Event-Driven Metamorphoses of P Systems

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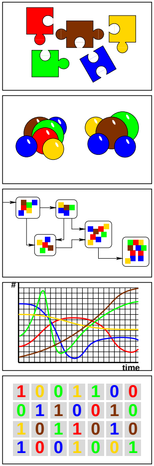
Outline

Event-Driven Metamorphoses of P Systems

- Motivation
- Mass-action kinetics
- P systems Π_{PMA}
- Transitions between P systems Π_{PMA}
- Example 1:
  Partially self-reproducible register machines
- Example 2:
  Artificial network evolution
- Outlook and acknowledgement



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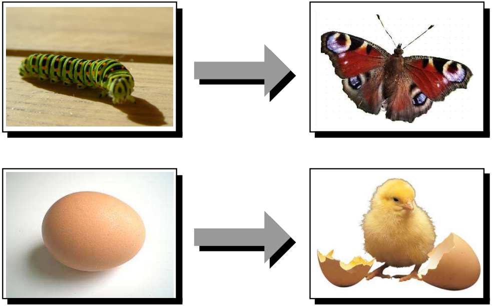
Plasticity = Structural Dynamics

Some biological examples

- Metamorphosis
- Mutational self-replication
- Population dynamics
- Synaptic plasticity
- Photosynthesis



Structure includes: set of reactions or behavioural rules

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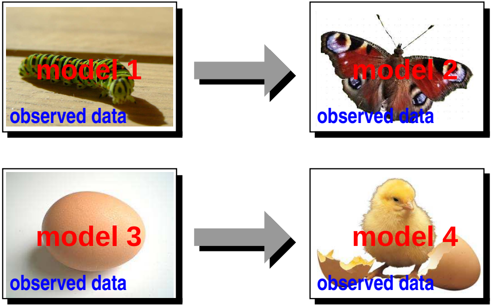

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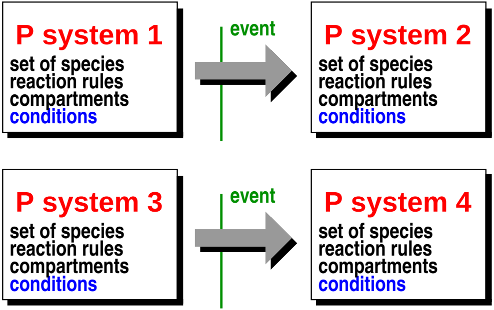

Structure includes: set of reactions or behavioural rules

Mass-Action Kinetics: Background

Modelling Temporal Behaviour of Chemical Reaction Networks

Assumption: number of effective reactant collisions Z proportional to reactant concentrations (Guldberg 1867)

$A + B \xrightarrow{\hat{k}} C$ .... $Z_C \sim [A]$ and $Z_C \sim [B]$, so

$$Z_C \sim [A] \cdot [B]$$

Production rate generating C:

$$v_{prod}([C]) = \hat{k} \cdot [A] \cdot [B]$$

Consumption rate of C: ...... $v_{cons}([C]) = 0$

$$\frac{d\,[C]}{d\,t} = v_{prod}([C]) - v_{cons}([C])$$

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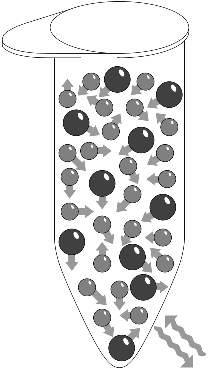
Initial conditions: $[C](0), [A](0), [B](0)$ to be set



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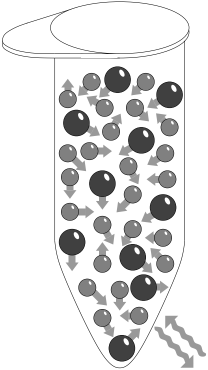

