The Silicon Cell approach to building detailed kinetic models of biological systems



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#### The Silicon Cell (SiC)

A silicon cell model is a computer replica of (part of) a living cell. It is based on experimentally determined rate laws and parameter values.

aim: To understand systems behavior as a function of its components characteristics

http://www.siliconcell.net

#### Will it ever work?

Chances of success improve dramatically by trying



#### A kinetic model of Yeast glycolysis





Can yeast glycolysis be understood in terms of *in vitro* kinetics of the constituent enzymes? Testing biochemistry

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#### Yeast glycolysis, structure Linear pathway, one independent flux, twelve independent variables, three conserved moieties. Reactions, i.e. substrates and products of the different steps, are well known.

Differential equations of all variables can be set up as a function of the individual rate equations:

d(GAP[t])/dt = vALD + vTPI - vGAPdh



#### Rate equations

Enzymology is a well established discipline!

If known take enzyme kinetic mechanism from literature. Measure for specific strain and conditions the kinetic parameters.

Example: PFK

#### Monod, Wymann, Changeux model









#### Building the model

- Kinetic types are taken from literature.
- Kinetic parameters are fitted using the experimental in vitro data.
- Enzyme concentrations are determined in cell extracts

# With this structure the kinetic model does not reach a steady state.

Let's compare to experimental data.





Flux	Experiment	Model
mmol min <sup>-1</sup> L <sup>-1</sup> cyt	•	
Glucose uptake	108	88
Ethanol efflux	135	129
Concentration		
mmol L <sup>1</sup> cyt		
G6P	2.45	1.07
F6P	0.62	0.11
F16bP	5.51	0.60
DHAP	0.81	0.74
3PGA	0.90	0.36
2PGA	0.12	0.04
PEP	0.07	0.07
Pvr	1.85	8.52
ATP	2.52	2.51
ADP	1.32	1.29
AMP	0.25	0.30
NAD	1.20	1.55
NADH	0.39	0.04

Bifurcation in detailed

glycolytic model



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Lower GLT activity

#### Building the Silicon Cell; a modular approach

- · SiC replicas of modules in metabolism
- Link modules to build the Silicon Cell

validation parameters context independent, mechanistic

modules should be defined on the basis of validation criteria; separation, structural, time, flux, ..

## Combining models

Important that the parameter values are context independent.

G6P

#### Not SiC:

Fit a parameter set of an incomplete model to a systemic data set.

If glycerol branch would be added to the core model, all parameter values would have to be fitted again Parameter values have no mechanistic meaning

#### SiC:

parameters have real meaning, value independent of model in which they are used

#### Adding detail to the glycerol branch

APPLIED AND ENVIRONMENTAL MICROBIOLOGY, Sept. 2002, p. 4448–4456 0099-224002300.00+0 DOI: 10.1128/AEMA8.9.4448–4456.2002 Copyright © 2002, American Society for Microbiology. All Rights Reserved

> Metabolic Control Analysis of Glycerol Synthesis in Saccharomyces cerevisiae Garth R. Cronwright,<sup>1+</sup> Johann M. Rohwer,<sup>2</sup> and Bernard A. Prior<sup>1</sup>

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Gartin R. Cronwright, Johann M. Konwer, and Bernard A. Prior Department of Microbiology<sup>1</sup> and Department of Biochemistry,<sup>2</sup> Stellenbosch University Matikhand 7602, South Africa

#### Adding new pathways

Eur. J. Biochem. 268, 3930-3936 (2001) © FEBS 2001

*In situ* kinetic analysis of glyoxalase I and glyoxalase II in *Saccharomyces cerevisiae* 

Ana Margarida Martins<sup>1</sup>, Pedro Mendes<sup>2</sup>, Carlos Cordeiro<sup>1,3</sup> and Ana Ponces Freire<sup>1,3</sup>

Integrated model prediction was more accurate than the model with the simple branch kinetics

#### Keeping track of all these models

Many different models No standardized model description Different simulation engines

#### JWS Online



Database of models Models can be run via client-server system Used for reviewing models by journals Link to SBML, YSBN, BMBF

#### JWS Online

Accessible and executable via the internet (Windows, Apple, Linux), all you need is a browser and java runtime environment (J2RE), 3 mirror sites:

Africa: http://jjj.biochem.sun.ac.za Europe: http://jjj.bio.vu.nl North America: http://jjj.vbi.vt.edu; caltech 2005

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#### Cell cycle model Tyson et al., 2001



# Understanding the system/model: MCA

System/model so complex and complicated that one needs a higher level language to study it.

MCA, allows for a high level quantitiative description, e.g. list the 5 most important enzymes responsible for systemic steady state behavior.

MCA, in addition to description also allows for understanding, expression of Control Coefficients in Elasticity Coefficients.

### Building the Silicon Cell

#### Integration of research efforts

To model a whole cell, efforts must be combined: e.g. agreement on cell strain, growth conditions, coordination, standards,

Combining top-down and bottom-up approaches

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