

Modelling a posttranslational biochemical oscillator

Chris Banks



PEPA club, May 2013

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- give an overview of modelling a biochemical oscillator in $c\pi$
 - joint work with Daniel Seaton, Millar Lab, SynthSys
 - model from Jolley et al., Cell Reports 2, Oct 2012

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- show some of the experiments we have performed
 - especially making use of compositionality and high-level language abstraction

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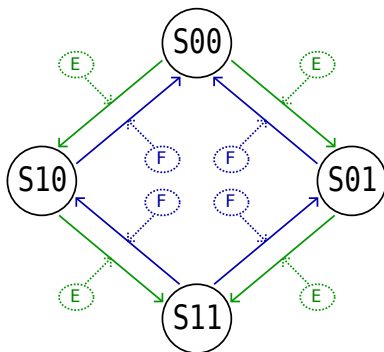
- give an overview of modelling a biochemical oscillator in $c\pi$
 - joint work with Daniel Seaton, Millar Lab, SynthSys
 - model from Jolley et al., Cell Reports 2, Oct 2012
- show some of the experiments we have performed
 - especially making use of compositionality and high-level language abstraction
- define some experiments to be done using *LBC*
 - especially those which would be non-trivial to program by hand

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- a theoretical posttranslational biochemical oscillator
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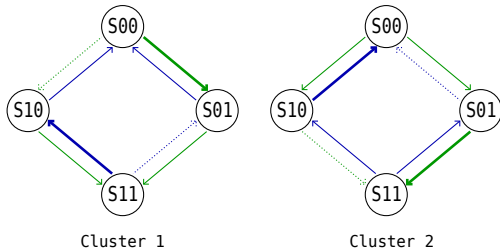


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- common to both: symmetry, cycles

The $c\pi$ model

Substrate:

$$S00 \triangleq (\nu M_{00}) s00a\langle be \rangle.(u.S00 + ra.S01) \\ + s00b\langle be \rangle.(u.S00 + rb.S10)$$

$$S01 \triangleq (\nu M_{01}) s01e\langle be \rangle.(u.S01 + r.S11) \\ + s01f\langle bf \rangle.(u.S01 + r.S00)$$

$$S10 \triangleq (\nu M_{10}) s10e\langle be \rangle.(u.S10 + r.S11) \\ + s10f\langle bf \rangle.(u.S10 + r.S00)$$

$$S11 \triangleq (\nu M_{11}) s11a\langle bf \rangle.(u.S11 + ra.S01) \\ + s11b\langle bf \rangle.(u.S11 + rb.S10)$$

The $c\pi$ model

Enzymes:

$$E \triangleq e(x).x.E$$

$$F \triangleq f(x).x.F$$

Process (mixture):

$$\Pi \triangleq c_{S00} \cdot S00 \parallel c_E \cdot E \parallel c_F \cdot F$$

Global affinity net:

$$M = \{s00a \leftrightarrow e, s00b \leftrightarrow e, s01e \leftrightarrow e, s10e \leftrightarrow e, \\ s01f \leftrightarrow f, s10f \leftrightarrow f, s11a \leftrightarrow f, s11b \leftrightarrow f\}$$

How complexation works:

$$S00 \triangleq (\nu M_{00}) s00a\langle be \rangle.(u.S00 + ra.S01) \\ + s00b\langle be \rangle.(u.S00 + rb.S10)$$

$$E \triangleq e(x).x.E$$

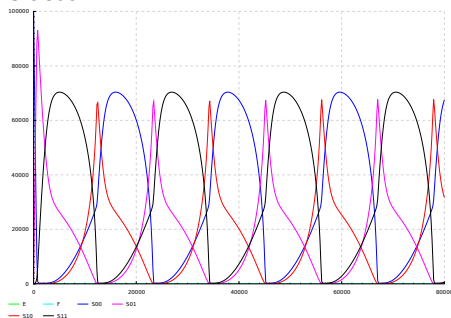
$$M_{00} = \{be \leftrightarrow u, be \leftrightarrow ra, be \leftrightarrow rb\}$$

