Can a Biologist fix a Radio?
Yuri Lazebnik. Cancer Cell. 2002 Sep;2(3):179-82.

Artificial Biochemistry

Stochastic Collectives

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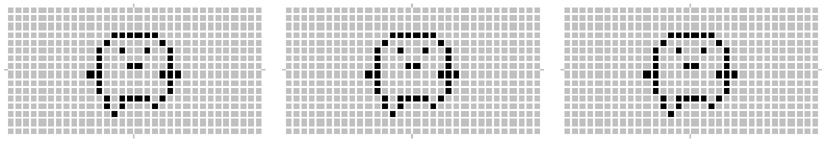
Trento, 2006-05-22..26

www.luca.demon.co.uk/ArtificialBiochemistry.htm

Stochastic Collectives



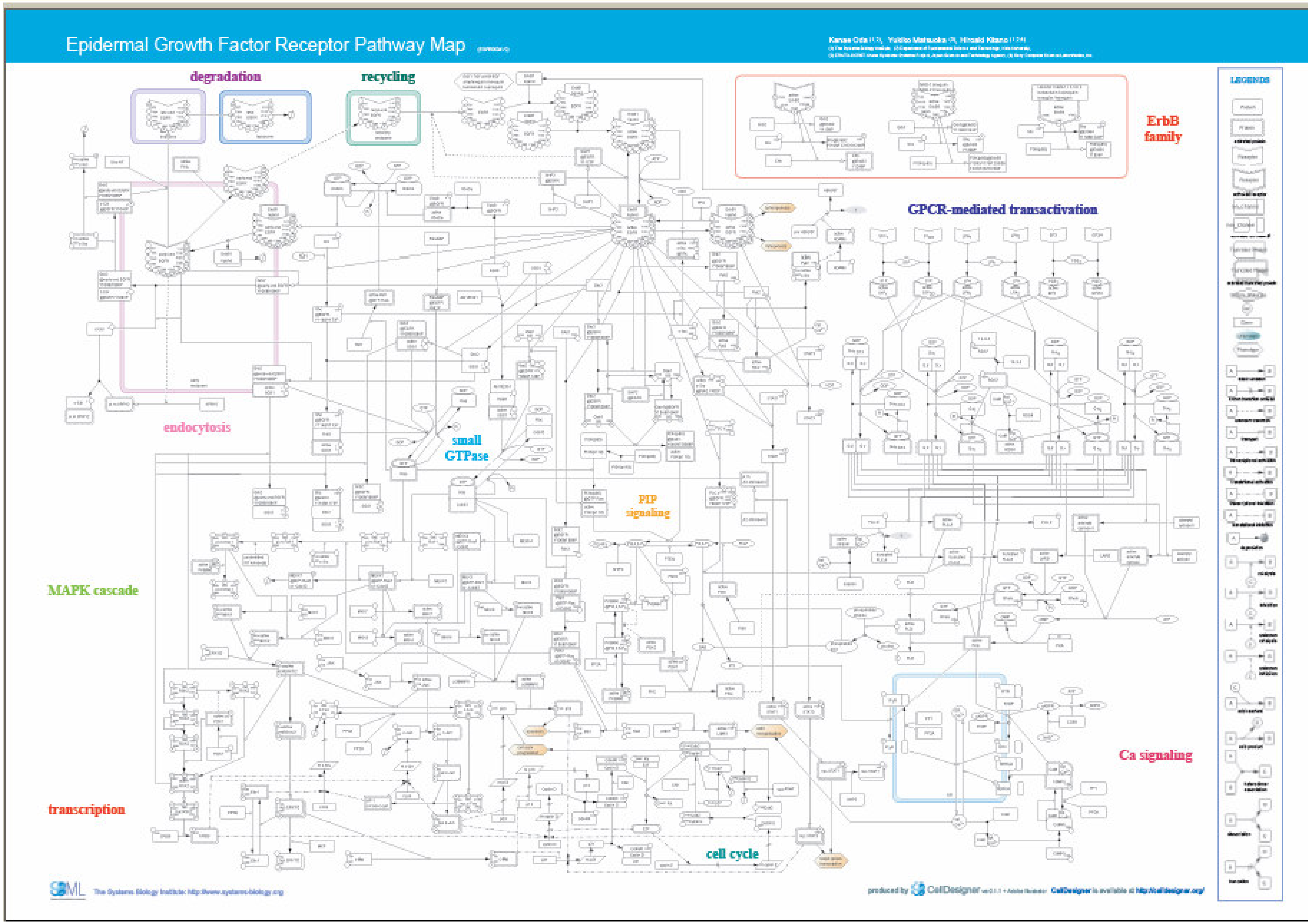
Stochastic Collectives

- "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 ("finite state" and "collective")
    - Cf. "multi-agent systems" and "swarm intelligence"

