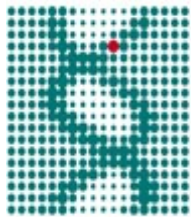


Parallelised Monte-Carlo simulation of large biological networks using the EGEE grid

Christoph Wierling

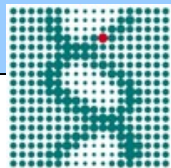
wierling@molgen.mpg.de



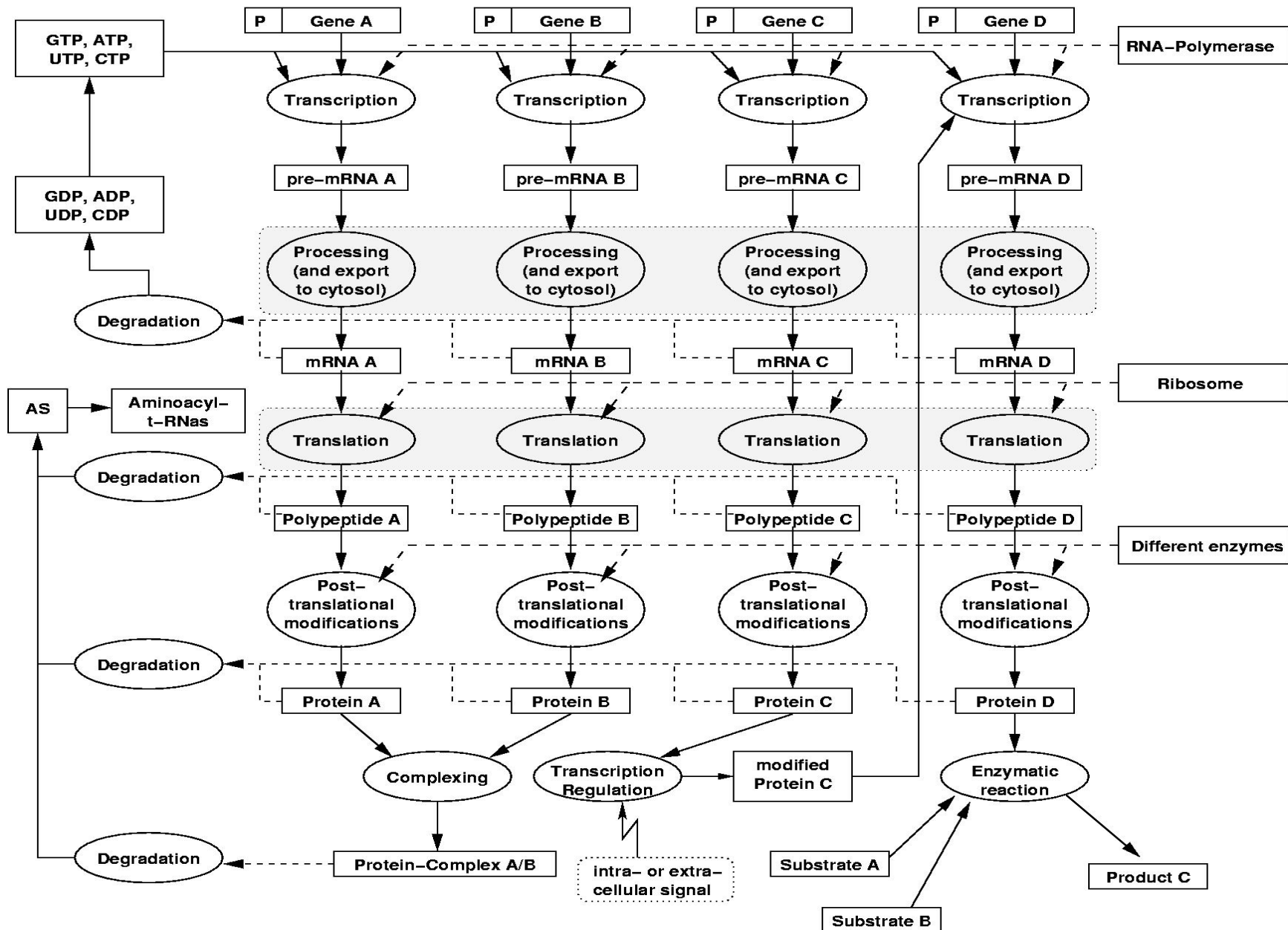
**Max-Planck-Institut
für molekulare Genetik**

