How the Cell Cycle Computes

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Dublin, 2012-05-25
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Outline

- Analyzing molecular networks
  - Various biochemical/bioinformatical techniques can tell us something about network structures.
  - We try do discover the function of the network, or to verify hypotheses about its function.
  - We try to understand how the structure is dictated by the function and other natural constraints.
- The Cell-Cycle Switches and Oscillators
  - Some of the best studied molecular networks.
  - Important because of their fundamental function (cell division) and preservation across evolution.

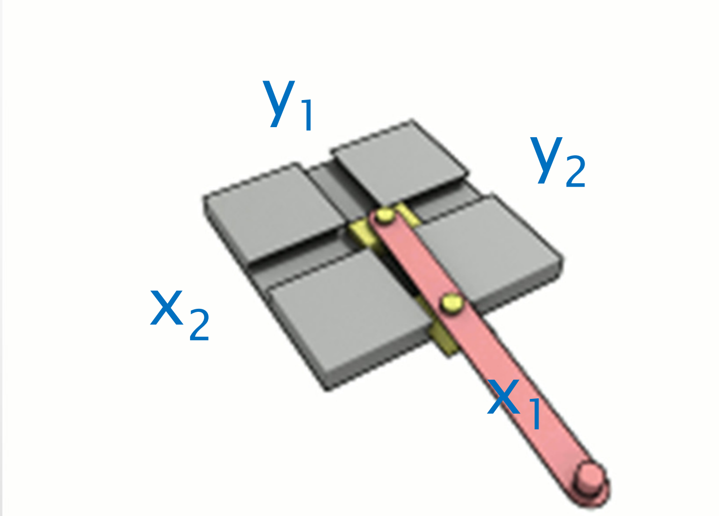
Oscillators

- Basic in Physics, studied by simple *phenomenological* (not structural) ODE models.
- Non-trivial in Chemistry: it was only discovered in the 20's (Lotka) that chemical systems can oscillate: before it was thought impossible in closed systems. Shown experimentally only in the 50's.
- Mechanics (since antiquity) and modern Electronics (as well as Chemistry) must engineer the *network structure* of oscillators.
- Biology: all natural cycles. Here we must reverse engineer their network structure.
- Computing: how can populations of agents (read: molecules) interact (network) to achieve oscillations?

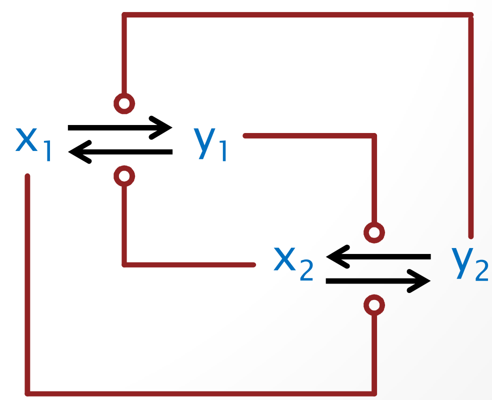
The Trammel of Archimedes

- A device to draw ellipses
  - Two interconnected **switches**.
  - When one switch is on (off) it flips the other switch on (off). When the other switch is on (off) it flips the first switch off (on).
  - The amplitude is kept constant by mechanical constraints.

The function



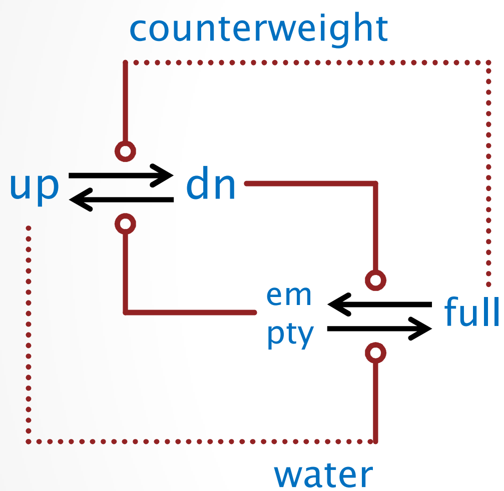
The network



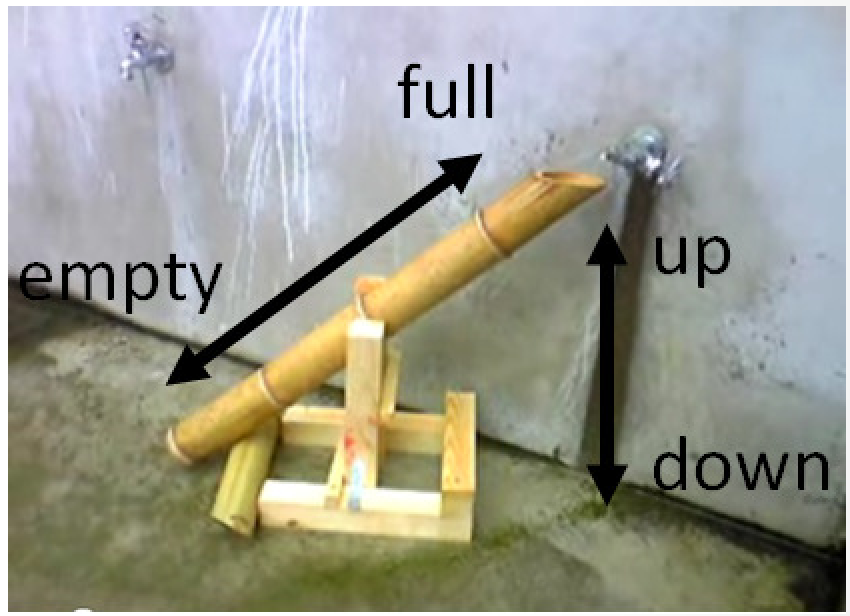
en.wikipedia.org/wiki/Trammel_of_Archimedes