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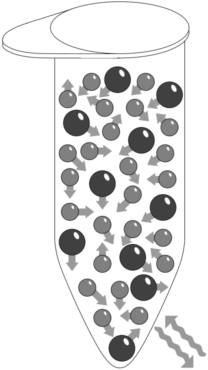

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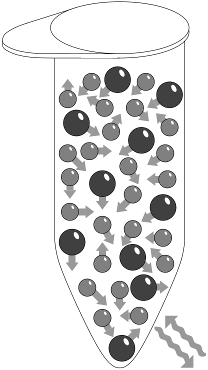

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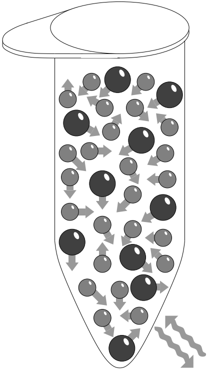

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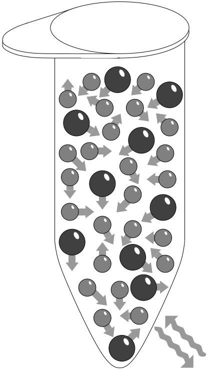


Mass-Action Kinetics: General ODE Model

Chemical reaction system

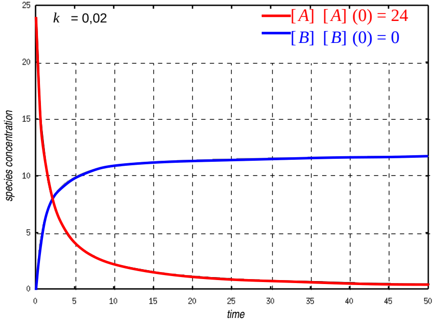
$$\begin{aligned}
a_{1,1}S_1 + a_{2,1}S_2 + \ldots + a_{n,1}S_n &\xrightarrow{\hat{k}_1} b_{1,1}S_1 + b_{2,1}S_2 + \ldots + b_{n,1}S_n \\
a_{1,2}S_1 + a_{2,2}S_2 + \ldots + a_{n,2}S_n &\xrightarrow{\hat{k}_2} b_{1,2}S_1 + b_{2,2}S_2 + \ldots + b_{n,2}S_n \\
&\vdots \\
a_{1,h}S_1 + a_{2,h}S_2 + \ldots + a_{n,h}S_n &\xrightarrow{\hat{k}_h} b_{1,h}S_1 + b_{2,h}S_2 + \ldots + b_{n,h}S_n,
\end{aligned}$$

results in ordinary differential equations

$$\frac{d\,[S_i]}{d\,t} = \sum_{\nu=1}^{h} \left(\hat{k}_\nu \cdot (b_{i,\nu} - a_{i,\nu}) \cdot \prod_{l=1}^{n} [S_l]^{a_{l,\nu}} \right) \quad \text{with} \quad i = 1, \ldots, n.$$

Mass-Action Kinetics: A Simple Example

$$2A + 0B \xrightarrow{\hat{k}_1} 0A + 1B$$



ODE system

$$\frac{d\,[A]}{d\,t} = -2 \cdot \hat{k}_1 \cdot [A]^2$$

$$\frac{d\,[B]}{d\,t} = \hat{k}_1 \cdot [A]^2$$

Analytic solution

$$[A](t) = \left(2\hat{k}_1 t + \frac{1}{[A](0)}\right)^{-1} \quad \text{iff} \quad [A](0) > 0 \quad \text{else} \quad [A](t) = 0$$

$$[B](t) = \left(-2\left(2\hat{k}_1 t + \frac{1}{[A](0)}\right)\right)^{-1} + \frac{[A](0)}{2} + [B](0)$$

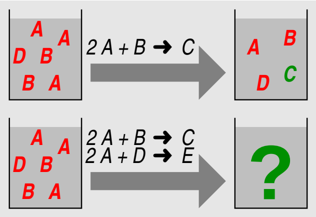
P Systems Π_{PMA}

Why?