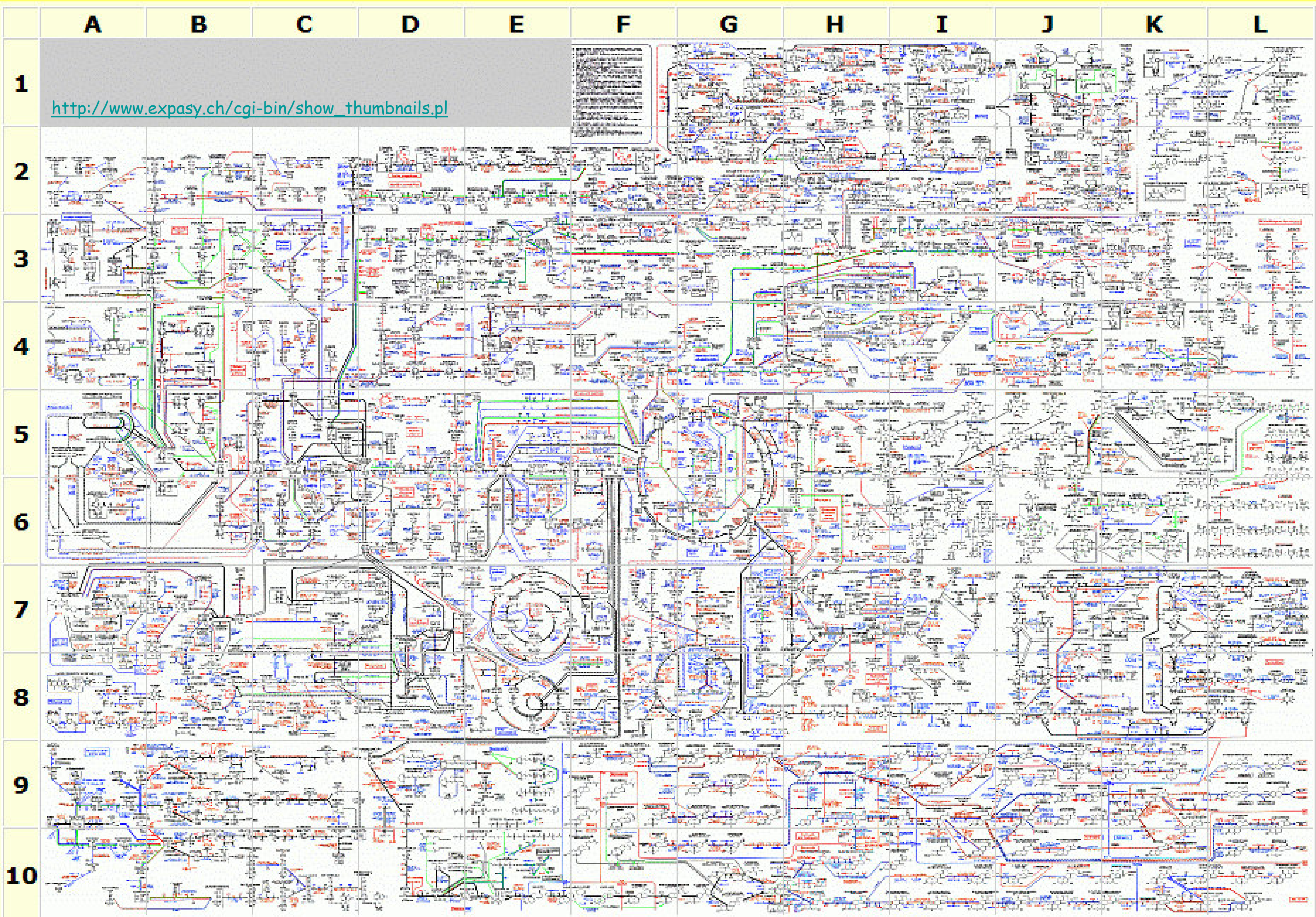
- "Stochastic":
  - Interactions have *rates*
    - Not quite discrete (hundreds or thousands of components)
    - Not quite continuous (non-trivial stochastic effects)
    - Not quite hybrid (no "switching" between regimes)

- 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



Even More State Transitions



Reverse Engineering Nature

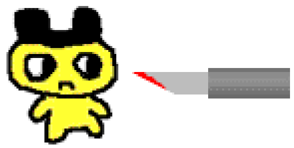
- That's what Systems Biology is up against
  - Exemplified by a technological analogy:

How often do I have to exercise my Tamagotchi?
Every Tamagotchi is different. However we do recommend exercising at least three times a day

- Tamagotchi: a technological organism
  - Has inputs (buttons) and outputs (screen/sound)
  - It has state: happy or needy (or hungry, sick, dead…)
  - Has to be petted at a certain rate (or gets needy)
  - Each one has a slightly different behavior

- Reverse Engineering Tamagotchi
  - Running experiments that elucidate their behavior
  - Building models that explain the experiments

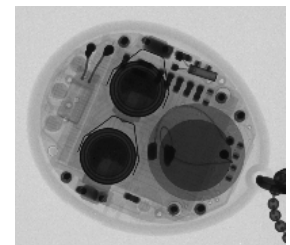
- Applications
  - Engineering: Can we build our own Tamagotchi?
  - Maintenance: Can we fix a broken Tamagotchi?



Understanding T.Nipponensis

- Tamagotchi Nipponensis: a stochastic interactive automaton
  - 40 million sold worldwide; discontinued in 1998
  - Still found "in the wild" in Akihabara
  - New version in 2004: they communicate!

- Traditional scientific investigations fail
  - Design-driven understanding fails
    - We cannot read the manual (Japanese)
    - What does a Tamagotchi "compute"? What is its "purpose"?
    - Why does it have 3 buttons?
  - Mechanistic understanding fails
    - Few moving parts. Removing components mostly ineffective or "lethal"
    - The "tamagotchi folding problem" (sequence of manufacturing steps) is too hard and gives little insight on function

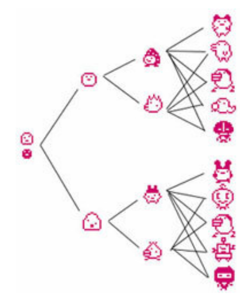


Tamagotchi X-ray

  - Behavioral understanding fails
    - Subjecting to extreme conditions reveals little and may void warranty
    - Does not answer consistently to individual stimuli, nor to sequences of stimuli
    - There are stochastic variations between individuals

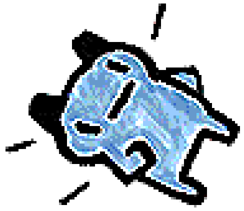
Tamagotchi Surgery
http://necrobones.com/tamasurg/

  - Ecological understanding fails
    - Difficult to observe in its native environment (kids' hands)
    - Mass produced in little-understood automated factories
    - It evolved by competing with other products in the baffling Japanese market
  - Mathematical understanding fails
    - What differential equations does it obey? (Uh?)



A New Approach

- "Systems Technology" of T. Nipponensis
  - High-throughput experiments (get all the information you possibly can)
    - Decode the entire software and hardware
    - Take sequences of tamagotchi screen dumps under different conditions
    - Put 300 in a basket and shake them; make statistics of final state