The Shishi Odoshi

- A Japanese scarecrow (lit. scare-deer)
  - Used by Bela Novak to illustrate the cell cycle switch.



empty + up → up + full
up + full → full + dn
full + dn → dn + empty
dn + empty → empty + up

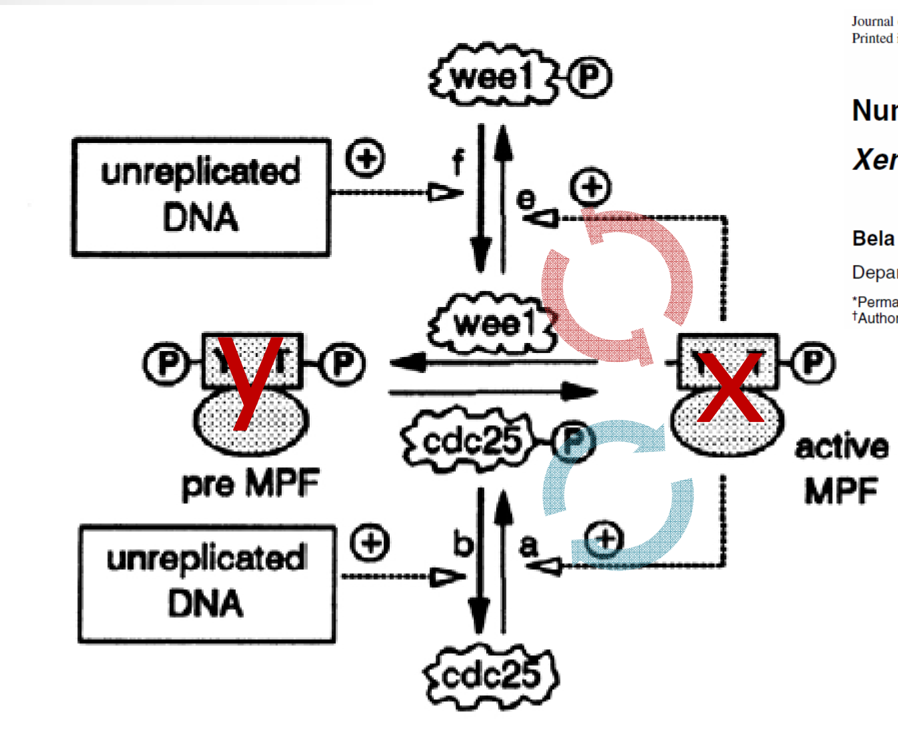


http://www.youtube.com/watch?v=VbvecTIftcE&NR=1&feature=fvwp

Outer switched connections replaced by constant influxes: tap water and gravity.

The Cell Cycle Switch

- At the core of the cell-cycled oscillator.
  - This network is universal in all Eukaryotes [P. Nurse].



Journal of Cell Science 106, 1153-1168 (1993)
Printed in Great Britain © The Company of Biologists Limited 1993

Numerical analysis of a comprehensive model of M-phase control in *Xenopus* oocyte extracts and intact embryos

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- Double positive feedback on x
- Double negative feedback on x
- No feedback on y
  ???

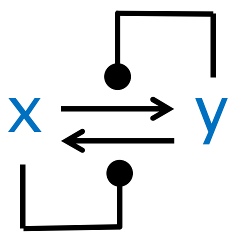
  - Well studied. But why this structure?

How to Build a Switch

- What is a "good" switch?
  - We need first a *bistable* system: one that has two *distinct* and *stable* states. I.e., given *any* initial state the system must *settle* into one of two states.
  - The settling must be *fast* (not get stuck in the middle for too long) and *robust* (must not spontaneously switch back).
  - Finally, we need to be able to *flip* the switch: drive the transitions by external inputs.

A Bad Algorithm

- Direct x–y competition
  - x catalyzes the transformation of y into x
  - y catalyzes the transformation of x into y



$$x + y \rightarrow x + x$$
$$y + x \rightarrow y + y$$

- This system is bistable, but
  - Convergence to a stable state is *slow* (a random walk).
  - *Any* perturbation of a stable state can initiate a random walk to the other stable state.

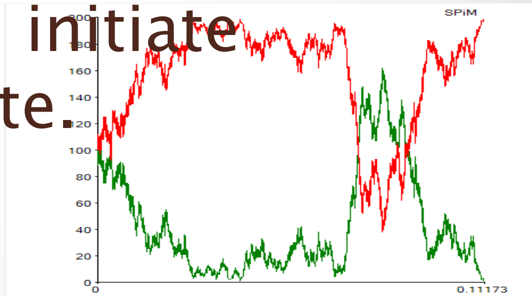
```
directive sample 0.0002
1000
directive plot x(); y(); b()

val rt = 10.0
new xcat@rt:chan
new ycat@rt:chan

let x() =
  do !xcat; x()
  or ?ycat; y()

and y() =
  do !ycat; y()
  or ?xcat; x()

run 100 of x()
run 100 of y()
```



A Very Good Algorithm

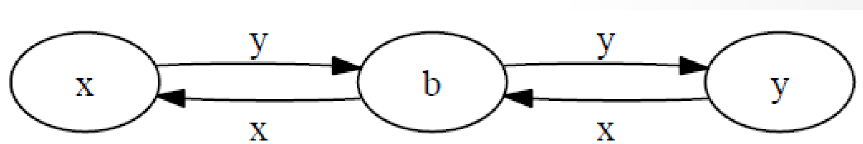
- Approximate Majority
  - Decide which of two populations is in majority
- A fundamental 'population protocol'
  - Agents in a population start in state x or state y.
  - A pair of agents is chosen randomly at each step, they interact ("collide") and change state.
  - The whole population must eventually agree on a majority value (all x or all y) with probability 1.

Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

We analyze the behavior of the following population protocol with states $Q = \{b, x, y\}$. The state b is the **blank** state. Row labels give the initiator's state and column labels the responder's state.

	x	b	y
x	(x, x)	(x, x)	(x, b)
b	(b, x)	(b, b)	(b, y)
y	(y, b)	(y, y)	(y, y)



Third 'undecided' state.

Properties

- With high probability, for n agents

[Angluin et al. http://www.cs.yale.edu/homes/aspnes/papers/disc2007-eisenstat-slides.pdf]

  - The number of state changes before converging is O(n log n)
  - The total number of <u>interactions</u> before converging is O(n log n)
  - The final outcome is correct if the initial disparity is ω(sqrt(n) log n)

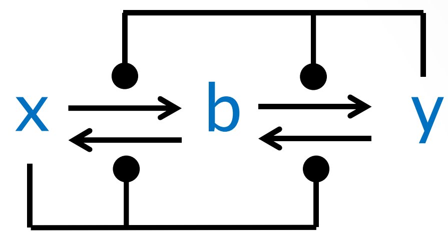
- The algorithm is the fastest possible
  - Must wait Ω(n log n) steps in expectation for all agents to interact

- Logarithmic time bound
  - Parallel time is the number of steps divided by the number of agents.
  - In parallel time the algorithm converges with high probability in O(log n).
  - That is true for any initial conditions, even x=y!

"Although we have described the population protocol model in a sequential light, in which each step is a single pairwise interaction, interactions between pairs involving different agents are independent and may be thought of as occurring in parallel. In measuring the speed of population protocols, then, we define 1 unit of parallel time to be jV j steps. The rationale is that in expectation, each agent initiates 1 interaction per parallel time unit; this corresponds to the chemists' idealized assumption of a well-mixed solution."
Distributed Computing 21(2):87-102.

Chemical Implementation

$x + y \rightarrow y + b$
$y + x \rightarrow x + b$
$b + x \rightarrow x + x$
$b + y \rightarrow y + y$

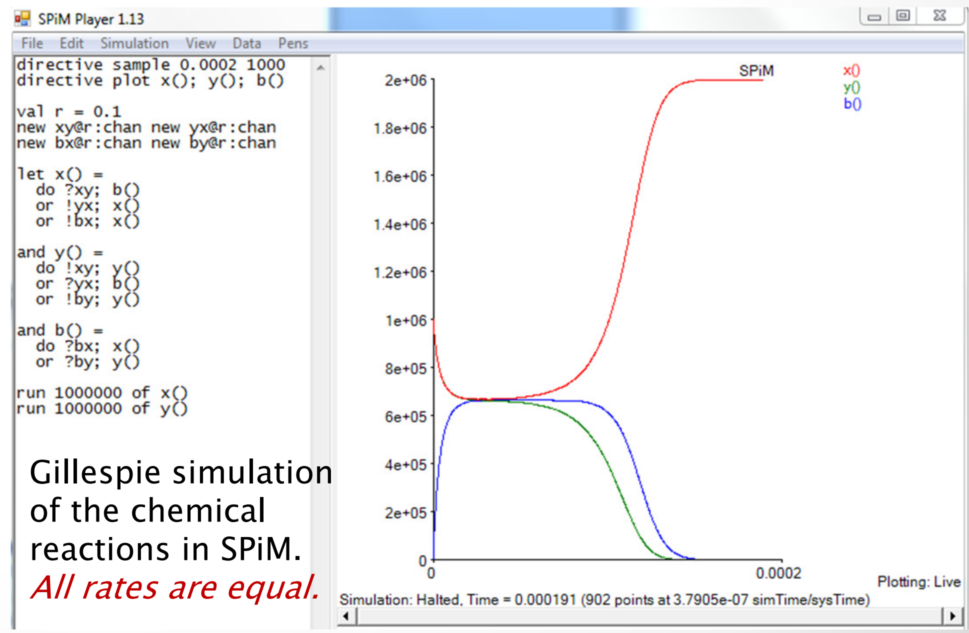


Worse case test: start with x=y.

Bistable
Even when x=y! (stochastically)

Fast
O(log n) convergence time

Robust
$\omega(\sqrt{n} \log n)$ majority wins whp



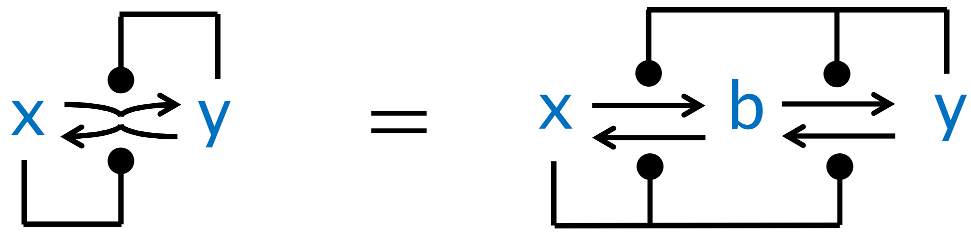
Gillespie simulation of the chemical reactions in SPiM.
All rates are equal.

