Added value of systems biology

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Eawag: Das Wasserforschungsinstitut des ETH-Bereichs
Water for ecosystems

Water for humans

Strategies for balanced use of water between ecosystems and human use
Selenium
Selenium

Health effects from www.meta-synthesis.com/webbook/35_pt/pt09.jpg
Selenium for humans
Selenium for humans

Selenocysteine/ Selenoproteins

\[
\begin{align*}
\text{H}_2\text{N} & - \text{CO} \\
\text{HSe} & - \text{OH}
\end{align*}
\]
Selenium for humans

Selenocysteine/Selenoproteins

H₂N

O

H₃Se

OH

Concentration of element in diet →

Biological function (%)

0

50

100

Death

Deficient

Optimum

Toxic

Death

30 - 900 μg per day
Selenium for humans

Selenocysteine/Selenoproteins

Keshan, Kashin-Beck
Selenium for humans

Selenocysteine/Selenoproteins

Keshan, Kashin-Beck

Concentration of element in diet → 30 - 900 µg per day
Precipitation main source of soil selenium

Hypothesis:
The climate plays an important role in the selenium distribution
Sources of selenium in the atmosphere

Winkel et al. (2012) Environmental Science and Technology
Green algae as source of atmospheric selenium

Chlamydomonas reinhardtii

Vriens et al. (2016) GASRTA
Amouroux et al. (2001) Earth Planet Sci Lett
Wen et al. (2007) Atmos Environ
Experimental design

Uptake of selenium

50 ml, 24 h

- Selenate – Se(VI)
- Selenite – Se(IV)
- Phosphate
- Sulphate

Methylation of selenium

10 ml, 0:1h:15h

- Selenate – Se(VI)
- Selenite – Se(IV)

Measurement of intra and extracellular speciation of selenium (GC-MS, ICP-MS)
Observation

Data

Interpretation/explanation:
Uptake of selenite faster than selenate

Interpretation/explanation:
Sulphate lowers uptake of selenate

Interpretation/explanation:

1) Selenate uses sulphate transporters for uptake
Phosphate lowers uptake of selenite

Interpretation/explanation:

1) Selenite uses phosphate transporter for uptake.
2) Phosphate indirectly affects uptake of selenite.
Different dynamics of selenate and selenite uptake

Interpretation/explanation:

1) Selenate uses a single transporter, while selenite uses more transporters which are potentially under intracellular selenium control.
Methylation of selenium mirrors uptake

70-90% of all intracellular Se is methylated.

1) Methylation is very efficient.
Methylation of selenium mirrors uptake

70-90% of all intracellular Se is methylated.  

1) Methylation is very efficient.
Intracellular speciation of selenium depends on selenium source

Interpretation/explanation:

1) Metabolization reactions depends on source of selenium.
2) At high intracellular concentration, methylation less efficient.
Why use mathematical modeling of biological processes?

- **PARAMETRIZATION** – reaction rates of all reactions in the model (assumption: known model structure)

- **HYPOTHESES DIFFERENTIATION** – which are the processes that dominate your experimental system (no model -> uncomplete understanding)

- **EXPERIMENTAL DESIGN**
  (if you can’t pick a hypothesis based on current data, what new data will do the job?)

- **PREDICTION/EXTRAPOLATION**
  (what will occur in the future, in a new situation)
Family of simple models
Family of simple models
Family of simple models
Family of simple models
Family of simple models

Vriens et al. (2016) ES&T
Family of simple models

- Selenate
- Selenite
- Phosphate
- Selenate transporter
- Selenite transporter
- Volatiles
- Se0
- Cell

Relationships:
- Selenate transporter to selenate
- Selenite transporter to selenite
- Selenite to volatiles
- Se0 to volatiles
Family of simple models

- Selenate
- Selenite
- Phosphate
- Selenate transporter
- Selenite transporter
- Se0
- Volatiles
Top model
(best fit to dynamic experimental data, lowest number of parameters)
Top model

- Selenite 75 μM
- Selenite 30 μM
- Selenate 75 μM
- Selenate 30 μM

Graphs showing intracellular and extracellular Se concentrations over exposure time.
New interpretation/change in interpretation

1) Reduction of intracellular selenate to selenite slowest reaction
2) Se(0) is produced only at very high levels of intracellular selenium
New interpretation/change in interpretation

1) Selenite uses phosphate transporters for uptake

2) Phosphate indirectly influences uptake of selenite.

