

Cell Signalling P Systems with Discretised Reaction Kinetics

T.Hinze¹ T.Lenser² G.Escuela² I.Heiland¹ S.Schuster¹

{thomas.hinze,heiland.ines,stefan.schu}@uni-jena.de

{thorsten.lenser,gabi.escuela}@uni-jena.de

Friedrich Schiller University Jena

¹Department Bioinformatics at
School of Biology/Pharmacy

²Bio Systems Analysis Group

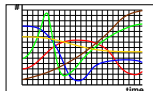
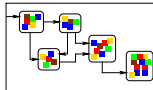
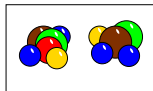
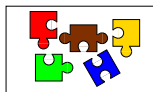
19. Theorietag
Automaten und Formale Sprachen



Outline

Cell Signalling P Systems with Discretised Reaction Kinetics

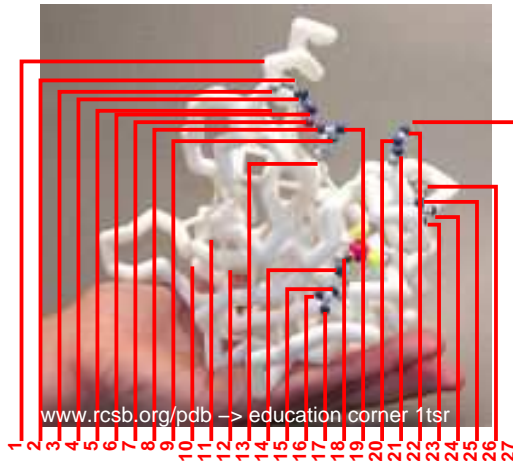
1. Motivation
2. Cell signalling modules (CSM)
3. P system framework Π_{CSM}
4. Case study KaiABC oscillator:
A circadian clock
5. Outlook and acknowledgement



1	0	0	1	1	0	0
0	1	1	0	0	1	0
1	0	1	1	0	1	0
1	0	0	1	0	0	1

Combinatorial Explosion of Protein Activation States

- Tumor suppressor protein p53: 27 phosphorylation sites
- Up to $2^{27} = 34,217,728$ distinguishable activation states
- Each state: individual constituent of reaction network



Cell Signalling Module

Characteristics

- Intracellular reaction network acting as functional unit
- Composed of proteins carrying phosphorylation sites
- Interactions between individual activation states

Facts

- Dynamical behaviour essential to understand function
- Often partially unknown
- Reconstruction as challenging task in systems biology
- Reverse engineering by integrative approach

Idea to manage complexity:

Capturing each protein by a specific string-object

instead of separate species per activation state

Specification of String-Objects

Assuming two alphabets: V (for protein names), V' (for protein properties); w.l.o.g $\#, \neg, * \notin V \cup V'$

Syntax for string-objects by regular set

$$S = V^+ \cdot (\{\#\} \cdot ((V')^+ \cup \{\neg\} \cdot (V')^+ \cup \{*\}))^*$$

Protein properties

- x : property x present (e.g. specific phosphate attached)
- $\neg x$: property x absent (e.g. specific phosphate removed)
- $*$: placeholder for arbitrary property setting

Examples

- $\text{prot1}\#\text{p}\#*\#\neg\text{p}$ (subsumes activation states of prot1)
- $\text{KaiC}\#\neg\text{KaiA}\#\text{KaiB}\#\text{4}$ (prot. complex, 4 ligands attached)

⇒ **Application of reaction rules requires string matching**

Π_{CSM} : System Components

Let $\langle S \rangle$ be the set of all multisets over S .

$$\Pi_{\text{CSM}} = (V, V', R_1, \dots, R_r, f_1, \dots, f_r, A, C, \Delta\tau)$$

with

$R_i \in \langle S \rangle \times \langle S \rangle$ is a reaction rule
 composed of two finite multisets

$f_i : \langle S \rangle \rightarrow \mathbb{N}$ is a function corresponding to
 discrete kinetics of reaction R_i

$A \in \langle S \rangle$ is a multiset of axioms representing
 the initial molecular configuration

$C \in \mathbb{R}_+$ spatial capacity of the module (vessel or compartment)

