Chemical Organization Theory

How are living systems organized?

How do they evolve?

Peter Dittrich
Bio Systems Analysis Group
FSU Jena
Bio Systems Analysis Group

Use computational approaches to explain complex *dynamical* phenomena found in living systems

- **ESIGNET – Evolving Cell Signalling Networks *in silico***
  (T. Hinze, T. Lenser, EU)

- **Chemical Network Theory and Simulation***
  (P. Speroni d.F., F. Cenler, BMBF)

- **Systems Analysis of the Cell Cycle***
  (B. Ibrahim, DAAD)

- **Organic Computing: Chemical Programming***
  (N. Matsumaru, DFG)

- **Semantics of Biological Models***
  (Ch. Knüpfer, RLS)

- **Autonomous Experimentation***
  (N. Matsumaru, BMBF)
How is life (and its origin) organized?

1. What is the bio-chemical organization of an organism?

2. How did the bio-chemical organization of the pre-prebiotic soup evolved?
Quality (not quantity)
Q1

How does the lattice of organizations of an organism looks like?

lattice of organizations = organizational structure
What is an answer?

Reaction Systems
Example Level IV: Catalytic Flow System
Example Level IV:
Catalytic Flow System

\[
\begin{align*}
&+ \rightarrow + \\
&+ \rightarrow \\
\end{align*}
\]
(catalytic)
Example Level IV:
Catalytic Flow System

\[ \text{(catalytic)} \]
Example Level IV: Catalytic Flow System

(catalytic)
Example Level IV: Catalytic Flow System

\[ \frac{dx_1}{dt} = k_2 x_2 x_2 \]
\[ \frac{dx_2}{dt} = k_1 x_1 x_2 \]
Example Level IV: Catalytic Flow System

```
\[ \frac{dx_1}{dt} = k_2 x_2 x - x_1 \Phi \]
\[ \frac{dx_2}{dt} = k_1 x_1 x_2 - x_2 \Phi \]
```

dilution flux $\Phi$

"reaction network"
Chemical Organization Theory
"Chemical Organization"

Organization :=

a set of molecules that is
(algebraically) closed and
self-maintaining

There is no reaction producing
any other molecules
than the member of the set.

Within the set, all molecules
consumed by a reaction
can be reproduced by a reaction.

[Speroni di Fenizio/Dittrich (2005/7)
inspired by Fontana, Buss, Rössler, Eigen, Kauffman, Maturana, Varela, Uribe]
Fixed Point and Organization

**Theorem**

Given a fixed point of the ODE describing the dynamics of a reaction system, then the set of molecules represented by that fixed point is an organization.

[Dittrich/Speroni di Fenizio, (2005,2007)]
Practical View

Reaction network

Chemical Organization Theory

Organization
All Organizations

Chemical Organization Theory

Reaction network

Organizations

Organization
Lattice of Organizations

Hasse diagram of the organizations

Reaction network

Chemical Organization Theory

Organizations
Generate Organization

Chemical Organization Theory

Reaction network

G_O({3, 4}) = ?

Hasse diagram of the organizations

{1, 2, 3, 4}

{1}

{2, 3}

{}
Generate Organization

Chemical Organization Theory

\[ G_{\text{Org}}(\{3, 4\}) = \{1\} \]

Hasse diagram of the organizations

Organizations

Reaction network

„generate organization“
Union of Organizations

Hasse diagram of the organizations

Chemical Organization Theory

"generate organization"

G_{Org}(\{3, 4\}) = \{1\}

\{1\} \cup O \{2, 3\} := G_{Org}(\{1\} \cup \{2, 3\})

"union of organizations"
Self-maintenance

• Organization :=
  closed & self-maintaining
  set of (molecular) species
**Example 1**

\[ a + b \rightarrow 2b \]
\[ a + c \rightarrow 2c \]
\[ b \rightarrow d \]
\[ c \rightarrow d \]
\[ b + c \rightarrow e \]
\[ \rightarrow a \]
Example 1

Organization \{a, b, d\}
Example 1

Organization \{a, b, d\}
Example 1

Organization \{a, b, d\}

1. Find flux vector

outside of org. = 0
Example 1

Organization \{a, b, d\}

1. Find flux vector

outside of org. = 0
inside of org. > 0
Example 1

Organization \{a, b, d\}

1. Find flux vector
   \[\text{outside of org.} = 0\]
   \[\text{inside of org.} > 0\]

2. Check production rates
   \[\text{outside of org.} = 0 \text{ (closure)}\]
Example 1

Organization \{a, b, d\}

1. Find flux vector
   outside of org. = 0
   inside of org. > 0

2. Check production rates
   outside of org. = 0 (closure)
   inside of org. $\geq 0$ (self-maint.)
Example 1

All Organizationen
Example 1

All Organizationen
Example 1

All Organizationen

Diagram showing connections between nodes labeled a, b, c, d, and e.
Example 1

All Organizationen

Diagram showing relationships between entities a, b, c, d, and e.
Example 1

Hasse diagram of organizations
"Überlappende Hierarchie"
Theorem: Fixed points are instances of organizations