3) Single transporter for selenate, multiple for selenite
New interpretation/change in interpretation

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NEW: Extrapolation of the model to inorganic concentrations of selenium found in the environment matches environmental observations.

NEW: Adds credibility to green algae being sources of atmospheric selenium.
New interpretation/change in interpretation

1. Some methylated selenium is lost during the experiment.
2. Either loss to the environment or degradation in the medium likely.
Added value of systems biology?

- PARAMETRIZATION
- HYPOTHESES DIFFERENTIATION
- EXPERIMENTAL DESIGN
- PREDICTION/EXTRAPOLATION
Added value of systems biology?

- PARAMETRIZATION
- HYPOTHESES DIFFERENTIATION
- EXPERIMENTAL DESIGN
- PREDICTION/EXTRAPOLATION
Added value of systems biology?

- Parametrization
- Hypotheses differentiation
- Experimental design
- Prediction/Extrapolation
Added value of systems biology?

- PARAMETRIZATION
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Intermezzo
Molecular mechanisms of toxicity of silver in Chlamydomonas

Pillai et al. (2014) PNAS
Input data for a co-expression network

Sources of public data

ArrayExpress (EMBL-EBI)\(^1\)
GEO (Gene Expression Omnibus, NCBI)\(^2\)
SRA (Sequence Read Archive, NCBI)\(^3\)

<table>
<thead>
<tr>
<th>cerium dioxide nanoparticles</th>
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<td>heat shock</td>
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<td>heat shock, hemin and Mg-protoporphyrin</td>
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<td>Electrophilic stress</td>
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<td>Silver, silver nanoparticles</td>
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<td>Light irradiation</td>
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<td>Sulphur stress</td>
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<tr>
<td>Sulphur starvation</td>
</tr>
<tr>
<td>nitrogen starvation</td>
</tr>
<tr>
<td>Copper</td>
</tr>
<tr>
<td>Oxidative stress</td>
</tr>
<tr>
<td>CO(_2)</td>
</tr>
<tr>
<td>Nitrogen starvation</td>
</tr>
<tr>
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<td>Iron starvation</td>
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The neighbourhood of copper transporters
Preliminary experiments

% Photosynthesis Inhibition vs. Control

50nM
100nM
Novel gene for silver tolerance

- Putative phosphate transporter
- Crr1
- Wild type
- Putative zinc finger
- Ctr1
- FAP154 – unknown function (similar to flagellar associated protein)
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Graphs showing photosynthetic efficiency and internal silver concentration as a function of Ag concentration.
Systems biology makes everything clearer
Predpostavke modelov

1) Struktura modela se med poskusom ne spremeni (brez regulacije)
2) Celice med poskusom ne rastejo (realno ca. 15%)
3) Začetna koncentracija Se v celici = 0 (realno samo zelo nizka)
4) Selenat in selenit ne prehajata v celico z difuzijo
5) Začetna koncentracija metiliranega selena = 0
6) Vse metilirane vrste Se obravnavane kot ena sama
7) Izven celice ni redukcije/oksidacije (nismo detektirali)
Družina modelov

1) Primerjava modelov z AIC, BIC
2) Analize identifikacije parametrov (profile likelihood)
3) Optimizacija: metoda omejenega koraka + genetski algoritem
4) Orodji: Matlab + PottersWheel
Brez toksičnosti

![Graph 1: Mean cell volume vs. Exposure time](image1)
![Graph 2: Culture size vs. Exposure time](image2)