$\Delta\tau \in \mathbb{R}_+$ time discretisation interval



Π_{CSM} : Matching

Let \mathcal{S} be a string-object syntax. Two string-objects match iff there is at least one common wild card-free representation:

$$\text{Match} \subseteq \mathcal{S} \times \mathcal{S}$$

$$\text{Match} = \bigcup_{m \in \mathbb{N}} \{ (p \# p_1 \# p_2 \dots \# p_m, s \# s_1 \# s_2 \dots \# s_m) \mid (p = s) \wedge \forall j \in \{1, \dots, m\} : [(p_j = s_j) \vee (p_j = *) \vee (s_j = *) \vee ((p_j = \neg q) \wedge (s_j \neq q)) \vee ((s_j = \neg q) \wedge (p_j \neq q))]] \}$$

- *Match* is a symmetric relation
- Requires minimal similarity between string-objects with incomplete information
- Uncertainty interpreted as arbitrary replacement by available properties

Π_{CSM} : Matching

Let **S** be a string-object syntax. Two string-objects match iff there is at least one common wild card-free representation:

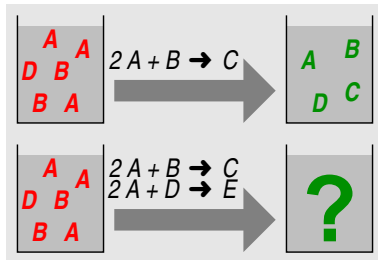
Example

C#D#p	C#D#-p	C#T#p	C#T#-p	C##p	C#D##	C##*	E##*
■				■	■	■	
	■				■	■	
		■		■		■	
			■			■	
■		■		■	■	■	
■	■			■	■	■	
■	■	■	■	■	■	■	
							■

$V = \{C, E\}$
 $V' = \{D, T, p\}$

Π_{CSM} : Dynamical System Behaviour (I)

- Successive progression of configuration $L_t \in \langle S \rangle$ over time $t \in \mathbb{N}$ starting from axioms A
- $\Delta\tau$: span between t and $t + 1$
- Conflict handling by prioritisation of reaction rules



$$L_0 = L_{0,0} = A$$

$$L_{t,1} = \begin{cases} L_{t,0} \ominus \text{Reactants}_{t,1} \uplus \text{Products}_{t,1} & \text{if } \text{Reactants}_{t,1} \subseteq L_{t,0} \\ L_{t,0} & \text{otherwise} \end{cases}$$

⋮

$$L_{t+1} = L_{t,r} = \begin{cases} L_{t,r-1} \ominus \text{Reactants}_{t,r} \uplus \text{Products}_{t,r} & \text{if } \text{Reactants}_{t,r} \subseteq L_{t,r-1} \\ L_{t,r-1} & \text{otherwise} \end{cases}$$

Π_{CSM} : Dynamical System Behaviour (II)

Estimation of multisets $Reactants_{t,j}$ and $Products_{t,j}$ at time t concerning reaction $R_j = (A_j, B_j) \in \langle S \rangle \times \langle S \rangle$ denoted



includes

- **Matching** between string-objects in L_t and those in A_j
- Consideration of **stoichiometry** captured by multisets A_j, B_j
- Evaluation of **kinetic law** expressed by scalar function f_j

$$Reactants_{t,j} = \biguplus_{e_1 \in Match(a_1)} \dots \biguplus_{e_p \in Match(a_p)} f_j(\{(e_1, \infty), \dots, (e_p, \infty)\} \cap L_{t,j-1}) \cdot \{(e_1, A_j(a_1)), \dots, (e_p, A_j(a_p))\}$$

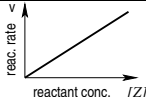
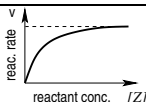
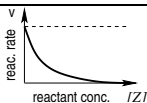
$$Products_{t,j} = \biguplus_{e_1 \in Match(a_1)} \dots \biguplus_{e_p \in Match(a_p)} f_j(\{(e_1, \infty), \dots, (e_p, \infty)\} \cap L_{t,j-1}) \cdot \{(b_1, B_j(b_1)), \dots, (b_q, B_j(b_q))\}$$

Π_{CSM} : Discrete Reaction Kinetics

Scalar function f_j provides number of turns for application of reaction rule R_j . Rate constant: $k_j = \hat{k}_j \cdot C \cdot \Delta\tau$ (Euler).

$$f_j(L_t) = \left[k_j \prod_{\forall \alpha \in Match(A_j) \cap Match(L_t) : (R_j = (A_j, B_j))} \hat{f}(L_t(\alpha))^{|Match(A_j) \cap \{(\alpha, \infty)\}|} \right]$$