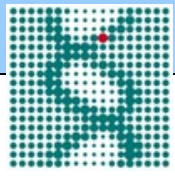


**Department – Vertebrate Genomics
Bioinformatics Group - Herwig
Berlin, Germany**



Cellular Processes





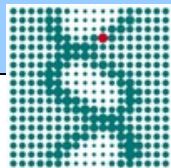
Modelling and Data Resources

Data required for modelling:

- Information about the *substrates* and *products* of a reaction and its *stoichiometry*
- Information about the catalyzing *enzyme* and its *kinetics*
- Information about the reactants and enzyme *concentrations*

Databases:

- KEGG (Kyoto Encyclopedia of Genes and Genomes)
- Reactome
- Transpath (Database of signal transduction pathways)
- SRS (Sequence Retrieval System)
- BioCyc
- Kinetikon (Kinetics database)
- Database of experimental data (Expression data, Protein/Protein interaction, ...)



PyBioS

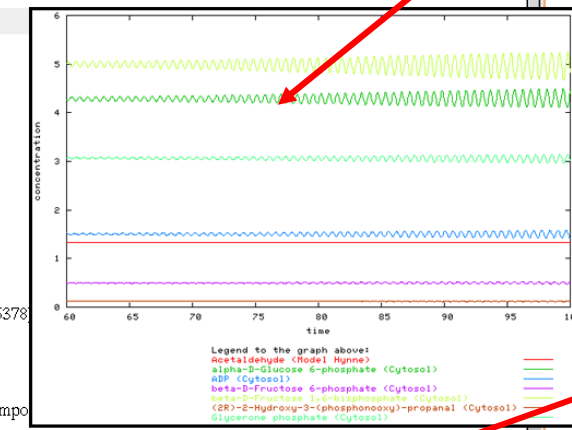
(<http://pybios.molgen.mpg.de>)

Detailed hierarchical model

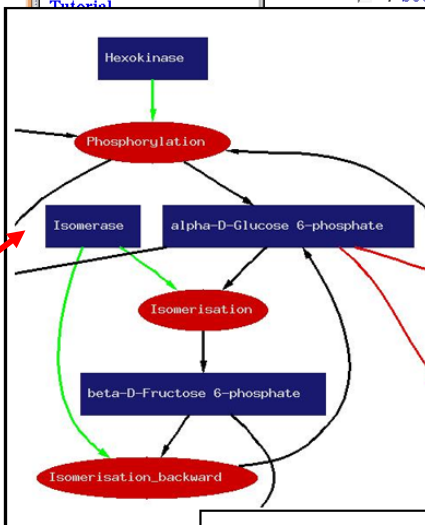
Diagram of simulation results

The screenshot shows the PyBioS web interface in a Mozilla browser. The address bar shows <http://pybios.molgen.mpg.de/biolab>. The interface has several tabs: View, Network, Reactions, Simulation, Populate, Analyse, and Export/Import. The 'Simulation Environment at /biolab/chris2/Hynne' is active. A tree view on the left shows the hierarchy: cell (Cell.cell1) containing CytoplasmMembrane (Compartment.CytoplasmMembrane), Cytoplasm (Compartment.Cytoplasm), and Cytosol (Compartment.Cytosol). Under Cytosol, various molecules are listed, including alpha-D-Glucose, alpha-D-Glucose 6-phosphate, beta-D-Fructose 6-phosphate, ATP, ADP, AMP, and beta-D-Fructose 1,6-bisphosphate.

Model repository



List of reactions



Reactions

Phosphorylation (Hexokinase): irreversible kinetic
 $1 \text{ alpha-D-Glucose} + 1 \text{ ATP} \rightarrow 1 \text{ alpha-D-Glucose 6-phosphate} + 1 \text{ ADP}$

Isomerisation_backward (Isomerase): irreversible kinetic
 $1 \text{ beta-D-Fructose 6-phosphate} \rightarrow 1 \text{ alpha-D-Glucose 6-phosphate}$

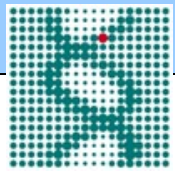
Isomerisation (Isomerase): irreversible kinetic
 $1 \text{ alpha-D-Glucose 6-phosphate} \rightarrow 1 \text{ beta-D-Fructose 6-phosphate}$

Phosphorylation (Phosphofruktokinase): irreversible kinetic
 $1 \text{ beta-D-Fructose 6-phosphate} + 1 \text{ ATP} \rightarrow 1 \text{ beta-D-Fructose 1,6-bisphosphate}$

