Modelling a circadian clock with HYPE

Vashti Galpin
Laboratory for Foundations of Computer Science
University of Edinburgh

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Outline

HYPE

- no stochastic events, different semantics

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- set of variables $\{X_1, \ldots, X_n\}$ for continuous values

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- well-defined subcomponents

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- obtain controlled system $\Sigma \underset{*}{\bowtie} \underline{\mathrm{init}}.Con$

Operational semantics

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- generates labelled transition system over configurations

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$$\frac{\mathrm{d}X_i}{\mathrm{d}t} = \sum \{ r \times [\![I(\vec{Y})]\!] \mid \mathrm{iv}(\iota) = X_i \text{ and } \sigma(\iota) = (r, I(\vec{Y})) \}$$

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- initial mode and first event $\underline{\text{init}}$

Circadian clocks

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- consider very simple example, *Ostreococcus tauri*

Circadian clock for *Ostreococcus tauri*

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- hybrid – different behaviour depending on light conditions

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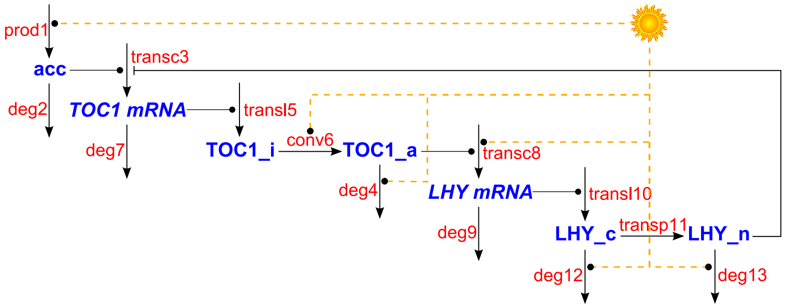

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  - T_m, T_i, T_a – mRNA and proteins for TOC1
  - L_m, L_c, L_n – mRNA and proteins for LHY
- what are the flows?
- how do they differ from light to dark?

HYPE model

- three events:

$$
\begin{aligned}
\mathrm{ec}(\underline{\mathsf{init}}) &= (\mathit{true}, (T' = t_0 \wedge (\text{initial values})) \\
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\end{aligned}
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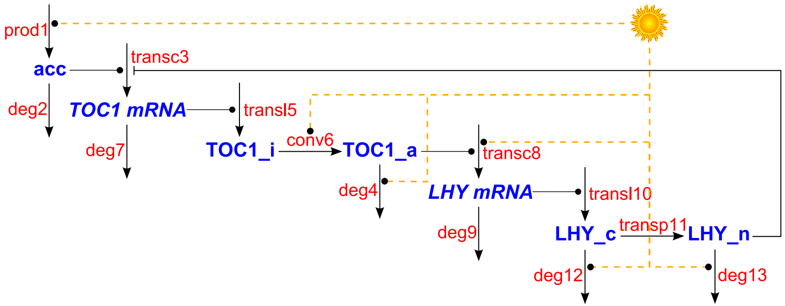
- one subcomponent for each influence
- if not light-sensitive then only $\underline{\mathit{init}}$ event required

Degradation flows – not light-sensitive



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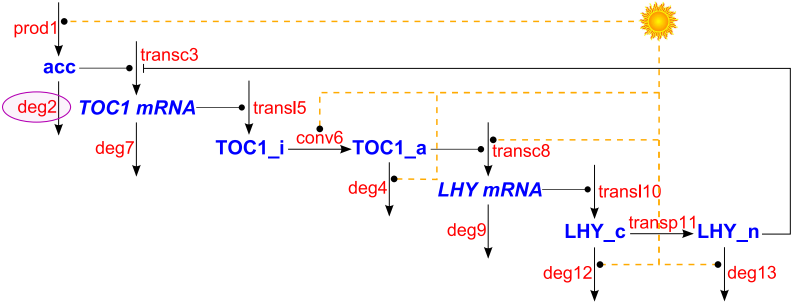

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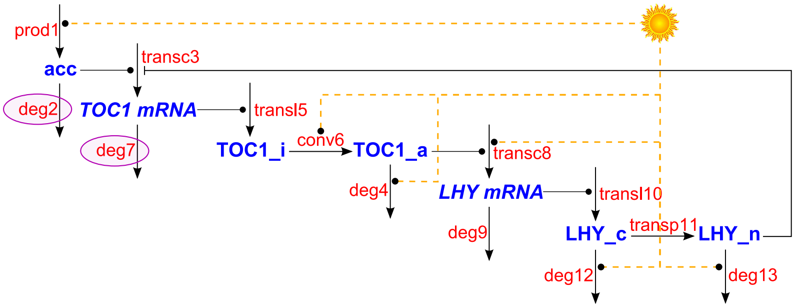