Back to the Cell Cycle

- The AM algorithm has great properties for settling a population into one of two states.
- But that is not what the cell cycle uses to switch its populations of molecules.
- Or is it?

Step 1: the AM Network

Abbreviated notation:

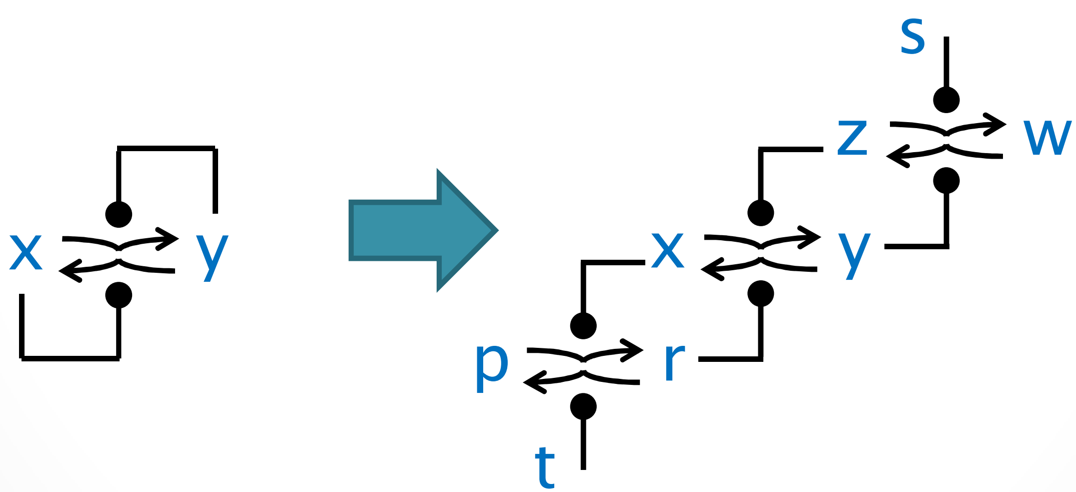


- Autocatalysis, and especially intricate autocatalysis, is not commonly seen in nature. Presumably, it's hard:

$$b + x \to x + x$$
$$b + y \to y + y$$

Step 2: remove auto-catalysis

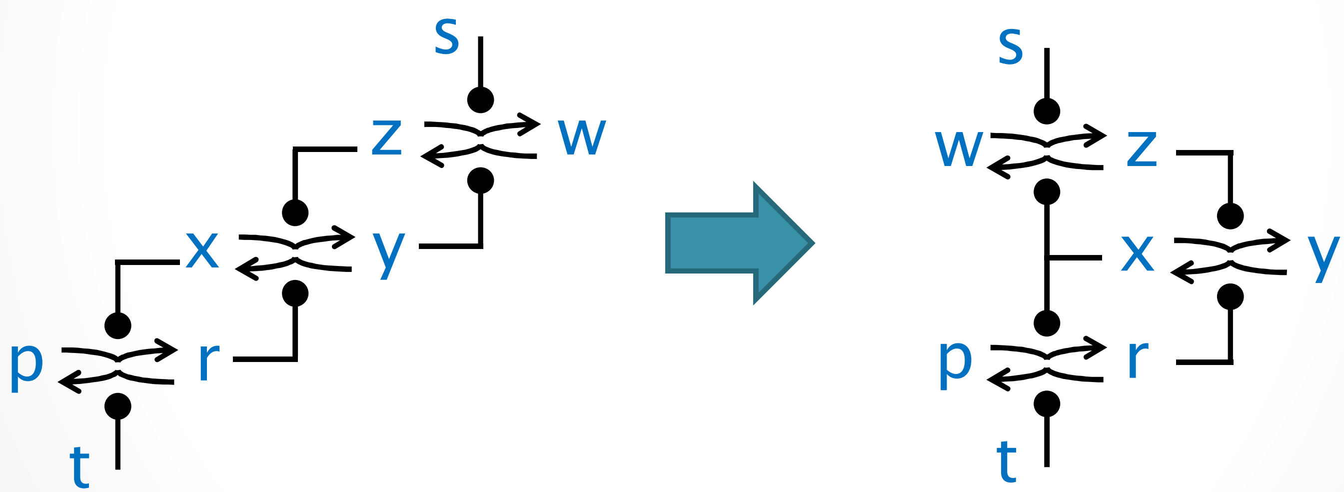
- Replace autocatalysis by mutual (simple) catalysis, introducing intermediate species z, r.
  - Here z breaks the y auto-catalysis, and r breaks the x auto-catalysis, while preserving the feedbacks.
  - z and r need to 'relax back' (to w and p) when they are not catalyzed: s and t provide the back pressure.



- Still, x and y (two states of the same molecule) are distinct active catalysts: that is not common in nature either.

