Backtracking Membrane Systems Unravel Stable Oscillations in Distributed Reaction Networks

Thomas Hinze[1], **Thorsten Lenser**[2], **Ines Heiland**[1], **Stefan Schuster**[1]

[1]Department of Bioinformatics at School of Biology and Pharmacy, Friedrich-Schiller University Jena

[2]Bio Systems Analysis Group at Department of Computer Science, Friedrich-Schiller University Jena

{hinze,thlenser,iheiland,schuster}@minet.uni-jena.de

seit 1558

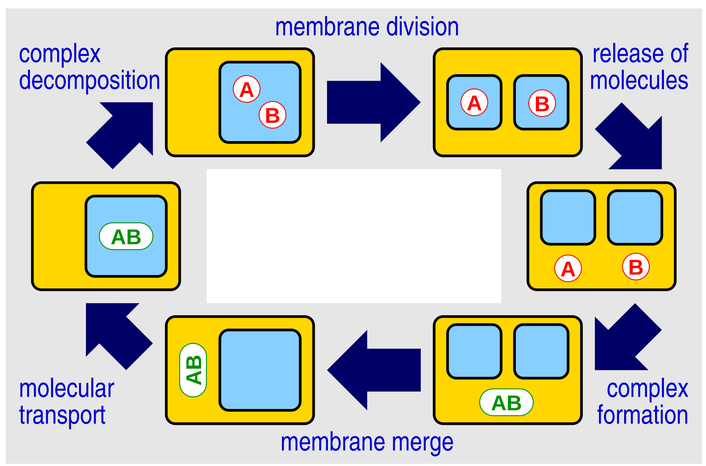
JCB Jena Centre for Bioinformatics

FORSYS Forschungseinheiten der Systembiologie

Motivation: Impetus of Oscillations in the Sciences

Oscillations are essential for the function of numerous systems in biology as well as engineering [1, 9, 12]. A common property of these systems lies in their necessity to synchronise and coordinate inherent chemical or physical activities based on periodically iterated trigger signals. In order to sustain a stable oscillatory signal behaviour, a **cyclic process succession** is required that is characterised by at least one positive or negative **feedback loop**. The delayed signal evaluation enables a concerted alternation between effects caused by the process chain and counteractions initiated by the feedback. External stimuli or stochasticity might affect signal oscillations resulting from a process cycle.

Motivated by the need for an appropriate toolbox covering description, simulation, and analysis of discontinuously considered biological reaction processes, we extend the concept of **membrane systems** [11] towards an underlying **backtracking mechanism** able to explore the nature of sustained oscillations including **alternations in compartmental structure** like in the following artificial example:



In particular, we expect to gain insight into aspects of **chronobiology** by **reverse engineering** using backtracking membrane systems. This approach can benefit from the reduced parameter space and from the flexibility regarding structural dynamics.

State-of-the-Art: Analysis of Oscillating Signals in Continuous Mathematical Models

Within the domain of strictly continuous signals quantified by real numbers, modelling and analysis of oscillating behaviour has been well-studied [9]. Chemical reaction networks assumed to reside in a **homogeneous environment** give a typical example: Each **species** is represented by its **concentration** which is allowed to vary continuously over time. From the **static network topology** together with the stoichiometry of the reactions, a corresponding **ordinary differential equation system** (ODE) can be derived that specifies the **reaction rates** for each species [3]. Inclusion of parameterised **kinetic laws** accomplishes a mapping between species concentrations and effective reaction rates. The resulting ODE can be tested for **stability** with respect to the dynamical systems behaviour. To this end, the **eigenvalues** of the **Jacobian matrix** obtained from the ODE are sufficient [12]. **Limit cycles** indicate the oscillatory behaviour in detail.

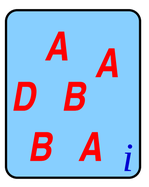
Looking Beyond: Discretisation for Capturing Structural Dynamics

Furthermore, there are different oscillatory scenarios in biological systems. On the one hand, periodicity might also be reflected in **temporal changes of the compartmental structure** like in cell cycle [8]. On the other hand, **complex signalling molecules** are often available in **low concentrations**. Both scenarios have in common to prevent pure ODE-based modelling techniques due to the **discrete manner of involved key entities**.

Membrane Systems: Algebraic Prerequisites

Membrane systems, pioneered by Gheorghe Păun [10, 11] and hence also called P systems, provide a discrete modelling approach to describe biological reaction systems composed of interconnected membranes. Each membrane delimits a spatial region in which chemical reactions can occur. Within a membrane i, molecular particles are formalised by a **multiset of objects** representing its **configuration** $\mathcal{L}_t^i$ at time point t.