Selected kinetic laws $\hat{f}([Z])$

Kinetics	Activation	Repression
Mass-Action (no saturation)	 <p>react. rate</p> <p>reactant conc. $[Z]$</p> <p>$\hat{f}([Z]) = [Z]$</p>	—
Michaelis-Menten (saturation)	 <p>react. rate</p> <p>reactant conc. $[Z]$</p> <p>$\hat{f}([Z]) = \frac{[Z]}{\Theta + [Z]}$</p>	 <p>react. rate</p> <p>reactant conc. $[Z]$</p> <p>$\hat{f}([Z]) = \left(1 - \frac{[Z]}{\Theta + [Z]}\right)$</p>

Circadian Clocks

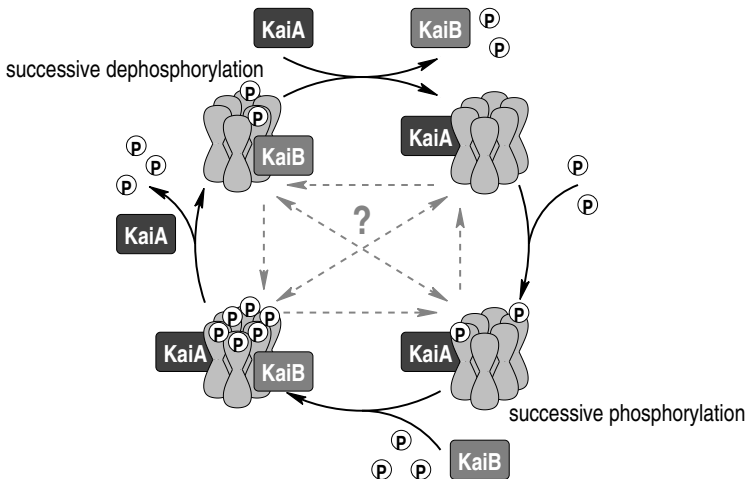
Characteristics

- Self-sustained biochemical oscillators
- Period of approx. 24 hours persisting under constant environmental conditions (e.g. constant darkness)
- Temperature compensation within physiological range
- Capability of entrainment by external stimuli (e.g. light/dark or temperature cycles)
- Reaction system with at least one feedback loop

High scientific impact because . . .

- Circadian clock as a potential universal property of life
- Self-sustainability and high precision of bio-oscillators
- Chronobiological control systems for manifold processes
- Several independent evolutionary origins assumed

KaiABC Oscillator: Reaction Cycle



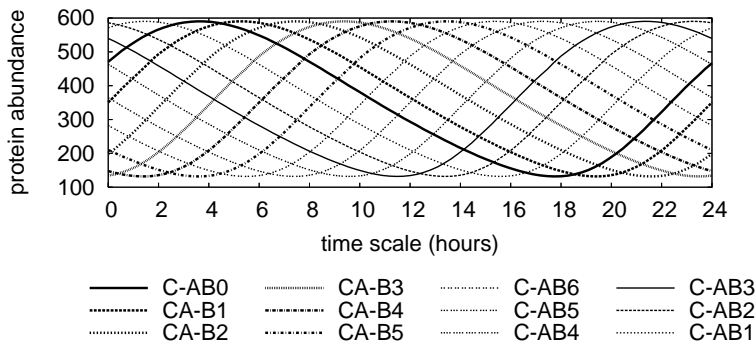
Incomplete information about interphase feedback loops

