Spanish congress of Chemical Engineering Departments
Barcelona., September 9th 2011t.S

Multiscale modeling of process dynamics in large-scale bioreactors

Spanish congress of Chemical Engineering Department.

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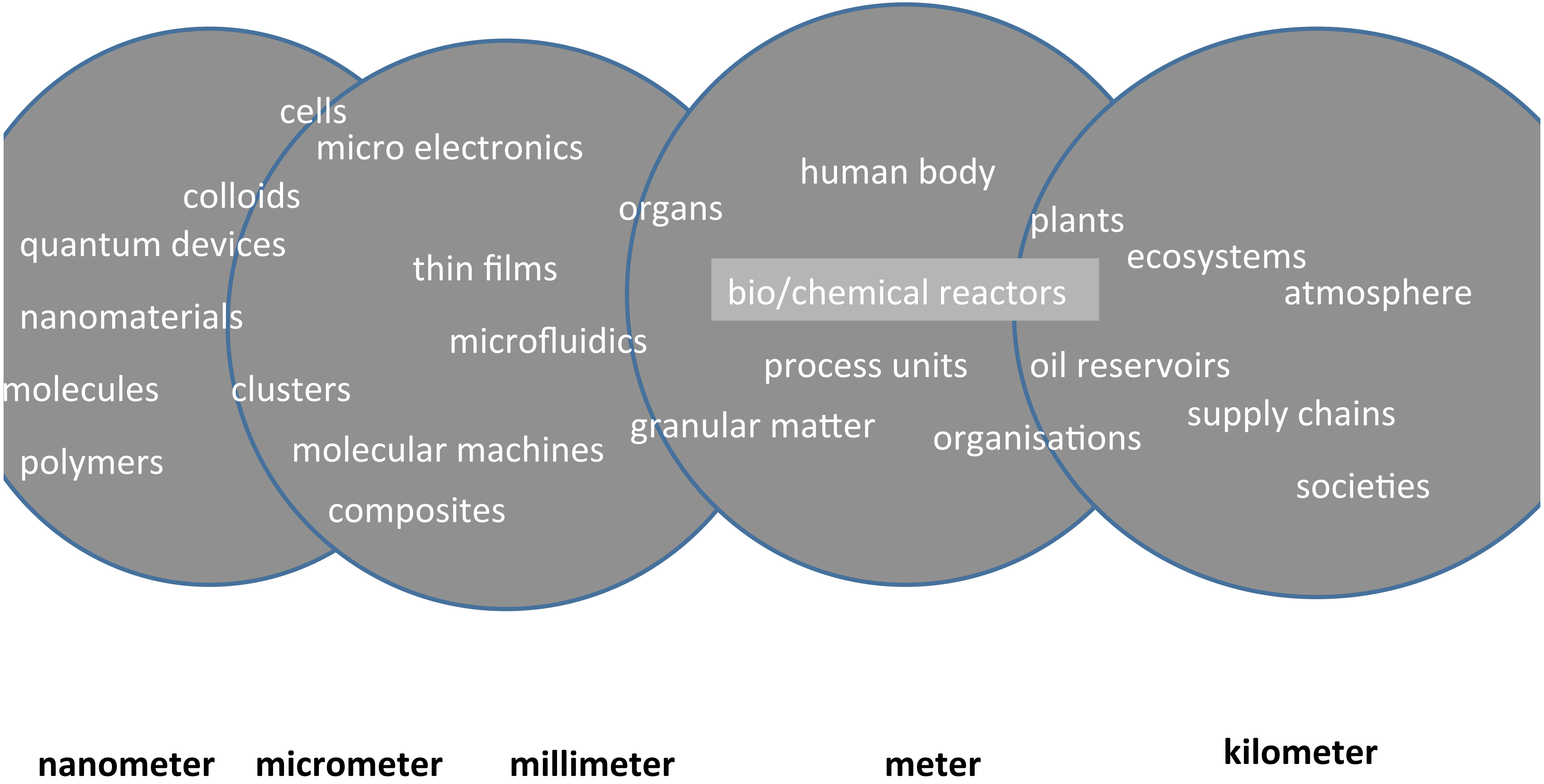
NGI Visiting Stipendiate, The Netherlands

„Benchmarking the Research Competitiveness of the United States in Chemical Engineering“

2007

Range of length scales covered by chemical engineering

(according to Julio M. Ottimo, AIChE Journal 2011)