- Allow coupling of systems in terms of system transitions
- Adopt systems description by reaction networks
- Discretise mass-action kinetics

Aspects considered for single system

- Suitability for small amounts of reacting particles (e.g. cell signalling)
- Compliance with mass conservance for undersatisfied reaction scenarios
- Determinism by strict prioritisation of rewriting rules
- Obtaining simple computational units
- Symbol objects
- Spatial globality in single well-stirred vessel



P Systems Π_{PMA}: Definition

$$\Pi_{\text{PMA}} = (V, \Sigma, [_1]_1, L_0, R)$$

- V .... system alphabet
- $\Sigma \subseteq V$ .... terminal alphabet
- $[_1]_1$ .... compartmental structure
- $L_0 \subset V \times (\mathbb{N} \cup \{\infty\})$ .... multiset for initial configuration
- $R = \{r_1, \ldots, r_h\}$ .... set of reaction rules

Each reaction rule r_i consists of two multisets and rate constant (reactants E_i, products P_i, k_i) such that

$$r_i = (\{(A_1, a_1), \ldots, (A_n, a_n)\}, \{(B_1, b_1), \ldots, (B_n, b_n)\}, k_i).$$

We write in chemical denotation:

$$r_i : a_1 A_1 + \ldots + a_n A_n \xrightarrow{k_i} b_1 B_1 + \ldots + b_n B_n$$

$\Longrightarrow$ Index i specifies priority of r_i: $r_1 > r_2 > \ldots > r_h$.

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$$r_i : a_1\,A_1 + \ldots + a_n\,A_n \xrightarrow{k_i} b_1\,B_1 + \ldots + b_n\,B_n$$

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P Systems Π_{PMA}: Discretised Mass-Action Kinetics

Mapping of rate constant $\hat{k}_i$ from ODE model

$$k_i = \frac{\hat{k}_i}{\mathrm{V}^{|E_i|}} \cdot \Delta t$$

with V: volume of reaction vessel, Δt: time discretisation interval

Considering reactions $r_1, \ldots, r_h$ consecutively
Iteration scheme for reaction $r_i = (E_i, P_i, k_i)$

$$\begin{aligned} L_{t,0} &= L_t \\ L_{t,i} &= L_{t,i-1} \ominus \{\text{multiplicity of reactant particles iff available}\} \\ &\qquad\quad \uplus \{\text{multiplicity of generated product particles}\} \\ L_{t+1} &= L_{t,h} \end{aligned}$$

Multiplicities depend on $L_{t,i-1}, E_i, P_i, k_i$

Transitions between P Systems Π_{PMA}

State transition system $\mathcal{A}$

- Each P system Π_{PMA} represents a state in $\mathcal{A}$
- State transitions in $\mathcal{A}$ initiated by triggering events with regard to time $(t = \tau)$ or species concentration as $([a] = \kappa)$

$\mathcal{A} = (Q, T, I, \Delta, F)$

$Q = \{\Pi^{(j)}_{\text{PMA}} \mid (j \in A) \wedge (A \subseteq \mathbb{N})\}$ ....states

$T \subseteq \{(t = \tau) \mid (\tau \in B) \wedge (B \subseteq \mathbb{N})\} \cup$ ....input alphabet

$\{([a]\ \text{cmp}\ \kappa) \mid (\kappa \in \mathbb{N}) \wedge (a \in V^{(j)}) \wedge$ ..cmp: $=, <, \leq, \ldots$

$(\Pi^{(j)}_{\text{PMA}} = (V^{(j)}, \Sigma^{(j)}, [_1]_1, L^{(j)}_0, R^{(j)}) \in Q) \wedge (j \in A)\}$

$I \subseteq Q$ ....initial states

$\Delta \subseteq Q \times T \times Q$ ....transition relation

$F \subseteq Q$ ....final states

Transitions between P Systems Π_{PMA}

P system transition $\Pi_{\text{PMA}}^{(j)} \overset{c}{\mapsto} \Pi_{\text{PMA}}^{(m)} \in \Delta$ in detail