$$ES_{00a} \equiv (be.E \mid u.S00 + ra.S01)$$

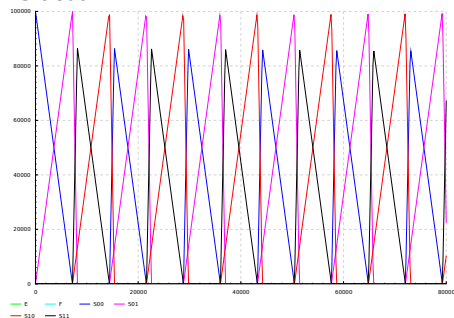
Similar for the other phosphorylation states.

- The $c\pi$ model generates the same ODE structure as in the paper
 - therefore we produce the same dynamics.

Cluster1



Cluster 2



Now we have a high-level language model

- we can much more easily make structural changes to the model
- it is trivial to compose models

Experiment idea:

- what happens when clocks are composed?
- different ways we can compose clocks?

Composing identical clocks – sharing enzymes

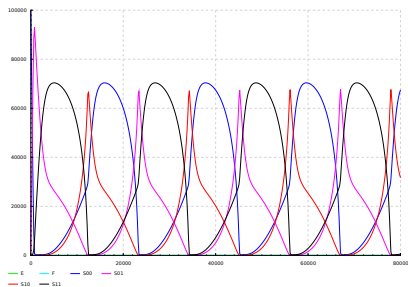
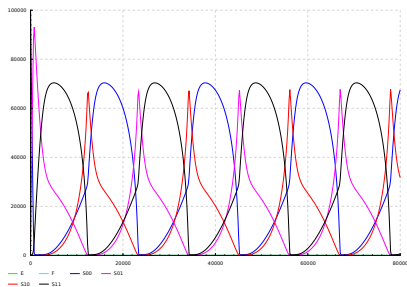
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$$\Pi \triangleq c_{S00} \cdot S00 \parallel c_{T00} \cdot T00 \parallel c_E \cdot E \parallel c_F \cdot F$$

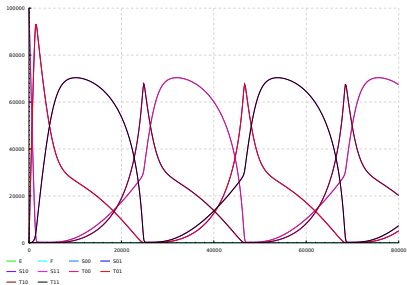
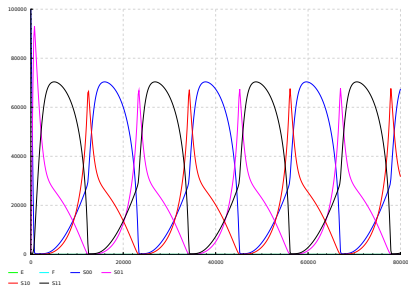
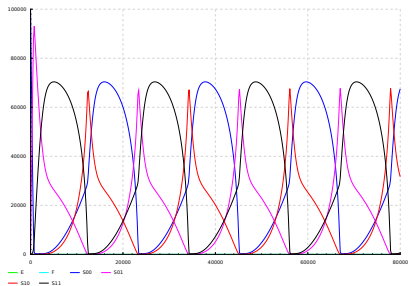
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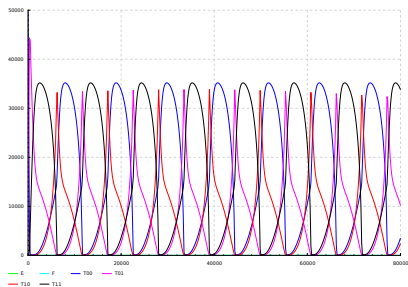
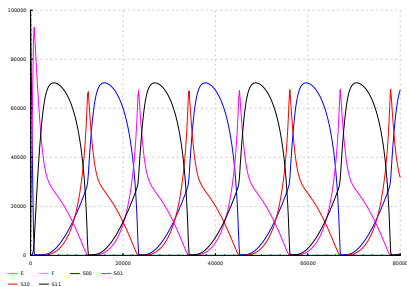
Composing identical clocks – sharing enzymes



