Computation by Synthetic Cell Signaling and Oscillating Processes Modelled using Mass-Action Kinetics

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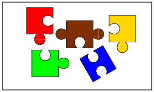
Mol.Biol.of Centrosomes & Cilia

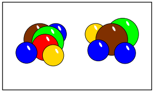
Computability in Europe
(CiE 2009)

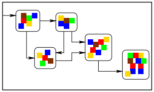
Outline

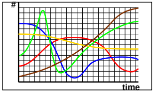
Computation by Synthetic Cell Signaling

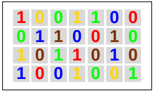
1. Motivation
2. Chemical information processing: Cell signaling
3. Mass-action kinetics
4. Deterministic register machine (RAM)
5. Chemical RAM representation
   - Clock
   - Master-slave flip-flops
   - Registers
   - Program control
6. Example 1: Integer addition
7. Example 2: Maximum of three nat. numbers
8. Outlook and acknowledgement











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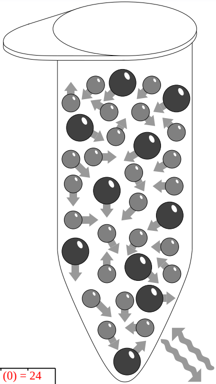
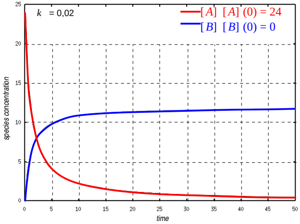
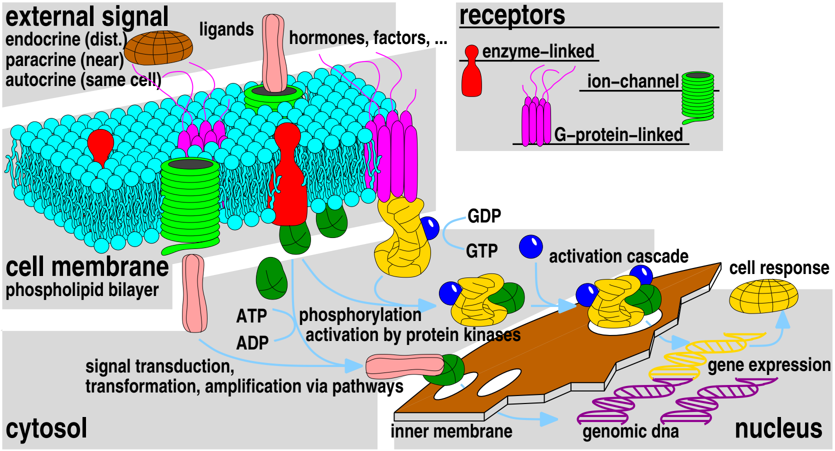
Motivation

- Chemical/Molecular computing
- Potential high capacity and density of molecular data storage
- Exploring similarities to biological information processing
- Identification of computational units in biological systems
- Artificial evolution of reaction networks towards specific tasks

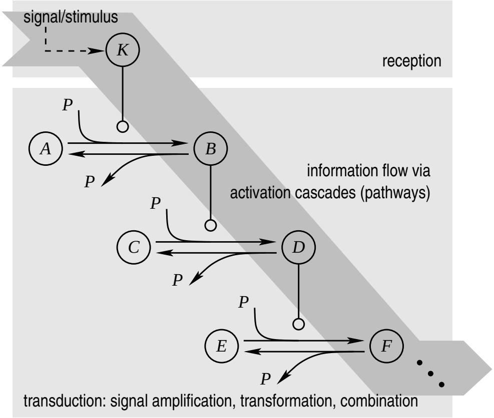




Biological Principles of Cell Signaling

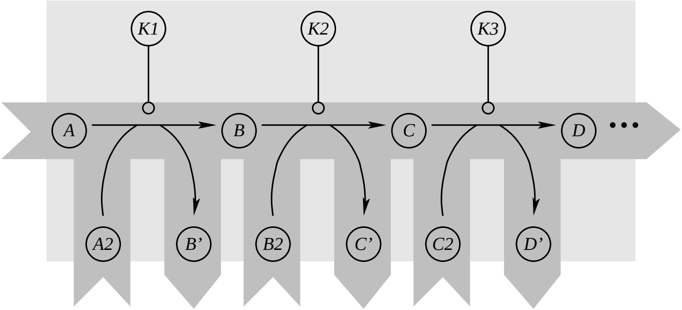


Typical Information Flow in Cell Signaling



- Motif: stepwise protein activation by phosphorylation
- Cascadization of motifs for signal transduction, amplification, transformation, combination