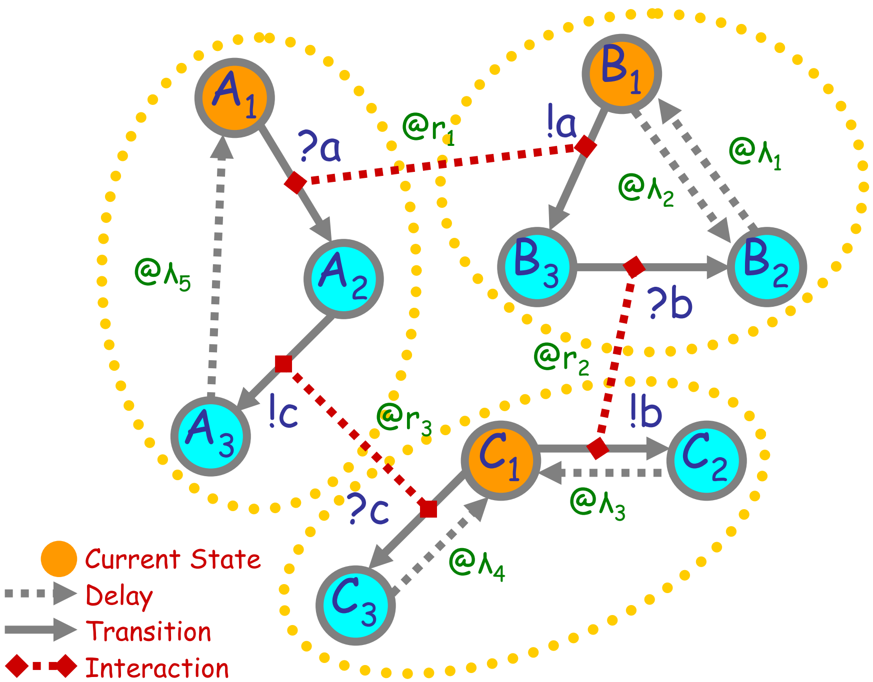
  - Modeling (organize all the information you got)
    - Ignore the "folding" (manufacturing) problem
    - Ignore materials (it's just something with buttons, display, and a *program*.)
    - Abstract until you find a conceptual model (ah-ha: it's a stochastic automaton).

- Do we understand what stochastic automata collectives can do?

Communicating Tamagotchi

Automata Collectives

Interacting Automata



new $a@r_1$
new $b@r_2$
new $c@r_3$
} Communication channels

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

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

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

$A_1 \mid B_1 \mid C_1$ } The system and initial state

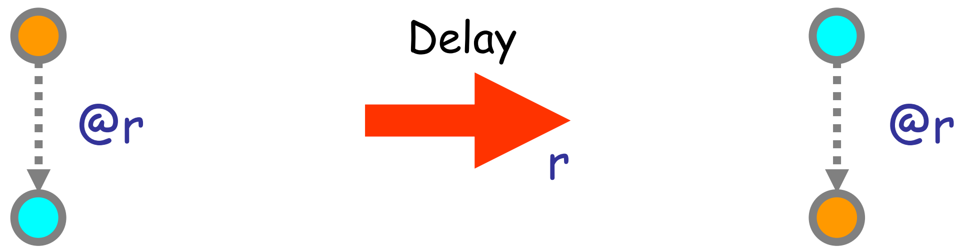
Communicating automata: a graphical FSA-like notation for "finite state restriction-free π-calculus processes". *Interacting* automata do not even exchange values on communication.

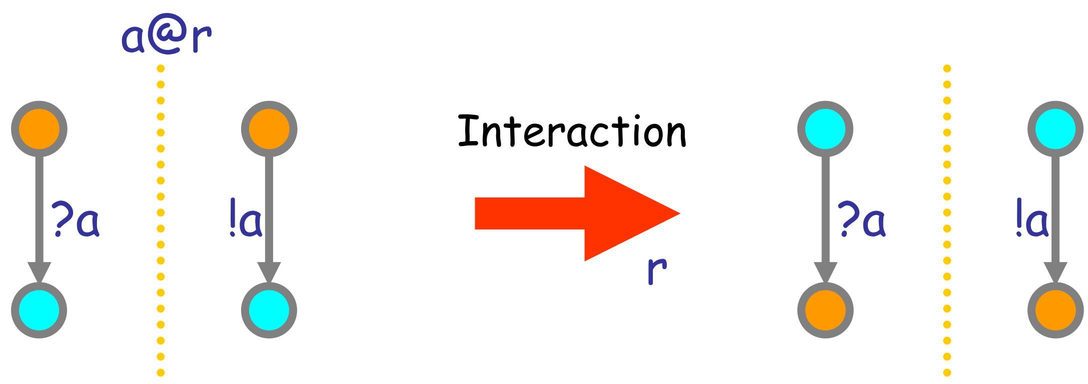
The stochastic version has *rates* on communications, and delays.

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

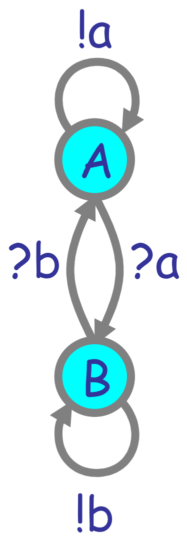
Analyzable by standard Markovian techniques, by first computing the "product automaton" to obtain the underlying finite Markov transition system. [Buchholz]

Interacting Automata Transition Rules





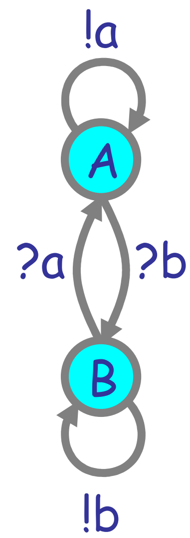
Groupies and Celebrities



Celebrity

(does not want to be like somebody else)

```
directive sample 0.1 1000
directive plot A(); B()

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

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

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

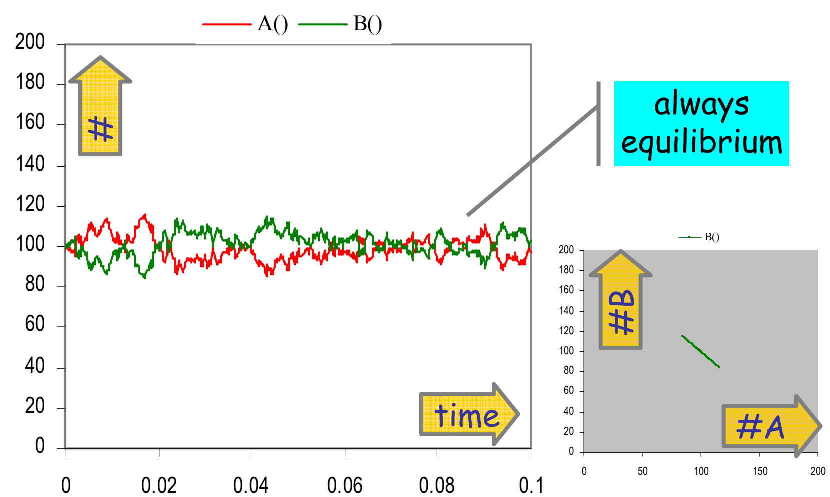


Groupie

(wants to be like somebody different)

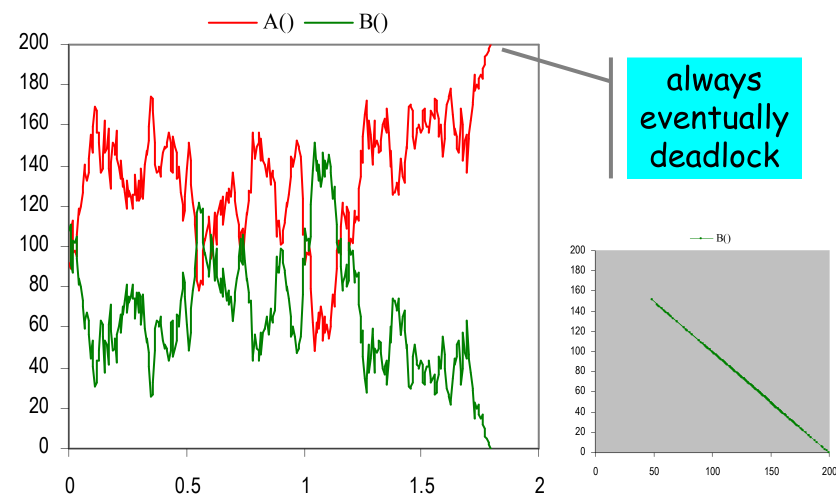
```
directive sample 5.0 1000
directive plot A(); B()