Step 3: only one active state

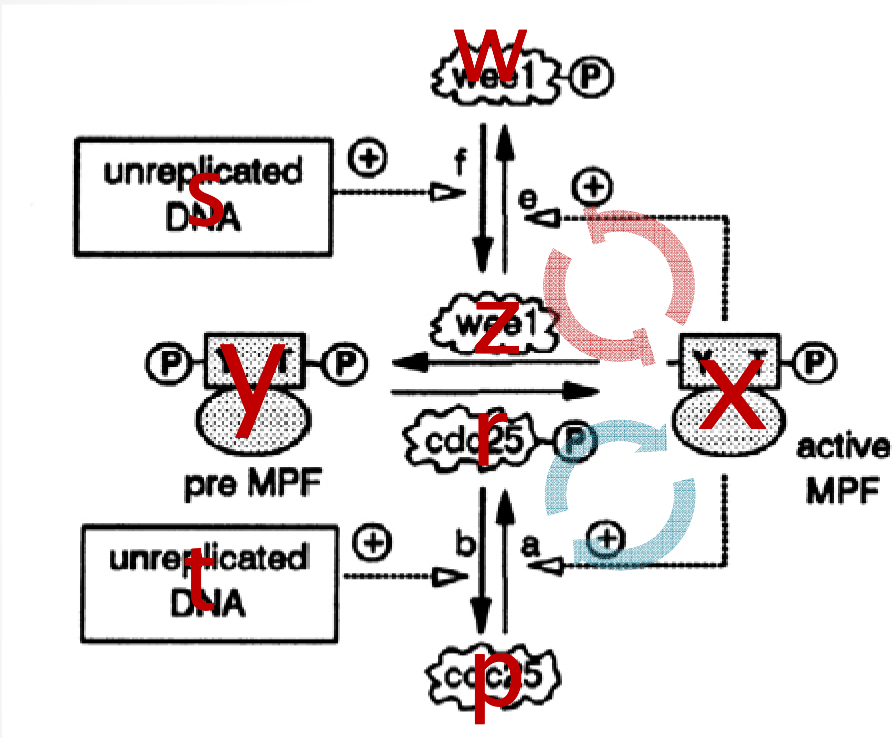
- Remove the catalytic activity of y.
  - Instead of y activating itself through z, we are left with z activating y (which remains passive). Hence, to deactivate y we now need to deactivate z. Since x 'wants' to deactivate y, we make x deactivate z.

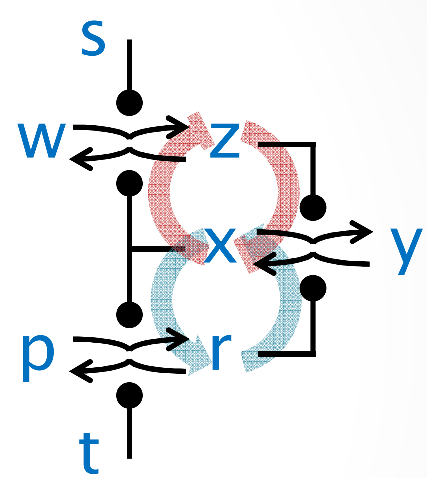


- All species now have one active (x,z,r) and one inactive (y,w,p) form. This is 'normal'.

Network Structure

- … and that *is* the cell-cycle switch!





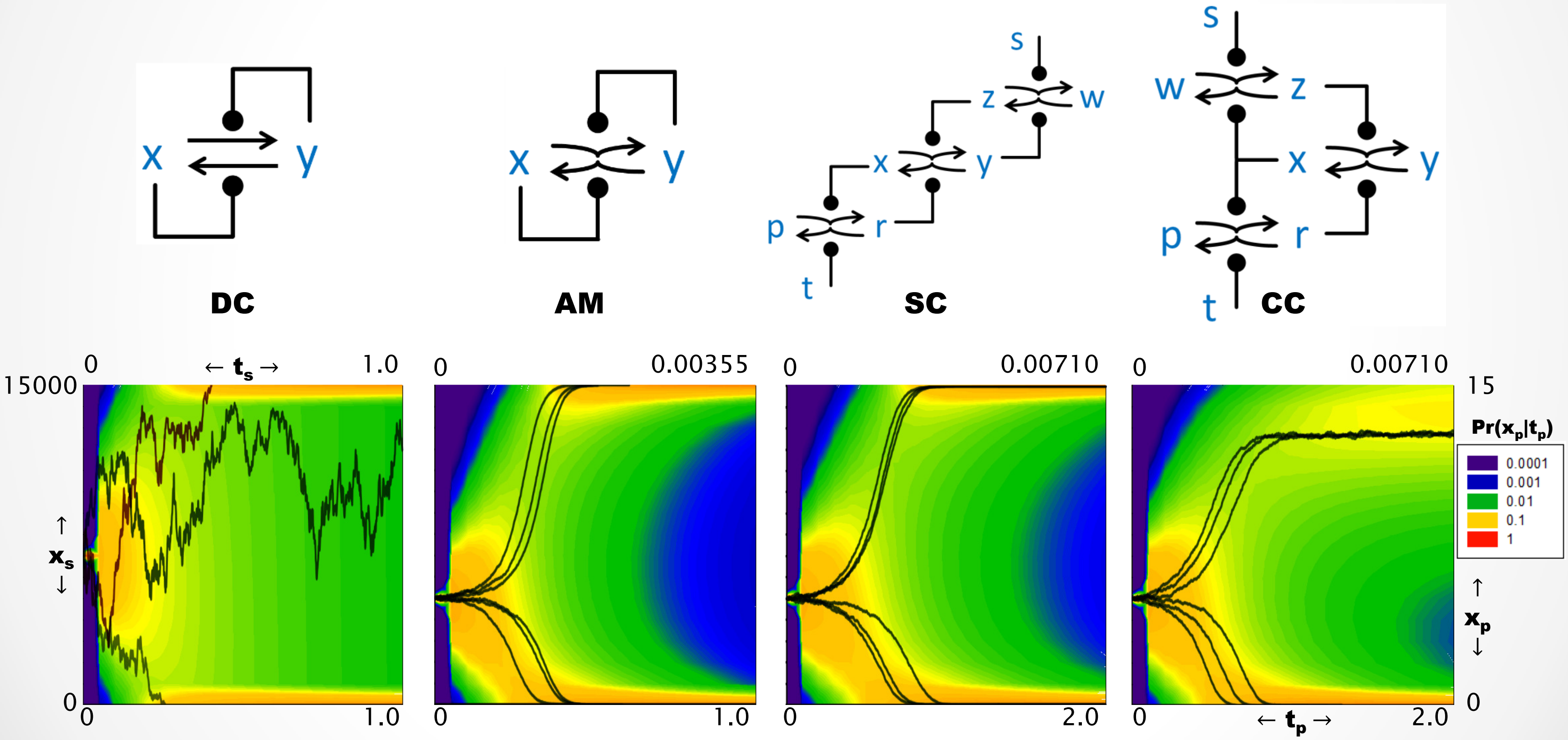
(Some of the bistable states can be enzymatic rather than multi-site phosporylations as in AM.)