Typical Information Flow in Metabolic Networks



- Sequence of catalyzed reactions
- Reactants and products usually not acting as catalysts

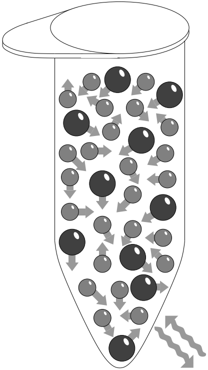
Mass-Action Kinetics: Background

Modeling Temporal Behavior 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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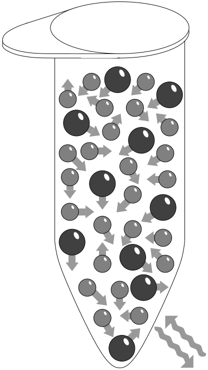

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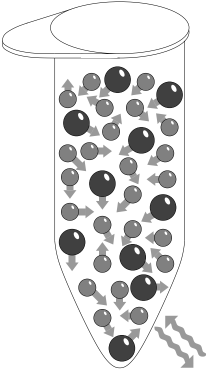

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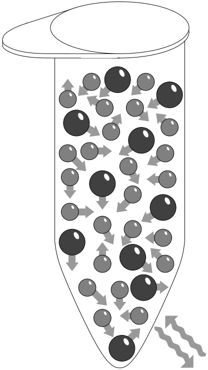

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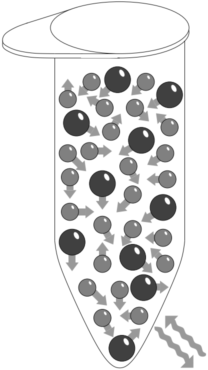

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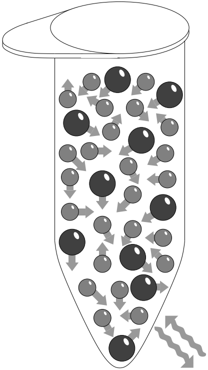

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Mass-Action Kinetics: General ODE Model

Chemical reaction system

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

results in ordinary differential equations

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

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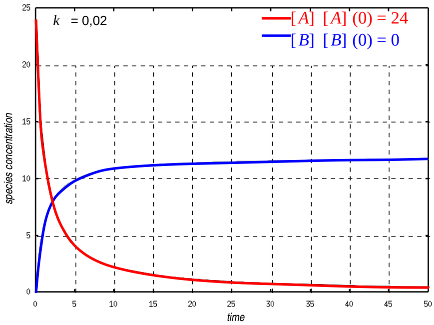
Mass-Action Kinetics: A Simple Example

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



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

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

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

T. Hinze, M. Sturm. Rechnen mit DNA. ISBN 978-3-486-27530-5, Oldenbourg Wissenschaftsverlag, 2004

Register Machine (RAM)

- Syntactical denotation of components
  $RAM = (R, L, P, \#_0)$
  - $\#_0$: jump label of first instruction
  - P: program (finite set of instructions)
  - L: finite set of jump labels $L = \{\#_0, \ldots, \#_n\}$
  - R: finite set of registers $R = \{\mathrm{R}_1, \ldots, \mathrm{R}_m\}$, $\mathrm{R}_k \in \mathbb{N}$
- Available instructions
  - $\#_i$: INC R_k $\#_j$ — increment register R_k, jump to $\#_j$
  - $\#_i$: DEC R_k $\#_j$ — decrement register R_k, jump to $\#_j$
  - $\#_i$: IFZ R_k $\#_j$ $\#_p$ — if $\mathrm{R}_k = 0$ jump to $\#_j$ else jump to $\#_p$
  - $\#_i$: HALT — terminate program and output
- Useful assumptions
  - Consecutive indexing of jump labels and registers
  - Determinism
  - Initialization of registers at start
  - Output of all m registers when HALT