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:



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.

A stochastic collective of groupies:

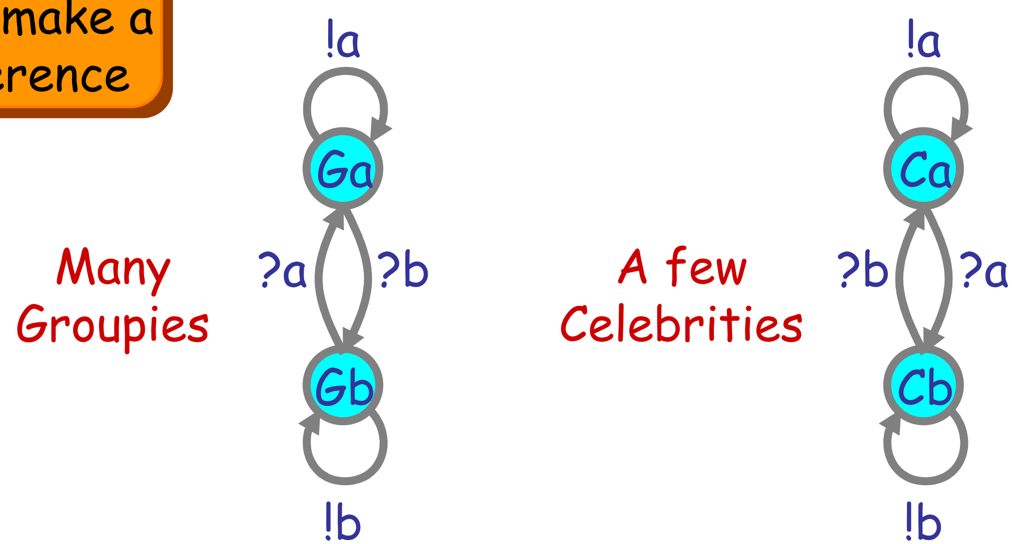


Unstable because within an A majority, an A has difficulty finding a B to emulate, but the few B's have plenty of A's to emulate, so the majority may switch to A. Leads to deadlock when everybody is in the same state and there is nobody different to emulate.

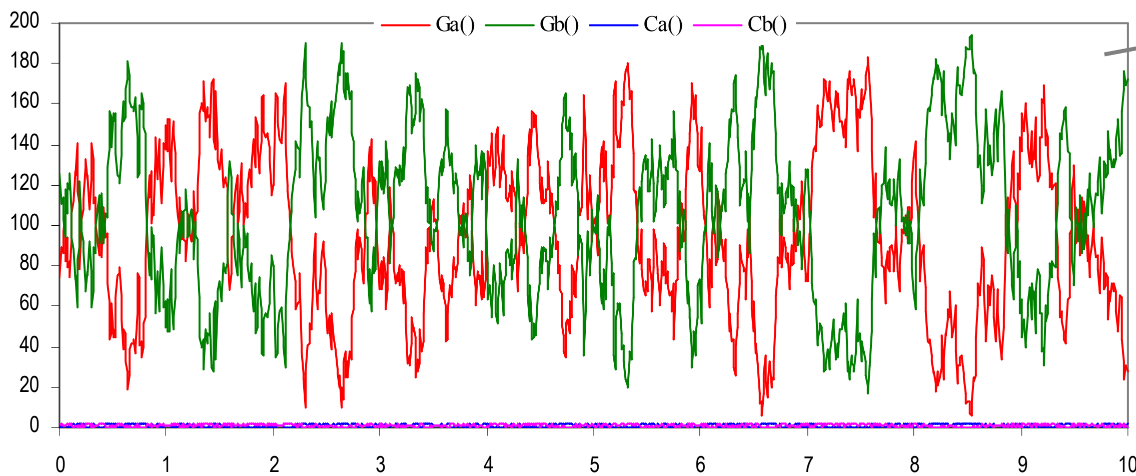
Both Together

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

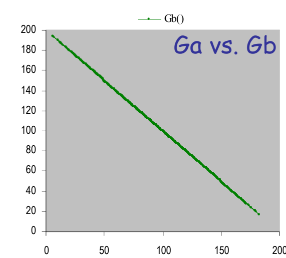
A way to break the deadlocks: Groupies with just a few Celebrities




```
directive sample 10.0 1000
directive plot Ga(); Gb(); Ca(); Cb()

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

let Ca() = do !a; Ca() or ?a; Cb()
and Cb() = do !b; Cb() or ?b; Ca()

let Ga() = do !a; Ga() or ?b; Gb()
and Gb() = do !b; Gb() or ?a; Ga()

run    1 of (Ca() | Cb())
run 100 of (Ga() | Gb())
```

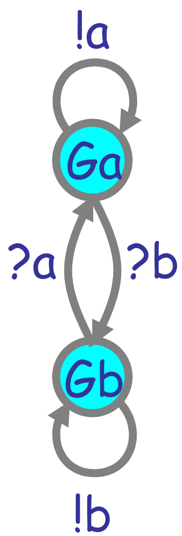


never deadlock

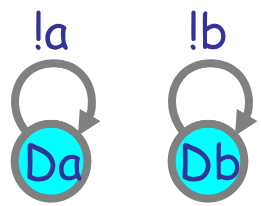


Doped Groupies

A similar way to break the deadlocks: destabilize the groupies by a small perturbation.

