The Continuous π-Calculus

An Algebra for Biochemical Modelling

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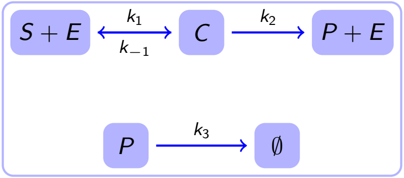
School of Informatics
University of Edinburgh

14 Oct 2008, CMSB

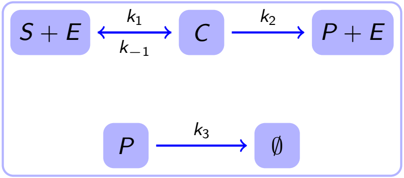
joint work with Ian Stark

Outline

Ordinary Differential Equations

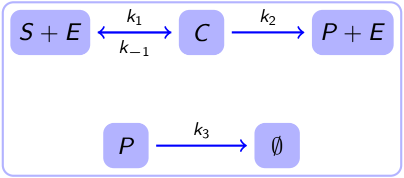


Ordinary Differential Equations



$$\begin{aligned}
\frac{d[S]}{dt} &= -k_1[S][E] + k_{-1}[C] \\
\frac{d[E]}{dt} &= -k_1[S][E] + k_{-1}[C] + k_2[C] \\
\frac{d[C]}{dt} &= k_1[S][E] - k_{-1}[C] - k_2[C] \\
\frac{d[P]}{dt} &= k_2[C] - k_3[P]
\end{aligned}$$

Ordinary Differential Equations



$$\frac{d[S]}{dt} = -k_1[S][E] + k_{-1}[C]$$
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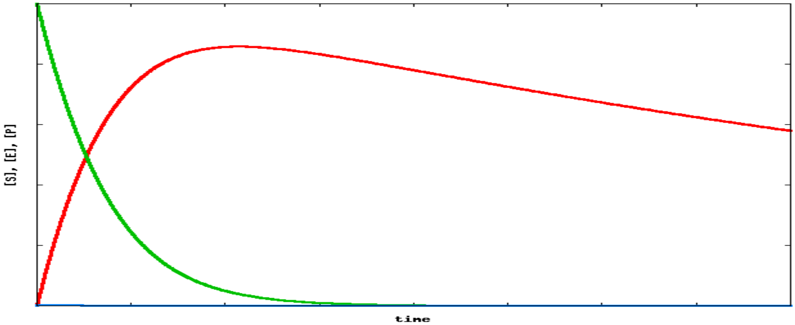
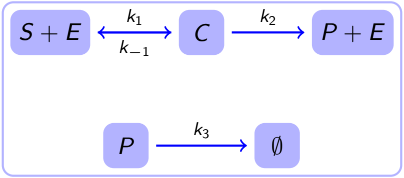


Process Algebras



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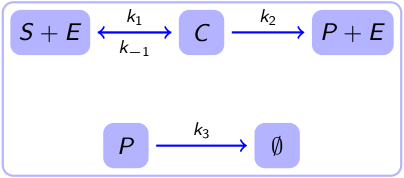
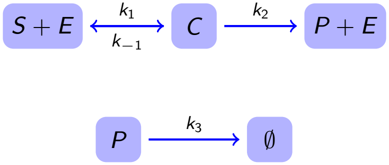
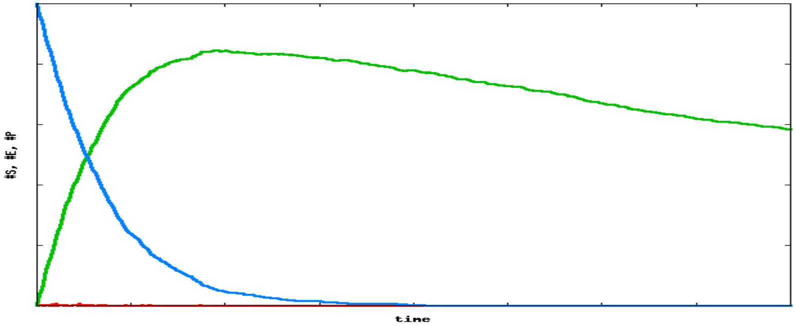