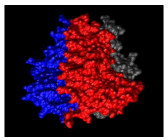


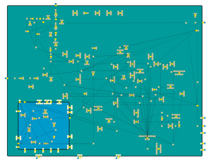
Multi-scale modeling in biomedicine

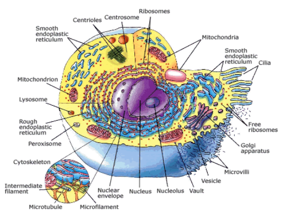
1nm

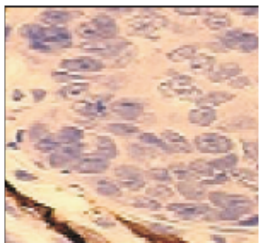
1m

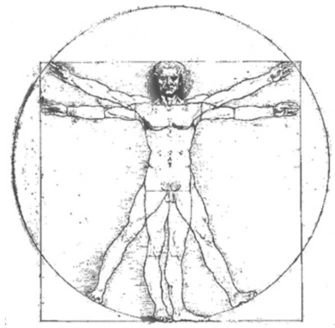
10 orders of magnitude











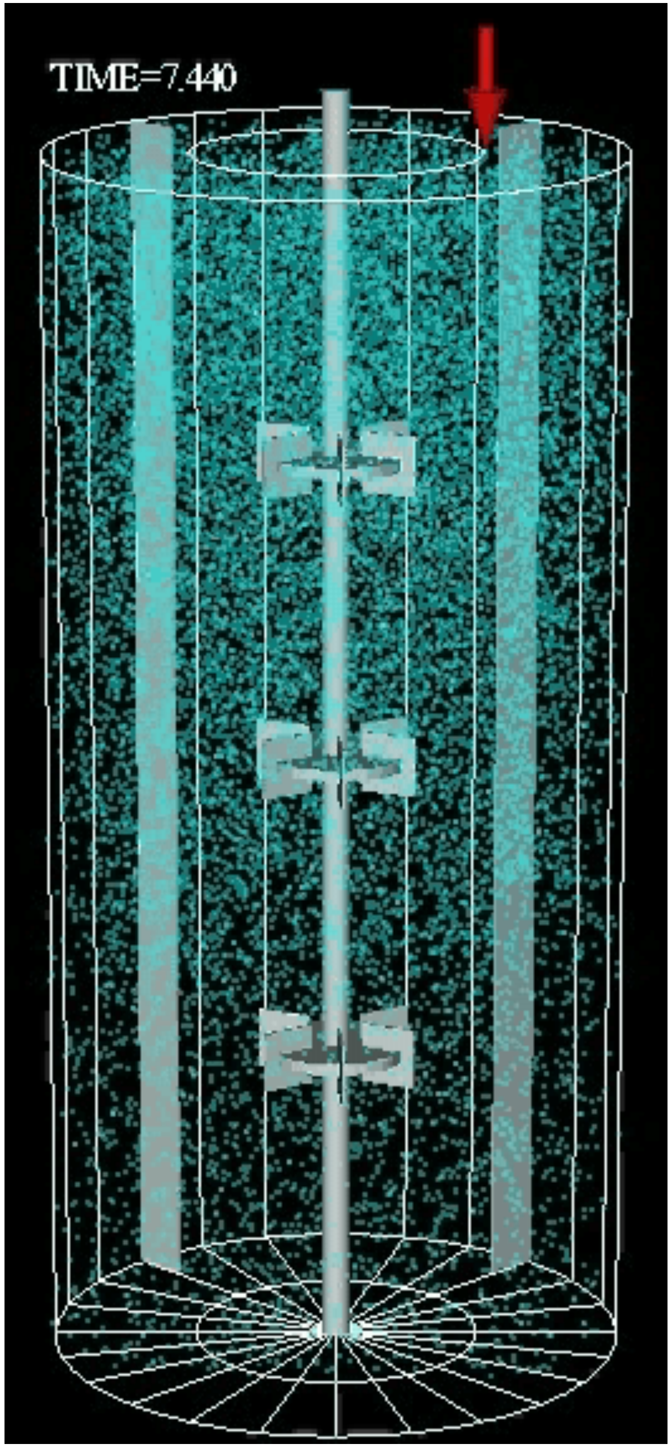
proteins networks cells tissues organs human body

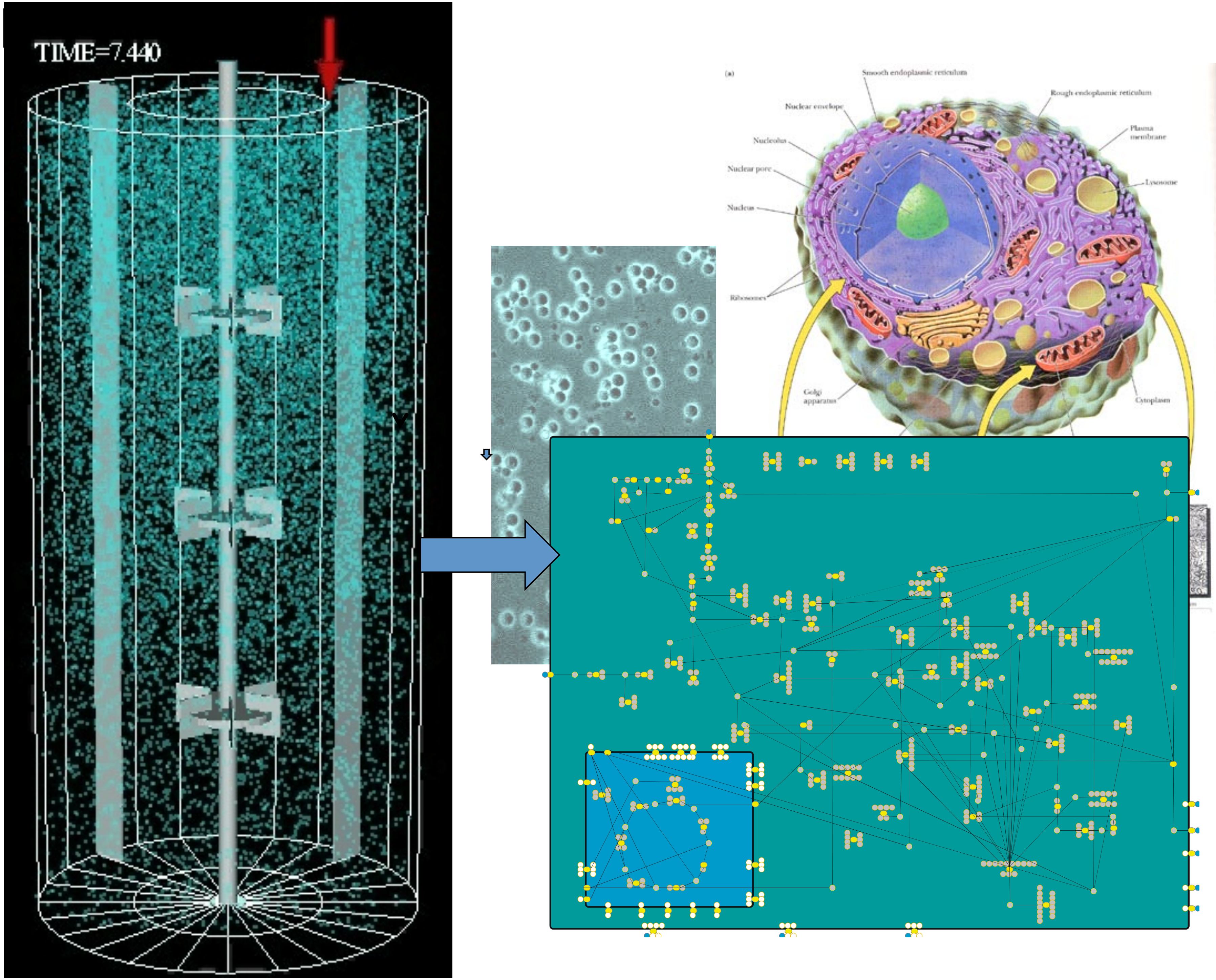
Temporal scales

1μs (ion channel gating) 10^9s (human life)