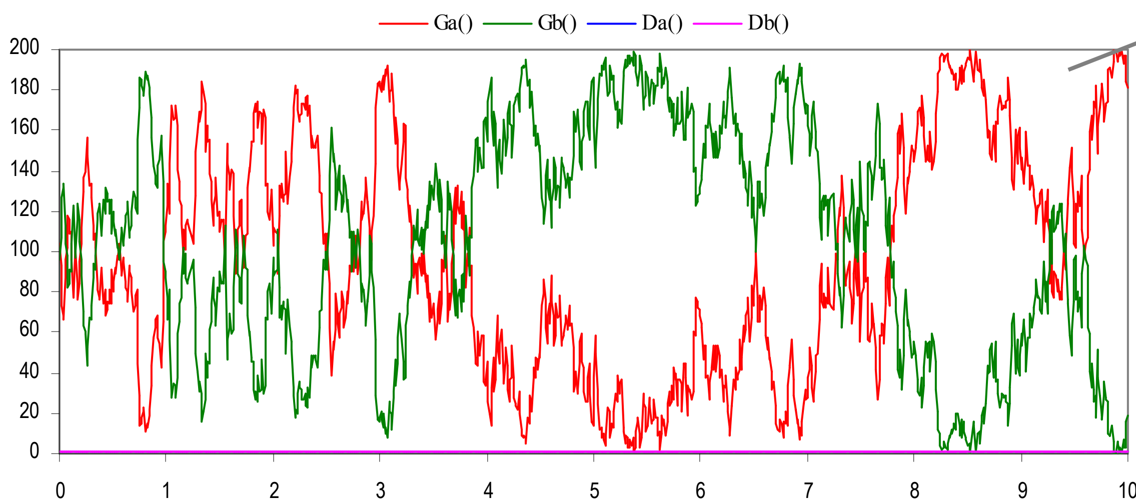


Groupie

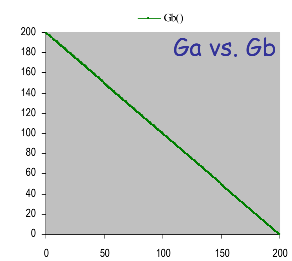


Doping[1]

```
directive sample 10.0 1000
directive plot Ga(); Gb(); Da(); Db()

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

let Ga() = do !a; Ga() or ?b; Gb()
and Gb() = do !b; Gb() or ?a; Ga()

let Da() = !a; Da()
and Db() = !b; Db()

run  1 of (Da() | Db())
run 100 of (Ga() | Gb())
```



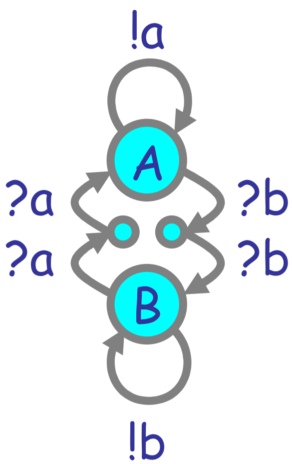
never deadlock

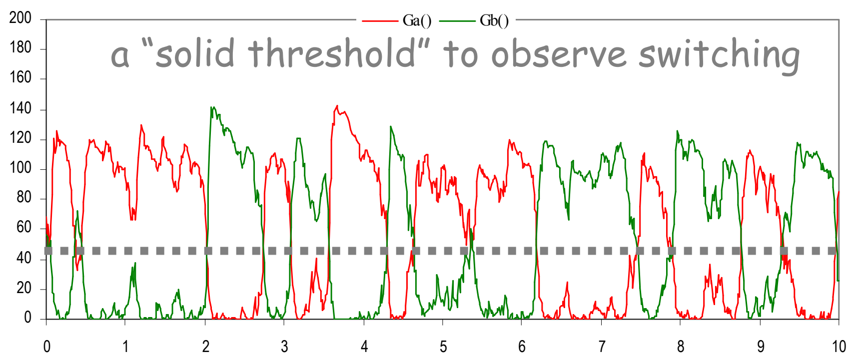


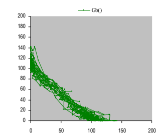
[1]A technical term in microelectronics

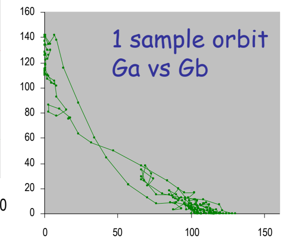
Hysteric Groupies

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

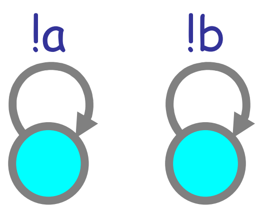






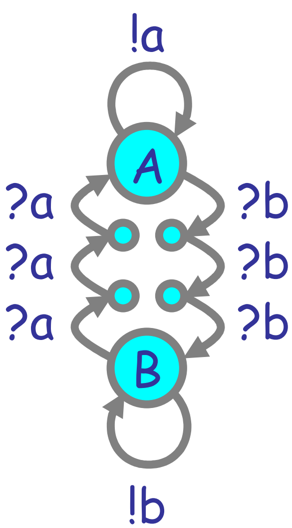


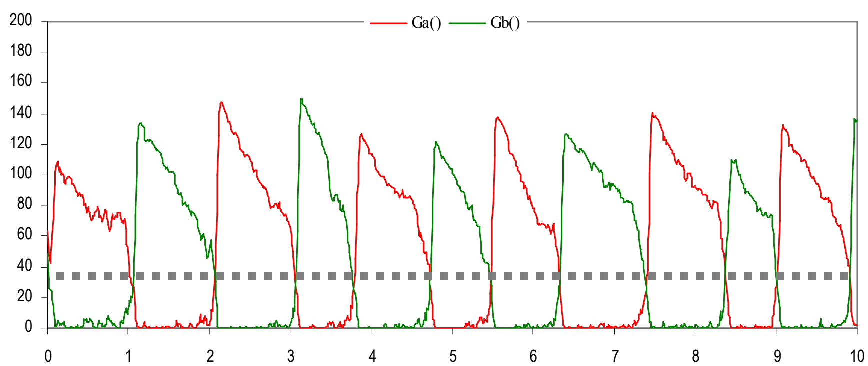

```
directive sample 10.0 1000
directive plot Ga(); Gb()

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

let Ga() = do !a; Ga() or ?b; ?b; Gb()
and Gb() = do !b; Gb() or ?a; ?a; Ga()

let Da() = !a; Da()
and Db() = !b; Db()

run 100 of (Ga() | Gb())
run   1 of (Da() | Db())
```

