HYPE applied to the modelling of hybrid biological systems

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24 May 2008

Introduction

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  - discrete behaviour

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  - view genes as on or off

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  - single gene in the cell with multiple mRNA and proteins
  - the Repressilator [Elowitz and Leibler, 2000]

Biological background

- DNA, genes

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- negative feedback cycle
  - each gene produces a protein
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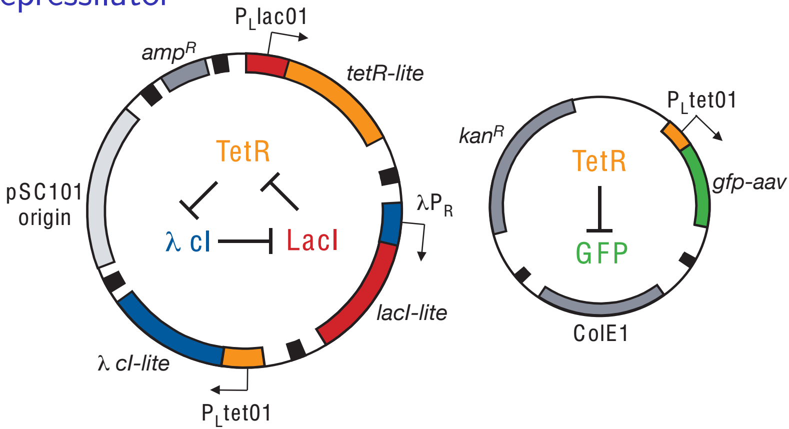
  - other gene cannot produce its protein
- quantities of proteins oscillate over time

The Repressilator



M.B. Elowitz and S. Leibler, A synthetic oscillatory network of transcriptional regulators, *Nature*, 403, 335-338.

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$Gene_A$

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$$Gene_A \xrightarrow[trs_A]{} mRNA_A$$

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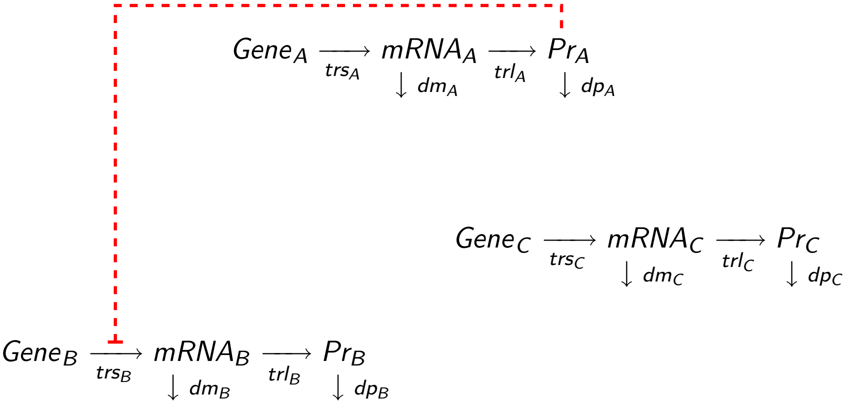

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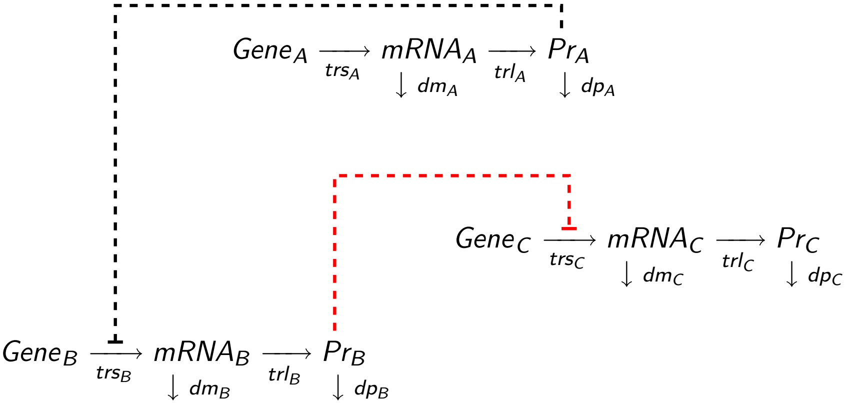