From $\Pi_{\text{PMA}}^{(j)} = (V^{(j)}, \Sigma^{(j)}, [_1]_1, L_0^{(j)}, R^{(j)})$

To $\Pi_{\text{PMA}}^{(m)} = (V^{(m)}, \Sigma^{(m)}, [_1]_1, L_0^{(m)}, R^{(m)})$

Triggered by $c \in T$:

$$\begin{aligned}
V^{(m)} &= V^{(j)} \cup AdditionalSpeciesV_{(j,m)} \setminus VanishedSpeciesV_{(j,m)} \\
\Sigma^{(m)} &= \Sigma^{(j)} \cup AdditionalSpecies\Sigma_{(j,m)} \setminus VanishedSpecies\Sigma_{(j,m)} \\
L_0^{(m)} &= L_t^{(j)} \uplus \{(a,0) \mid a \in AdditionalSpeciesV_{(j,m)}\} \\
R^{(m)} &= R^{(j)} \uplus AdditionalReactions_{(j,m)} \ominus VanishedReactions_{(j,m)}
\end{aligned}$$

Re-prioritisation of reaction rules if necessary

Example 1

Chemical register machine (RAM) with self-reproducible components

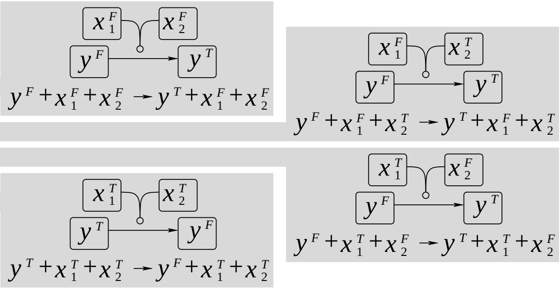
- Construction of chemical reaction networks for boolean logic gates
- Introduction of a chemical clock by oscillating reactions
- Specification of a chemical master-slave flip-flop (MSFF)
- Utilise chemical master-slave flip-flop as 1-bit storage unit (initial register)
- Extend registers if needed by integration of further 1-bit storage units (self-replicable components)
- Transform register machine program into chemical program control (INC, DEC, IFZ, HALT)
- Sequential as well as parallelised register machine chemistry

Chemical Implementation of Boolean Variables and Logic Gates

Chemical reaction network for NAND

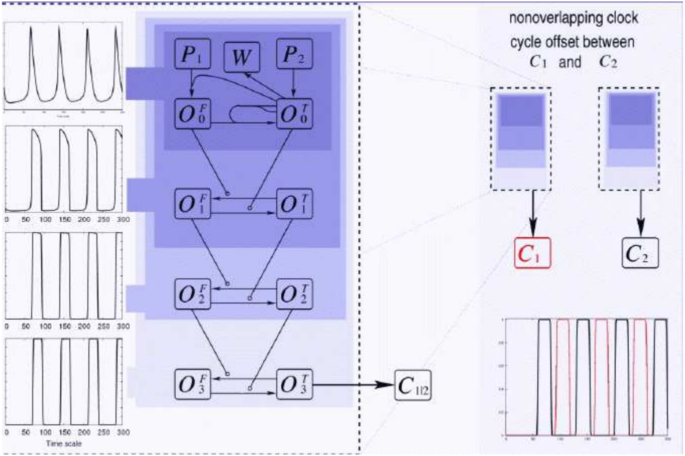
Boolean variable z represented by two correlated species Z^T and Z^F