- The question is: did we preserve enough *function* through our *network transformations*?

Convergence Analysis

Switches as Computational Systems – Convergence

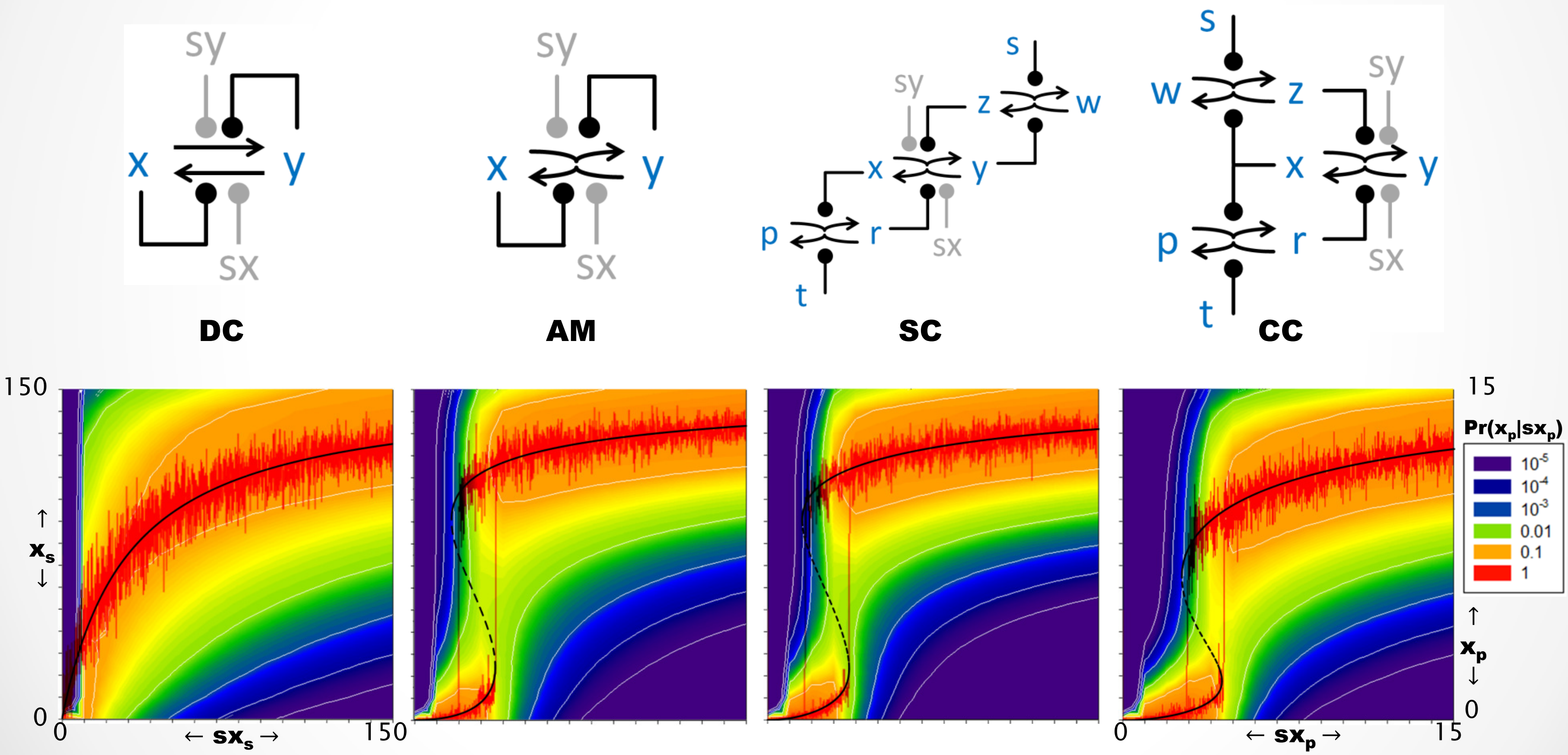
Techniques: Stochastic Simulation and Probabilistic Modelchecking