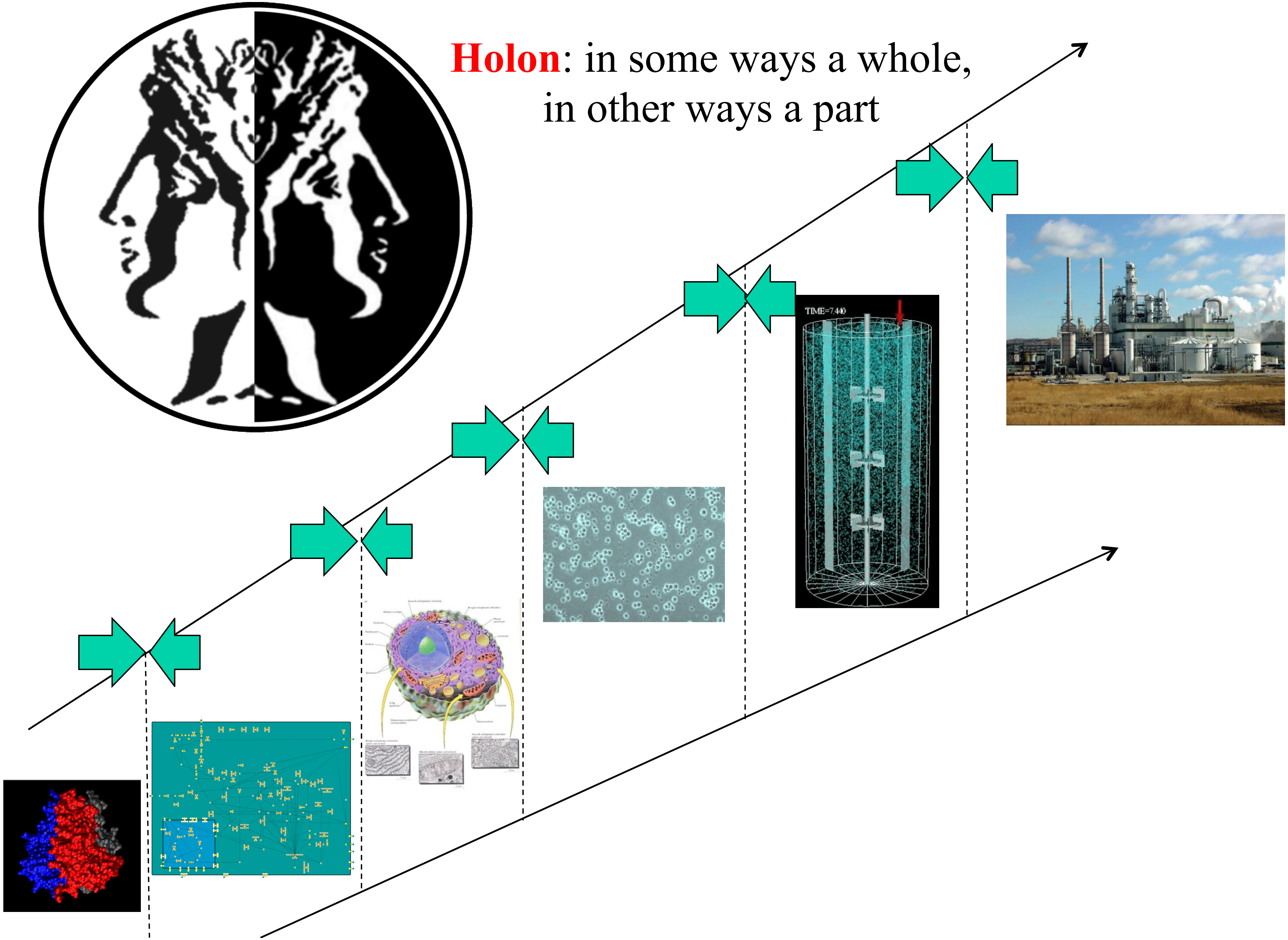
16 orders of magnitude

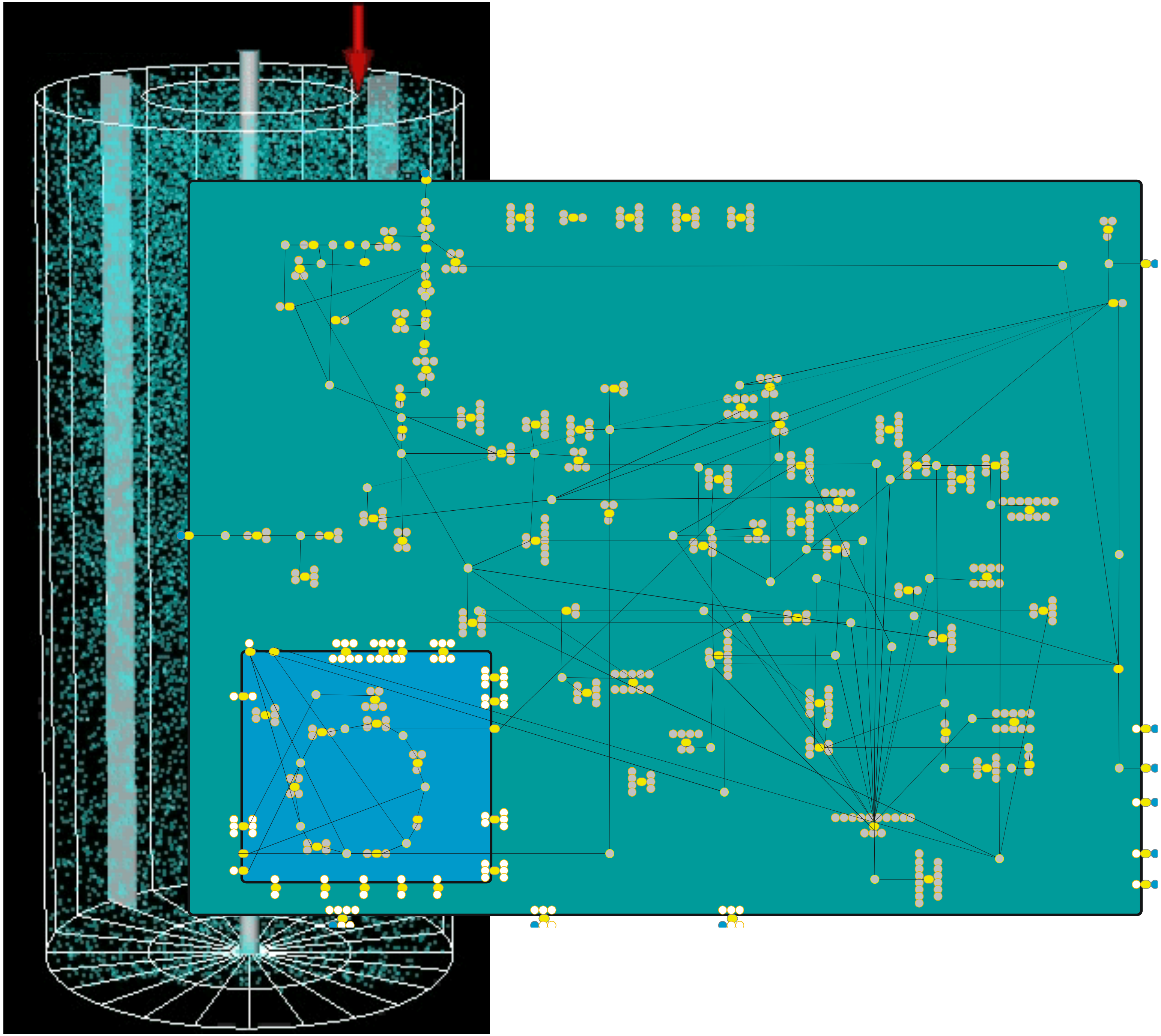
[redacted]