$$\mathrm{S} \triangleq \mathrm{a}(\mathrm{x},\mathrm{y}).(\mathrm{x}.\mathrm{S} + \mathrm{y}.\mathrm{P})$$
$$\mathrm{E} \triangleq (\nu\, \mathrm{u})(\nu\, \mathrm{r})\overline{\mathrm{a}}(\mathrm{u},\mathrm{r}).(\overline{\mathrm{u}}.\mathrm{E} + \overline{\mathrm{r}}.\mathrm{E})$$
$$\mathrm{P} \triangleq \tau.\mathbf{0}$$
$$\mathrm{S} \mid \ldots \mid \mathrm{S} \mid \mathrm{E} \mid \ldots \mid \mathrm{E}$$

Process Algebras



$$S \triangleq a(x, y).(x.S + y.P)$$
$$E \triangleq (\nu\, u)(\nu\, r)\overline{a}(u, r).(\overline{u}.E + \overline{r}.E)$$
$$P \triangleq \tau.\mathbf{0}$$
$$S \mid \ldots \mid S \mid E \mid \ldots \mid E$$



ODEs vs PAs

ODEs:

PAs:

ODEs vs PAs

ODEs:

- continuous

PAs:

- discrete

ODEs vs PAs

ODEs:

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- deterministic

PAs:

- discrete
- non-deterministic/stochastic

ODEs vs PAs

ODEs:

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- monolithic

PAs:

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- modular (compositional)

ODEs vs PAs

ODEs:

- continuous
- deterministic
- monolithic
- specify dynamics

PAs:

- discrete
- non-deterministic/stochastic
- modular (compositional)
- specify interactions

ODEs vs PAs

ODEs:

- continuous
- deterministic
- monolithic
- specify dynamics
- very popular

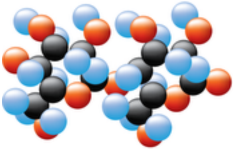
PAs:

- discrete
- non-deterministic/stochastic
- modular (compositional)
- specify interactions
- relatively unknown

Syntax: species and processes

Species:

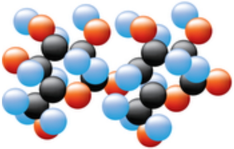
$$
\begin{aligned}
A, B ::= \quad & \mathbf{0} \mid \pi_1.A_1 + \cdots + \pi_n.A_n \\
& D(\vec{a}) \mid A \mid B \mid (\nu M)A
\end{aligned}
$$



Syntax: species and processes

Species:

$$A, B ::= \mathbf{0} \mid \pi_1.A_1 + \cdots + \pi_n.A_n \mid D(\vec{a}) \mid A \mid B \mid (\boldsymbol{\nu} M)A$$



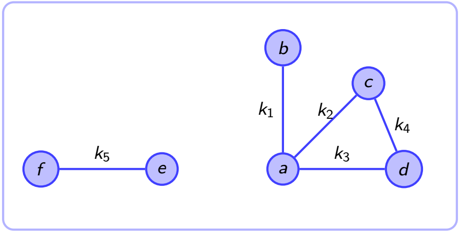
Processes:

$$P, Q ::= c \cdot A \mid P \parallel Q \qquad c \in \mathbb{R}_{\geq 0}$$

(thus P is an element of $\mathbb{R}^{\mathcal{S}}$)

Syntax: affinity networks

Names represent protein interaction sites.



An affinity network gives their interaction structure.

Semantics

$\frac{dP}{dt}$: immediate behaviour

- element of $\mathbb{R}^{\mathcal{S}}$
- equivalent to an ODE system

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$\partial\mathbf{P}$: interaction potential

- element of $\mathbb{R}^{\mathcal{S}\times\mathcal{C}\times\mathcal{N}}$
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$$\partial(P \parallel Q) \triangleq \partial P + \partial Q$$

$$\frac{d(P \parallel Q)}{dt} \triangleq \frac{dP}{dt} + \frac{dQ}{dt} + \partial P \oplus \partial Q$$

Semantics

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$$\partial(P \parallel Q) \triangleq \partial P + \partial Q$$