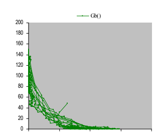


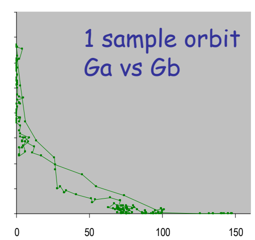
(Still with doping)

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



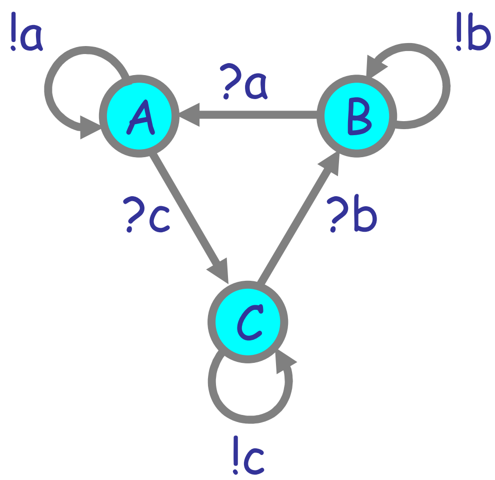




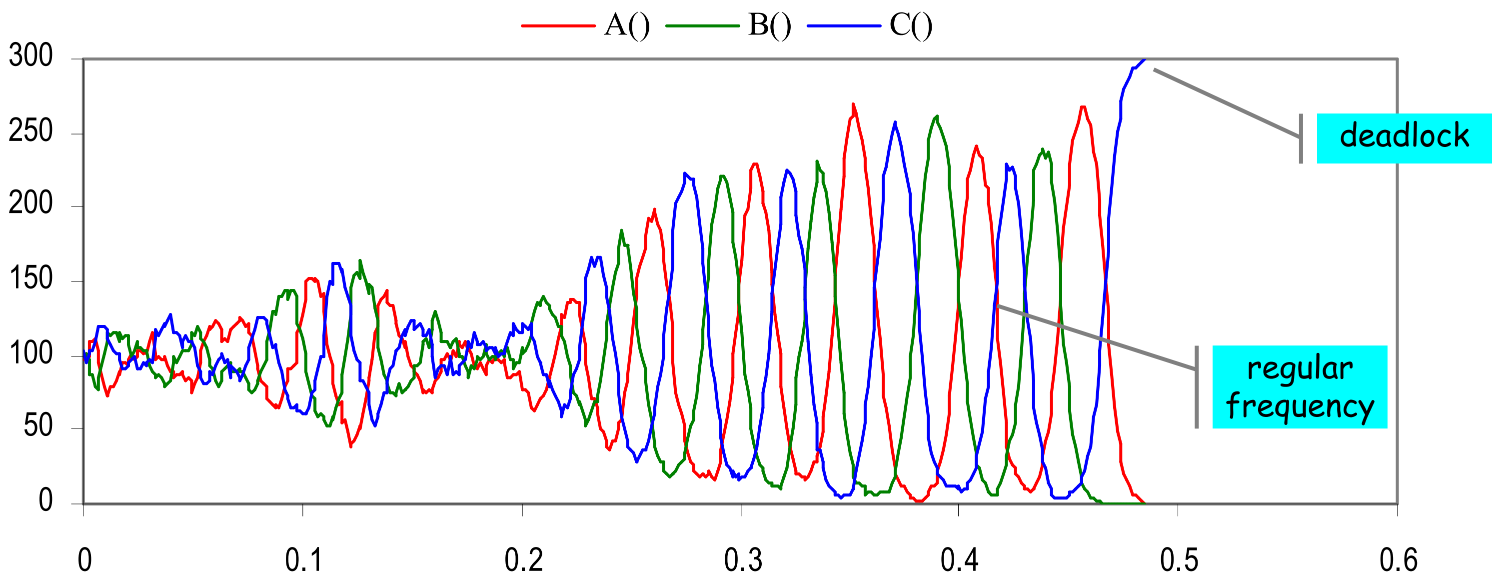



```
directive sample 10.0 1000
directive plot Ga(); Gb()

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; ?a; Ga()

let Da() = !a; Da()
and Db() = !b; Db()

run 100 of (Ga() | Gb())
run   1 of (Da() | Db())
```

