,b)$
$\text{Tr}(b) = !b; \text{Tr}(b) \oplus \tau_\gamma; 0$
$\text{Neg}(x(r),y(r)) \mid \text{Neg}(y(r),z(r)) \mid \text{Neg}(z(r),x(r))$

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

$\text{Neg}(x,y) \rightarrow^c \text{Tr}/y + \text{Neg}/x,y$
$\text{Neg}/y,z \rightarrow^c \text{Tr}/z + \text{Neg}/y,z$
$\text{Neg}/z,x \rightarrow^c \text{Tr}/x + \text{Neg}/z,x$
$\text{Tr}/x + \text{Neg}/x,y \rightarrow^c \text{Tr}/x + \text{Inh}/x,y$
$\text{Tr}/y + \text{Neg}/y,z \rightarrow^c \text{Tr}/y + \text{Inh}/y,z$
$\text{Tr}/z + \text{Neg}/z,x \rightarrow^c \text{Tr}/z + \text{Inh}/z,x$
$\text{Inh}/x,y \rightarrow^h \text{Neg}/x,y$
$\text{Inh}/y,z \rightarrow^h \text{Neg}/y,z$
$\text{Inh}/z,x \rightarrow^h \text{Neg}/z,x$
$\text{Tr}/x \rightarrow^0 \text{0}$
$\text{Tr}/y \rightarrow^0 \text{0}$
$\text{Tr}/z \rightarrow^0 \text{0}$
$\text{Neg}/x,y + \text{Neg}/y,z + \text{Neg}/z,x$

A fine stochastic oscillator over a wide range of parameters.

Analytically not an oscillator!

Blossey-Cardelli-Phillips.
GMA ≠ CME
\[ A+A \rightarrow^{2r} A \quad =? \quad A+A \rightarrow^{r} 0 \]

\[ [A]^* = -2k[A]^2 \quad \Rightarrow \quad [A]^* = -2k[A]^2 \]

\[
\begin{align*}
\text{\( k = \frac{r\gamma}{2} \)} & \quad \text{\( A+A \rightarrow^{2k} A \)} & \quad \text{\( [A]_0 = \frac{2}{\gamma} \)} \\
\text{\( A+A \rightarrow^{2r} A \)} & \quad \text{\( A+A \)} & \quad \text{\( A+A \rightarrow^{r} 0 \)} & \quad \text{\( k = \frac{r\gamma}{2} \)} \\
\text{\( A+A \rightarrow^{2r} A \)} & \quad \text{\( A+A \)} & \quad \text{\( A+A \rightarrow^{r} 0 \)} & \quad \text{\( k = \frac{r\gamma}{2} \)} \\
\text{\( 2r \)} & \quad \text{\( A \)} & \quad \text{\( r \)} & \quad \text{\( 0 \)}
\end{align*}
\]
... as Automata

\[ [A]^\bullet = -2r\gamma[A]^2 \]

\[ [A]^\bullet = -4k[A]^2 \]

\[ k = r\gamma/2 \]

\[ A + A \rightarrow^4 k A \]

\[ [A]^0 = 2/\gamma \]

\[ A + A \rightarrow^4 r A \]

\[ A + A \rightarrow 4r A \]

\[ A = ?a_r;0 \oplus !a_r;A \]

\[ A | A \]

\[ A = ?a(2r);0 \oplus !a(2r);A \]

\[ A | A \]

\[ A = ?a(r);0 \oplus !a(r);0 \]

\[ A | A \]

\[ A = ?a(2r);0 \oplus !a(2r);A \]

\[ A | A \]

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Conclusions
Conclusions

- **Compositional Models**
  - Accurate (at the “appropriate” abstraction level).
  - Manageable (so we can scale them up by composition).

- **Interacting Automata**
  - Complex global behavior from simple components.
  - Bridging individual and collective behavior.
  - Connections to classical Markov theory, chemical Master Equation, and Rate Equation.

- **PolyAutomata (not shown)**

- **Mapping out “the whole system”**
  - Through an “artificial biochemistry” (a scalable mathematical and computational modeling framework) to investigate “real biochemistry” on a large scale.