Auto-generated interaction diagram of the model

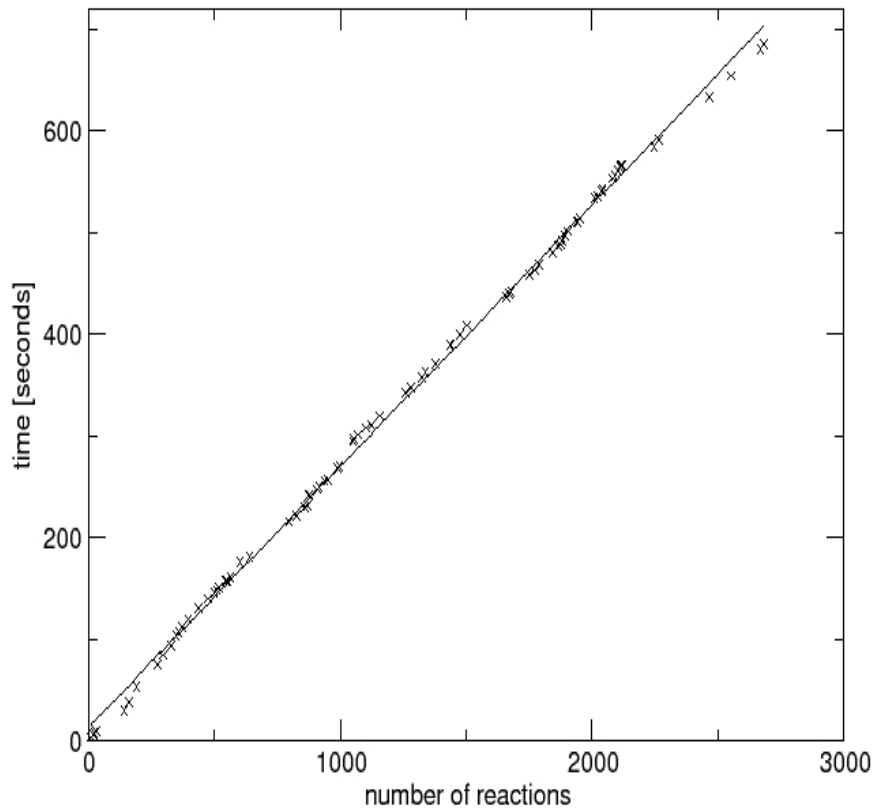
$$\text{Phosphorylation.Vm} * [\text{alpha-D-Glucose}] * \frac{[\text{ATP}]}{K_DGlc * K_ATP + K_Glc * [\text{ATP}] + K_ATP * ([\text{alpha-D-Glucose}] + [\text{alpha-D-Glucose}] * [\text{ATP}]}$$