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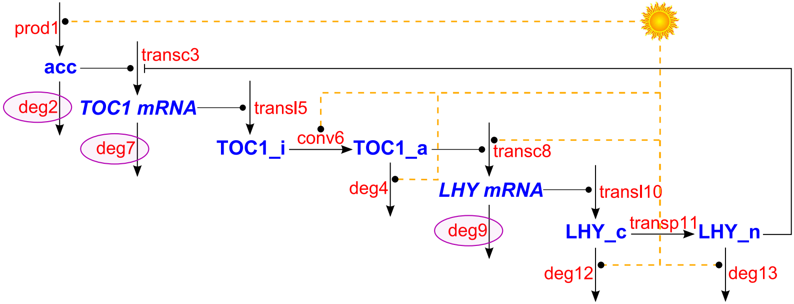

Degradation flows – not light-sensitive

- deg2: degradation of *acc*
  - mass action

$$I_{A,2}(A) \stackrel{def}{=} \underline{\text{init}}{:}(\iota_{A,2}, -r_2, linear(A)).I_{A,2}(A)$$

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- deg7: degradation of TOC1 mRNA
  - mass action

$$I_{T_m,7}(T_m) \stackrel{def}{=} \underline{\text{init}}{:}(\iota_{T_m,7}, -r_7, linear(T_m)).I_{T_m,7}(T_m)$$

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- deg9: degradation of LHY mRNA
  - mass action

$$I_{L_m,9}(L_m) \stackrel{def}{=} \underline{\mathrm{init}}{:}(\iota_{L_m,9}, -r_9, \mathit{linear}(L_m)).I_{L_m,9}(L_m)$$

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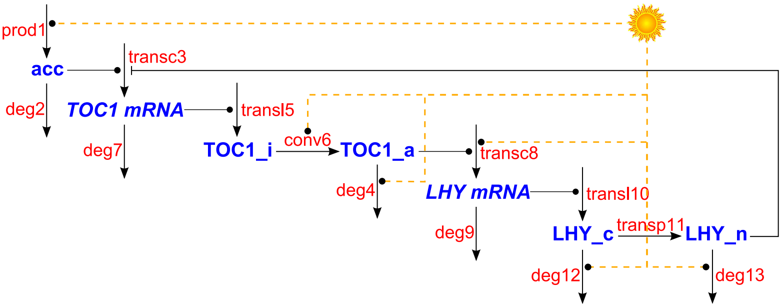

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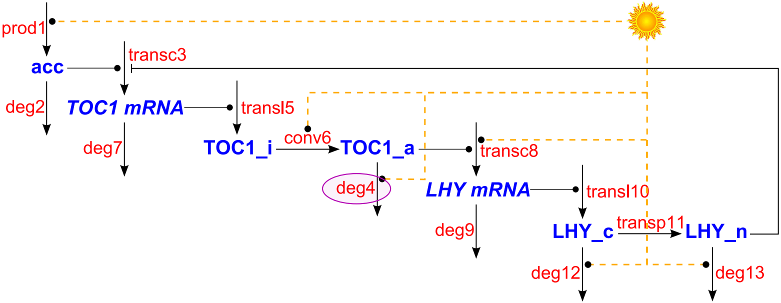

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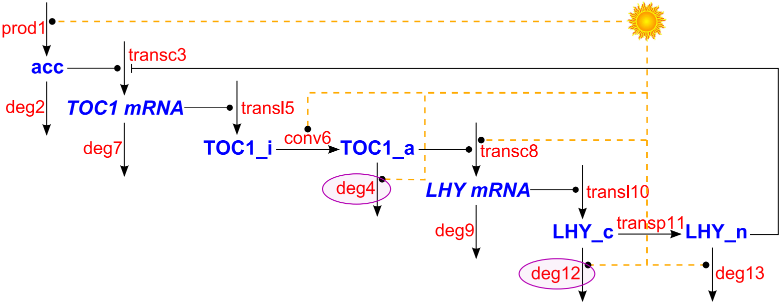