The Model Π_{KaiABC} at a Glance

$$\begin{aligned} \Pi_{KaiABC} &= (V, V', R_1, \dots, R_{17}, f_1, \dots, f_{17}, A, C, \Delta\tau) \\ V &= \{A, B, C\} \dots \dots \dots \text{identifiers of proteins KaiA, KaiB, KaiC} \\ V' &= \{A, B\} \cup \dots \dots \dots \text{KaiA, KaiB within a complex associated to KaiC} \\ &\quad \{0, 1, 2, 3, 4, 5, 6\} \dots \dots \text{number of attached phosphates} \\ R_1 &= C\# \neg A\#B\#0 + A \longrightarrow C\#A\# \neg B\#1 + B \\ R_2 &= C\#A\# * \#1 + A \longrightarrow C\#A\# * \#2 + A \\ R_3 &= C\#A\# * \#2 + A \longrightarrow C\#A\# * \#3 + A \\ R_4 &= C\#A\# * \#3 + A \longrightarrow C\#A\# * \#4 + A \\ R_5 &= C\#A\# * \#4 + A \longrightarrow C\#A\# * \#5 + A \\ R_6 &= C\#A\# \neg B\#5 + B \longrightarrow C\# \neg A\#B\#6 + A \\ R_7 &= C\# * \#B\#6 + B \longrightarrow C\# * \#B\#5 + B \\ R_8 &= C\# * \#B\#5 + B \longrightarrow C\# * \#B\#4 + B \\ R_9 &= C\# * \#B\#4 + B \longrightarrow C\# * \#B\#3 + B \\ R_{10} &= C\# * \#B\#3 + B \longrightarrow C\# * \#B\#2 + B \\ R_{11} &= C\# * \#B\#2 + B \longrightarrow C\# * \#B\#1 + B \\ R_{12} &= C\# * \#B\#1 + B \longrightarrow C\# * \#B\#0 + B \\ R_{13} &= C\# \neg A\#B\#* + A \longrightarrow C\#A\# \neg B\#* + B \\ R_{14} &= C\#A\# \neg B\#* + B \longrightarrow C\# \neg A\#B\#* + A \\ R_{15} &= A \longrightarrow \emptyset \\ R_{16} &= B \longrightarrow \emptyset \\ R_{17} &= C\# * \# * \#* \longrightarrow \emptyset \\ &\dots \end{aligned}$$

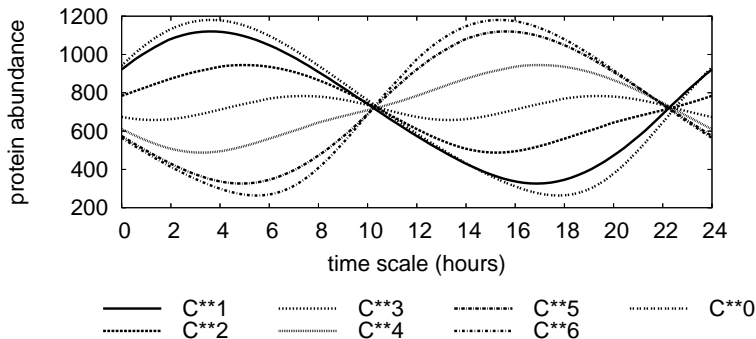
Discrete Michaelis-Menten kinetics

Simulation Results: Individual KaiABC Subproducts



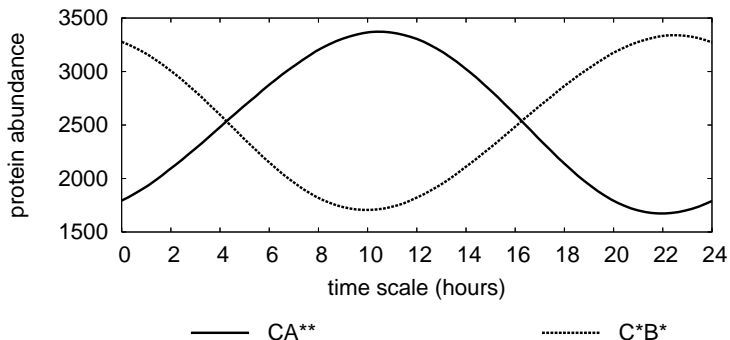
Temporal courses of 12 specific KaiABC subproducts representing the process status of the reaction cycle. Kinetic parameters and initial amounts adjusted in a way to obtain a period of ≈ 24 hours and symmetry among individual oscillations.

Focussing on the Level of Phosphorylation



Temporal courses of KaiABC subproducts subsumed by their level of phosphorylation ranging from 0 to 6. Kinetic parameters and initial amounts adjusted in a way to obtain a period of ≈ 24 hours and symmetry among individual oscillations.

Focussing on KaiABC Complex Formation



Temporal courses of KaiABC subproducts separated into two groups by association of KaiA resp. KaiB to KaiC. Kinetic parameters and initial amounts adjusted in a way to obtain a period of ≈ 24 hours and symmetry among individual oscillations.

Outlook

Conclusions

- String-objects denoted by regular expressions can manage descriptive complexity of protein binding states
- Coping with incomplete information by means of integrative approach
- Practicability for application in systems biology

Further work

- Extending the system by symmetry-breaking assumptions
 - Premature association/dissociation
 - Spontaneous dephosphorylation
 - Monomer shuffle, . . .
- Integration of temperature within the model
- Perturbance analysis of the model

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