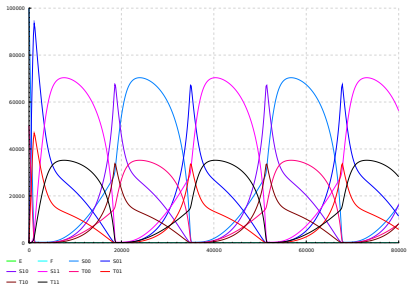
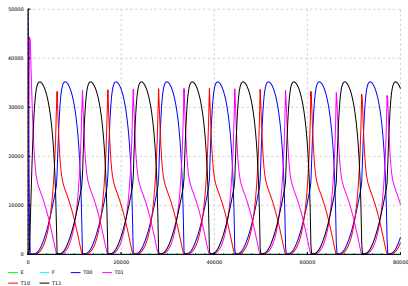
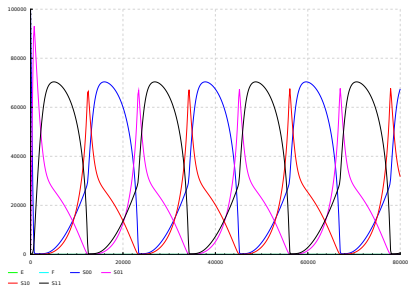
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Composing identical clocks – sharing only kinase