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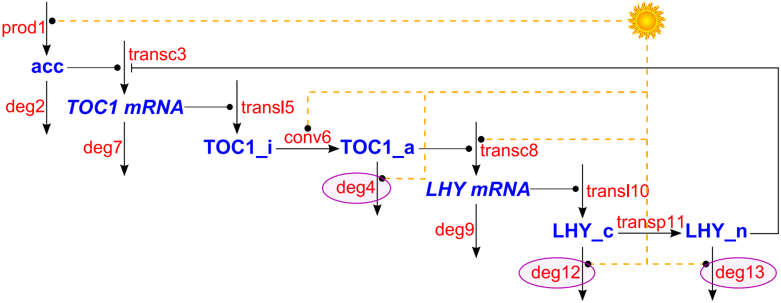

Degradation flows – light-sensitive

- deg4: degradation of activated TOC1
  - mass action

$$
\begin{aligned}
I_{T_a,4}(T_a) \stackrel{def}{=} \; & \underline{\text{light}}{:}(\iota_{T_a,4}, -l_4, \mathit{linear}(T_a)).I_{T_a,4}(T_a) + \\
& \underline{\text{dark}}{:}(\iota_{T_a,4}, -d_4, \mathit{linear}(T_a)).I_{T_a,4}(T_a) + \\
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\end{aligned}
$$

- deg12: degradation of cytosolic LHY
  - mass action

$$
\begin{aligned}
I_{L_c,12}(L_c) \stackrel{def}{=} \ & \underline{\text{light}}:(\iota_{L_c,12}, -l_{12}, linear(L_c)).I_{L_c,12}(L_c) + \\
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\end{aligned}
$$

Degradation flows – light-sensitive (continued)

- deg13: degradation of nuclear LHY
  - mass action

$$
\begin{aligned}
I_{L_n,13}(L_n) \stackrel{\mathit{def}}{=}\ & \underline{\text{light}}{:}(\iota_{L_n,13}, -l_{13}, \mathit{linear}(L_n)).I_{L_n,13}(L_n) + \\
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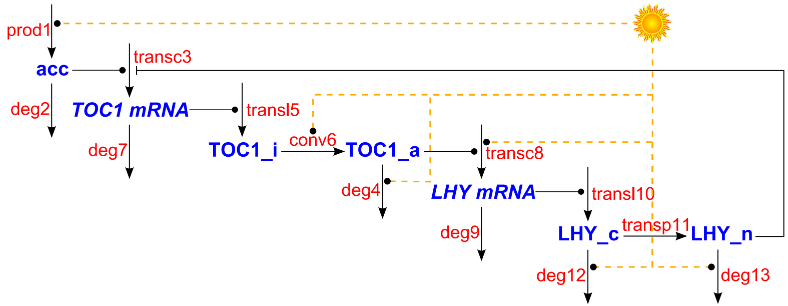

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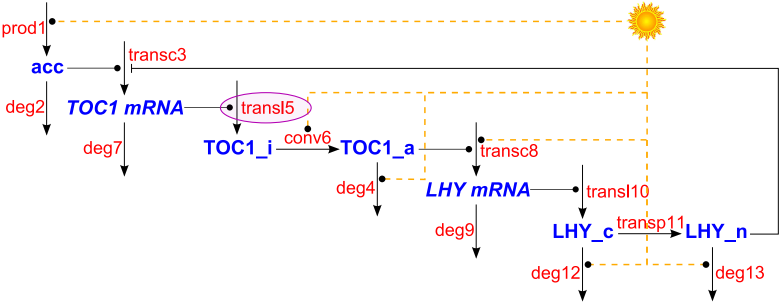

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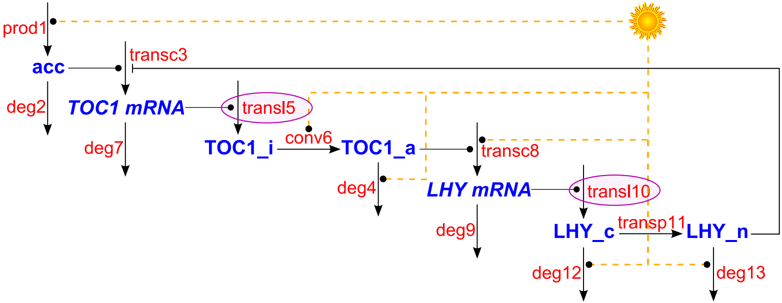