Steady State Analysis

Switches as Dynamical Systems – Steady State Response

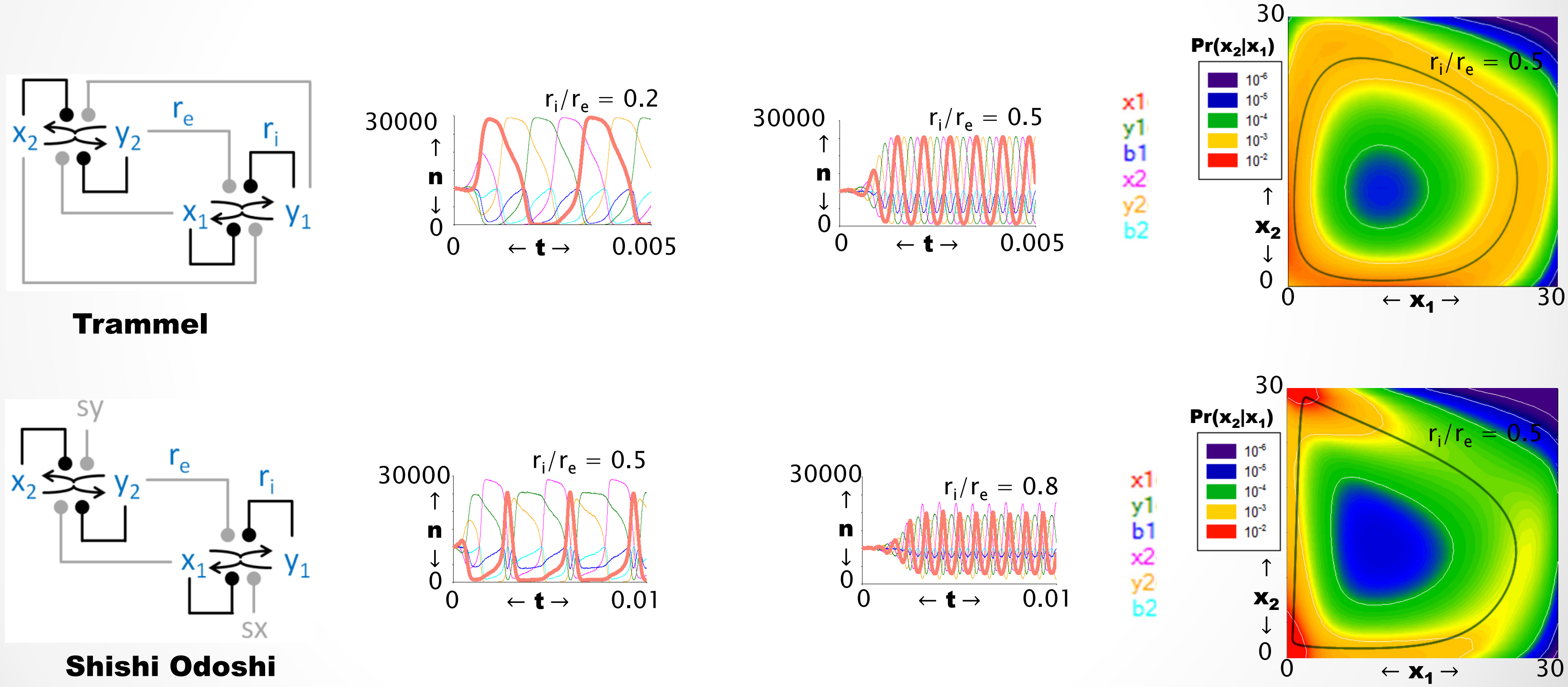
Techniques: as above, plus Dynamical Systems Theory