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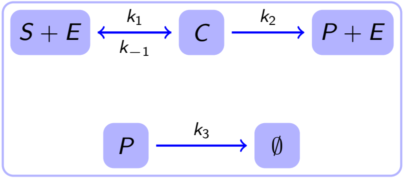
$$1_{A \xrightarrow{x} F} \oplus 1_{B \xrightarrow{y} G} \triangleq Aff(x,y)(\langle F \cdot G\rangle - \langle A\rangle - \langle B\rangle)$$

Example: a simple chemical reaction network



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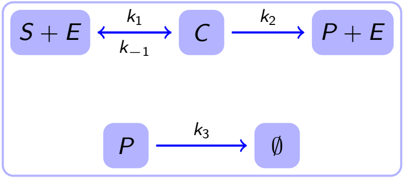

$$
\begin{aligned}
\mathtt{S} &\triangleq \mathtt{a(x,y).(x.S + y.P)} \\
\mathtt{E} &\triangleq (\boldsymbol{\nu}\ \mathtt{M})\mathtt{b}\langle\mathtt{u},\mathtt{r}\rangle\mathtt{.act.E} \\
\mathtt{P} &\triangleq \tau@\mathtt{k_3}.\mathbf{0}
\end{aligned}
$$

$$\mathtt{c_E} \cdot \mathtt{E} \parallel \mathtt{c_S} \cdot \mathtt{S}$$

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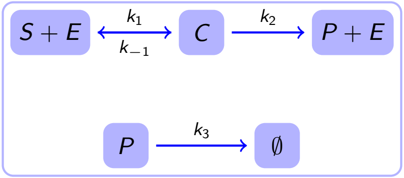
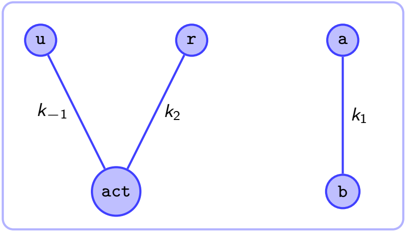


$$\mathtt{S} \triangleq \mathtt{a}(\mathtt{x},\mathtt{y}).(\mathtt{x}.\mathtt{S} + \mathtt{y}.\mathtt{P})$$
$$\mathtt{E} \triangleq (\boldsymbol{\nu}\ \mathtt{M})\mathtt{b}\langle \mathtt{u},\mathtt{r}\rangle.\mathtt{act}.\mathtt{E}$$
$$\mathtt{P} \triangleq \tau @ \mathtt{k}_3.\mathbf{0}$$
$$\mathtt{c}_\mathtt{E} \cdot \mathtt{E} \parallel \mathtt{c}_\mathtt{S} \cdot \mathtt{S}$$



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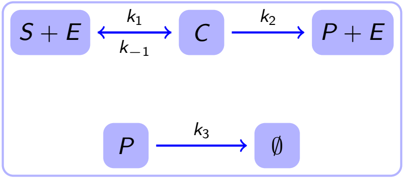

$$\mathtt{S} \triangleq \mathtt{a(x,y).(x.S + y.P)}$$
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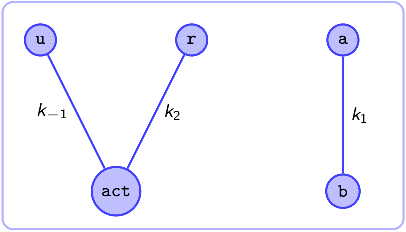
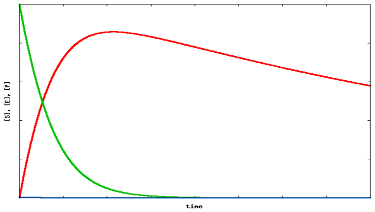
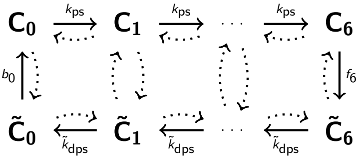
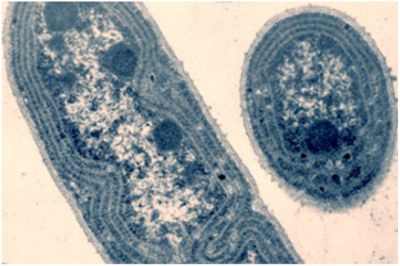
$$\mathtt{c_E} \cdot \mathtt{E} \parallel \mathtt{c_S} \cdot \mathtt{S}$$

