Hybrid Systems and Systems Biology

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(joint work with Luca Bortolussi)

June 7th, 2008

Outline

1. Hybrid Systems: definition and sample applications to Systems Biology;
2. a Stochastic Process Algebra (SPA) for biological modeling: *sCCP*;
3. efficiency: from sCCP to ODE's;
4. being more “discrete”: the circadian clock.

Hybrid Systems

Many real systems have a double nature. They:

- evolve in a continuous way,
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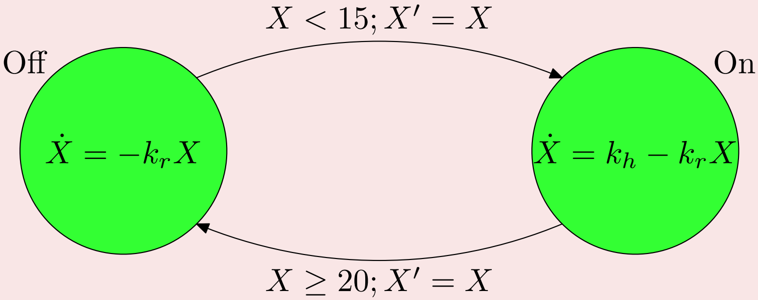
Modeling?

hybrid systems/automata

The Example

A thermostat model



Hybrid Automata - Syntax

Alur et al. 1992

Definition (Hybrid Automaton - Syntax)

A tuple $H = \langle Z, Z', \mathcal{V}, \mathcal{E}, Inv, Dyn, Act, Reset \rangle$ where:

- Z and Z' are varibles in $\mathbb{R}^k$
- $\langle \mathcal{V}, \mathcal{E} \rangle$ is a graph
- Each $v \in \mathcal{V}$ is labelled by $Inv(v)[Z]$ and $Dyn(v)[Z, Z', T]$
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$Dyn(v)[Z, Z', T]$ is a formula of the form $Z' = p_v(Z, T)$, where p_v is the solution of the vectorial field $\mathcal{P}(v)$.

Hybrid Automata - Intuitively

Finite Automata *plus Time*

- in *mode* v, Z must always satisfy $Inv(v)[Z]$
- H evolves from Z to Z' in time T when $Dyn(v)[Z, Z', T]$
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Time flows when *within* states:

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Definition (Discrete Transition)

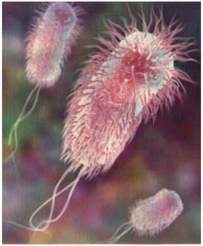
$$\langle v, r \rangle \xrightarrow{\langle v,u \rangle}_D \langle u, s \rangle \iff$$

$\langle v, u \rangle \in \mathcal{E}$ and $Inv(v)[r]$, $Act(\langle v, u \rangle)[r]$, $Reset(\langle v, u \rangle)[r, s]$, and $Inv(u)[s]$ hold.

Examples of use of HS for Systems Biology

Escherichia coli

- a bacterium detecting the food concentration through a set of receptors;
- moving by flagellar rotations.



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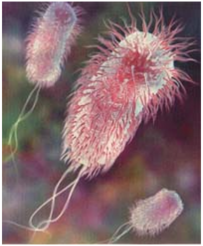

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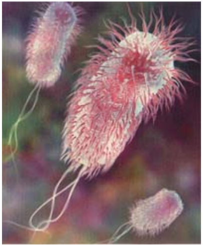

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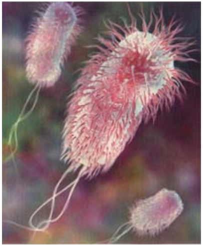

Depending on the concentration of attractans and repellents, E. coli responds to stimuli in one of two ways:

- "RUNS" – it moves in a straight line by moving its flagella counterclockwise (CCW)
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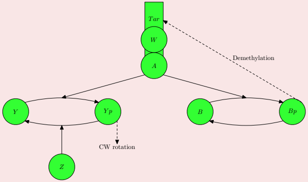
E. Coli Model