Definition (Multiset): *Let F be a set. A multiset over F is a mapping $\mathcal{F} : F \to \mathbb{N} \cup \{\infty\}$ that specifies the multiplicity of each element $a \in F$.*
Example: $\mathcal{L}_t^i = \{(A,3),(B,2),(C,0),(D,1)\}$

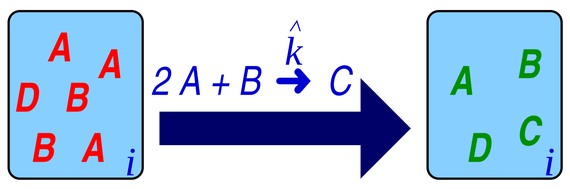


Reaction Rules

Dedicated **term-rewriting mechanisms** simultaneously execute **reaction rules** associated to each membrane by application of multiset operations:

Difference: $\mathcal{F} \ominus \mathcal{G} := \{(a, \max(\mathcal{F}(a) - \mathcal{G}(a), 0)) \mid a \in F \setminus G\}$
Sum: $\mathcal{F} \uplus \mathcal{G} := \{(a, \mathcal{F}(a) + \mathcal{G}(a)) \mid a \in F \cup G\}$

Example:

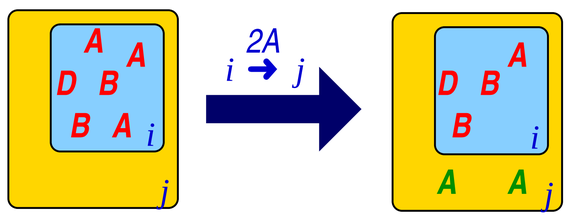


$$\begin{aligned}\mathcal{L}_{t+1}^i &= \mathcal{L}_t^i \ominus \{(A, 2\cdot\hat{k}),(B,1\cdot\hat{k})\} \uplus \{(C,1\cdot\hat{k})\} \text{ with } \hat{k}=1\\ &= \{(A,3),(B,2),(C,0),(D,1)\} \ominus \{(A,2),(B,1)\} \uplus \{(C,1)\}\\ &= \{(A,1),(B,1),(C,1),(D,1)\}\end{aligned}$$

Here, $\hat{k}$ reflects possible effects of discretised kinetic laws.

Transportation Rules

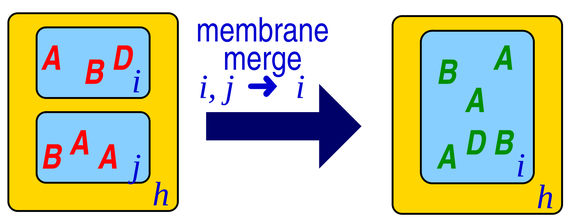
Supplementary **transportation rules** control the exchange of objects among membranes.
Example:



$$\begin{aligned}\mathcal{L}_{t+1}^i &= \mathcal{L}_t^i \ominus \{(A,2)\}\\ &= \{(A,3),(B,2),(C,0),(D,1)\} \ominus \{(A,2)\}\\ &= \{(A,1),(B,2),(C,0),(D,1)\}\\ \mathcal{L}_{t+1}^j &= \emptyset \uplus \{(A,2)\} = \{(A,2)\}\end{aligned}$$

Structural Rules

Structural rules afford directed manipulations of the membrane structure like membrane dissolution, division, transportation, or creation from molecular constituents. Accordingly, capturing aspects of structural dynamics is seen as an advantageous feature of membrane systems [2, 5, 6, 7].
Example:



$$\begin{aligned}[h[i]_i[j]_j]_h &\to [h[i]_i]_h \quad \ldots\ldots \text{update compartmental structure}\\ \mathcal{L}_{t+1}^i &= \mathcal{L}_t^i \uplus \mathcal{L}_t^j,\ \mathcal{L}_{t+1}^j = \emptyset \quad \ldots\ldots \text{update configurations}\\ \mathcal{R}_{t+1}^i &= \mathcal{R}_t^i \uplus \mathcal{R}_t^j,\ \mathcal{R}_{t+1}^j = \emptyset \quad \ldots\ldots \text{update reaction rules}\\ \mathcal{T}_{t+1}^i &= \mathcal{T}_t^i \uplus \mathcal{T}_t^j|_{j\to i},\ \mathcal{T}_{t+1}^j = \emptyset \quad \ldots \text{transportation rules}\end{aligned}$$