\[ \dot{x} = f(x) \quad x = \begin{pmatrix} a \\ b \\ c \\ d \\ e \end{pmatrix} \]

fixed point / (stationary solution)

\[ 0 = f(x^0) \quad x^0 = \begin{pmatrix} 4 \\ 7 \\ 0 \\ 11 \\ 0 \end{pmatrix} \]

{ a, b, d }
How does the lattice of organizations of an organism looks like?

organizational structure = lattice of organizations
Trivially, all organisms have at least one organization

\[ S + O \rightarrow 2O + W \]

\{S, O, W\}

\{S\}
Is there more?

\[ S + O_1 \xrightarrow{\text{à}} 2O_1 + W \]
\[ S + O_2 \xrightarrow{\text{à}} 2O_2 + W \]
\[ \text{à S} \]
\[ \text{à Oà} \]
\[ \text{à Wà} \]
Is there more?

\[ S + O_1 \rightarrow 2O_1 + W \]
\[ S + O_1 + O_2 \rightarrow 2O_2 + W \]
\[ \rightarrow S \]
\[ \rightarrow O \]
\[ \rightarrow W \]
How does the lattice organizations in an organism looks like?

- number?
- height?
- size distribution?
We looked at a couple of network models of “real” systems

• photochemistries  
  (dead, closed but not isolated systems)
• metabolism
• regulated metabolism
• lambda-phage
• HIV - immunesystem
Population Dynamics

HIV Immunesystem Model
Test-bed: HIV Virus Dynamics

simulation model of HIV replication (4 ODEs)

\[ \frac{dx}{dt} = \lambda - dx - \beta xy \]
\[ \frac{dy}{dt} = \beta xy - ay - pyz \]
\[ \frac{dz}{dt} = cxyw - cqyw - bw \]
\[ \frac{w}{dt} = cqyw - hw \]

\[ \lambda, \beta, a, p, c, b, h \]

uninfected CD4+ T cells → infected CD4+ T cells → CTL precursors → CTL effectors

CTL = cytotoxic T lymphocytes

[Wodarz/Nowak, PNAS 96:14464,1999]
HIV Dynamics: Mathematical analysis

HIV Dynamics Graphs:

- Immune system destroyed
- Virus defeated

- CD4+ T cell
- Infected CD4+ T cell
- CTL precursors
- CTL effectors

Time (days) vs. Concentration (arbitrary units)
HIV – Immunsystem Populationsmodell

Modell nach: C.D. Wodarz, M. A. Nowak, PNAS 96 (1999), 14464-13369
HIV – Immunsystem Populationsmodell

T-Zelle + infizierte-T-Zelle à 2 infizierte-T-Zelle

Modell nach: C.D. Wodarz, M. A. Nowak, PNAS 96 (1999), 14464-13369
HIV – Immunsystem Populationsmodell

T-Zelle + infizierte T-Zelle + CTL-Pre \rightarrow T-Zelle + infizierte T-Zelle + 2 CTL-Pre

Modell nach: C.D. Wodarz, M. A. Nowak, PNAS 96 (1999), 14464-13369
HIV – Immunsystem Populationsmodell

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HIV - Immunsystem Populationsmodell

Modell nach: C.D. Wodarz, M. A. Nowak, PNAS 96 (1999), 14464-13369
Organisation := abgeschlossen und selbsterhaltend

Organisation := (algebraisch) abgeschlossene und selbsterhaltende Molekülmenge

Alle Organisationen

Organisationshierarchie


Explain medication strategy ...