Details of the kinetics

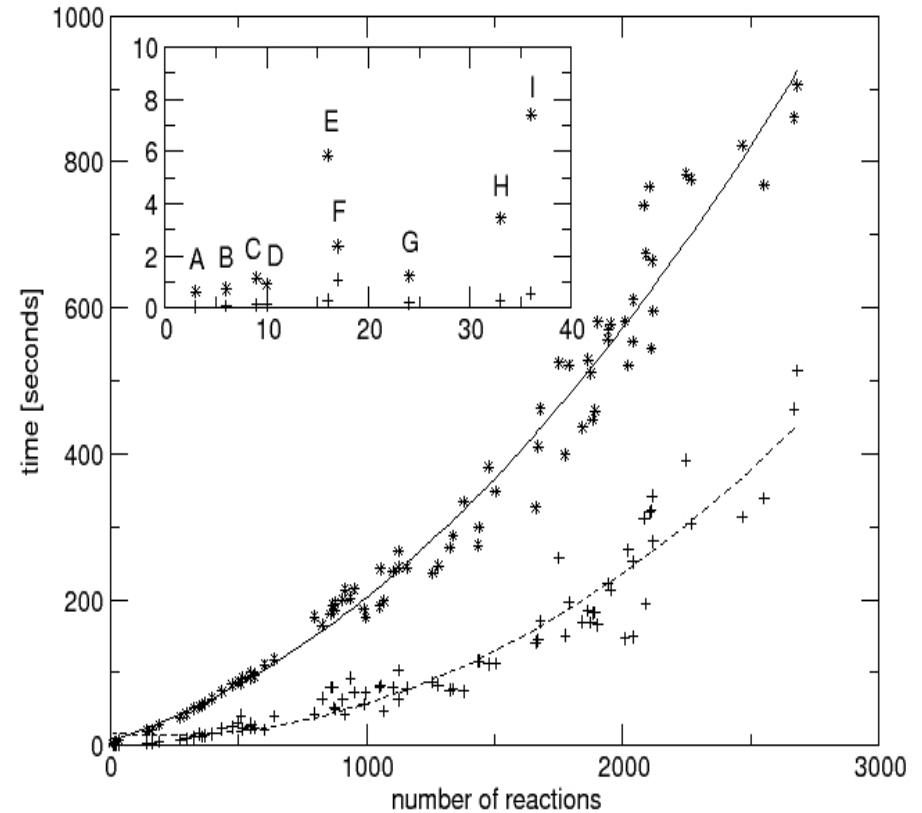


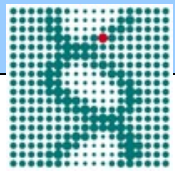
Scaling of Model Population and Simulation

Population



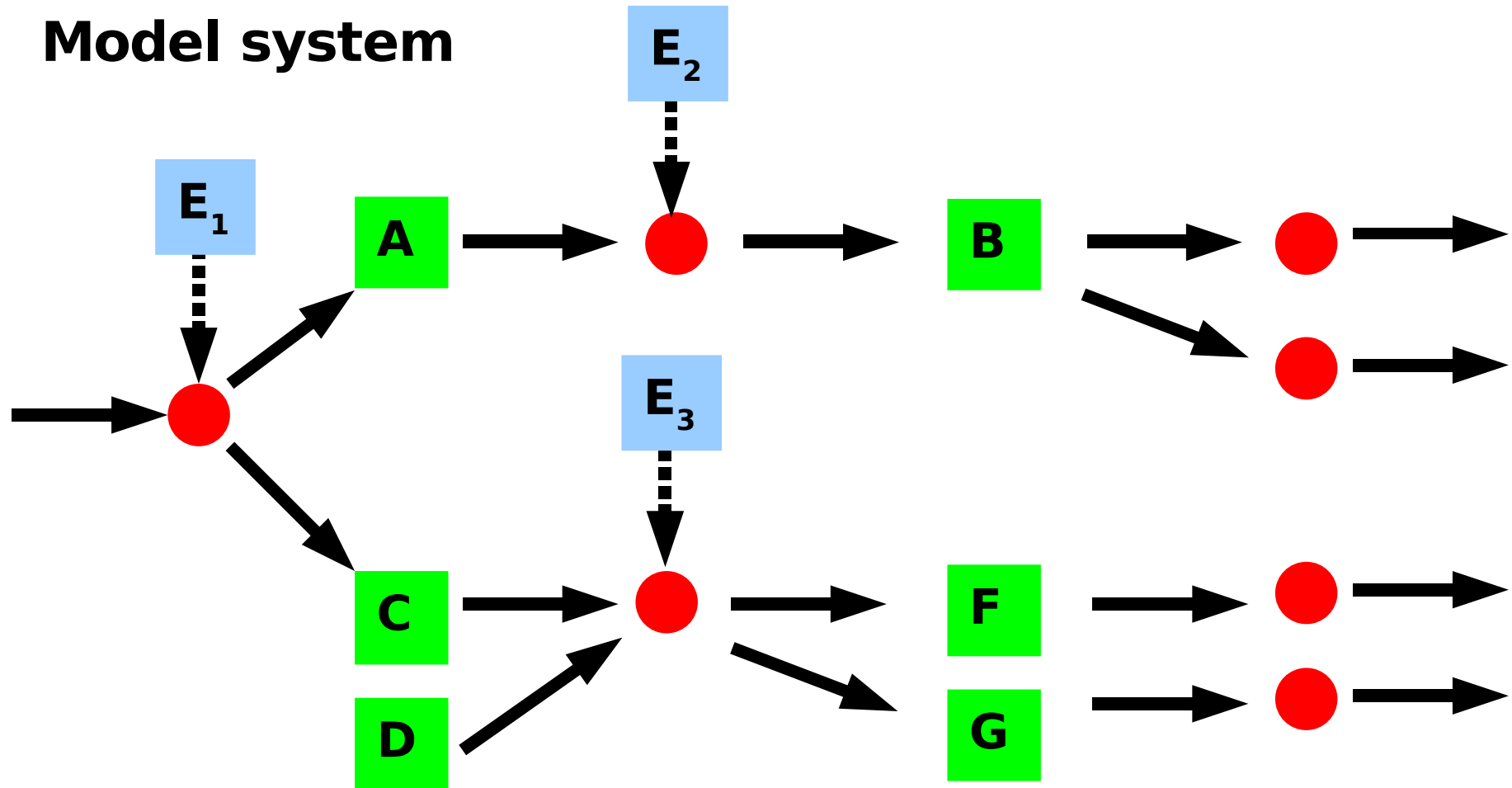
Simulation



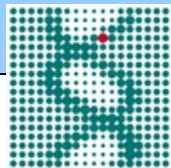


Simulation studies in EGEE grid (I)