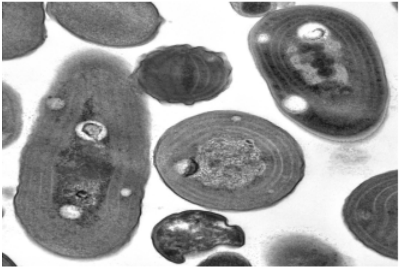


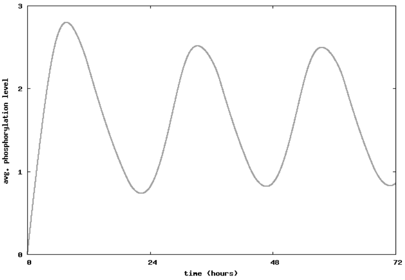


The KaiABC circadian clock of *Synechococcus elongatus*





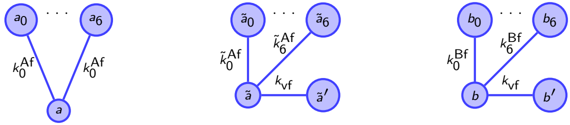




The model

$$
\begin{aligned}
C_i &\triangleq (\nu M_i)(\tau@k_{\text{ps}}.C_{i+1}+\tau@f_i.\tilde{C}_i+\tau@k_{\text{dps}}.C_{i-1}+a_i\langle act_i\rangle.(u_i.C_i+r_i.C_{i+1}))\\
\tilde{C}_i &\triangleq \tau@\tilde{k}_{\text{ps}}.\tilde{C}_{i+1}+\tau@b_i.C_i+\tau@\tilde{k}_{\text{dps}}.\tilde{C}_{i-1}+b_i.b'.B\tilde{C}_i\\
B\tilde{C}_i &\triangleq \tau@\tilde{k}_{\text{ps}}.B\tilde{C}_{i+1}+\tau@k_i^{\text{Bb}}.(\tilde{C}_i|B|B)+\tau@\tilde{k}_{\text{dps}}.B\tilde{C}_{i-1}+\tilde{a}_i.\tilde{a}'.AB\tilde{C}_i\\
AB\tilde{C}_i &\triangleq \tau@\tilde{k}_{\text{ps}}.AB\tilde{C}_{i+1}+\tau@\tilde{k}_i^{\text{Ab}}.(B\tilde{C}_i|A|A)+\tau@\tilde{k}_{\text{dps}}.AB\tilde{C}_{i-1}\\
A &\triangleq a(x).x.A+\tilde{a}.\mathbf{0}\\
B &\triangleq b.\mathbf{0}
\end{aligned}
$$

$$\mathbf{P} \triangleq \mathbf{c_A}\cdot\mathbf{A} \parallel \mathbf{c_B}\cdot\mathbf{B} \parallel \mathbf{c_C}\cdot\mathbf{C_0}$$



The model: no autonomous phosphorylation

$$C_i \triangleq (\nu M_i)(\tau@k_{\text{ps}}.C_{i+1} + \tau@f_i.\tilde{C}_i + \tau@k_{\text{dps}}.C_{i-1} + a_i\langle act_i\rangle.(u_i.C_i + r_i.C_{i+1}))$$

$$\tilde{C}_i \triangleq \tau@\tilde{k}_{\text{ps}}.\tilde{C}_{i+1} + \tau@b_i.C_i + \tau@\tilde{k}_{\text{dps}}.\tilde{C}_{i-1} + b_i.b'.B\tilde{C}_i$$

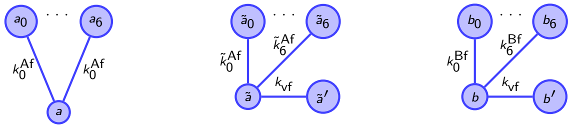
$$B\tilde{C}_i \triangleq \tau@\tilde{k}_{\text{ps}}.B\tilde{C}_{i+1} + \tau@k_i^{\text{Bb}}.(\tilde{C}_i|B|B) + \tau@\tilde{k}_{\text{dps}}.B\tilde{C}_{i-1} + \tilde{a}_i.\tilde{a}'.AB\tilde{C}_i$$

$$AB\tilde{C}_i \triangleq \tau@\tilde{k}_{\text{ps}}.AB\tilde{C}_{i+1} + \tau@\tilde{k}_i^{\text{Ab}}.(B\tilde{C}_i|A|A) + \tau@\tilde{k}_{\text{dps}}.AB\tilde{C}_{i-1}$$

$$A \triangleq a(x).x.A + \tilde{a}.\mathbf{0}$$

$$B \triangleq b.\mathbf{0}$$

$$\mathbf{P} \triangleq \mathbf{c_A \cdot A} \parallel \mathbf{c_B \cdot B} \parallel \mathbf{c_C \cdot C_0}$$