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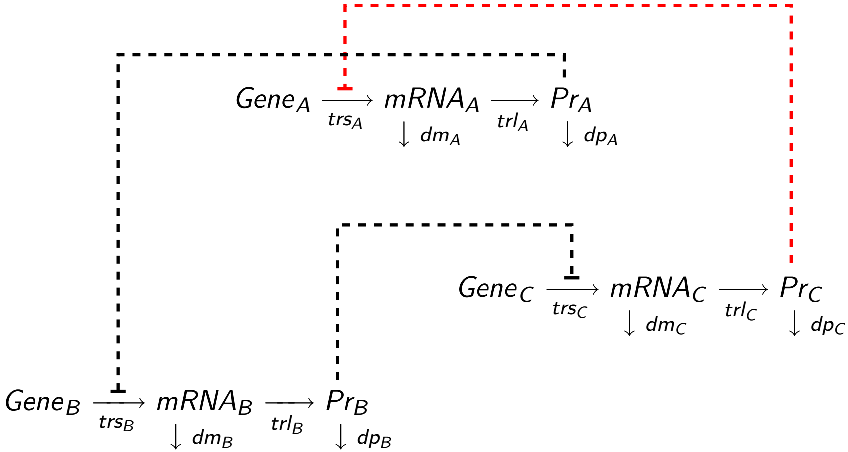

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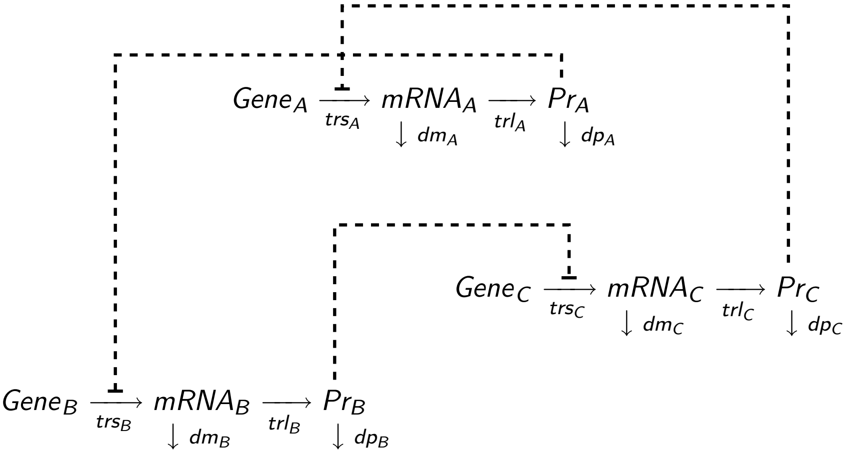

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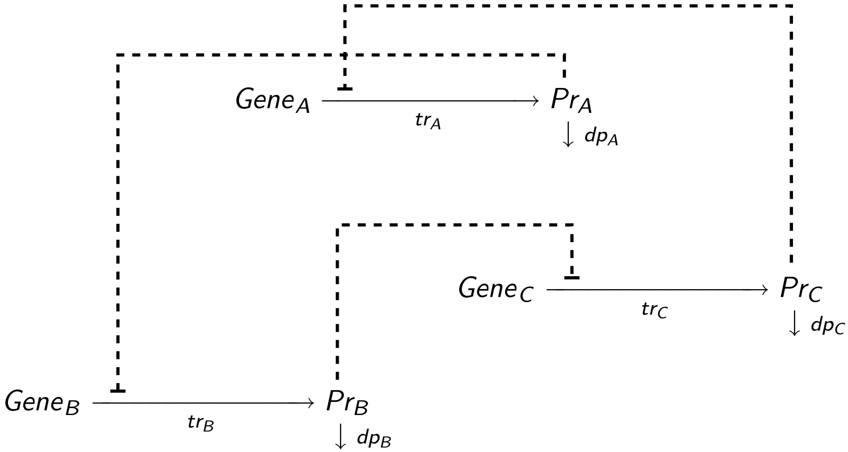