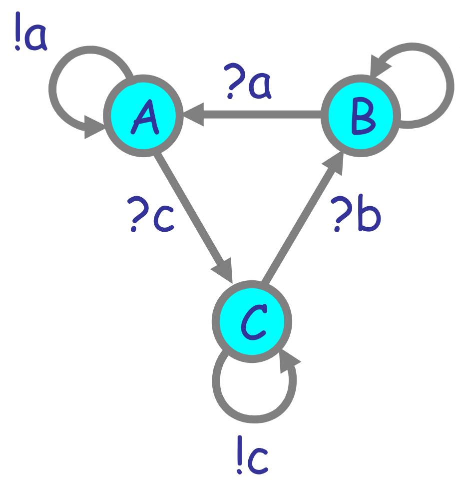
3-Way Groupies

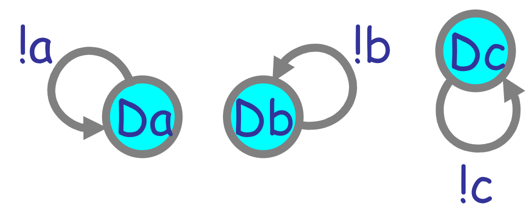



```
directive sample 2.0 10000
directive plot A(); B(); C()

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

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

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

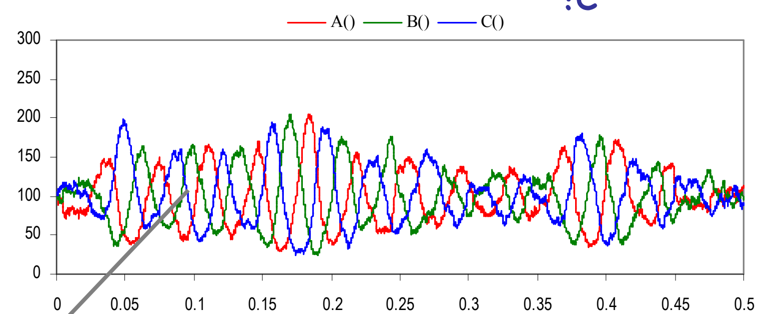


Doped 3-Way Groupies



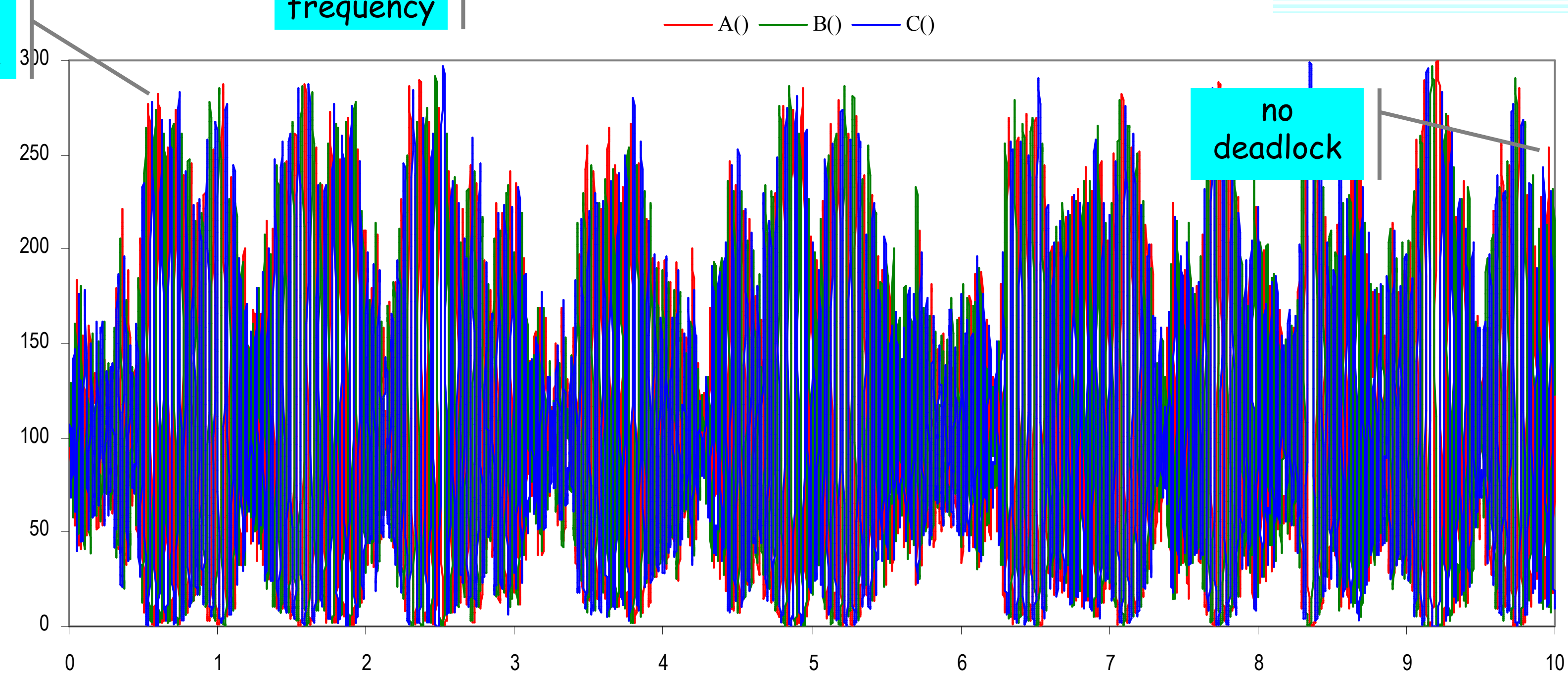



```
directive sample 10.0 10000
directive plot A(); B(); C()

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

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

let As() = !a; As()
and Bs() = !b; Bs()
and Cs() = !c; Cs()