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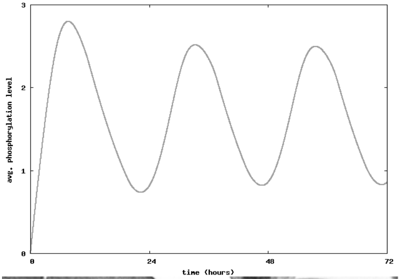

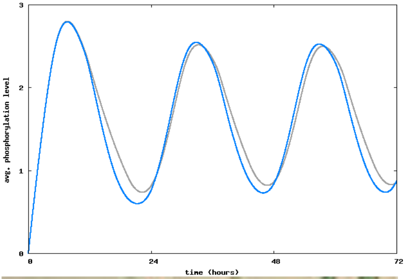

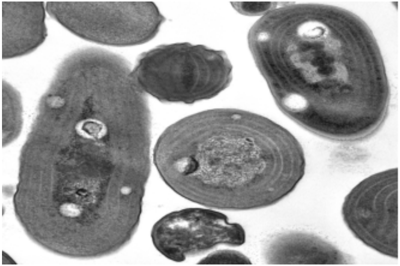

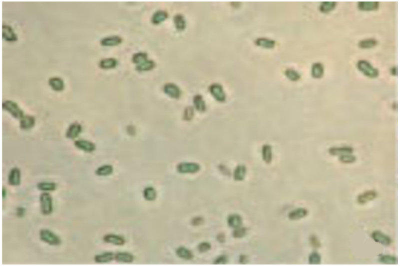

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$$C_i \triangleq (\nu M_i)(\tau @ k_{\mathrm{ps}}.C_{i+1} + \tau @ f_i.\tilde{C}_i + \tau @ k_{\mathrm{dps}}.C_{i-1} + a_i\langle act_i\rangle.(u_i.C_i + r_i.C_{i+1}))$$

$$\tilde{C}_i \triangleq \tau @ \tilde{k}_{\mathrm{ps}}.\tilde{C}_{i+1} + \tau @ b_i.C_i + \tau @ \tilde{k}_{\mathrm{dps}}.\tilde{C}_{i-1} + b_i.b'.B\tilde{C}_i$$

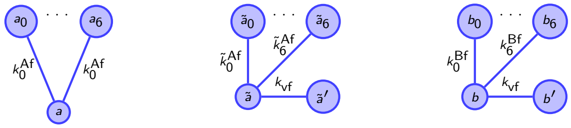
$$B\tilde{C}_i \triangleq \tau @ \tilde{k}_{\mathrm{ps}}.B\tilde{C}_{i+1} + \tau @ k_i^{\mathrm{Bb}}.(\tilde{C}_i|B|B) + \tau @ \tilde{k}_{\mathrm{dps}}.B\tilde{C}_{i-1} + \tilde{a}_i.\tilde{a}'.AB\tilde{C}_i$$

$$AB\tilde{C}_i \triangleq \tau @ \tilde{k}_{\mathrm{ps}}.AB\tilde{C}_{i+1} + \tau @ \tilde{k}_i^{\mathrm{Ab}}.(B\tilde{C}_i|A|A) + \tau @ \tilde{k}_{\mathrm{dps}}.AB\tilde{C}_{i-1}$$

$$A \triangleq a(x).x.A + \tilde{a}.\mathbf{0}$$

$$B \triangleq b.\mathbf{0}$$

$$\mathbf{P} \triangleq \mathbf{c_A \cdot A} \parallel \mathbf{c_B \cdot B} \parallel \mathbf{c_C \cdot C_0}$$