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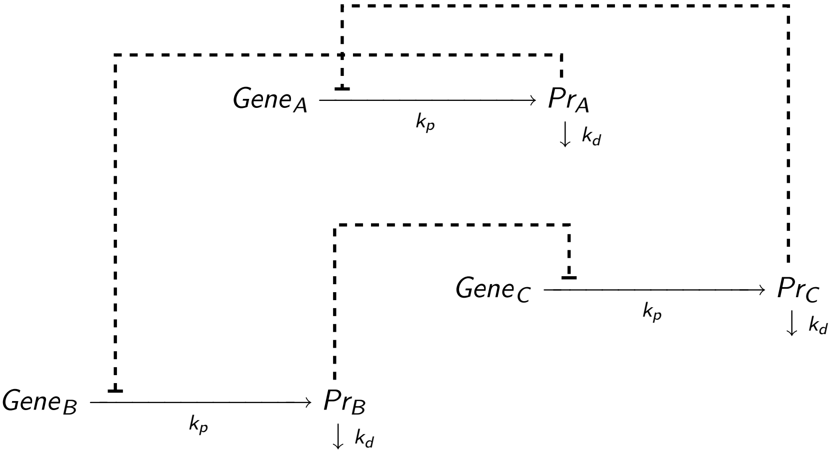

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- activities — influences on continuous aspects, flows

$$\alpha \in \mathcal{A} \qquad \alpha(\vec{X}) = (\iota, r, I(\vec{X}))$$

influence name (ι), rate (r), influence type ($I(\vec{X})$) with $[\![I(\vec{X})]\!] = f(\vec{X})$

where $\vec{X}$ is a formal parameter.

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- not stochastic

The Repressilator in HYPE

- degradation

$$G_A^{degr}(X) \stackrel{def}{=} \underline{\text{init}} : (d_A, -k_d, linear(X)).G_A^{degr}(X)$$

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$$\begin{aligned} G_A^{prod} &\stackrel{def}{=} \underline{\text{init}} : (p_A, k_p, const).G_A^{prod} \\ &+ \underline{\text{express}}_A : (p_A, k_p, const).G_A^{prod} \\ &+ \underline{\text{inhibit}}_A : (p_A, 0, const).G_A^{prod} \end{aligned}$$

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- composed

$$Gene_A(X) \stackrel{def}{=} (G_A^{degr}(X) \underset{\{\underline{\mathrm{init}}\}}{\bowtie} G_A^{prod})$$

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- "controller"

$$Con_A \stackrel{def}{=} \underline{\text{inhibit}}_A.\underline{\text{express}}_A.Con_A$$

The Repressilator in HYPE (cont.)

$$Rep \stackrel{def}{=} (Gene_A(A_B) \underset{\underline{\text{init}}}{\bowtie} Gene_B(B_C) \underset{\underline{\text{init}}}{\bowtie} Gene_C(C_A)) \underset{L}{\bowtie} \underline{\text{init}}.(Con_A \parallel Con_B \parallel Con_C)$$

$$L = \{\underline{\text{init}}, \underline{\text{inhibit}}_A, \underline{\text{inhibit}}_B, \underline{\text{inhibit}}_C, \underline{\text{express}}_A, \underline{\text{express}}_B, \underline{\text{express}}_C\}$$

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$$ec(\underline{\text{init}}) = (true, (A_B = c_A \wedge B_C = c_B \wedge C_A = c_C))$$

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$$ec(\underline{\text{init}}) = (true, (A_B = c_A \wedge B_C = c_B \wedge C_A = c_C))$$
$$ec(\underline{\text{inhibit}}_A) = (C_A > p, T) \qquad ec(\underline{\text{express}}_A) = (C_A \leq p, T)$$