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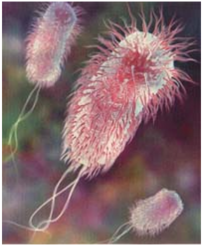

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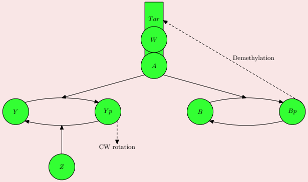

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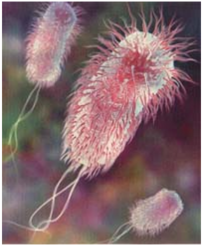

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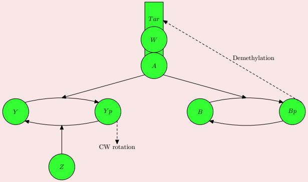
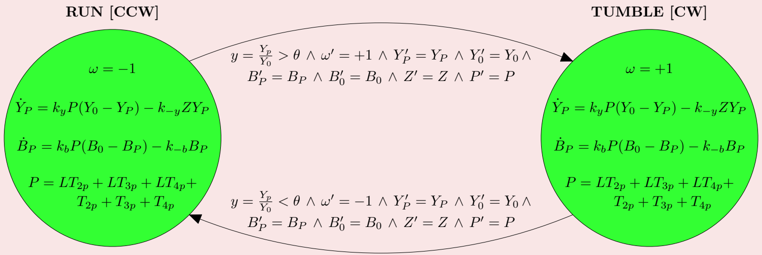


Examples of use of HS for Systems Biology

E. coli IDA Model



A. Casagrande et al., *Independent Dynamics Hybrid Automata in Systems Biology*, AB('05) Tokyo, 2005

Examples of use of HS for Systems Biology

Parameters in Genetic Regulatory Networks

- Use “well behaving” differential equations (e.g. piece-wise multi affine functions);
- use temporal logic to express dynamical properties;
- partition the parameters’space in such a way to guarantee validity of temporal properties.
- PM-Systems *Model Checking Genetic Regulatory Networks with Applications to Synthetic Biology*, G. Batt and C. Belta

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(Typical) Key Property

Theorem (Multiaffine functions on hyperrectangular polytopes) f multiaffine function and P hyperrectangular polytope:

$$f(P) \quad \subseteq \quad \mathrm{hull}(\{f(v) \mid v \in \mathcal{V}_P\}),$$

that is $\forall x \in P$, $f(x)$ is a linear combination of the values of f at vertices of P.

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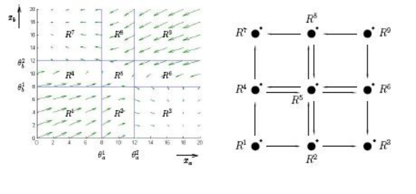

Examples of use of HS for Systems Biology

Switching among simulation techniques

Use different simulation techniques as the number of molecule varies;

1. stochastic simulation for low numbers;
2. ode simulation for high numbers;

Alur et al. *Hybrid Modeling and Simulation of Biochemical Networks*

Modeling: Stochastic vs. Diff. Equations

Differential Equations

- mature
- computationally affordable (*one* run)

Stochastic *something*

- precise
- computationally costly (*many* runs!)

A *Bridge*: our attempt

First step

Use a Stochastic version of Concurrent Constraint Programming as Discrete Stochastic starting tool.

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Second step

Introduce Hybrid Systems.

Modes of the HS $\Leftrightarrow$ Combinations of Stochastic choices

Dynamics $\Leftrightarrow$ *Ad-hoc* edge's variables with activations constrained by rates

Stochastic Concurrent Constraint Programming

What is

- A SPA with a computational “twist”.
- Maintains a form of local storage.
- Keeps separated the description of interactions and the management of data for computations.
- (Naturally) Introduce functional rates.

Concurrent Constraint Programming

Constraint Store

- In this process algebra, the main objects are **constraints** , which are *formulae over an interpreted first order language* (i.e. $X = 10$, $Y > X - 3$).
- Constraints can be added to a "container", the constraint store, but can never be removed.