The model: weaker KaiA binding

$$C_i \triangleq (\boldsymbol{\nu} M_i)(\tau @ k_{\text{ps}}.C_{i+1} + \tau @ f_i.\tilde{C}_i + \tau @ k_{\text{dps}}.C_{i-1} + a_i\langle act_i\rangle.(u_i.C_i + r_i.C_{i+1}))$$

$$\tilde{C}_i \triangleq \tau @ \tilde{k}_{\text{ps}}.\tilde{C}_{i+1} + \tau @ b_i.C_i + \tau @ \tilde{k}_{\text{dps}}.\tilde{C}_{i-1} + b_i.b'.B\tilde{C}_i$$

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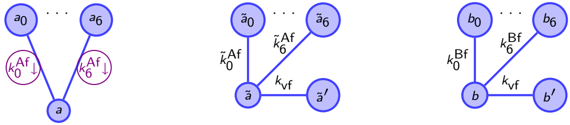
$$AB\tilde{C}_i \triangleq \tau @ \tilde{k}_{\text{ps}}.AB\tilde{C}_{i+1} + \tau @ \tilde{k}_i^{\text{Ab}}.(B\tilde{C}_i|A|A) + \tau @ \tilde{k}_{\text{dps}}.AB\tilde{C}_{i-1}$$

$$A \triangleq a(x).x.A + \tilde{a}.\mathbf{0}$$

$$B \triangleq b.\mathbf{0}$$

$$\mathbf{P} \triangleq \mathbf{c_A \cdot A} \parallel \mathbf{c_B \cdot B} \parallel \mathbf{c_C \cdot C_0}$$



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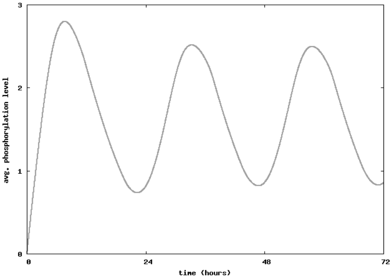
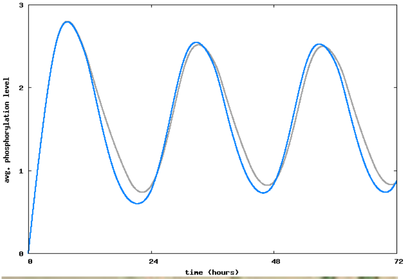
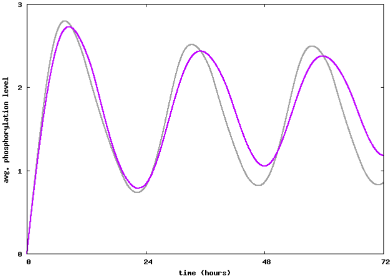
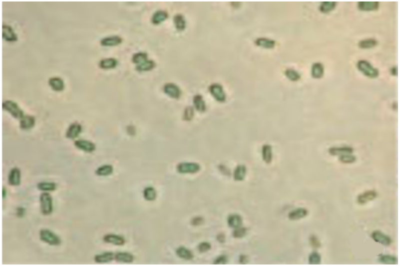


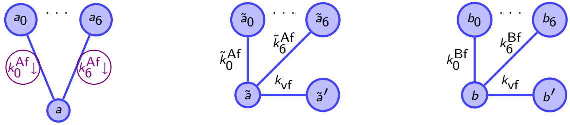






The model: weaker KaiA binding

$$
\begin{aligned}
C_i &\triangleq (\nu M_i)(\tau@k_{ps}.C_{i+1}+\tau@f_i.\tilde{C}_i+\tau@k_{dps}.C_{i-1}+a_i\langle act_i\rangle.(u_i.C_i+r_i.C_{i+1})) \\
\tilde{C}_i &\triangleq \tau@\tilde{k}_{ps}.\tilde{C}_{i+1}+\tau@b_i.C_i+\tau@\tilde{k}_{dps}.\tilde{C}_{i-1}+b_i.b'.B\tilde{C}_i \\
B\tilde{C}_i &\triangleq \tau@\tilde{k}_{ps}.B\tilde{C}_{i+1}+\tau@k_i^{Bb}.(\tilde{C}_i|B|B)+\tau@\tilde{k}_{dps}.B\tilde{C}_{i-1}+\tilde{a}_i.\tilde{a}'.AB\tilde{C}_i \\
AB\tilde{C}_i &\triangleq \tau@\tilde{k}_{ps}.AB\tilde{C}_{i+1}+\tau@\tilde{k}_i^{Ab}.(B\tilde{C}_i|A|A)+\tau@\tilde{k}_{dps}.AB\tilde{C}_{i-1} \\
A &\triangleq a(x).x.A+\tilde{a}.\mathbf{0} \\
B &\triangleq b.\mathbf{0} \\
\mathbf{P} &\triangleq \mathbf{c_A \cdot A} \parallel \mathbf{c_B \cdot B} \parallel \mathbf{c_C \cdot C_0}
\end{aligned}
$$