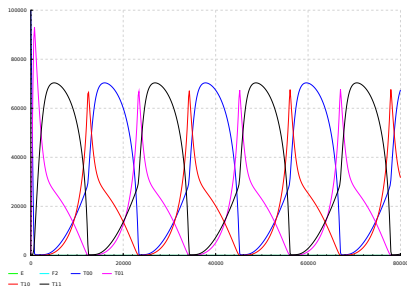
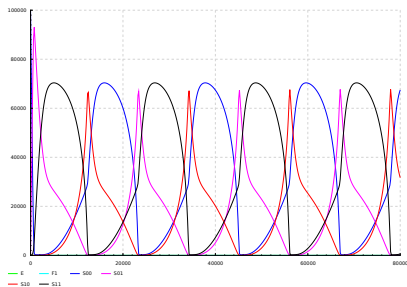
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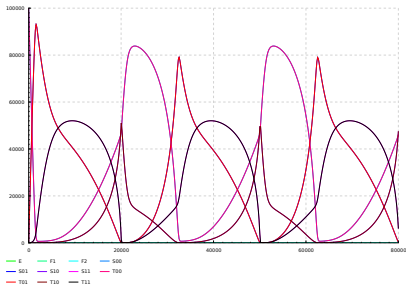
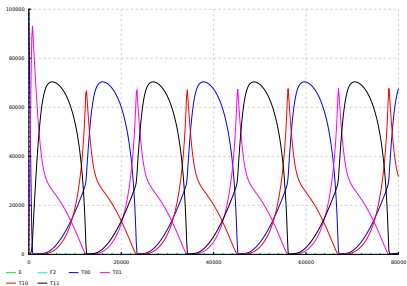
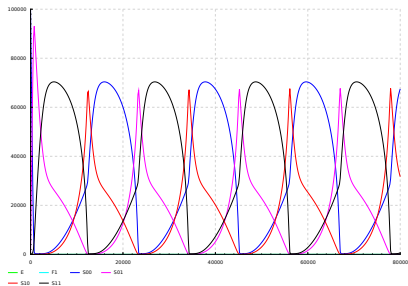
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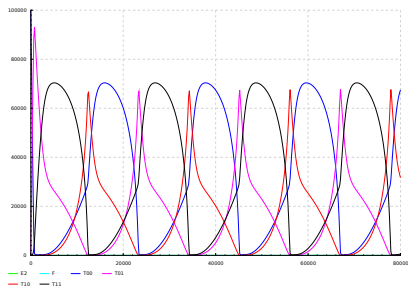
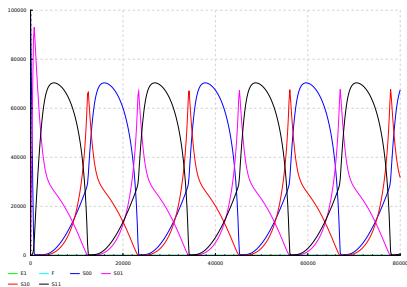
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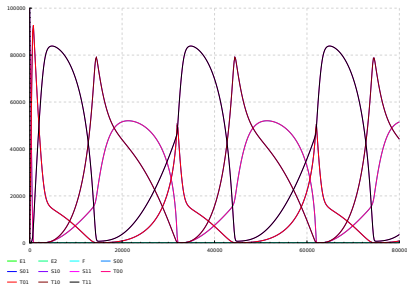
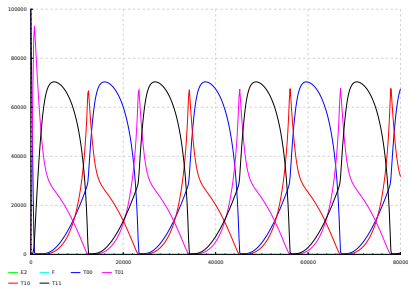
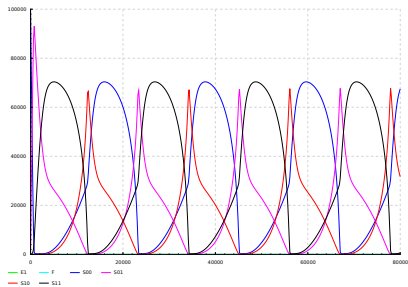
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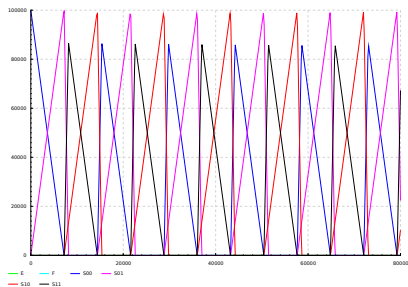
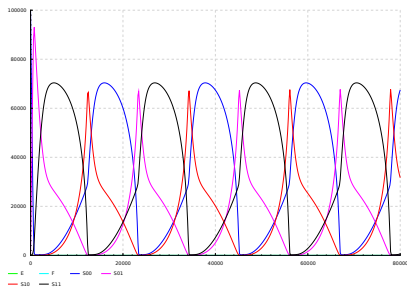
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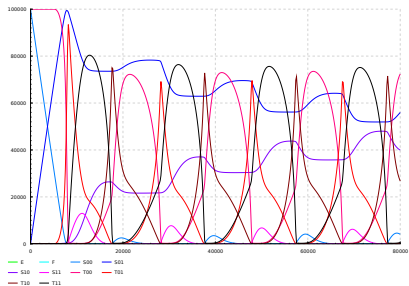
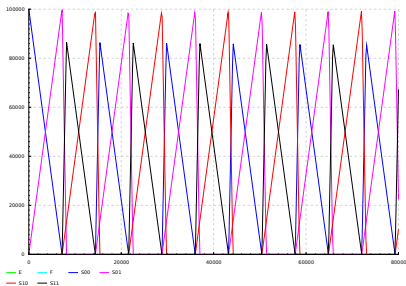
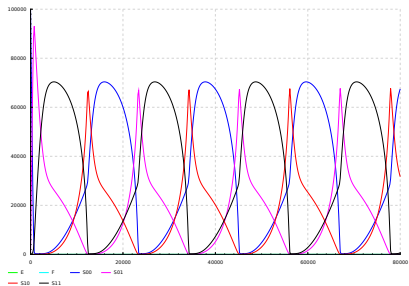
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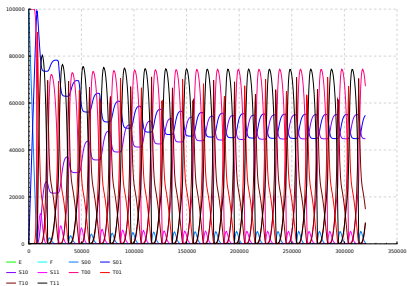
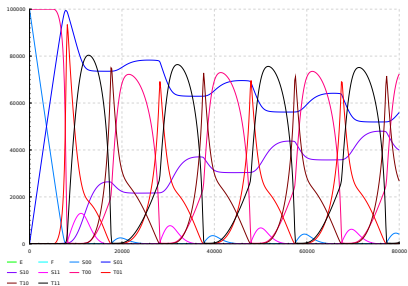
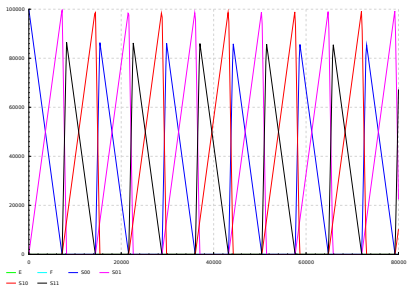