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Operational semantics

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- updating function: $\sigma[\iota \mapsto (r, I)]$

$$\sigma[\iota \mapsto (r, I)](x) = \begin{cases} (r, I) & \text{if } x = \iota \\ \sigma(x) & \text{otherwise} \end{cases}$$

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- change identifying function: $\Gamma : \mathcal{S} \times \mathcal{S} \times \mathcal{S} \rightarrow \mathcal{S}$

$$(\Gamma(\sigma, \tau, \tau'))(\iota) = \begin{cases} \tau(\iota) & \text{if } \sigma(\iota) = \tau'(\iota) \\ \tau'(\iota) & \text{if } \sigma(\iota) = \tau(\iota) \\ \text{undefined} & \text{otherwise} \end{cases}$$

Operational semantics (cont.)

Prefix with influence:

$$\frac{}{\langle \underline{a}:(\iota, r, I).E, \sigma\rangle \xrightarrow{\underline{a}} \langle E, \sigma[\iota \mapsto (r, I)]\rangle}$$

Prefix without influence:

$$\frac{}{\langle \underline{a}.E, \sigma\rangle \xrightarrow{\underline{a}} \langle E, \sigma\rangle}$$

Choice:

$$\frac{\langle E, \sigma\rangle \xrightarrow{\underline{a}} \langle E', \sigma'\rangle}{\langle E+F, \sigma\rangle \xrightarrow{\underline{a}} \langle E', \sigma'\rangle} \qquad \frac{\langle F, \sigma\rangle \xrightarrow{\underline{a}} \langle F', \sigma'\rangle}{\langle E+F, \sigma\rangle \xrightarrow{\underline{a}} \langle F', \sigma'\rangle}$$

Constant:

$$\frac{\langle E, \sigma\rangle \xrightarrow{\underline{a}} \langle E', \sigma'\rangle}{\langle A, \sigma\rangle \xrightarrow{\underline{a}} \langle E', \sigma'\rangle}(A \stackrel{def}{=} E)$$

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Operational semantics (cont.)

Parallel without synchronisation:

$$\frac{\langle E, \sigma \rangle \xrightarrow{\underline{a}} \langle E', \sigma' \rangle}{\langle E \underset{M}{\bowtie} F, \sigma \rangle \xrightarrow{\underline{a}} \langle E' \underset{M}{\bowtie} F, \sigma' \rangle} \quad \underline{a} \notin M$$

$$\frac{\langle F, \sigma \rangle \xrightarrow{\underline{a}} \langle F', \sigma' \rangle}{\langle E \underset{M}{\bowtie} F, \sigma \rangle \xrightarrow{\underline{a}} \langle E \underset{M}{\bowtie} F', \sigma' \rangle} \quad \underline{a} \notin M$$

Parallel with synchronisation:

$$\frac{\langle E, \sigma \rangle \xrightarrow{\underline{a}} \langle E', \tau \rangle \quad \langle F, \sigma \rangle \xrightarrow{\underline{a}} \langle F', \tau' \rangle}{\langle E \underset{M}{\bowtie} F, \sigma \rangle \xrightarrow{\underline{a}} \langle E' \underset{M}{\bowtie} F', \Gamma(\sigma, \tau, \tau') \rangle}$$

$\underline{a} \in M, \Gamma$ defined

Operational semantics (cont.)

Parallel without synchronisation:

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$$\frac{\langle F, \sigma \rangle \xrightarrow{\underline{a}} \langle F', \sigma' \rangle}{\langle E \underset{M}{\bowtie} F, \sigma \rangle \xrightarrow{\underline{a}} \langle E \underset{M}{\bowtie} F', \sigma' \rangle} \quad \underline{a} \notin M$$

Parallel with synchronisation:

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$\underline{a} \in M, \Gamma$ defined