The model: KaiA and KaiB can dimerize

$$C_i \triangleq (\boldsymbol{\nu} M_i)(\tau@k_{\mathrm{ps}}.C_{i+1} + \tau@f_i.\tilde{C}_i + \tau@k_{\mathrm{dps}}.C_{i-1} + a_i\langle act_i\rangle.(u_i.C_i + r_i.C_{i+1}))$$

$$\tilde{C}_i \triangleq \tau@\tilde{k}_{\mathrm{ps}}.\tilde{C}_{i+1} + \tau@b_i.C_i + \tau@\tilde{k}_{\mathrm{dps}}.\tilde{C}_{i-1} + b_i.b'.B\tilde{C}_i$$

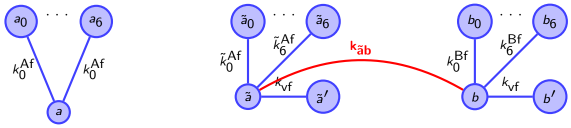
$$B\tilde{C}_i \triangleq \tau@\tilde{k}_{\mathrm{ps}}.B\tilde{C}_{i+1} + \tau@k_i^{\mathrm{Bb}}.(\tilde{C}_i|B|B) + \tau@\tilde{k}_{\mathrm{dps}}.B\tilde{C}_{i-1} + \tilde{a}_i.\tilde{a}'.AB\tilde{C}_i$$

$$AB\tilde{C}_i \triangleq \tau@\tilde{k}_{\mathrm{ps}}.AB\tilde{C}_{i+1} + \tau@\tilde{k}_i^{\mathrm{Ab}}.(B\tilde{C}_i|A|A) + \tau@\tilde{k}_{\mathrm{dps}}.AB\tilde{C}_{i-1}$$

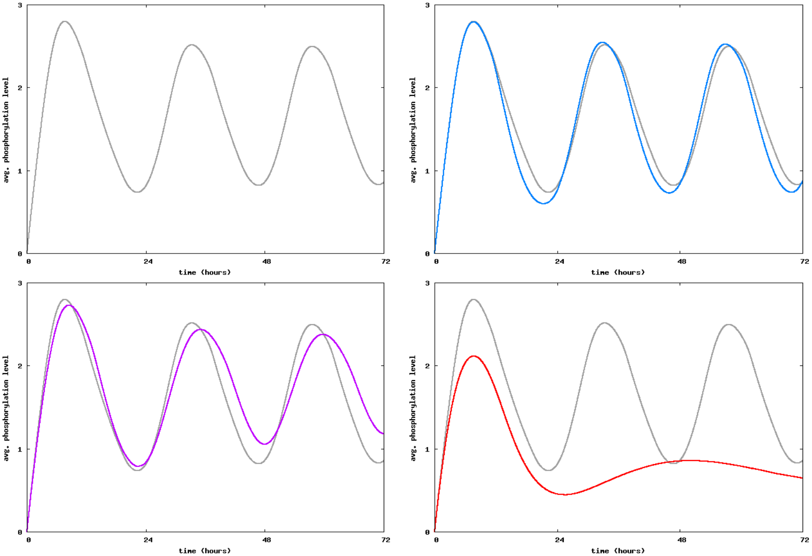
$$A \triangleq a(x).x.A + \tilde{a}.\mathbf{0}$$

$$B \triangleq b.\mathbf{0}$$

$$\mathbf{P} \triangleq \mathbf{c_A \cdot A} \parallel \mathbf{c_B \cdot B} \parallel \mathbf{c_C \cdot C_0}$$



The model: KaiA and KaiB can dimerize



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Appendix

Key references:

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