x_1	x_2	y
0	0	1
0	1	1
1	0	1
1	1	0



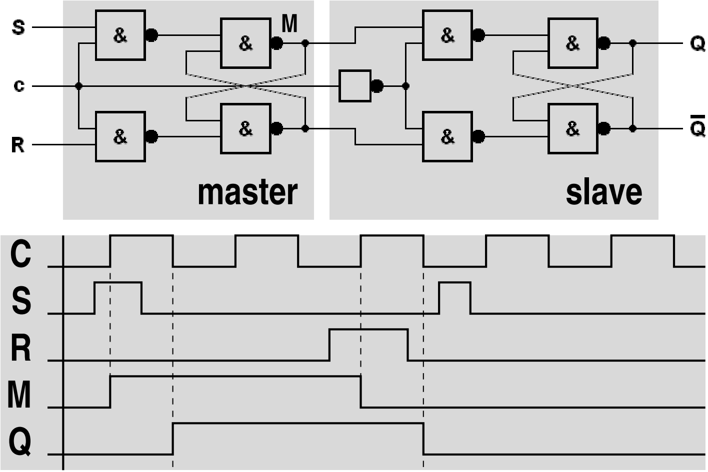
A Chemical Clock

- Based on Belousov-Zhabotinsky reactions
- Cascade of auxiliary reactions for fast-switching behaviour
- Two offset oscillators provide clock signals $[C_1]$ and $[C_2]$



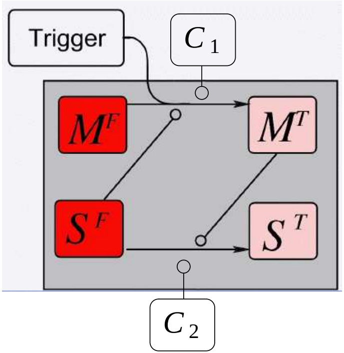
Master-Slave Flip-Flop

Reliable 1-bit storage unit, well-studied



Chemical MSFF Implementation

Two-stage switching from **FALSE** to **TRUE** using trigger species and offset clocks C_1 and C_2



species M^F, M^T: master bit value
species S^F, S^T: slave bit value

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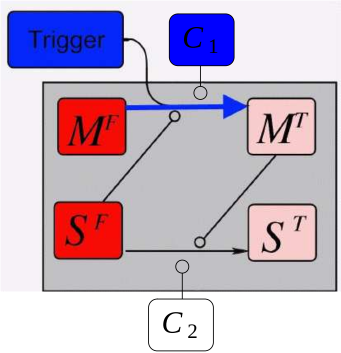

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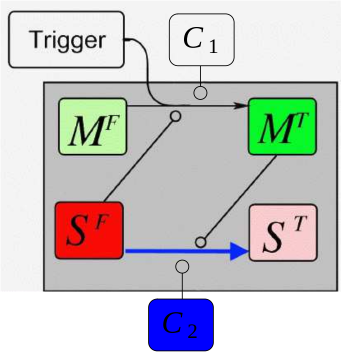

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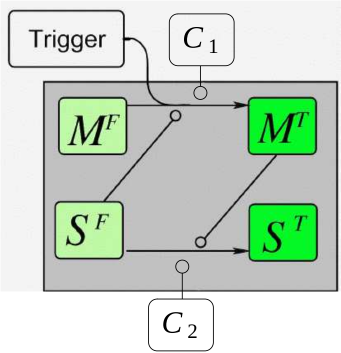

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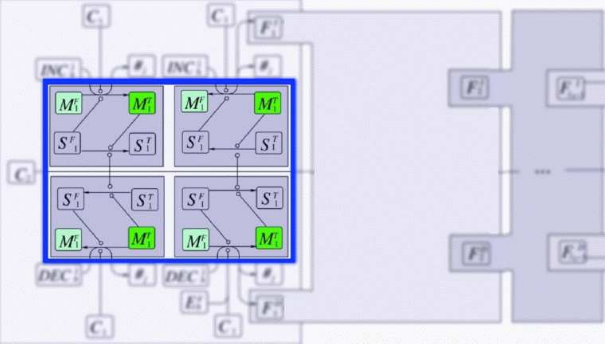
From MSFF to Register

- Four network motifs (all switching scenarios) form MSFF
- Chaining of MSFFs to build register of arbitrary length
- Assumption of MSFF as self-replicable modular unit