- Selenit: 30 μM, 75 μM
- Selenat: 30 μM, 75 μM
Predpostavke modelov

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8) Primerjava modelov z AIC
9) Analize identifikacije parametrov (profile likelihood)
10) Optimizacija: truste region + genetski algoritem
11) Orodja: Matlab + PottersWheel
<table>
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<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Description</th>
<th>Value constraint</th>
</tr>
</thead>
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<tr>
<td>( V_{\text{max}}^{\text{Se[VI]}} )</td>
<td>( \mu M \cdot h^{-1} )</td>
<td>Maximum flux for the uptake of Se[VI]</td>
<td>( 10^{-6} - 10^5 )</td>
</tr>
<tr>
<td>( K_M^{\text{Se[VI]}} )</td>
<td>( \mu M )</td>
<td>Michaelis constant for the uptake of Se[VI]</td>
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</tr>
<tr>
<td>( k_{P0A} )</td>
<td>( h^{-1} )</td>
<td>Rate of uptake of phosphate</td>
<td>( 10^{-6} - 10^3 )</td>
</tr>
<tr>
<td>( c_{\text{INH}} )</td>
<td>/</td>
<td>Inhibition constant of phosphate on the uptake of Se</td>
<td>( 10^{-6} - 10^3 )</td>
</tr>
<tr>
<td>( k_{RED} )</td>
<td>( h^{-1} )</td>
<td>Rate of reduction of Se[VI]</td>
<td>( 10^{-6} - 10^3 )</td>
</tr>
<tr>
<td>( k_{MET} )</td>
<td>( h^{-1} )</td>
<td>Rate of Se[IV] metabolism</td>
<td>( 10^{-6} - 10^3 )</td>
</tr>
<tr>
<td>( k_{DIFF} )</td>
<td>( h^{-1} )</td>
<td>Rate of diffusion of methylated Se through cell membrane</td>
<td>( 10^{-15} - 10^{-3} )</td>
</tr>
<tr>
<td>( k_{DEG} )</td>
<td>( h^{-1} )</td>
<td>Rate of loss of volatile Se</td>
<td>( 10^{-6} - 10^3 )</td>
</tr>
<tr>
<td>( V_{\text{max}}^{\text{Se[IV]} \rightarrow \text{Se[0]}} )</td>
<td>( \mu M \cdot h^{-1} )</td>
<td>Maximum flux for transformation of Se[IV] into Se[0]</td>
<td>( 10^{-6} - 10^5 )</td>
</tr>
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<td>( \mu M )</td>
<td>Michaelis constant for transformation of Se[IV] into Se[0]</td>
<td>( 10^{-2} - 10^5 )</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>/</td>
<td>Hill factor</td>
<td>( 10^0 - 10^{-5} )</td>
</tr>
<tr>
<td>( V_{\text{vial}} )</td>
<td>mL</td>
<td>Vial volume</td>
<td>10</td>
</tr>
<tr>
<td>( V_{\text{cell}} )</td>
<td>fL</td>
<td>Cell volume</td>
<td>200</td>
</tr>
<tr>
<td>( k_{SOA} )</td>
<td>( h^{-1} )</td>
<td>Rate of uptake of sulfate</td>
<td>( 10^{-6} - 10^3 )</td>
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<tr>
<td>( k_0 )</td>
<td>( h^{-1} )</td>
<td>Rate of transformation of Se[IV] into Se[0]</td>
<td>( 10^{-6} - 10^3 )</td>
</tr>
<tr>
<td>( k_{vol} )</td>
<td>( h^{-1} )</td>
<td>Rate of transformation of Se[0] into methylated Se</td>
<td>( 10^{-6} - 10^3 )</td>
</tr>
<tr>
<td>( k_{vol2} )</td>
<td>( h^{-1} )</td>
<td>Rate of transformation of methylated Se into Se[0]</td>
<td>( 10^{-6} - 10^3 )</td>
</tr>
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</table>
Se je zelo podoben S, metilirane S molecule so pomembne za globalni S cikel. Normalno je $S > 10^2$, vendar se Se veliko lažje metilira – zakaj?