- Medication strategy

Organisationsstruktur

{ T-Zelle, infizierte T-Zelle, CTL-Pre, CTL-Ef }

{ T-Zelle, infizierte T-Zelle }

{ T-Zelle }

## Compare models

<table>
<thead>
<tr>
<th>ODE Model</th>
<th>Reaction Network Model</th>
<th>Organizational Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>D: (D. S. Callaway, A. S. Perelson: Bull. Math. Biol. 64 (2002), 29–64.)</td>
<td>( \phi \to Q ) ( Q \to \phi ) ( x \to \phi ) ( y \to \phi ) ( v \to \phi ) ( x + v \to y + v ) ( y \to y + N_T v ) ( Q + v \to s x + v ) ( Q + B \to s x + B )</td>
<td>{Q,x,y,v,B}</td>
</tr>
<tr>
<td>( Q = \xi - \theta(v + B)Q ) ( \dot{x} = s\theta(v + B)Q - dx ) ( -(1 - \kappa)\beta x v ) ( \dot{y} = (1 - \kappa)\beta x v - ay ) ( \dot{v} = N_T \delta y - uv )</td>
<td>( P = 1 - \eta ) ( \phi \to x ) ( x \to \phi ) ( v_I \to \phi ) ( v_{NI} \to \phi ) ( x + v_I \to y + v_I ) ( y \to y + v_I )</td>
<td>{Q,x,B} {Q,x,y,v} {Q}</td>
</tr>
<tr>
<td>E: (A.S. Perelson, et al.: Science 271, 5255 (1996), 1582–1586.)</td>
<td>( \dot{x} = \lambda - dx - (1 - \kappa)kv_I x ) ( \dot{y} = (1 - \kappa)kv_I x - \delta y ) ( \dot{v}<em>I = (1 - \eta)N_T \delta x - cv_I ) ( \dot{v}</em>{NI} = \eta N_T \delta y - cv_{NI} )</td>
<td>0 ( \leq \kappa &lt; 1, 0 &lt; \eta &lt; 1 ) ( {x,y,v_I,v_{NI}} ) {x}</td>
</tr>
</tbody>
</table>

- N. Matsumaru, F. Centler, P. Speroni di Fenizio, P. Dittrich (2006); *it - Information Technology*, 48(3):1-9,
Evaluate model quality

Application of Organization Theory to Planetary Photochemistries

Mars

31 molecular species, 103 reactions

main component: CO₂ (95%)

http://www.fpsoftlab.com/images/screenshots/mars-640x480-1.jpg

Y. L. Yung and W. B. DeMore (1999)
Photochemistry of Planetary Atmospheres, Oxford University Press
Mars - Reaction Network File

... 
1 CO2 1 hv -> 1 CO 1 O  
2 O -> 1 O2  
1 O 1 O2 1 N2 -> 1 O3 1 N2  
1 O 1 O2 1 CO2 -> 1 O3 1 CO2  
1 O 1 O3 -> 2 O2  
1 O 1 CO -> 1 CO2  
1 O(1D) 1 O2 -> 1 O 1 O2  
1 O(1D) 1 O3 -> 2 O2  
1 O(1D) 1 O3 -> 1 O2 2 O  
1 O(1D) 1 H2 -> 1 H 1 OH  
1 O(1D) 1 CO2 -> 1 O 1 CO2  
1 O(1D) 1 H2O -> 2 OH  
2 H -> 1 H2  
1 H 1 O2 -> 1 HO2  
1 H 1 O3 -> 1 OH 1 O2  
1 H 1 HO2 -> 2 OH  
1 H 1 HO2 -> 1 H2 1 O2  
1 H 1 HO2 -> 1 H2O 1 O  
1 O 1 H2 -> 1 OH 1 H  
1 O 1 OH -> 1 O2 1 H  
...
Mars at Night

13 molecules
Mars at Daytime
Distribution of Organizations

Dayside

Nightside

Number of Organizations

Size (molecular species)
Randomizing the Network at daytime

A

Organizations (connected), mean of 50 runs

Number of Organizations

2 3 4 5 6 7 8

Permutations

0 20 40 60 80 100
How does the lattice of organizations of an organism look like?
Metabolic Models

- network from Palsson et al (?)
- analysis by C. Kaleta 2006
E. Coli Metabolism Model
E. coli Model (III)

synthesis of some dNTPs

lipid synthesis

ACP or hmrsACP

pyrimidine nucleotide synthesis

q8 (quinone)

central metabolism+

Minimal growth scenario:
D-Glucose, O₂, Fe₂⁺, NH₄⁺, H⁺, Pi, SO₄

analysis by C. Kaleta, F. Centler, 2006
E. coli Model (II) – Regulated Network

- Palsson/Covert
- Organization theory is able to predict growth phenotypes of various mutants quite nicely
- But the organizational structure is simple

\{S, O, W\}

- C. Kaleta, F. Centler, P. Speroni di Fenizio, P. Dittrich (2007), submitted
Overview

• Chemical Evolution

• Organizations in Space

• Chemical Information Processing and Chemical Programming
How did the bio-chemical organization of the pre-prebiotic soup evolved?

What is the characteristics of the organizational evolution? upward? downward? ...
A View of Chemical Evolution

\[ \cdot \quad X^g \quad \overset{\text{in the state space}}{\rightarrow} \quad X^{g+1} \quad \cdot \]

(actual evolution)
Actual Evolution

\[ \mathbf{X}_g \xrightarrow{\text{in the state space}} \mathbf{X}_{g+1} \]  
(Actual evolution)
Actual Evolution

\[ X_g \xrightarrow{\text{in the state space}} X_{g+1} \]

(actual evolution)
Actual Evolution

vs.