Agents

Agents can perform two basic operations on this store (asynchronously):

- Add a constraint (**tell** ask)
- Ask if a certain relation is entailed by the current configuration (**ask** instruction)

V. Saraswat, *Concurrent Constraint Programming*, MIT press, 1993

Syntax of CCP

$Program = Decl.A$

$D = \varepsilon \mid Decl.Decl \mid p(x) : -A$

$$
\begin{array}{ll}
A = & \mathbf{0} \\
\mid & \mathrm{tell(c).A} \\
\mid & \mathrm{ask(c_1).A_1 + ask(c_2).A_2} \\
\mid & A_1 \parallel A_2 \mid \exists_x A \mid p(x)
\end{array}
$$

Syntax of sCCP

Syntax of Stochastic CCP

$$Program = D.A$$

$$D = \varepsilon \mid D.D \mid p(\vec{x}) : -A$$

$$\begin{aligned} A &= \mathbf{0} \mid \text{tell}_\infty(c).A \mid M \mid \exists_x A \mid A \parallel A \\ M &= \pi.G \mid M + M \\ \pi &= \text{tell}_\lambda(c) \mid \text{ask}_\lambda(c) \\ G &= \mathbf{0} \mid \text{tell}_\infty(c).G \mid p(\vec{y}) \mid M \mid \exists_x G \mid G \parallel G \end{aligned}$$

L. Bortolussi, *Stochastic Concurrent Constraint Programming*, QAPL, 2006

Stochastic Rates

Rates are functions from the constraint store $\mathcal{C}$ to positive reals:

$$\lambda : \mathcal{C} \longrightarrow \mathbb{R}^+.$$

Rates can be thought as speed or duration of communications.

sCCP – technical details

Operational Semantics

- There are *two transition relations*, one instantaneous (finite and confluent) and one stochastic.
- Traces are sequences of events with variable time delays among them.

Discrete vs. Continuous Semantics

- The operational semantics is *abstract w.r.t. the notion of time*: we can map the labeled transition system into a discrete or a continuous time Markov Chain.

Implementation

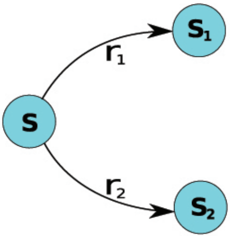
- We have an interpreter written in Prolog, using the *CLP engine of SICStus* to manage the constraint store.
- Efficiency issues.

Stream Variables

- *Quantities varying over time* can be represented in sCCP as unbounded lists.
- Hereafter: special meaning of $X = X + 1$.

Continuous Time Markov Chains

A **Continuous Time Markov Chain** (CTMC) is a direct graph with edges labeled by a real number, called the rate of the transition (representing the speed or the frequency at which the transition occurs).

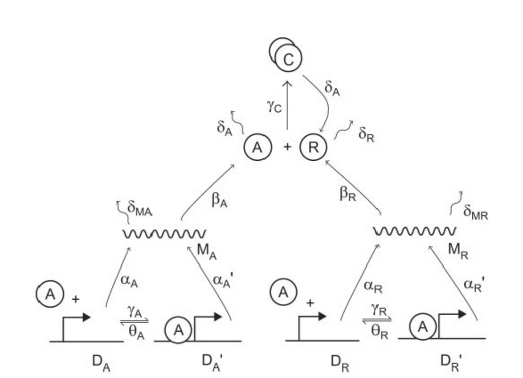


- In each state, we select the next state according to a *probability distribution* obtained normalizing rates (from S to S_1 with prob. $\frac{r_1}{r_1+r_2}$).
- The time spent in a state is given by an exponentially distributed random variable, with rate given by the *sum of outgoing transitions* from the actual node ($r_1 + r_2$).

Circadian Clock

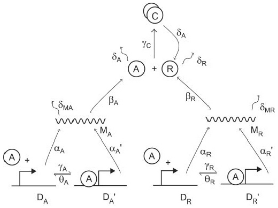
(J. M. G. Vilar, H. Yuan Kueh, N. Barkai, and S. Leibler. PNAS, 2002.)