Backtracking Membrane Systems: Description and Principle of Operation

A backtracking membrane system is an algebraic construct

$$\Pi = (V, S_0, C_0, \Delta\tau) \qquad \text{composed of}$$

V ..... system alphabet
S_0 ..... initial membrane structure
C_0 ..... initial configuration and rules for each membrane
M ..... finite global set of structural rules
$\Delta\tau$ ..... time discretisation intervall (time span $\langle t, t+1\rangle$)

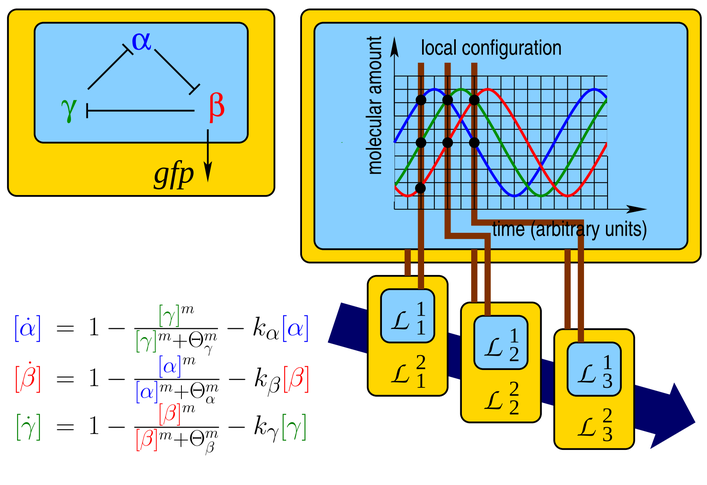
Alphabet V specifies the set of characters (symbols) from which object identifiers (nonempty finite strings $\in V^*$) are formed. This way, string objects are able to express simple complexes such as polymer chains. The **initial membrane structure** S_0, a sequentialised tree, comprises the spatial membrane nesting of the entire system. Within C_0, the **initial specification of each membrane** $i \in \{1,\ldots,|C_0|\}$ is formulated as a tuple of finite components $(\mathcal{L}_0^i, \mathcal{R}_0^i, \mathcal{T}_0^i)$ corresponding to the local configuration $\mathcal{L}_0^i$, reaction rules $\mathcal{R}_0^i$, and transportation rules $\mathcal{T}_0^i$. Multisets for educts and products along with a kinetic term (cf. $\hat{k}$) constitute each reaction in $\mathcal{R}_0^i$. The **dynamics** of Π is based on iterated turns reflecting the progression in discrete time steps. Each turn follows a fixed sequence of multiset operations in a **nondeterministic** way:

1. Identify reactants simultaneously within each membrane
2. Remove all reactant objects from the system
3. Add corresponding product objects obtained from the applied reaction rules
4. Change membrane structure if necessary
5. Move objects among membranes

After each time step, all resulting membranes renew their configurations. Together with the current topological membrane structure, they form the **overall configuration** of the entire system at the present point in time. The overall configuration contains the whole information about the process status of the entire system.

Identification and Analysis of Configurations Obtained from Derivation Tree

Within each time step, the entire system nondeterministically carries out a number of transitions from a common overall configuration into its successors. This is done because a membrane might contain too few objects to satisfy all matching reaction and transportation rules. Here, all subsets of satisfied transitions are considered separately which can cause a combinatorial explosion of configurations in the worst case. By **monitoring the overall configurations** over time, a **derivation tree** is obtained that provides a comprehensive data pool for further analysis by backtracking. **Stable oscillations** appear as recurring, but nonadjacent overall configurations along a path through the derivation tree. The simple example shown below demonstrates a discrete view on a reaction system with resulting configurations by means of the **repressilator**, a synthetic biological oscillator based on gene regulation [4] whose dynamics is commonly modelled using Hill kinetics:



$$\begin{aligned}[\dot{\alpha}] &= 1 - \frac{[\gamma]^m}{[\gamma]^m + \Theta_\gamma^m} - k_\alpha[\alpha]\\ [\dot{\beta}] &= 1 - \frac{[\alpha]^m}{[\alpha]^m + \Theta_\alpha^m} - k_\beta[\beta]\\ [\dot{\gamma}] &= 1 - \frac{[\beta]^m}{[\beta]^m + \Theta_\beta^m} - k_\gamma[\gamma]\end{aligned}$$

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