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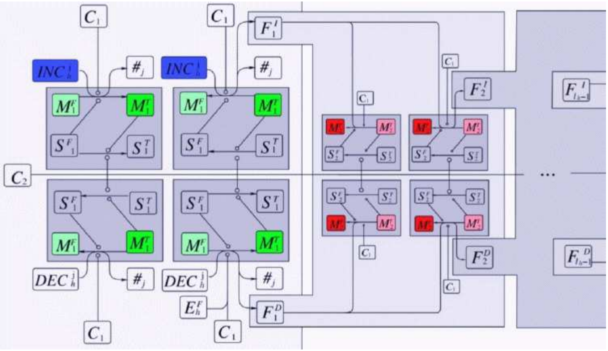

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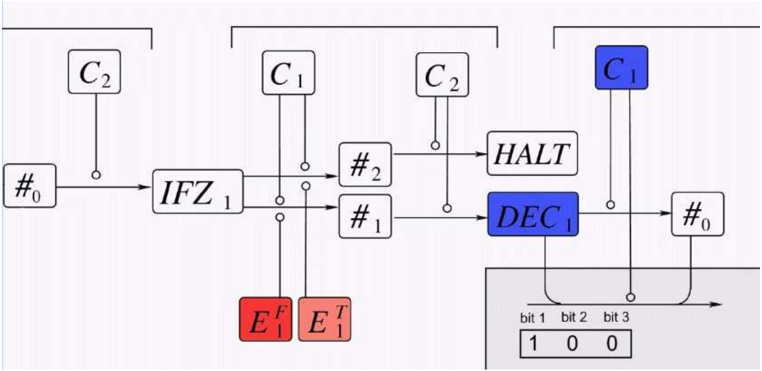
Chemical Program Control

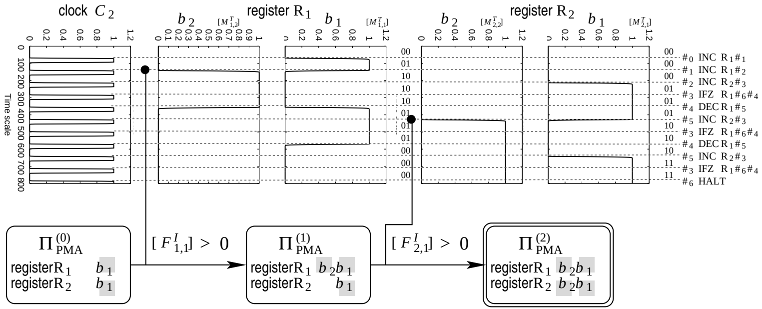
Simple example for sequential instruction flow:

$\#_0$: IFZ R_1 $\#_2$ $\#_1$
$\#_1$: DEC R_1 $\#_0$
$\#_2$: HALT



Simulation: Adding Binary Numbers

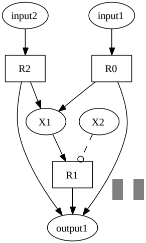
- Denotation of register machine by P systems Π_{PMA}
- Dynamical network behaviour emulates computation
- Stepwise extension of registers: system transitions
- Simulation carried out using CellDesigner (SBML)

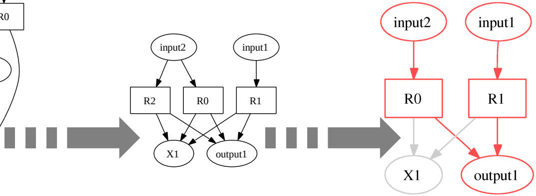


Example 2: Artificial Network Evolution

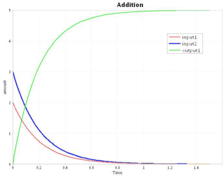
Task: addition of two positive real numbers

snapshots of artificial network evolution





- **R0**, **R1**, **R2** identify reactions
- **input1**, **input2**, **output1**: distinguished species
- **X1**, **X2**: auxiliary species
- Stepwise modification of network structure and kinetic parameters