run 100 of (A() | B() | C())
run 1 of (As() | Bs() | Cs())
```



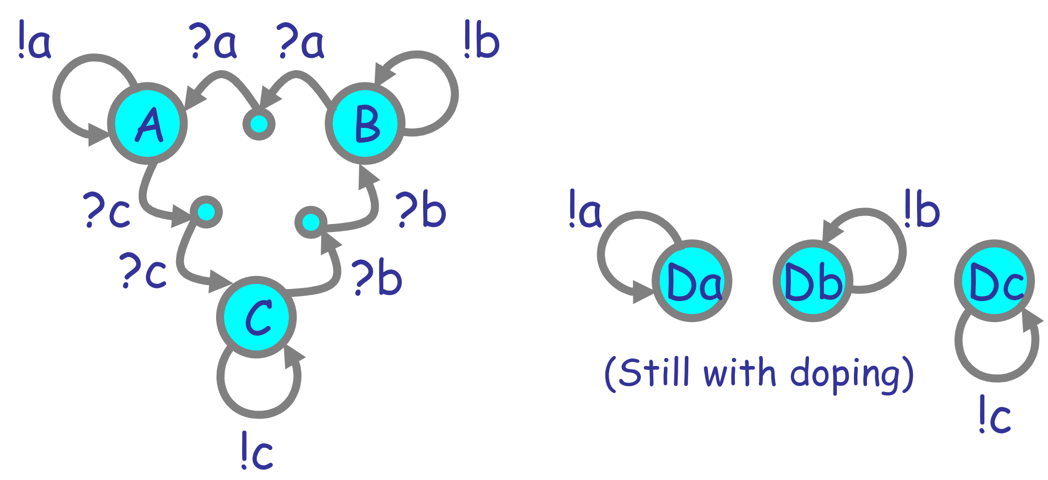
regular frequency

random amplitude



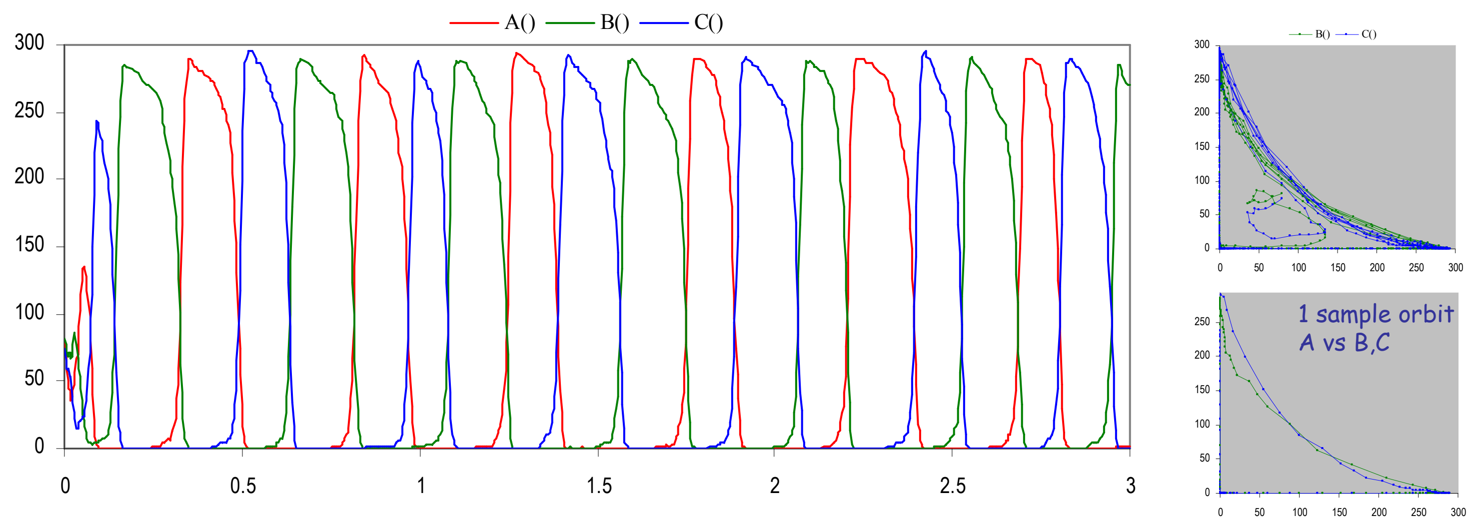
no deadlock

Hysteric 3-Way Groupies

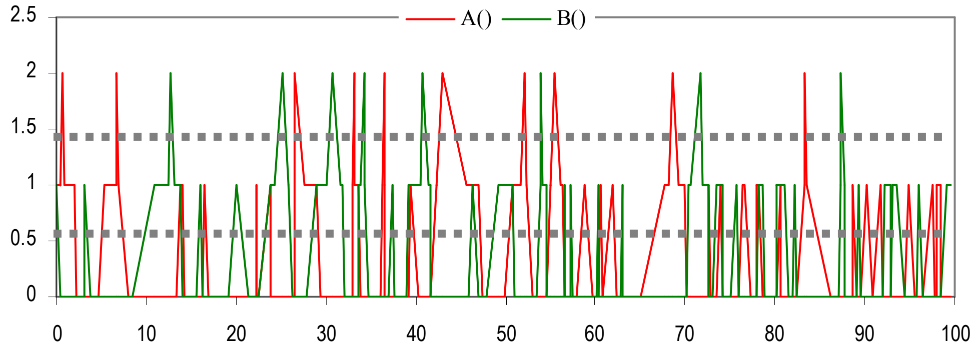



```
directive sample 3.0 1000
directive plot A(); B(); C()

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

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

let Da() = !a; Da()
and Db() = !b; Db()
and Dc() = !c; Dc()

run 100 of (A() | B() | C())
run 1 of (Da() | Db() | Dc())
```

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

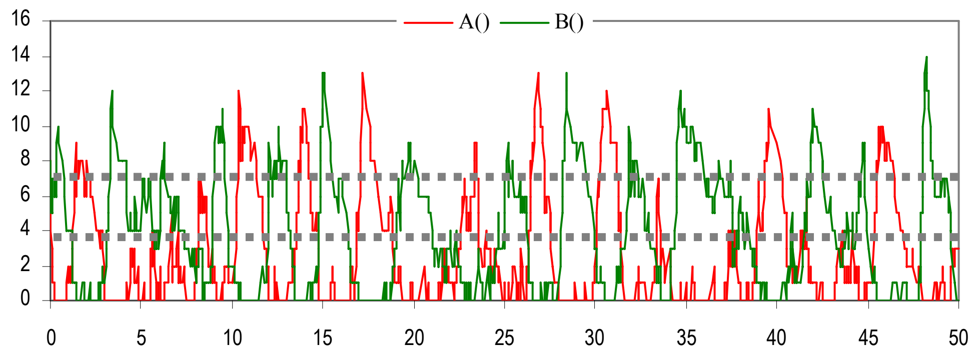


Oscillation as Emergence



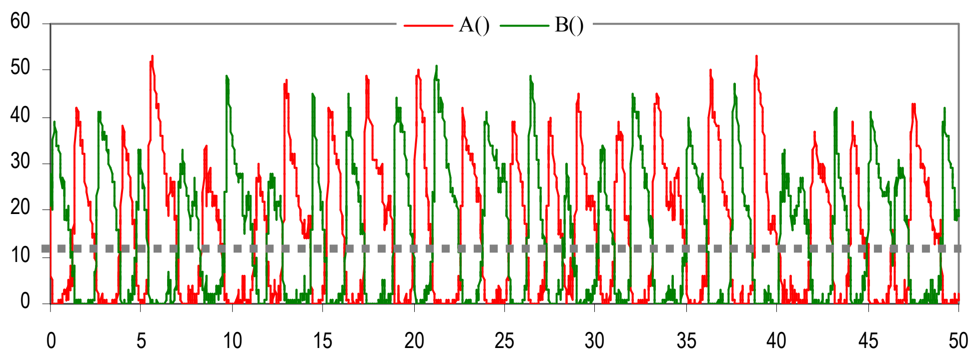
Just 2 processes do not oscillate regularly at all!

Without changing the components, interesting properties emerge with a critical size of the population.



Nor 16…

Dotted lines indicate cross sections where one may look for evidence of alternation.



Pretty good with 64…

```
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 As() = !a; As()
and Bs() = !b; Bs()

run 64 of (A() | B())
run   1 of (As() | Bs())
```

Summary

- Biological Systems
  - Assume they are stochastic automata collectives.
  - Try to reverse engineer them on that basis.
- Stochastic automata collective
  - Can have very puzzling behavior.
  - Stochastic “noise” can have macroscopic effects.
  - Macroscopic properties may “emerge”.
- Biological systems
  - Can have very puzzling behavior even if you know them completely.

Q?