A clock expressing proteins A and R with a stable period



Circadian Clock

- transcription and the translation phases are modeled explicitl.
- *A* is an enhancer for both genes
- *R* represses *A* forming *AR* and making *A* inactive
- *R* can be degraded only if it is not in complexed form while *A* can be degraded in any form



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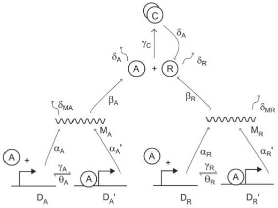

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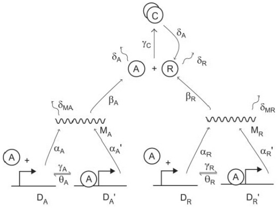

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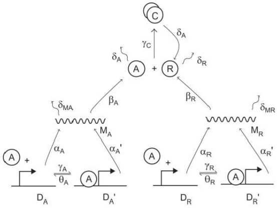

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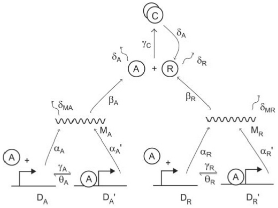

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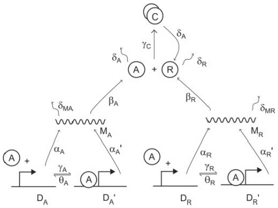

Robustness

The stochastic model is more robust as if internal noise was exploited by Nature to increase stability of function (i.e., for a clock, oscillations).

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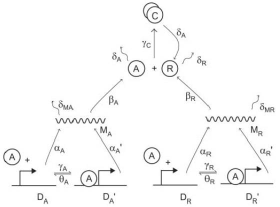

$\mathsf{p\_gate}(\alpha_A, \alpha'_A, \gamma_A, \theta_A, M_A, A) \parallel$
$\mathsf{p\_gate}(\alpha_R, \alpha'_R, \gamma_R, \theta_R, M_R, A) \parallel$
$\mathsf{reaction}(\beta_A, [M_A], [A]) \parallel$
$\mathsf{reaction}(\delta_{MA}, [M_A], []) \parallel$
$\mathsf{reaction}(\beta_R, [M_R], [R]) \parallel$
$\mathsf{reaction}(\delta_{MR}, [M_R], []) \parallel$
$\mathsf{reaction}(\gamma_C, [A, R], [AR]) \parallel$
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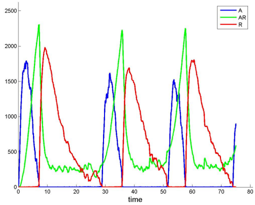
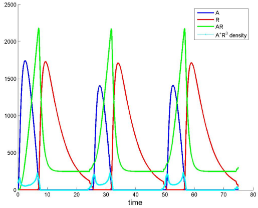
$\mathsf{reaction}(\delta_R, [R], [])$





From sCCP to ODE

What?

We want to associate a set of ODE to an sCCP program (written in a restricted syntax).

Why?

ODE can be numerically simulated faster than stochastic processes.

On the market...

There are (syntactic) methods to write set of ODEs for PEPA and stochastic π-calculus, looking at the speed of creation and destruction of terms (We did the same for sCCP).
However, the ODE can show a behavior different from that of SPA models.

J. Hillston, Fluid Flow Approximation of PEPA models, *QEST*, 2005.

L. Cardelli, From Processes to ODEs by Chemistry, 2006.

L. Bortolussi, A. Policriti. Connecting Process Algebras and Differential Equations for systems biology, 2006.

From sCCP to ODE: example

Idea

Collapse all instantaneous transitions following a stochastic one and add their updates to the edge's label denoting such a transition.