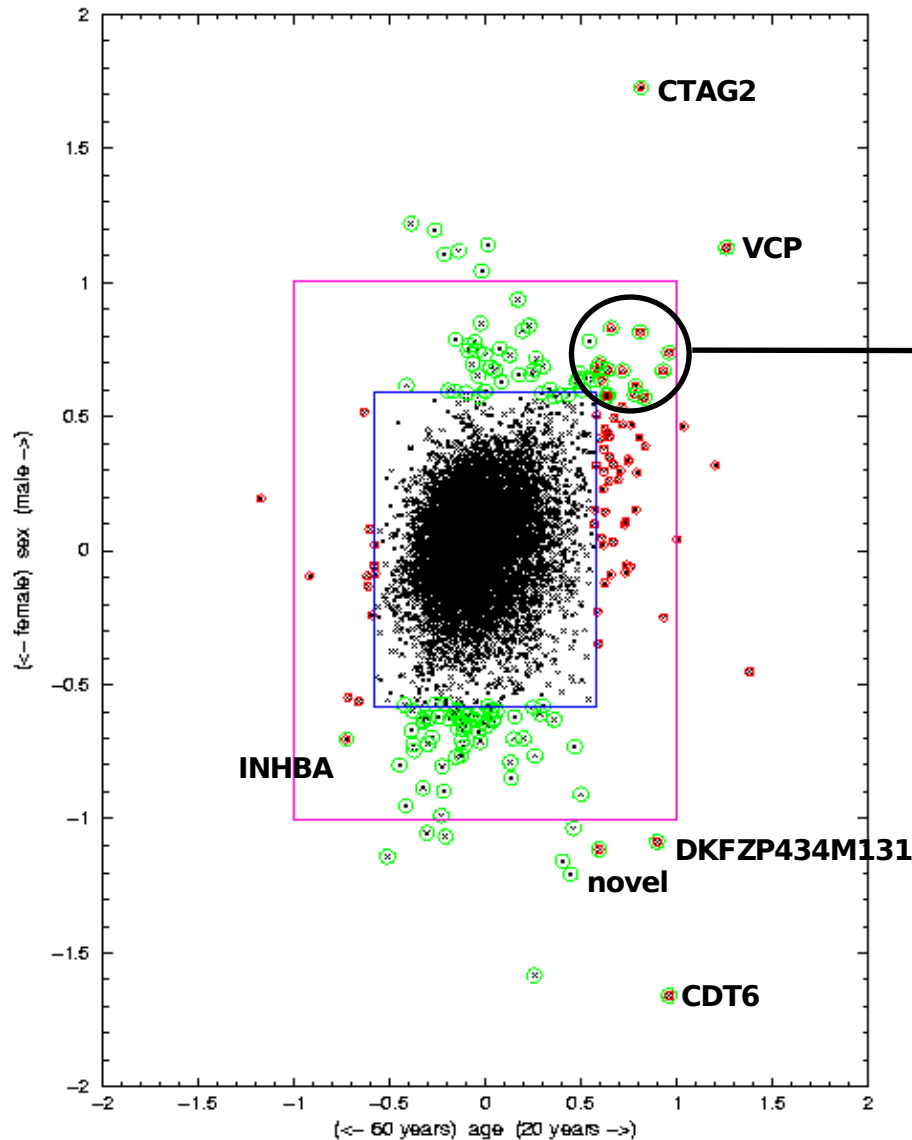
Model system



- Pure Metabolic Model: e.g. from KEGG (>1400 reactions)
- Metabolic & Signal-Transduction pathways: e.g. from Reactome (>1500)



Gene expression - modelling and simulation (I)