Chemical RAM with Self-Reproducible Components

1. Construction of chemical reaction networks for boolean logic gates
2. Introduction of a chemical clock based on oscillating reactions
3. Specification of a chemical master-slave flip-flop (MSFF)
4. Utilize chemical master-slave flip-flop as 1-bit storage unit (initial register)
5. Extend registers if needed by integration of further 1-bit storage units (self-replicable components)
6. Transform register machine program into chemical program control (INC, DEC, IFZ, HALT)

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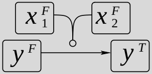
Chemical Implementation of Boolean Variables and Logic Gates

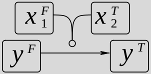
Boolean variable z represented by
two correlated species Z^T and Z^F

Chemical reaction network for NAND

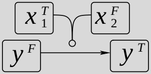
x_1	x_2	y
0	0	1
0	1	1
1	0	1
1	1	0



$$y^F + x_1^F + x_2^F \rightarrow y^T + x_1^F + x_2^F$$



$$y^F + x_1^F + x_2^T \rightarrow y^T + x_1^F + x_2^T$$



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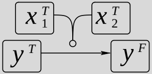

$$y^T + x_1^T + x_2^T \rightarrow y^F + x_1^T + x_2^T$$

T. Hinze, R. Fassler, T. Lenser, P. Dittrich. Register Machine Computations on Binary Numbers by Oscillating and Catalytic Chemical Reactions Modelled using Mass-Action Kinetics. International Journal of Foundations of Computer Science 20(3):411-426, 2009

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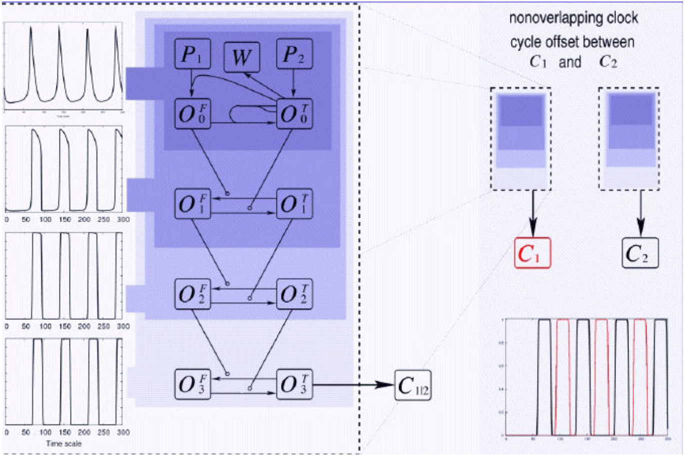
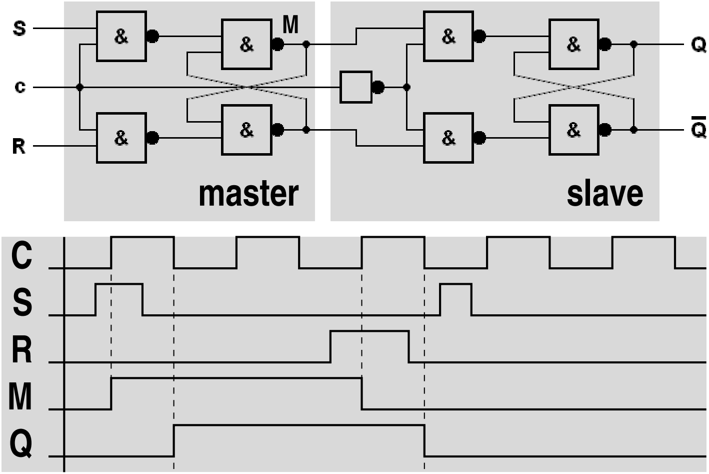
A Chemical Clock

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



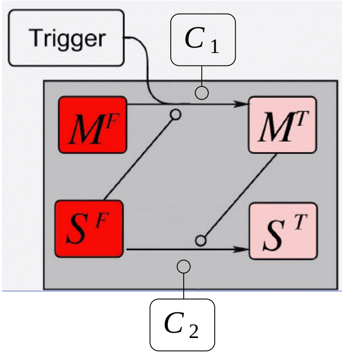
Master-Slave Flip-Flop (MSFF)

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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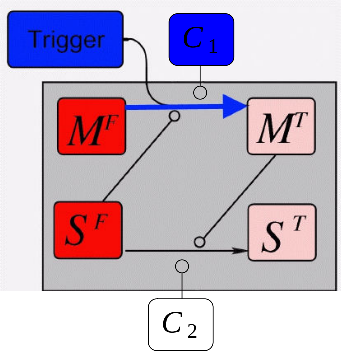