Oscillation Analysis

Switches in the context of larger networks

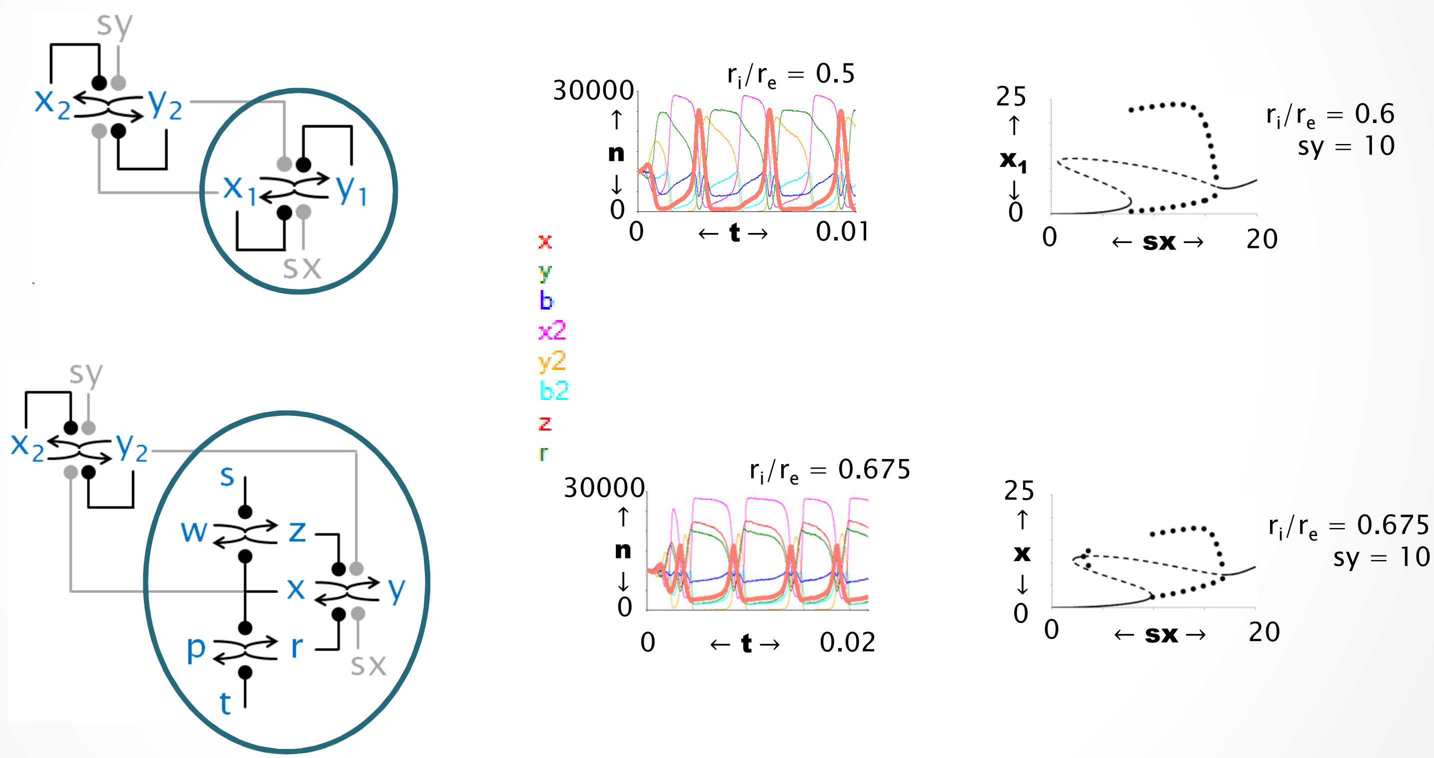
Techniques: time course, phase space



Modularity Analysis

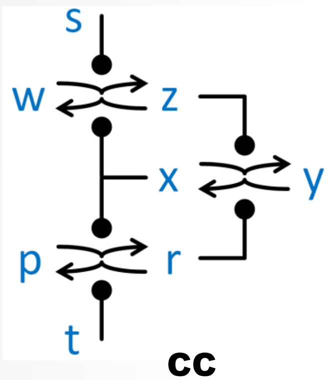
Contextual equivalence?

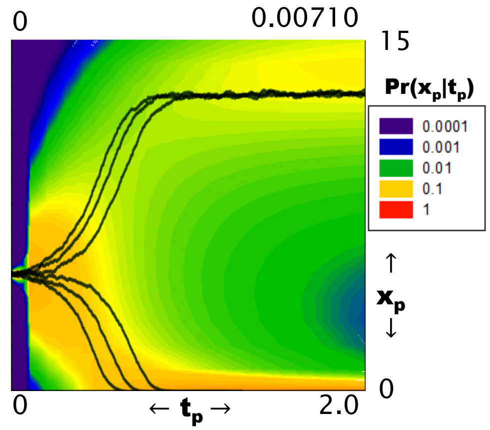
Techniques: time course, bifurcations



CC does not fully switch

We have seen that the output of CC does not go ‘fully on’ like AM:

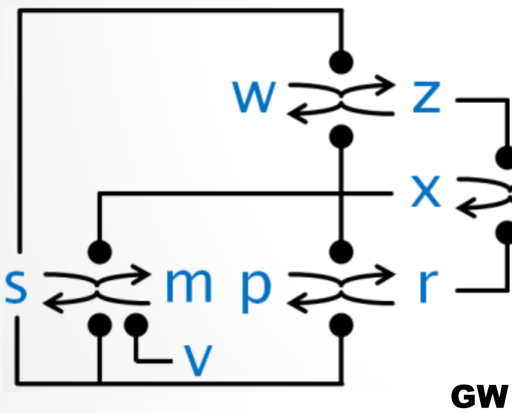


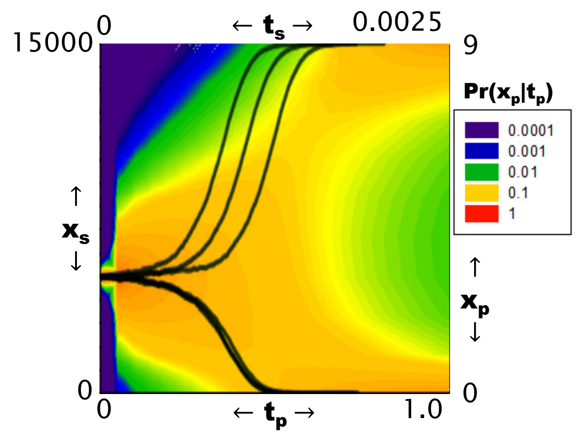


because s continuously inhibits s so that x cannot fully express.
This could be solved if x would inhibit s in retaliation.

But nature fixed that!

In fact nature has solved this problem: there is another known feedback loop in the cell cycle switch by which x suppresses s:



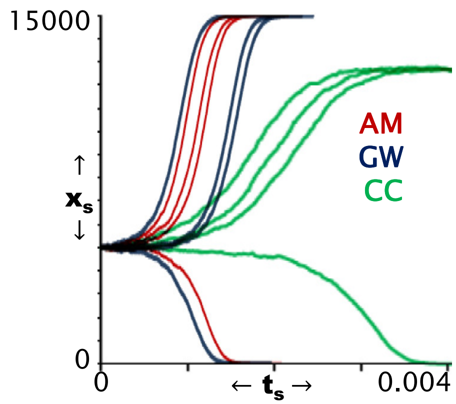


Full activation!

(Also, s and t happen to be the same molecule)

And made it fast too!

More surprising: the extra feedback also speeds up the decision time of the switch, making it about as good as the 'optimal' AM switch:



Nature really is trying very hard to implement the AM algorithm!

Conclusions

Summary

- Q (traditional): What kind of **dynamical system** is the cell-cycle switch?
- A (traditional): Bistability – ultrasensitivity – hysteresis …
  Focused on how unstructured sub-populations change over time.

- Q: What kind of **algorithmic system** is the cell-cylce switch?
- A: Interaction – complexity – convergence ...
  Focused on individual molecules as programmable, structured, algorithmic entities.