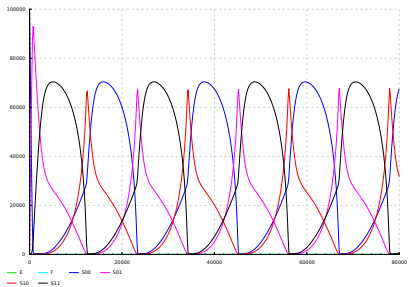
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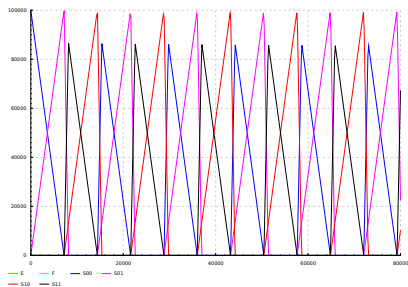
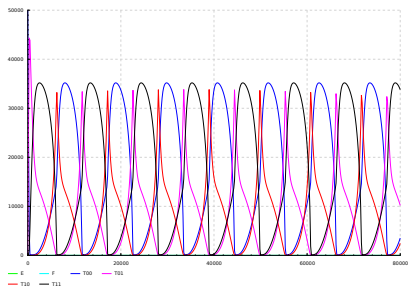
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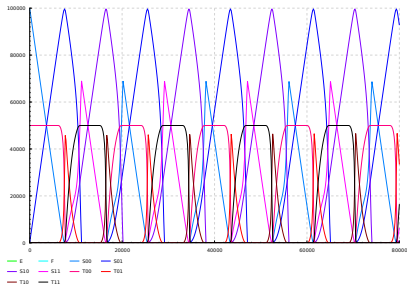
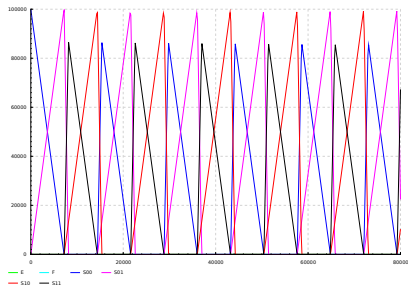
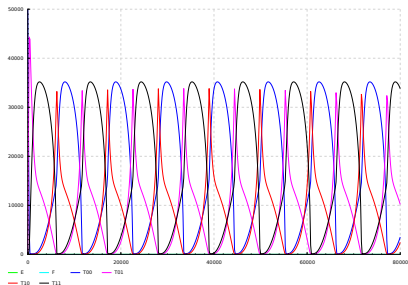
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Further experiments

- Composing the two clock types with different coupling.
- Composing clocks out of phase.
- Introducing inhibitors, etc.
- ???

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 - $Clock1 \models \mathbf{G}_t(Clock2 \triangleright \mathbf{F}_{10}\phi)$
 - Neatly expresses the experiment of composing with varying phase.
- The specified behaviour ϕ could be something which captures the kind of oscillation we see in these models
 - $\mathbf{G}_t\left(\mathbf{F}_p([S_{xx}] > c \wedge \mathbf{F}_p[S_{xx}] < c)\right)$

Finally, some requests:

- Please rigorously dissect!
- Any suggestions?