TIME=7.440
(a)
Smooth endoplasmic reticulum
Rough endoplasmic reticulum
Nuclear envelope
Nucleolus
Plasma membrane
Nuclear pore
Lysosome
Nucleus
Ribosomes
Golgi apparatus
Cytoplasm

Holon: in some ways a whole, in other ways a part





CFD

Computational Fluid Dynamics

&

CCD

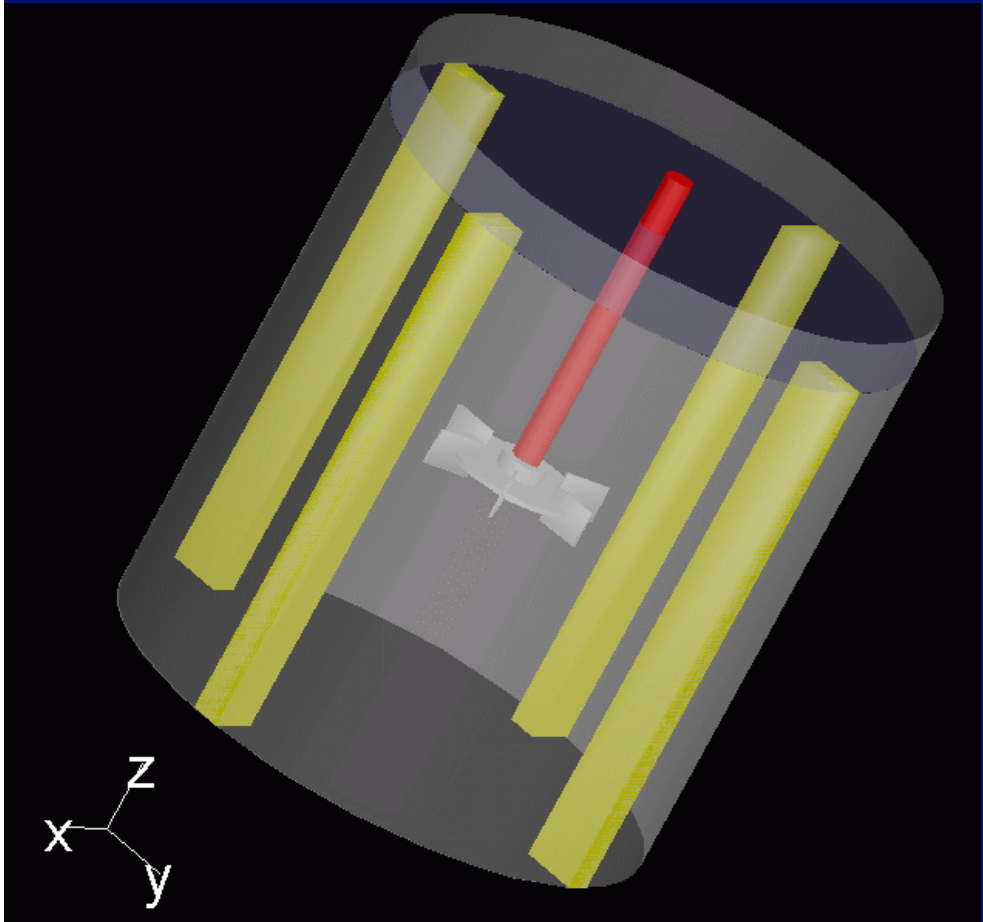
Computational Cellular Dynamics