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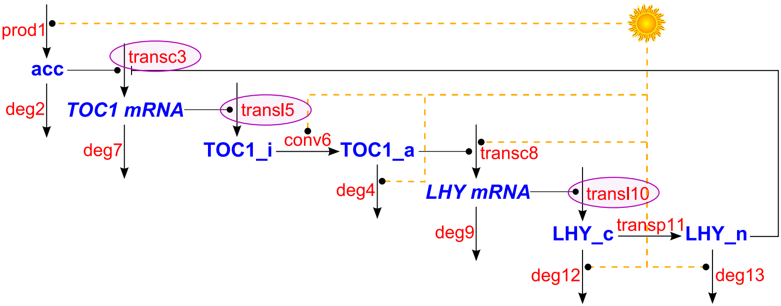

Production flows – not light sensitive

- transl5: translation of TOC1 mRNA to TOC1 protein
  - mass action

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- transl10: translation of LHY mRNA to LHY protein
  - mass action

$$I_{L_c,10}(L_m) \stackrel{def}{=} \underline{\text{init}}{:}(\iota_{L_c,10}, r_{10}, linear(L_m)).I_{L_c,10}(L_m)$$

Production flows – not light sensitive

- transl5: translation of TOC1 mRNA to TOC1 protein
  - mass action

$$I_{T_i,5}(T_m) \stackrel{def}{=} \underline{\mathrm{init}}{:}(\iota_{T_i,5}, r_5, linear(T_m)).I_{T_i,5}(T_m)$$

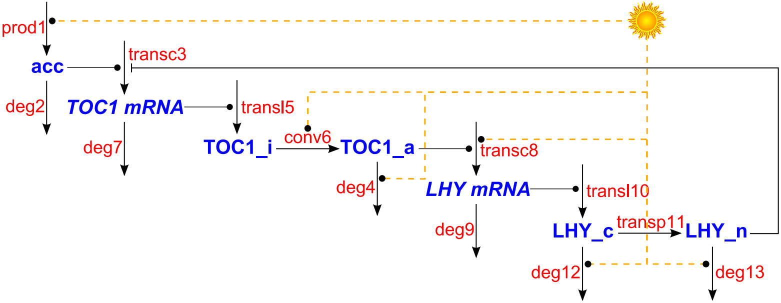
- transl10: translation of LHY mRNA to LHY protein
  - mass action

$$I_{L_c,10}(L_m) \stackrel{def}{=} \underline{\mathrm{init}}{:}(\iota_{L_c,10}, r_{10}, linear(L_m)).I_{L_c,10}(L_m)$$

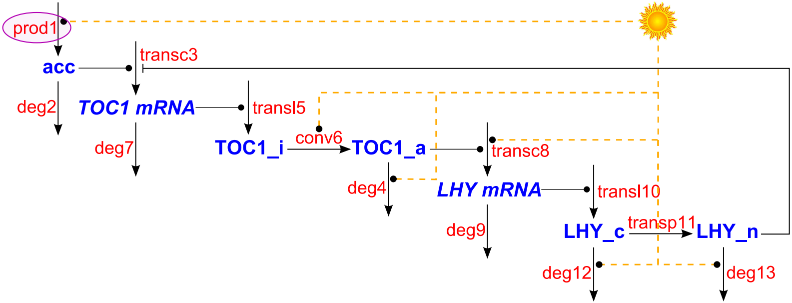
- transc3: transcription of TOC1 mRNA from TOC1 gene
  - not directly light sensitive, but enhanced by *acc*
  - inhibited by nuclear LHY
  - complex rate function

$$I_{T_m,3}(A, L_n) \stackrel{def}{=} \underline{\mathrm{init}}{:}(\iota_{T_m,3}, 1, g(A, L_n)).I_{T_m,3}(A, L_n)$$