Organizational Evolution
Organizational Evolution

Movement in the set of organizations
(organizational evolution)

Movement in the state space
(actual evolution)
Organizational Evolution

1. Upwards \([t_1 \rightarrow t_2]\)  
   \[O_{t_1} \subset O_{t_2}\]

Hasse diagram of organizations

Organizations

Dynamics
Organizational Evolution

1. Upwards \([t_1 \rightarrow t_2]\) \(O_{t_1} \subseteq O_{t_2}\)

2. Downwards \([t_2 \rightarrow t_3]\) \(O_{t_2} \supseteq O_{t_3}\)

Hasse diagram of organizations

Organizations

Dynamics
Organizational Evolution

1. Upwards \([t_1 \rightarrow t_2]\) 
   \[O_{t_1} \subset O_{t_2}\]

2. Downwards \([t_2 \rightarrow t_3]\)
   \[O_{t_2} \supset O_{t_3}\]

3. Sidewards \([t_1 \rightarrow t_3]\)
   otherwise

A set of existing species and an organization are not equivalent. e.g., \{2,3,4\}
Theoretical vs. Practical

• Theoretically:
  – Every possible species is known.
  – Entire reaction network is given.
  → Every possible organization can be calculated.
  → It is possible to define the dynamics on the ODE

• Practically:
  – **NOT** every possible species is known.
  – the entire network is **NOT** given.
  → **NOT** every possible organization can be calculated.
Perspective Change

Hasse diagram of the organizations

Organizations

Dynamics

t1 t2 t3
Perspective Change

Dynamics
Downward movement
Upward Movements
(adding mutations)
Q2

How did the bio-chemical organization of the pre-prebiotic soup evolved?

What is the characteristics of the organizational evolution? upward? downward? ...
Q2 - Notes

• There are two levels of chemical evolution.
  – Actual evolution
    (the actual vessel)
  – Organizational evolution
    (upward, downward, sideward movements)

• These levels are different.

• If the organizations are complex, a downward movement (organizational level) can lead to a state with a higher diversity (actual evolution).
Space plays a fundamental role in many natural bio-chemical processes.
Organizations in Space
Aspects of Space

- Membranes
- Clusters
- Waves
- Spatial Scales
Space

[P. Speroni di Fenizi, P. Dittrich, Chemical Organizations at Different Spatial Scales, LNCS, Springer, 2007]
Chemical Computing – Chemical Programming
Chemical Flip-Flop

\[ M = \{ a, A, b, B, c, C, d, D \} \]

\[
\begin{align*}
\text{a + d} & \rightarrow \text{C} & \text{b + c} & \rightarrow \text{D} & \text{a + A} & \rightarrow 0 \\
\text{a + D} & \rightarrow \text{C} & \text{b + C} & \rightarrow \text{D} & \text{b + B} & \rightarrow 0 \\
\text{A + d} & \rightarrow \text{C} & \text{B + c} & \rightarrow \text{D} & \text{c + C} & \rightarrow 0 \\
\text{A + D} & \rightarrow \text{c} & \text{B + C} & \rightarrow \text{d} & \text{d + D} & \rightarrow 0
\end{align*}
\]

256 possible sets of molecular species
Chemical Flip-Flop (with two inputs)

\[\begin{array}{c}
S & a & c & Q \\
\bar{R} & b & d & \bar{Q}
\end{array}\]

<table>
<thead>
<tr>
<th>S</th>
<th>R</th>
<th>Q_{t+1}</th>
<th>\bar{Q}_{t+1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Q_t</td>
<td>\bar{Q}_t</td>
</tr>
</tbody>
</table>

set
reset
hold

E

\{a, b, C, D\}

\[\begin{array}{l}
\emptyset \rightarrow a \\
\emptyset \rightarrow b
\end{array}\]

\{a, b\}

\{A, B, C, d\}

\[\begin{array}{l}
\emptyset \rightarrow a \\
\emptyset \rightarrow B
\end{array}\]

\{A, B\}

\{A, b, c, D\}

\[\begin{array}{l}
0 \rightarrow A \\
0 \rightarrow b
\end{array}\]
Flip-Flop dynamics

Concentrations [particles/10 ml]

0 10 20 30

∅—A, ∅—B (stay)
∅—A, ∅—b (reset)
∅—A, ∅—B (stay)
∅—a, ∅—B (set)

Concentrations [particles/10 ml]

0 50 100 150 200 250 300 350 400

Time [s]

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