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Reduced Transitions Systems

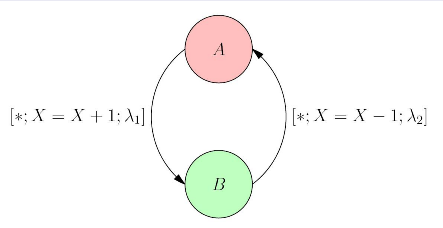
- Associate a labeled graph to each sequential component of an sCCP program:
  - EDGES are transitions and are labeled by a set of guards, a set of updates of variables of the store, and the corresponding rates;
  - NODES are stochastic choices.
- Procedure calls are resolved by inserting a copy of the called procedure.
- Syntactic restrictions are necessaries.

From sCCP to ODE: example

Example

A :- $\text{ask}_{\lambda_1}(\mathit{true}).\text{tell}_\infty(X = X + 1)$.B
B :- $\text{tell}_{\lambda_2}(X = X - 1)$.A

The RTS



From sCCP to ODE: example

Interaction matrix andx reaction vector

$$I = \begin{array}{c|cc} & t_1 & t_2 \\ \hline X & 1 & -1 \\ A & -1 & 1 \\ B & 1 & -1 \end{array} \qquad r = \begin{pmatrix} \lambda_1 \cdot A \\ \lambda_2 \cdot B \end{pmatrix}$$

$ode = I \cdot r$

$$ode \begin{cases} \dot{X} = \lambda_1 \cdot A - \lambda_2 \cdot B \\ \dot{A} = -\lambda_1 \cdot A + \lambda_2 \cdot B \\ \dot{B} = \lambda_1 \cdot A - \lambda_2 \cdot B \end{cases}$$

Example: a "distilled" Repressilator

$$\begin{array}{lll}
A :- & & \mathsf{tell}_{k_+}(X = X + 1).A \\
& + & \mathsf{ask}_{k_- X}(X > 0). \\
& & \qquad \mathsf{tell}_{\infty}(X = X - 1).A \\
& + & \mathsf{ask}_{k_0}(\mathit{true}).B
\end{array}$$

$$\begin{array}{lll}
B :- & & \mathsf{tell}_{k_-}(X = X + 1).B \\
& + & \mathsf{ask}_{k_+ X}(X > 0). \\
& & \qquad \mathsf{tell}_{\infty}(X = X - 1).B \\
& + & \mathsf{ask}_{k_0}(\mathit{true}).A
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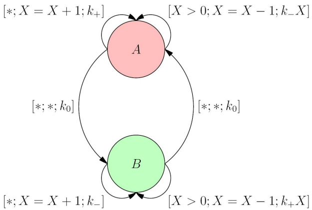

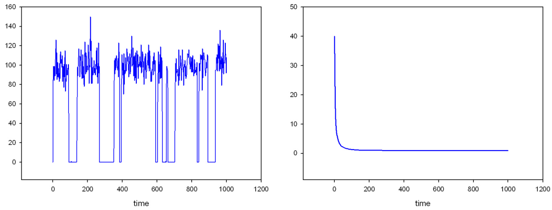

HA associated to an sCCP-ntwrk

Ideas

- localize the construction to looping edges in order to determine flow conditions;
- use (non constant) rates to govern variables associated to edges;
- use variables associated to edges in activation conditions.

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HA associated to an sCCP-ntwrk

$N = A_1 \parallel \ldots \parallel A_M$ be an sCCP-network.

Definition (sketch)

1. *control modes* $\Sigma = (\sigma_1, \ldots, \sigma_M)$;
2. *control edges* corresponding to non-looping arcs $t_{ij} \in T_i$ of $RTS(A_i)$;
3. *variables*: stream variables $X_1, \ldots, X_k$ of N, plus one variable $Y_{i,j}$ for each RTS-edge t_{ij};
4. *flow conditions* $ode_\Sigma = \sum_{i=1}^{M} ode_{i,\sigma_i}$, where $ode_{i,\sigma_i} = I_{i,\sigma_i} \cdot r_{i,\sigma_i}$. Moreover, if the label of t_{ij} is $(g_{ij}, c_{ij}, \lambda_{ij})$, $\dot{Y}_{ij} = \lambda_{ij}(X_1, \ldots, X_k)$;
5. *activation condition* corresponding to t_{ij}, is the predicate $g_{ij} \wedge Y_{ij} \geq 1$, where g_{ij} is the guard predicate of the transition;
6. resets corresponding to t_{ij}, with $c_{ij} = \bigwedge_{k=1}^{h_{ij}} X_{i_k} = X_{i_k} + \delta_{ij}$,