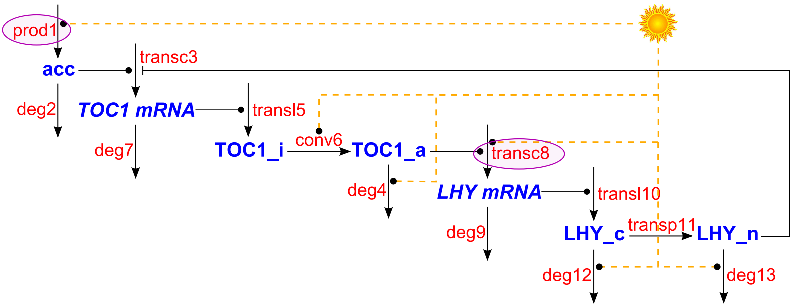
Production flows – light sensitive



Production flows – light sensitive



Production flows – light sensitive



Production flows – light sensitive

- prod1: production of *acc*, entirely light-sensitive

$$\begin{aligned} I_{A,1} \stackrel{def}{=} & \ \underline{\text{light}}{:}(\iota_{A,1}, l_1, constant).I_{A,1} + \\ & \underline{\text{dark}}{:}(\iota_{A,1}, 0, constant).I_{A,1} + \\ & \underline{\text{init}}{:}(\iota_{A,1}, 0, constant).I_{A,1} \end{aligned}$$

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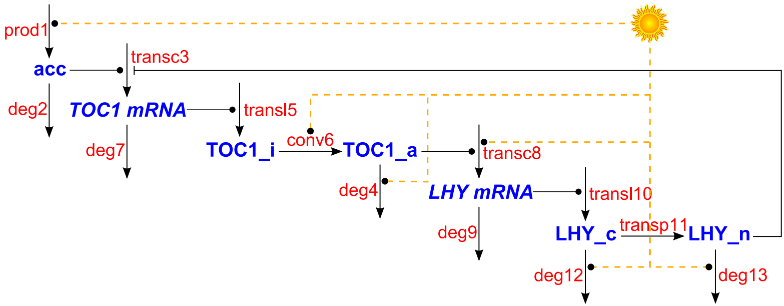
- transc8: transcription of LHY mRNA
  - enhanced by active TOC1 protein

$$\begin{aligned} I_{L_m,8}(T_a) &\stackrel{def}{=} \underline{\text{light}}{:}(\iota_{L_m,8}, 1, f(T_a)).I_{L_m,8}(T_a) + \\ &\quad \underline{\text{dark}}{:}(\iota_{L_m,8}, 1, f'(T_a)).I_{L_m,8}(T_a) + \\ &\quad \underline{\text{init}}{:}(\iota_{L_m,8}, 1, f'(T_a)).I_{L_m,8}(T_a) \end{aligned}$$

Conversion flows - light sensitive



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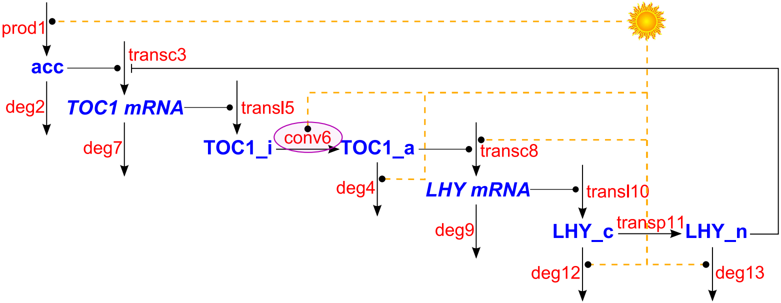

Conversion flows - light sensitive

- conv6: conversion of TOC1 protein from inactive to active
  - mass action

$$
\begin{aligned}
I_{T_i,6}(T_i) \stackrel{def}{=}\ & \underline{\text{light}}:(\iota_{T_i,6}, -l_6, \mathit{linear}(T_i)).I_{T_i,6}(T_i) + \\
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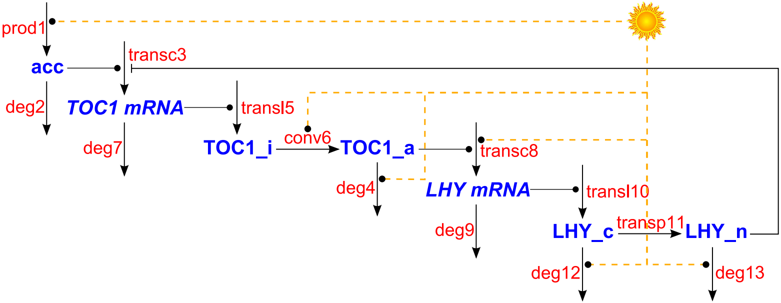
$$