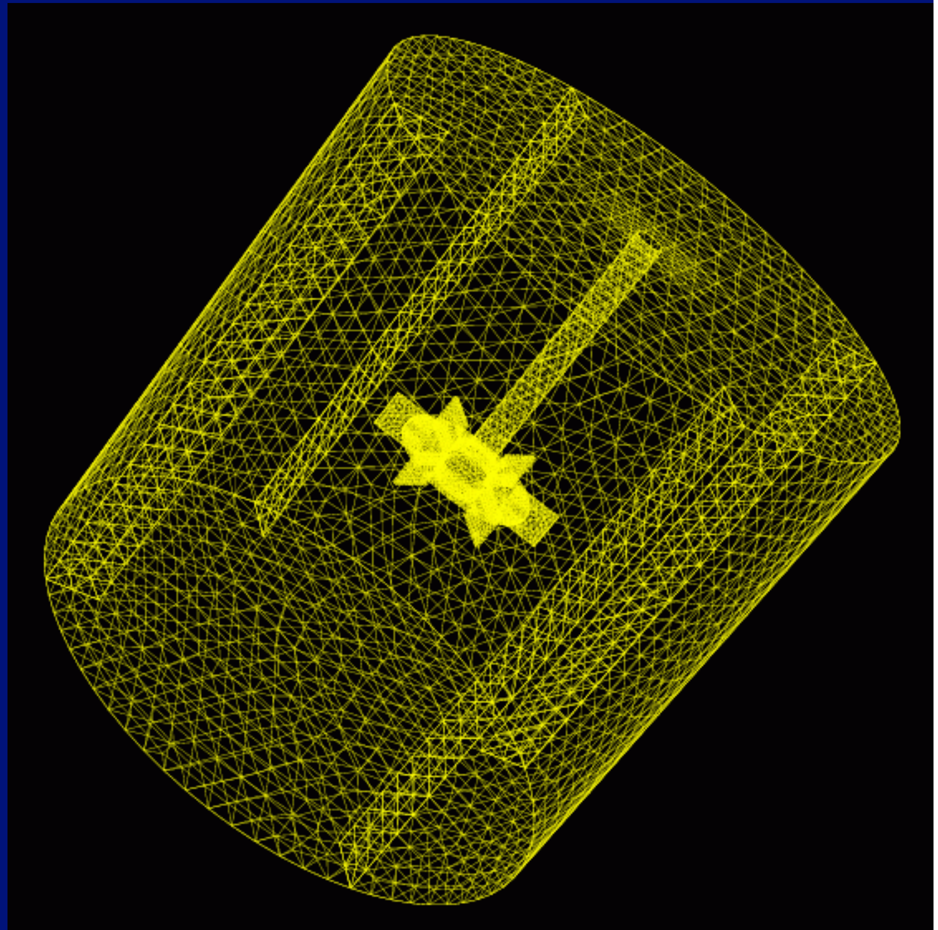
CFD

Computational Fluid Dynamics

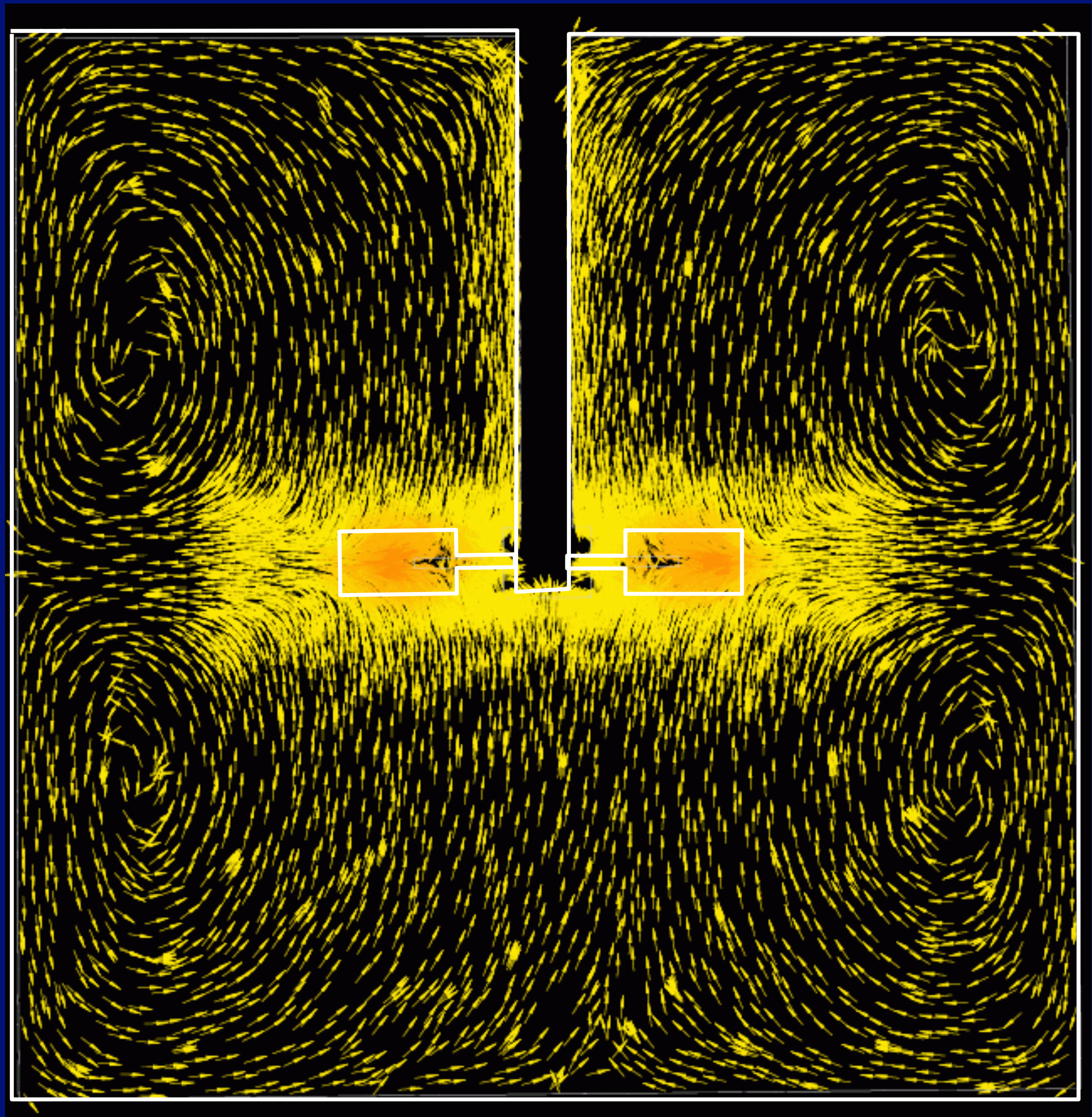
Modeling of mixing tank

Software package:Fluent

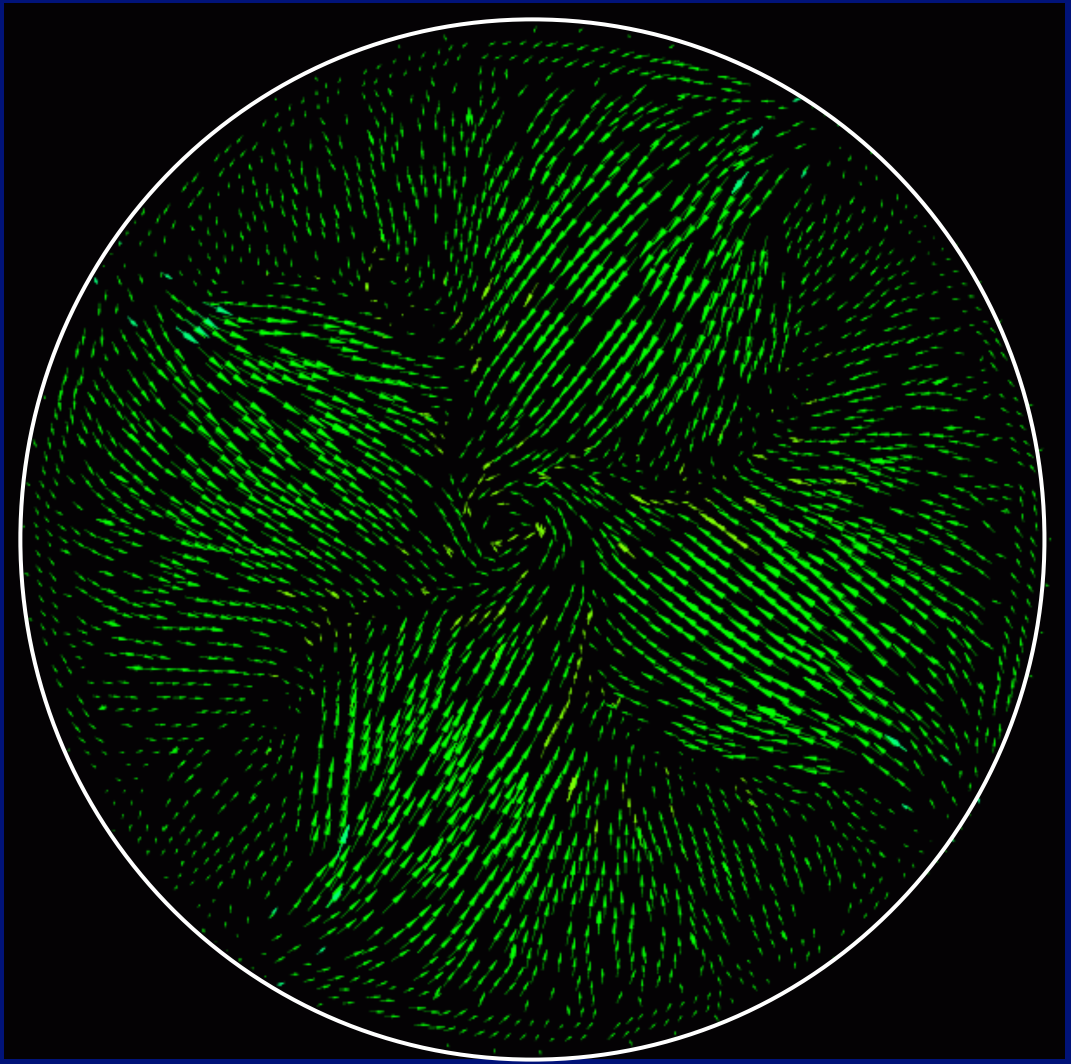




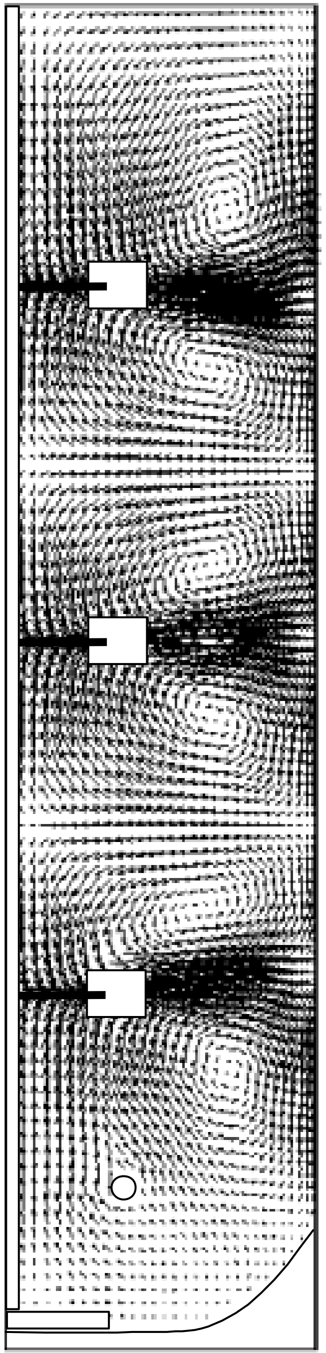
Velocity field (vertical section)

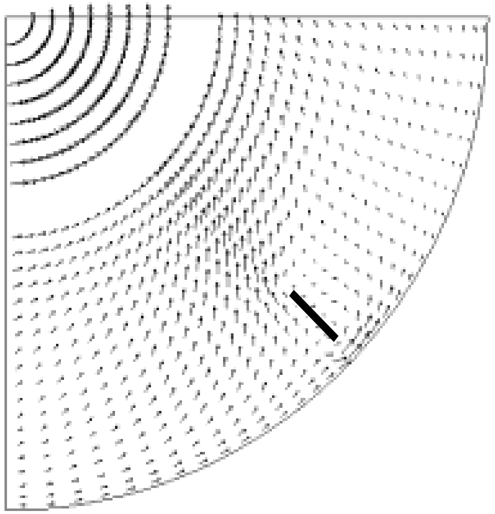


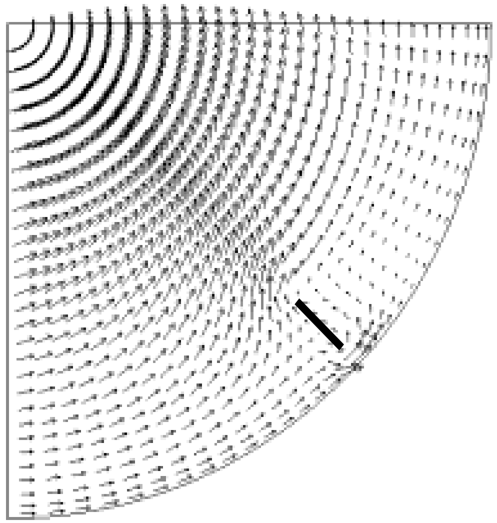
Velocity field (bottom)



Fluiddynamics in a 1500 l reactor with 900 l reaction volume







Simulation of metabolic overflow during fed batch operation

$$\frac{\partial C}{\partial t} + \frac{\partial (u_j C)}{\partial x_j} = \frac{\partial}{\partial x_j}\left(D_{eff} \frac{\partial C}{\partial x_j} \right) + S$$