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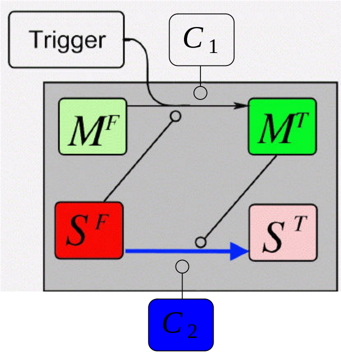

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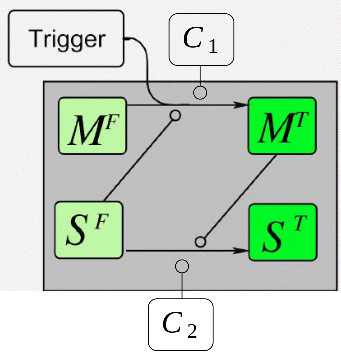

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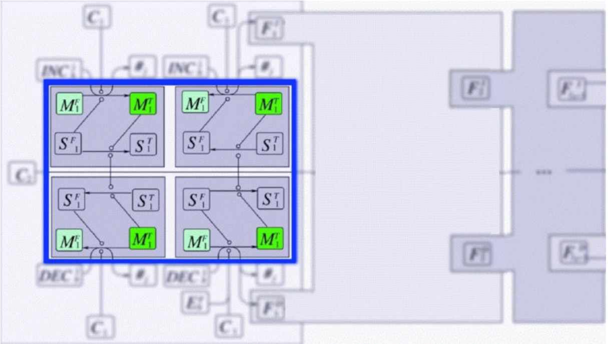
From MSFF to Register

- 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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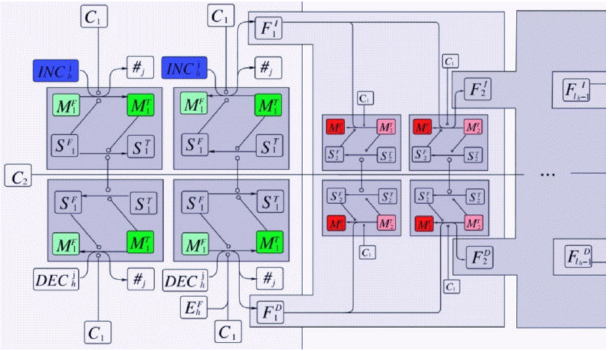


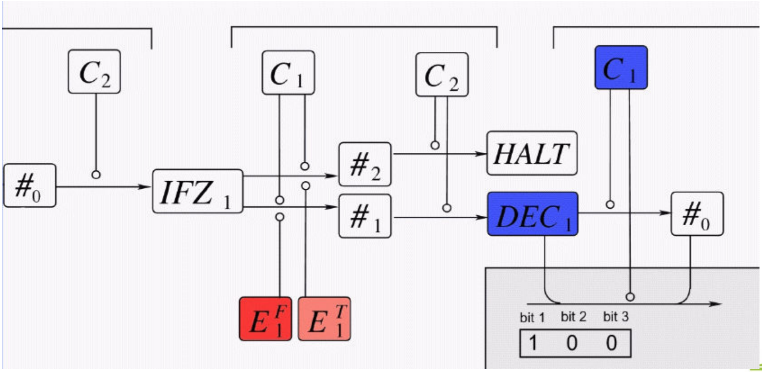
Chemical Program Control

Simple example for sequential instruction flow:

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

$\#_1$: DEC R_1 $\#_0$

$\#_2$: HALT



Chemical Program Control

Transformation scheme

instruction	reactions
$\#_i$: INC R_h $\#_j$	$\#_i + C_2 \xrightarrow{k_\mathrm{p}} INC_h^j + C_2$ $INC_h^j + C_1 \xrightarrow{k_\mathrm{b}} \#_j + C_1$
$\#_i$: DEC R_h $\#_j$	$\#_i + C_2 \xrightarrow{k_\mathrm{p}} DEC_h^j + C_2$ $DEC_h^j + C_1 \xrightarrow{k_\mathrm{b}} \#_j + C_1$
$\#_i$: IFZ R_h $\#_j$ $\#_q$	$\#_i + C_2 \xrightarrow{k_\mathrm{p}} IFZ_h^{j,q} + C_2$ $IFZ_h^{j,q} + E_h^T + C_1 \xrightarrow{k_\mathrm{s}} \#_j + E_h^T + C_1$ $IFZ_h^{j,q} + E_h^F + C_1 \xrightarrow{k_\mathrm{s}} \#_q + E_h^F + C_1$
$\#_i$: HALT	$\#_i + C_2 \xrightarrow{k_\mathrm{p}} HALT + C_2$