$$\left(\bigwedge_{k=1}^{h_{ij}} X'_{i_k} = X_{i_k} + \delta_{ij} \right) \wedge \left(\bigwedge_{t_{ij} \in T_i} Y'_{ij} = 0 \right).$$

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On activation conditions

Time varying rates $\lambda = \lambda(t)$

- introduce one variable Y_e for each edge e
- every transition constitute a *non-homogeneous Poisson process*
- we can define the *cumulative rate function*

$$\Lambda(t) = \int_{t_0}^{t} \lambda(s)ds,$$

- theory of non-homogeneous Poisson processes $\Rightarrow$ number of firings at time t behaves like a Poisson variable with rate equal to $\Lambda(t)$
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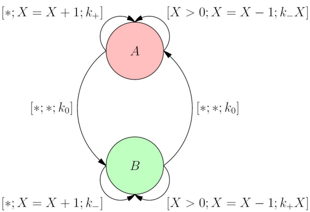
$[*; X = X+1; k_+]$
$[X > 0; X = X-1; k_- X]$
A
$[*; *; k_0]$
$[*; *; k_0]$
B
$[*; X = X+1; k_-]$
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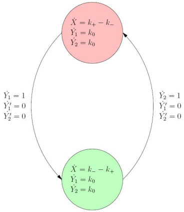
$\dot{X} = k_+ - k_-$
$\dot{Y}_1 = k_0$
$\dot{Y}_2 = k_0$
$\dot{Y}_1 = 1$
$\dot{Y}_1' = 0$
$\dot{Y}_2' = 0$
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$\dot{Y}_1 = k_0$
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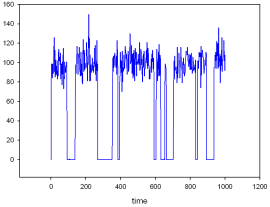
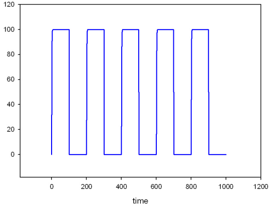

160
140
120
100
80
60
40
20
0
0
200
400
600
800
1000
1200
time


120
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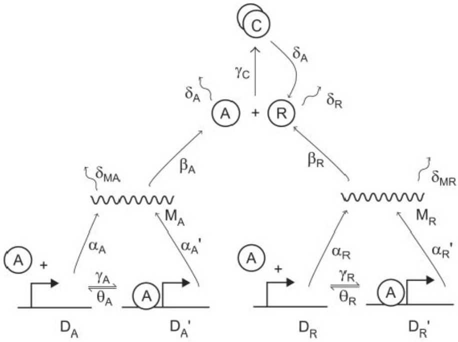
Circadian Clock: robustness



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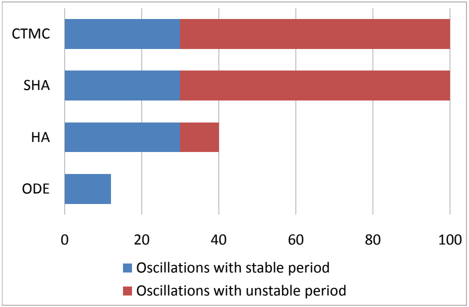

Figure: Stability with respect to β_R

Conclusions

- HS for: biochemical reactions, genetic networks, etc.
- SPA to ODE: problems (the stochastic component *averaged away*).
- Localize ODE's and maintain a discrete portion of the network: Hybrid Systems (with the *right* control variables).

Future

- Define a *lattice* of HSs.
- Formalize the behavioral properties to guide/determine the level of discreteness to maintain.