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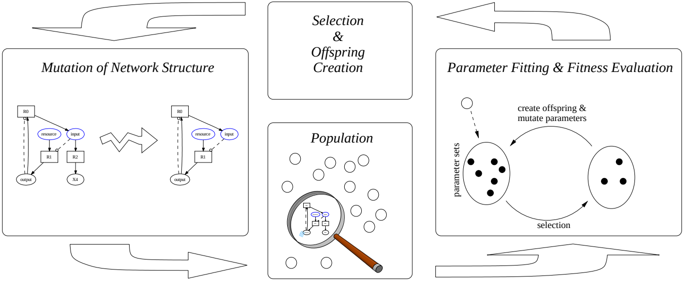
Two-Level Evolutionary Algorithm

- Separation of structural evolution from parameter fitting
- Idea: parameters can adapt to mutated network structure



- Upper level: network structure, analogue to graph-GP
- Lower level: parameter fitting using standard Evolution Strategy

⟹ All networks handled as SBML models

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Evolutionary Operators and Parameterisation

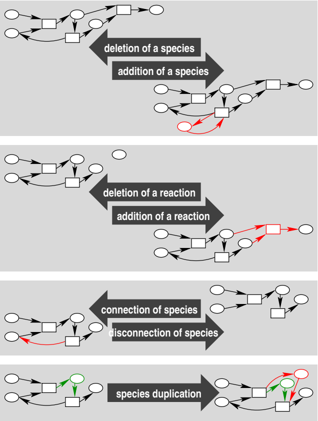
EA used here employs eight different mutations

Operators for structural evolution

- Addition/deletion of a species
- Addition/deletion of a reaction
- Connection/removal of an existing species to/from a reaction
- Duplication of a species with all its reactions (discussed in detail later)

Operator for parameter evolution

- Mutation of a randomly selected kinetic parameter by addition of a Gaussian variable



Further information on SBMLevolver software: www.esignet.net

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Outlook

Take home message

- Coordination of temporally local subsystems into common framework requires homogeneous approach
- P systems suit here: discreteness, combine different levels of abstraction
- Exploring structural dynamics in Systems Biology
- Understand/predict functionality of complex dynamical systems as a whole beyond molecular computing

Further work

- Comprise P systems of (selected) different classes and with compartmental structures into common transition framework

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Evolving Cell Signalling Networks *in silico*

European interdisciplinary research project

- University of Birmingham (Computer Science)
- TU Eindhoven (Biomedical Engineering)
- Dublin City University (Artificial Life Lab)
- University of Jena (Bio Systems Analysis)

SIXTH FRAMEWORK PROGRAMME

Objectives

- Study the computational properties of bionetworks
- Develop new ways to model and predict real bionetworks
- Gain new theoretical perspectives on real bionetworks

Computing facilities

- Cluster of 33 workstations
  (two Dual Core AMD Opteron™ 270 processors)

ESIGNET

Our Team for Bio Systems Analysis in Jena

Peter Dittrich (PI)

Thomas Hinze (PostDoc)

Gerd Grünert (PhD student)
Bashar Ibrahim (PhD student)
Thorsten Lenser (PhD student)
Naoki Matsumaru (PhD student)
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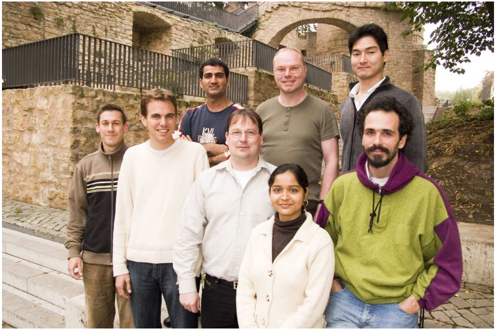
Franz Carlsen (research assistant)
Raffael Faßler (research assistant)
Christoph Kaleta (research assist.)
Stephan Richter (research assist.)



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Thank you for your attention. Questions? Remarks?

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