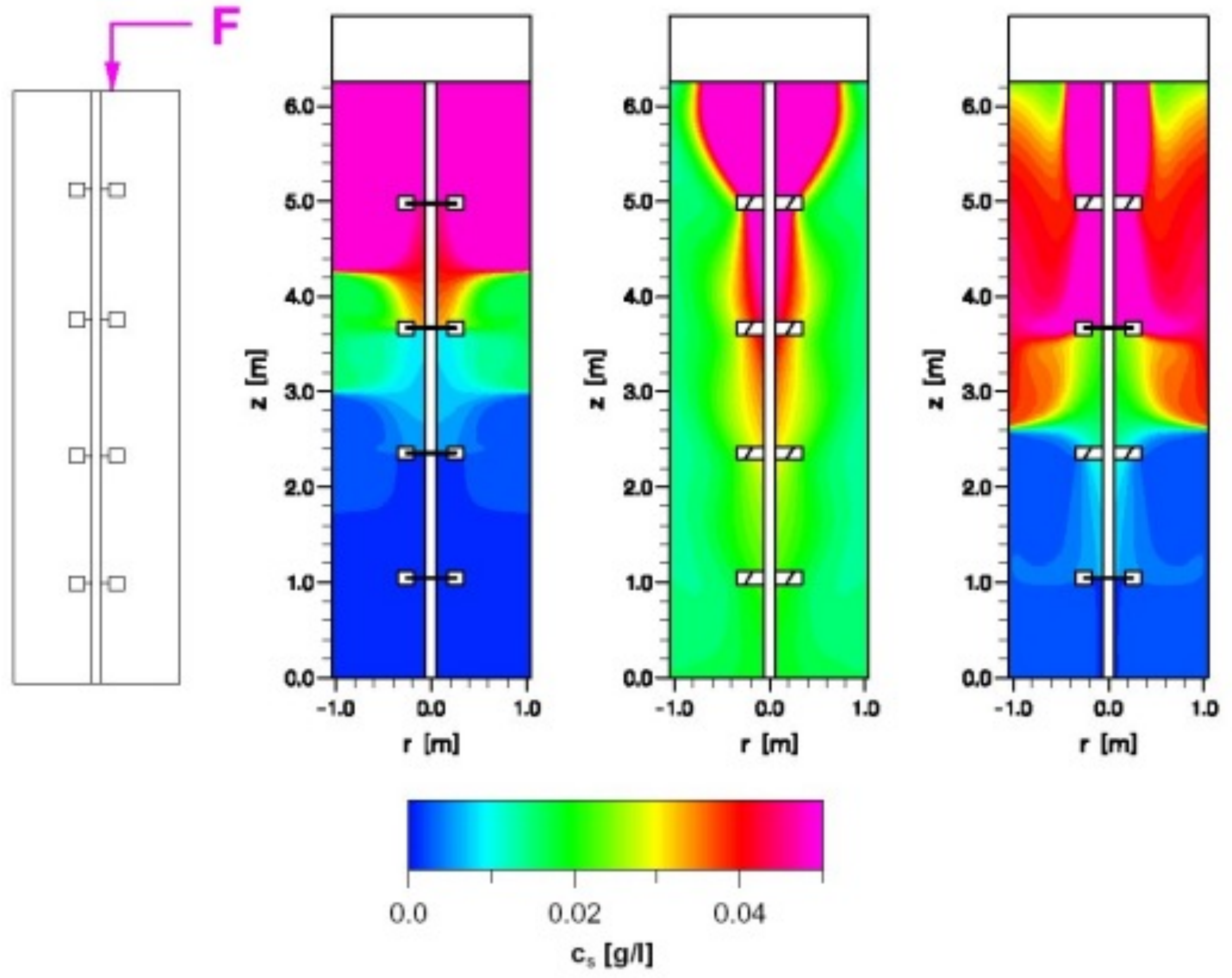
Substrate

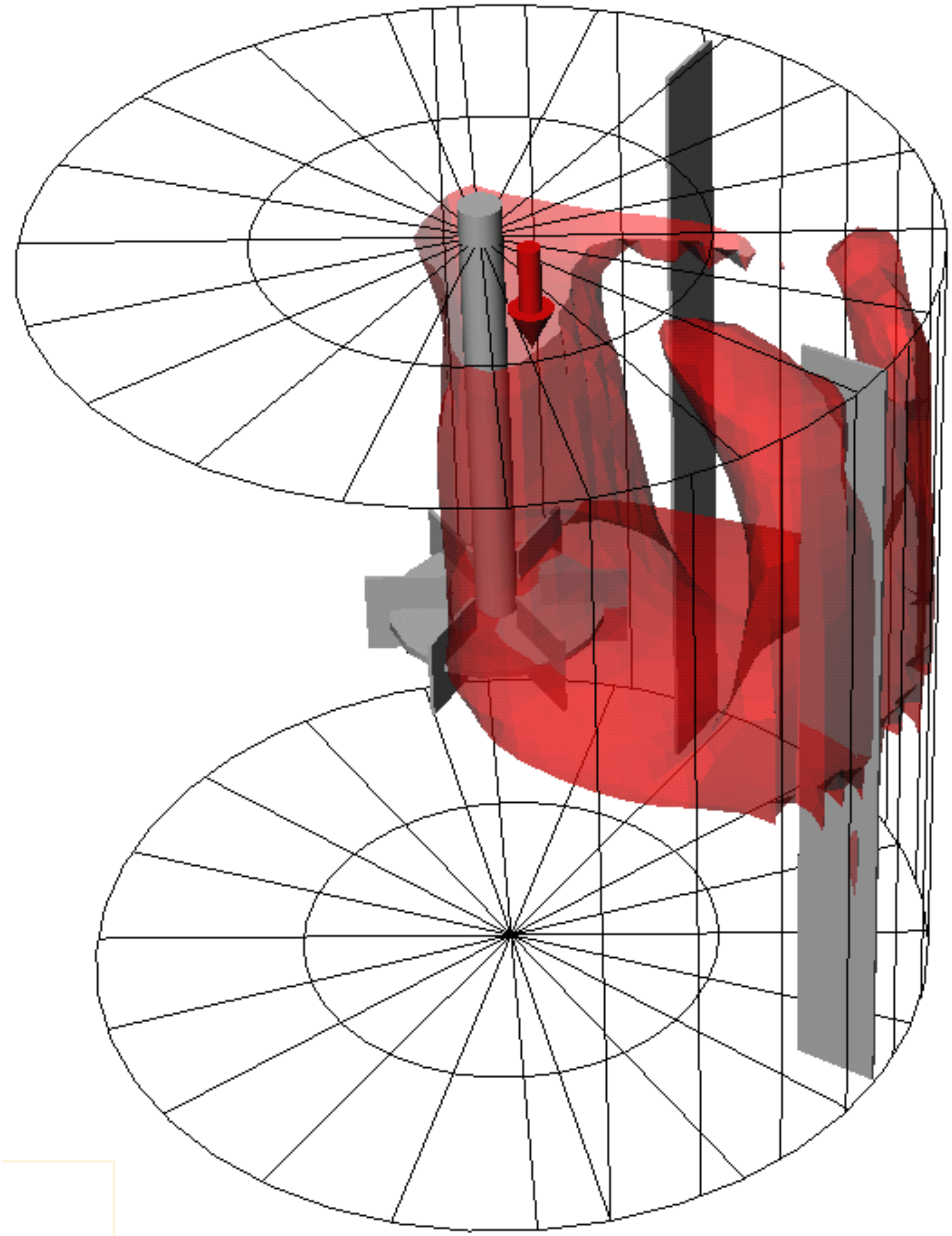
$$S = q_s^{\max} \frac{C_s}{K_s + C_s}$$