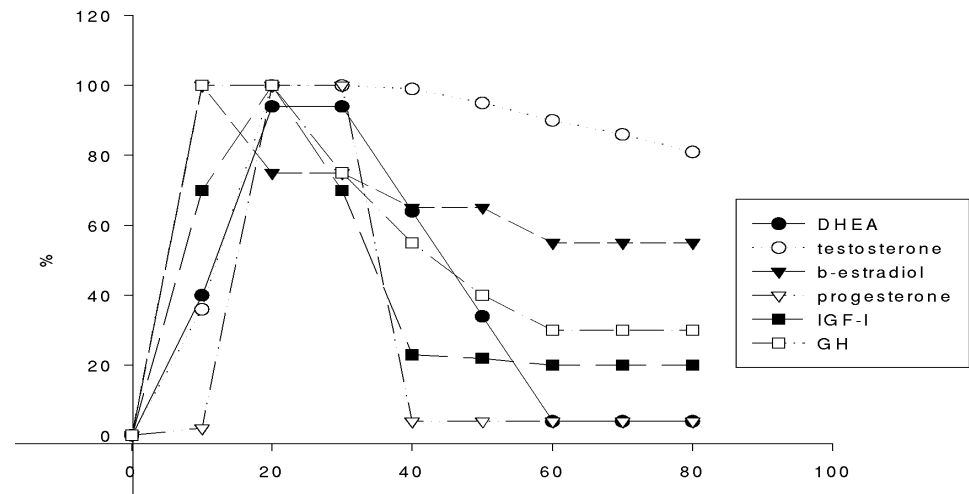


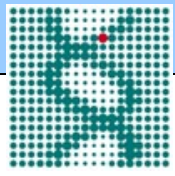
- HNRPU
- novel
- novel
- ACTN1
- HLA-C
- KIAA0090
- BRUNOL5
- novel
- EEF2
- FLJ12592
- MAP3K3
- NXN
- DHRC7
- C20orf172

Skin ageing project:

MPIMG (James Adjaye)
Charite CBF
Dermatology
(Prof. Christos Zouboulis)

Serum levels of hormones decline with age in human individuals:

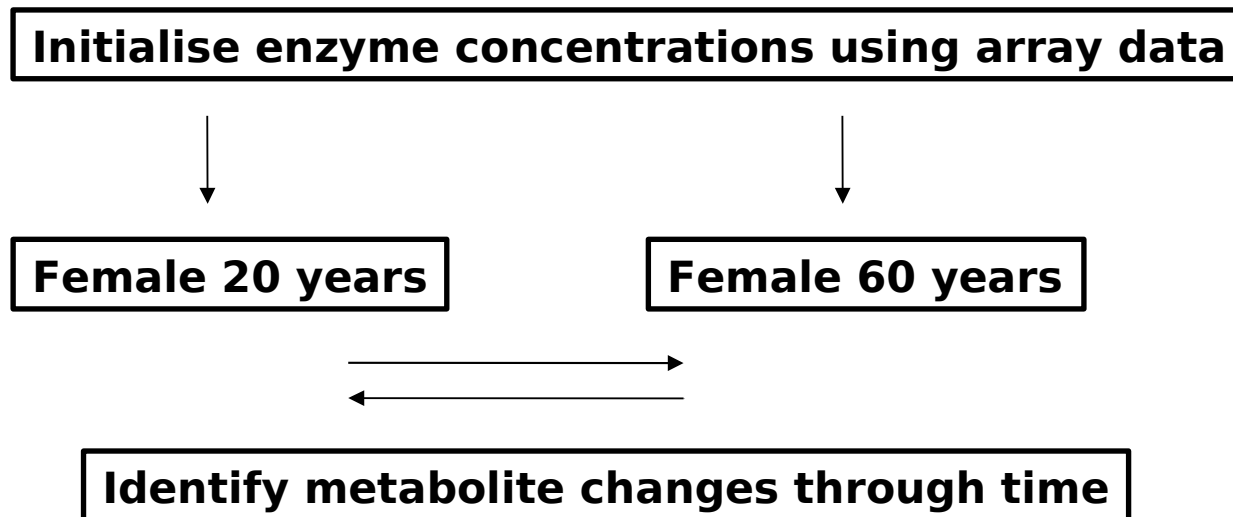


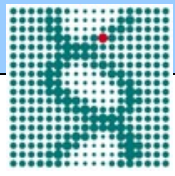


Gene expression – modelling and simulation (II)

KEGG database (<http://www.genome.ad.jp/kegg/kegg2.html>): 1,104 enzymes

- Ensembl chip: 745 (67%)
- Metabolic profiling of conditions (Example: Skin ageing project)
 - Condition 1: hormone-induced cell lines mimicking female 20 years old
 - Condition 2: hormone-induced cell lines mimicking female 60 years old





Gene expression – modelling and simulation (III)

1. Populate the metabolic reactions from KEGG (~1,600 objects and ~2,300 reactions)
(for example Carbohydrate Met., Energy Met., Lipid Met.); determines network topology