The Repressilator – transition derivation

$$\dfrac{\dfrac{\langle G_A^{degr}(A_B), \tau \rangle \xrightarrow{\underline{\text{init}}} \langle G_A^{degr}(A_B), \tau_1 \rangle \qquad \langle G_A^{prod}, \tau \rangle \xrightarrow{\underline{\text{init}}} \langle G_A^{prod}, \tau_2 \rangle}{\langle G_A^{degr}(A_B) \underset{\underline{\text{init}}}{\bowtie} G_A^{prod}, \tau \rangle \xrightarrow{\underline{\text{init}}} \langle G_A^{degr}(A_B) \underset{\underline{\text{init}}}{\bowtie} G_A^{prod}, \tau_3 \rangle}}{\langle Gene_A(A_B), \tau \rangle \xrightarrow{\underline{\text{init}}} \langle Gene_A(A_B), \tau_3 \rangle}$$

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\tau &= \{ d_A \mapsto *,\ p_A \mapsto *, \ldots \} \\
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The Repressilator – labelled transition system

8 configurations represent all possibilities with 8 distinct states

$$
\begin{aligned}
\sigma_0 &= D \cup \{p_A \mapsto (0, c),\ p_B \mapsto (0, c),\ p_C \rightarrow (0, c)\} \\
\sigma_1 &= D \cup \{p_A \mapsto (0, c),\ p_B \mapsto (0, c),\ p_C \mapsto (k_p, c)\} \\
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\sigma_4 &= D \cup \{p_A \mapsto (k_p, c),\ p_B \mapsto (0, c),\ p_C \mapsto (0, c)\} \\
\sigma_5 &= D \cup \{p_A \mapsto (k_p, c),\ p_B \mapsto (0, c),\ p_C \mapsto (k_p, c)\} \\
\sigma_6 &= D \cup \{p_A \mapsto (k_p, c),\ p_B \mapsto (k_p, c),\ p_C \mapsto (0, c)\} \\
\sigma_7 &= D \cup \{p_A \mapsto (k_p, c),\ p_B \mapsto (k_p, c),\ p_C \mapsto (k_p, c)\}
\end{aligned}
$$

where

$$D = \{d_A \mapsto (-1, I(A_B)), d_B \mapsto (-1, I(B_C)), d_C \mapsto (-1, I(C_A))\}$$

Hybrid semantics

- extract ODEs from each state σ in the lts of CS

$$CS_\sigma = \left\{ \text{ODE for variable } V \;\middle|\; V \in \mathcal{V} \right\} \text{ where}$$

$$\frac{dV}{dt} = \sum \left\{ r[\![I(\vec{W})]\!] \;\middle|\; iv(\iota) = V \text{ and } \sigma(\iota) = (r, I(\vec{W})) \right\}$$

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  - multiply its rate and influence function together

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  - for any influence name associated with V
  - determine from σ its rate and influence type
  - multiply its rate and influence function together
  - sum these over all associated influence names

The Repressilator – ODEs

$$\begin{aligned}\sigma_4 \;=\; \{ & d_A \mapsto (-1, linear(A_B)),\ p_A \mapsto (k_p, const), \\ & d_B \mapsto (-1, linear(B_C)),\ p_B \mapsto (0, const), \\ & d_C \mapsto (-1, linear(C_A)),\ p_C \mapsto (0, const)\}\end{aligned}$$

The ODEs for this state are

$$\frac{dA_B}{dt} = -k_d A_B + k_p, \quad \frac{dB_C}{dt} = -k_d B_C, \quad \frac{dC_A}{dt} = -k_d C_A$$

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Use ABC for this set of ODEs