Transportation flows – not light sensitive



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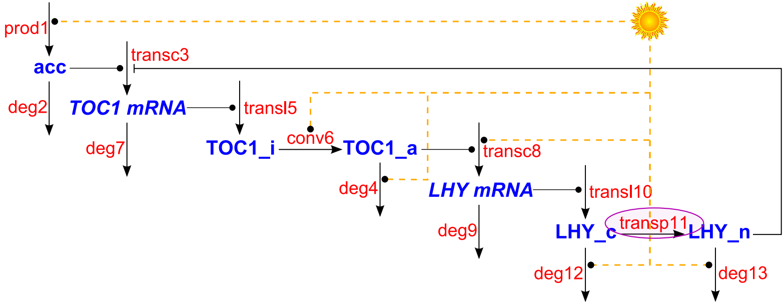

Transportation flows and time flow

- transp11: movement of LHY protein
  - from cytoplasm to nucleus
  - not light sensitive

$$I_{L_c,11}(L_c) \stackrel{def}{=} \underline{\text{init}}{:}(\iota_{L_c,11}, -r_{11}, \mathit{linear}(L_c)).I_{L_c,11}(L_c)$$

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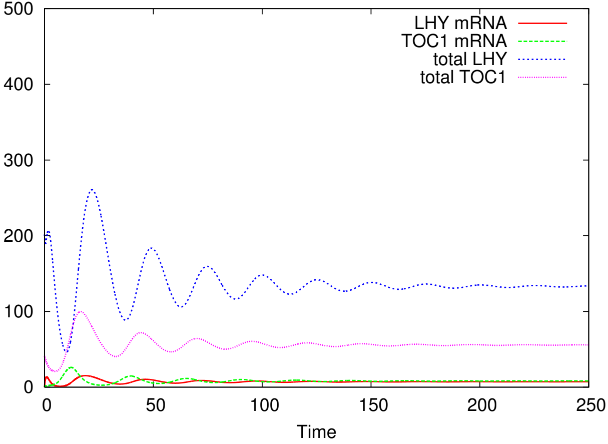
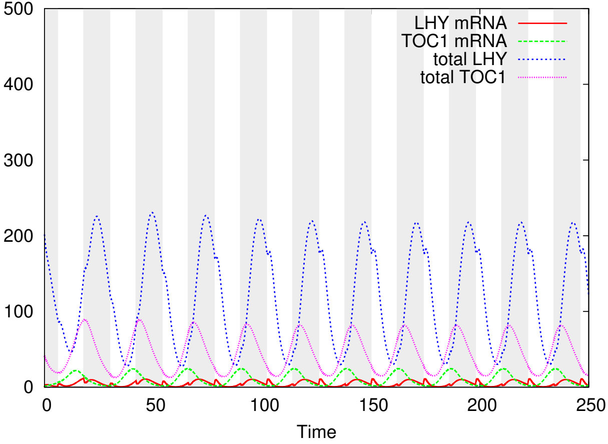
- construct controlled system from subcomponents and controller

Results – constant light



- identical to Bio-PEPA ODE output

Results – 12 hours light, 12 hours dark



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A different approach

- given a ODE biological model with hybrid behaviour

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- assumptions about model

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    - n species, $S_1, \ldots, S_n$

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  - circadian clock, choose light or dark conditions

A different approach (continued)

- form of each species ODE

$$\frac{dX_i}{dt} = \sum_{j=1}^{m} D[i,j]v[j] = \sum_{j=1}^{m} D[i,j]f_j(\vec{X})$$

A different approach (continued)

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$$I_{i,j}(\vec{X}) \stackrel{\mathit{def}}{=} \underline{\mathrm{init}} : (\iota_{i,j}, D[i,j], v[j]).I_{i,j}(\vec{X})$$

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- HYPE model, validate if possible

$$\left(\underset{*}{\bowtie}{}_{i=1}^{n} \left(\underset{*}{\bowtie}{}_{j=1}^{m} I_{i,j}(\vec{X}) \right) \right) \underset{*}{\bowtie} \underline{\mathrm{init}}.0$$

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$$\big(\Join_{*}\, {}_{i=1}^{n} \,(\Join_{*}\, {}_{j=1}^{m}\, I_{i,j}(\vec{X}))\big) \Join_{*} \underline{\mathrm{init}}.0$$

- defines redundant subcomponents whenever $D[i,j] = 0$, can omit

A different approach (continued)

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  - difference is variable parameters in subcomponents

Conclusions

- model of circadian clock of *Ostreococcus tauri*

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- further research: more examples

Thank you

This research was funded by the EPSRC SIGNAL Project