2. Fit a probability density for the initial concentrations (derived from array data):

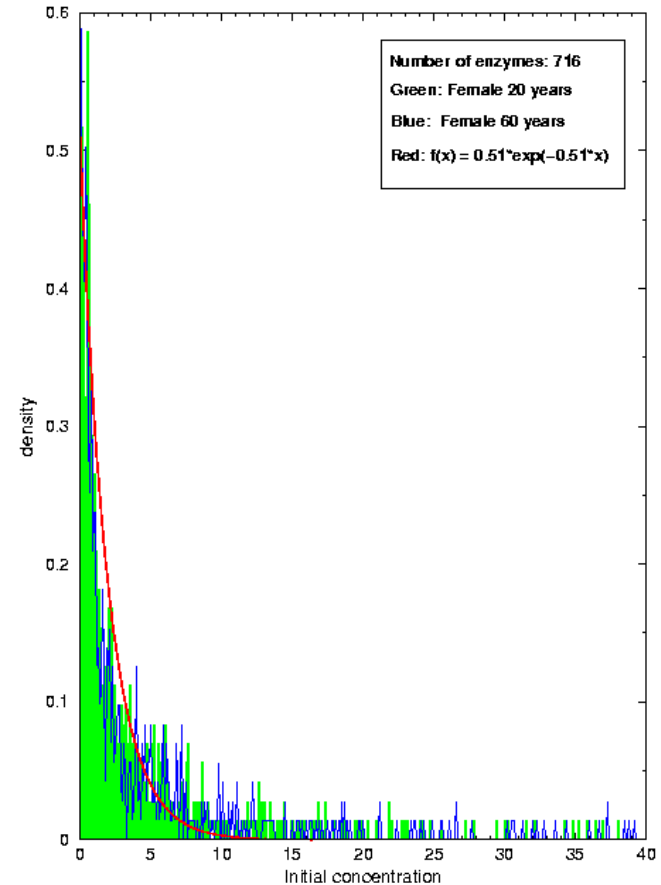
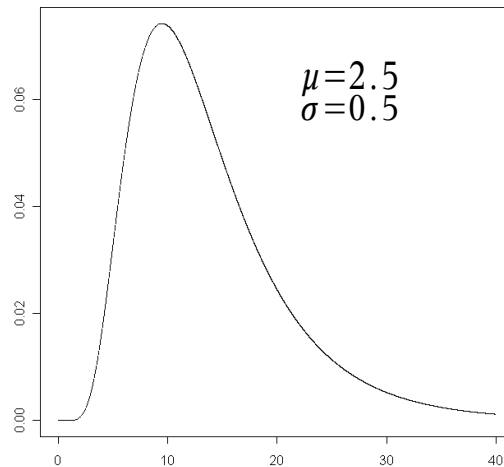
$$f(x) = 0.51 e^{-0.51x}$$

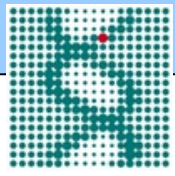
3. Assume a probability density for the kinetic constants

4. Run time series for the two conditions

5. Repeat step 3. and 4. twenty times

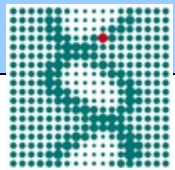
6. Identify changes in metabolite concentrations