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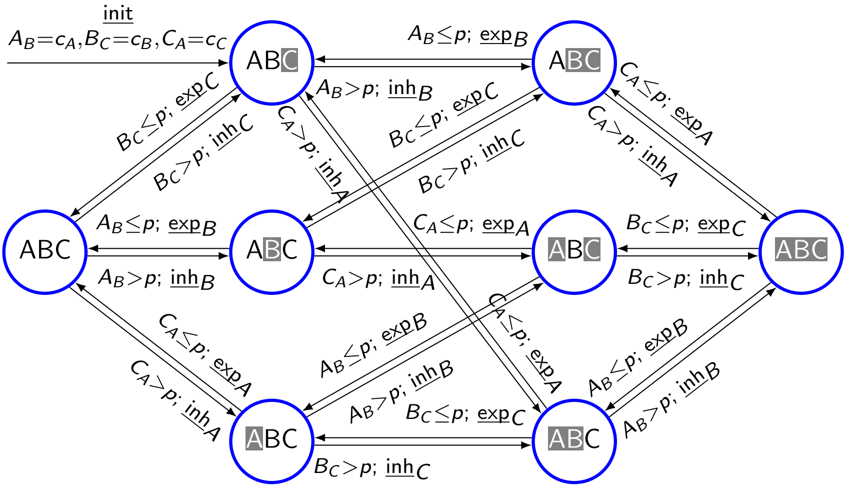
Likewise the ODEs for σ_3 would be ABC and for σ_7, ABC

The Repressilator – hybrid automaton



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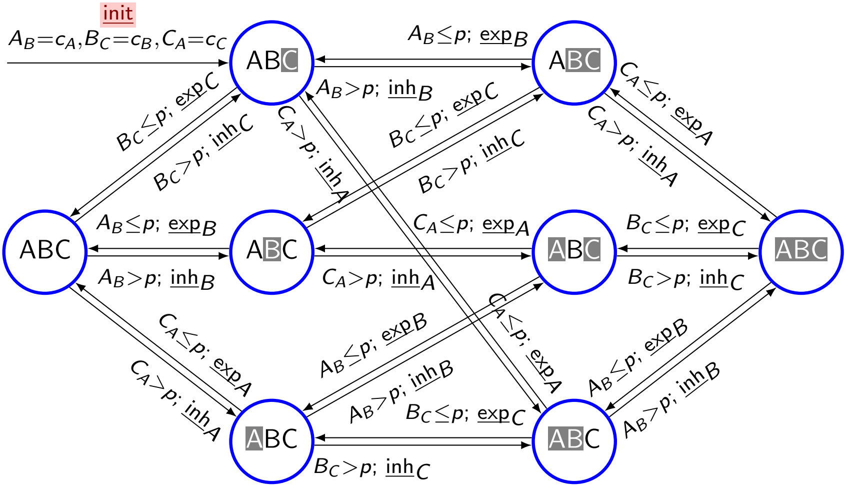

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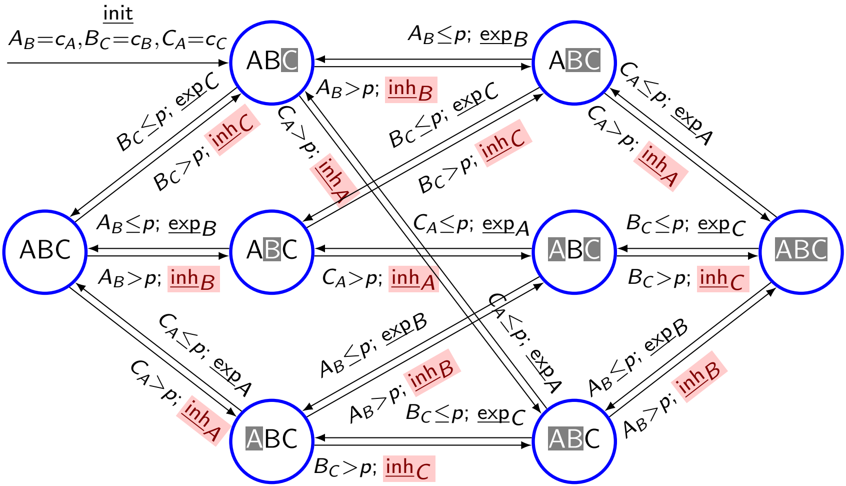