C_1, C_2: Species providing offset clock signals

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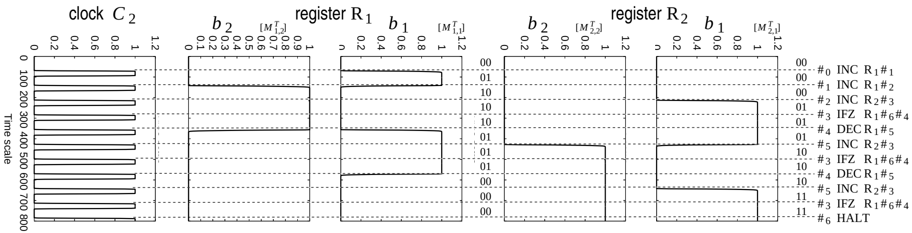
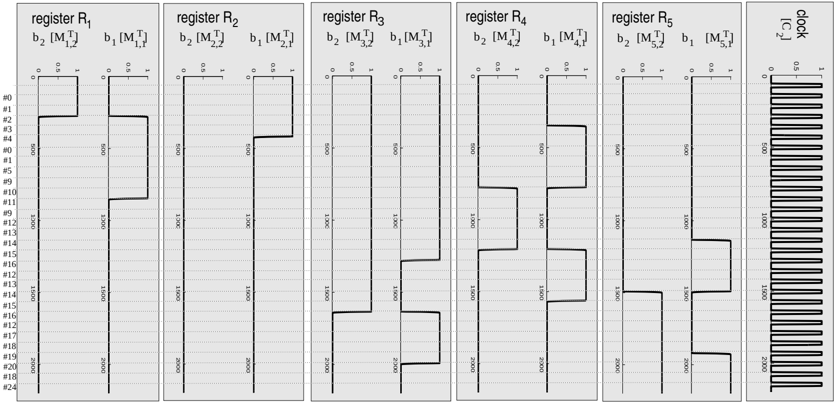
Example 1: Integer Addition “2 + 1"

- Initialization of registers R_1 and R_2 with summands
- $\mathrm{R}_2 := \mathrm{R}_2 + \mathrm{R}_1;\ \mathrm{R}_1 := 0$
- Bitwise extension of registers if needed
- Simulation carried out using CellDesigner (SBML)



Example 2: Maximum of Three Numbers "$\max(2, 1, 3)$"

- $R_5 := \max(R_1, R_2, R_3)$
- Idea: $R_4 := \max(R_1, R_2)$; $R_5 := \max(R_4, R_3)$
- Full network: 142 species and 223 reactions in total



R. Fassler, T. Hinze, T. Lenser, P. Dittrich. Construction of Oscillating Chemical Register Machines on Binary Numbers using Mass-Action Kinetics. In O.H. Ibarra, P. Sosik (Eds.), Proceedings PIWMC2008 in conjunction with DNA14, ISBN 978-80-7248-468-3, pp. 11-22, Silesian University Press, 2008

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Outlook

Take home message

- Pure chemical computers with self-reproducible components can reach Turing-completeness
- Oscillatory processes as universal clock generators
- Digital (based on two correlated species) vs. analog (concentration-based) encoding of data
- Chemical RAM: Framework for providing network prototypes with dedicated functionality for comparative studies (reverse engineering)

Further work

- Parallelization of chemical RAM following CREW strategy for memory access

Special Thanks go to . . .

... my coworkers

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Bio Systems Analysis Group, FSU Jena

Raffael Faßler
Department Bioinformatics, FSU Jena

Bashar Ibrahim
German Cancer Research Center

Stefan Schuster
Department Bioinformatics, FSU Jena

... the funding organization

German Federal Ministry of Education and Research, project 0315260A within Research Initiative in Systems Biology

Bundesministerium für Bildung und Forschung

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... you for your attention. Questions?