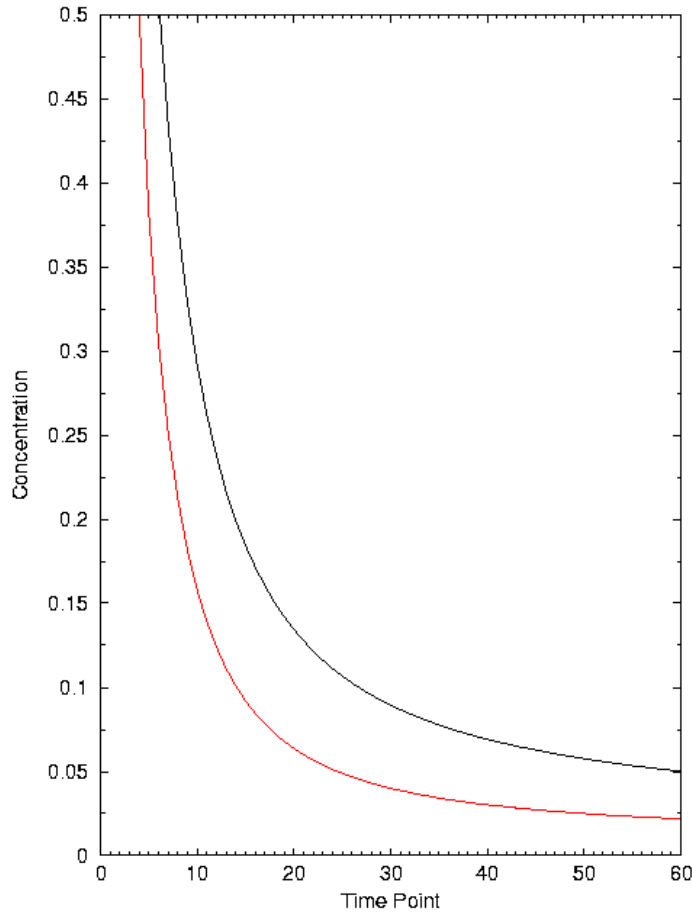


Gene expression – modelling and simulation (IV)

1. Squalene	2.16	decreased	Passi, S. et al. (2003) <i>Biofactors</i> 18:289-297, Andersson, M. et al. (1995) <i>Mech Ageing Dev</i> 85:1-14.
2. Leukotriene B4	1.60	decreased	Viggiano, D. et al. (1994) <i>Pediatr Res</i> 36:60-63.
3. Carnosine	0.51	increased	Hyland, P. et al. (2000) <i>Mech Ageing Dev</i> 121:203-215.
4. 3-hydroxy-3-methyl-glutaryl-CoA	0.64	increased	Pallottini, V. et al. (2003) <i>Biogerontology</i> 4:371-378.
5. Ubiquinone	1.00	unchanged	Andersson, M. et al. (1995) <i>Mech Ageing Dev</i> 85:1-14.
6. 4-hydroxybenzoate	1.06	unchanged	Andersson, M. et al. (1995) <i>Mech Ageing Dev</i> 85:1-14.



Gene expression – modelling and simulation (V)



Problems:

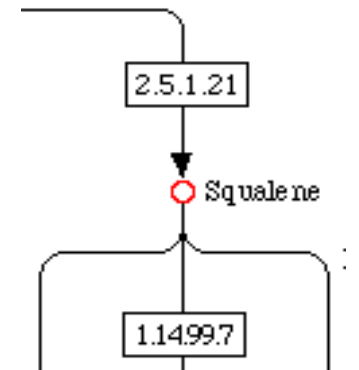
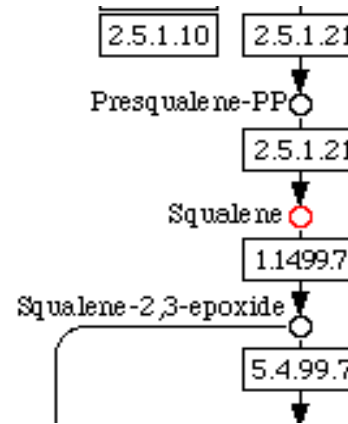
- no steady-state analysis
- many substrates approach zero concentration

Example: Squalene

Metabolic Processes:

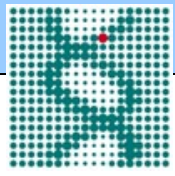
sterols, vitamin K,E biosynthesis

terpenoid biosynthesis



2.5.1.21	FDFT1 <i>squalene synthase</i>
1.1499.7	SQLE <i>squalene epoxidase</i>

F20	F60	Ratio	BG-Tags	P-Value
8.12	5.58	1.46	(>0.99 in both)	4.3*10 ⁻²
8.30	11.49	0.72	(>0.99 in both)	1.28*10 ⁻¹



Simulation studies in EGEE grid (II)

Applications

Cancer application

Melanoma celllines:

[**primary tumor** vs. **metastases** (tumor progression) vs. **control**]

Homepage of ESBIC-D (EU project):

<http://pybios.molgen.mpg.de/ESBIC-D>

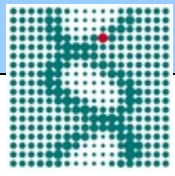
Type-2 diabetes

Mouse model (NZO):

[**standard diet** vs. **high fat diet**]

Nutrigenomik (BioProfile – BMBF – Germany):

http://www.molgen.mpg.de/~lh_bioinf/projects/Nutrigenomik/



Acknowledgement



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für molekulare Genetik**

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Prof. Dr. Hans Lehrach

Elisabeth Maschke-Dutz



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France**

Dr. Christophe Blanchet

Remi Mollon

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