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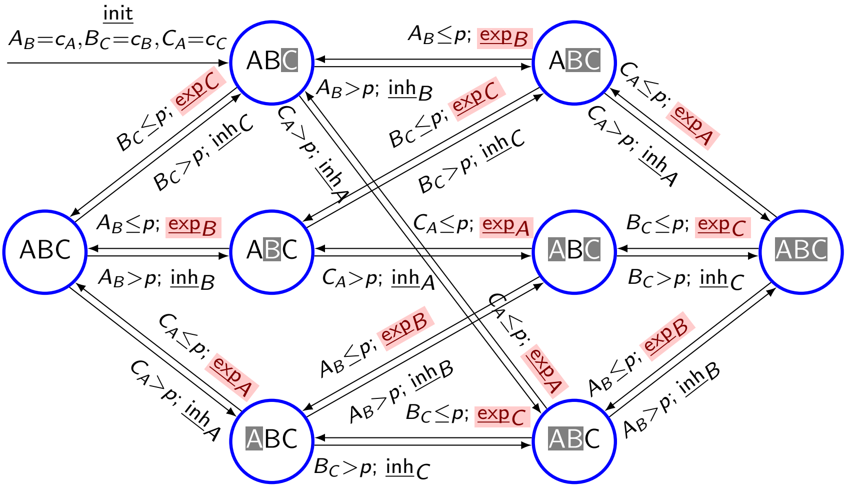
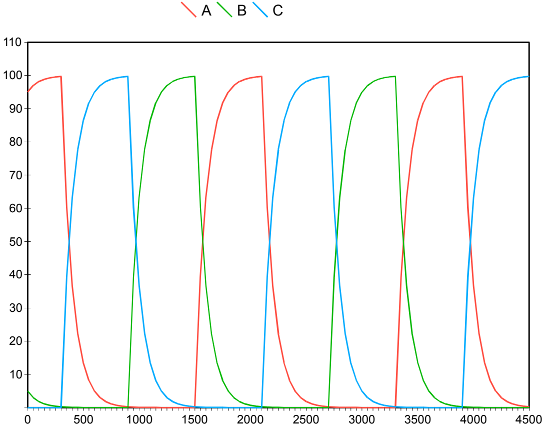


The Repressilator – protein levels over time



k_p=1.00 k_d=0.01

The Repressilator in ACP^{srt}_{hs}

- different style of modelling
- explicit ODEs

$$\begin{aligned}
\text{GeneA} &\stackrel{def}{=} (dA_B = c_A) \curvearrowright \text{OnA} \\
\text{OnA} &\stackrel{def}{=} (\,dA_B/dt = -k_d A_B + k_p\,) \curvearrowright \sigma^*_{\text{rel}} \\
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$$\text{Rep} \stackrel{def}{=} \text{GeneA} \parallel \text{GeneB} \parallel \text{GeneC}$$

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  - use of flows to obtain ODEs
  - separation of modelling concerns

Thank you

This research was funded by the EPSRC SIGNAL Project

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  - parameterised by formal variables $\vec{X}$

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- subcomponents: $S ::= \underline{\mathsf{a}} : \alpha . C_s \mid S + S \qquad \underline{\mathsf{a}} \in \mathcal{E}, \alpha \in \mathcal{A}$

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HYPE syntax (cont.)

- subcomponents: $S ::= \underline{a} : \alpha . C_s \mid S + S \qquad \underline{a} \in \mathcal{E}, \alpha \in \mathcal{A}$
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- controller: $M ::= \underline{a}.M \mid 0 \mid M + M \qquad \underline{a} \in \mathcal{E}$

  $Con ::= M \mid Con \underset{L}{\bowtie} Con \qquad L \subseteq \mathcal{E}$

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- controlled system: $ConSys ::= \Sigma \bowtie_L \underline{\text{init}}.Con \qquad L \subseteq \mathcal{E}$

HYPE syntax (cont.)

- HYPE model: $(ConSys, \mathcal{V}, \mathcal{X}, IN, IT, \mathcal{E}, \mathcal{A}, ec, iv, EC, ID)$

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    else $jump(e) = true$ and $urgent(e) = false$
- $init(v) = \begin{cases} res_{\underline{init}} & \text{if } v = \langle P, \sigma \rangle \text{ with primes removed} \\ false & otherwise \end{cases}$