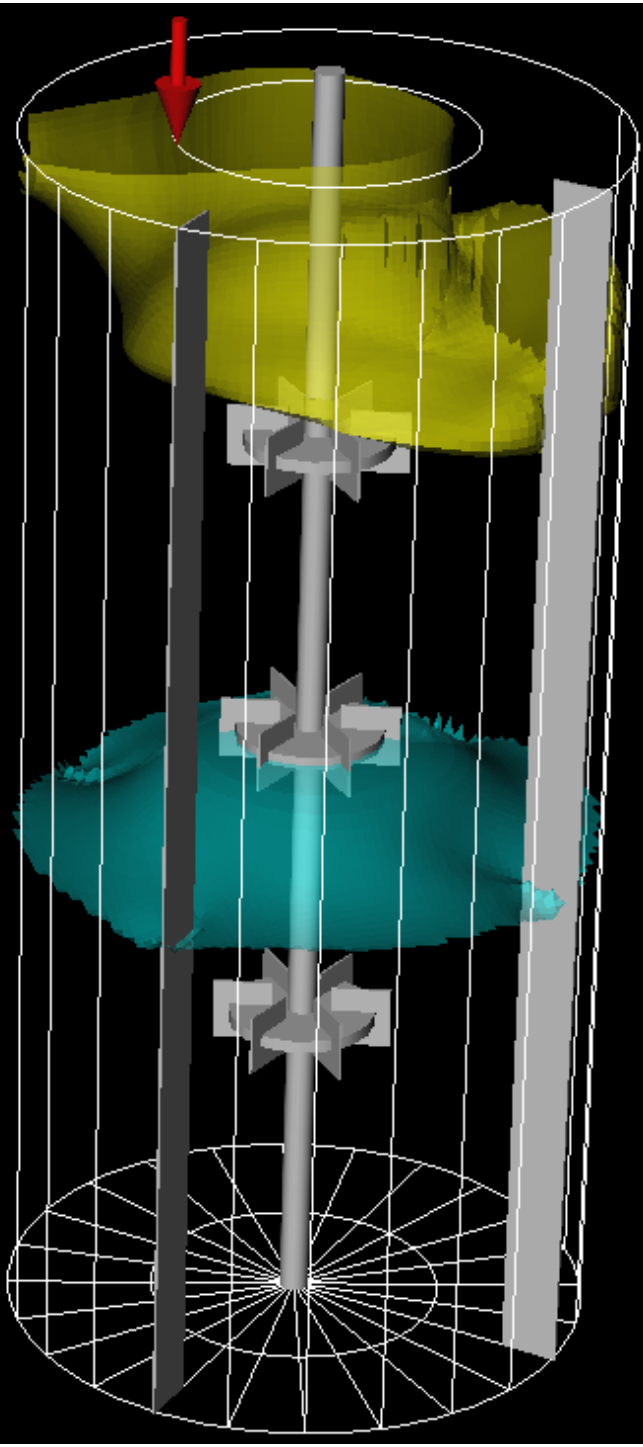
Product

$$S = q_s^{\max} \frac{\max(0, C_s - C_{s,krit})}{K_s + (C_s - C_{s,krit})}$$

Glucose concentration fields during fed-batch cultivation of *Saccharomyces cerevisiae*







Limitations

- **Analysis of systems behavior if biophase needs to be segregated into individual cells -> local interactions between microorganisms and their enviroment = *f* (intracellular state (history of the individuum))**

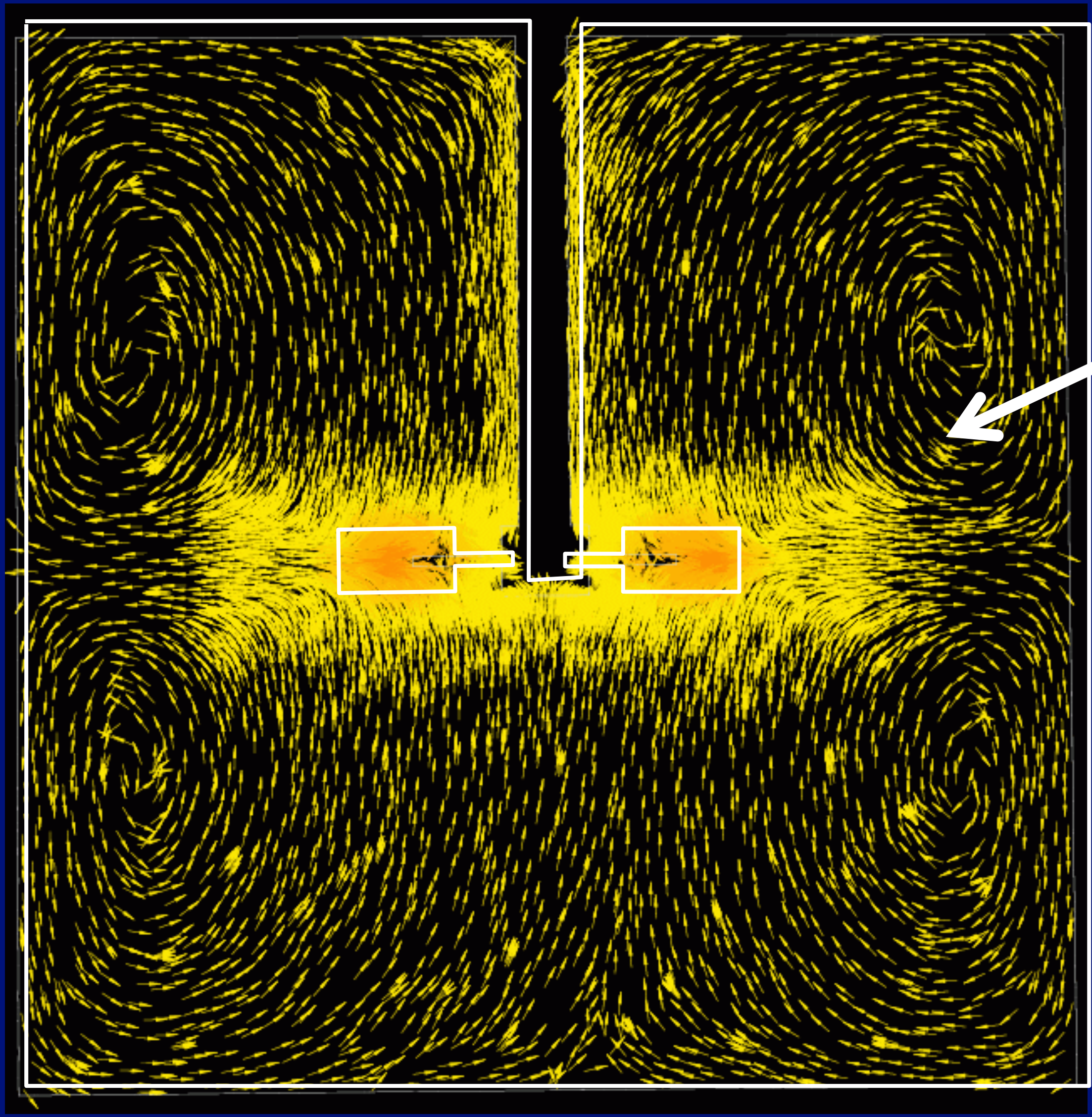
↓

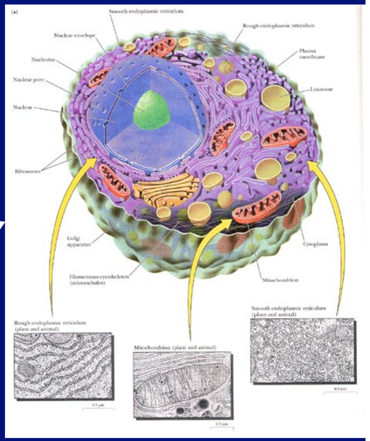
Lifelines of single cells in space and time

↓

Dynamic behavior of the population

Velocity field (vertical section)





Lagrange-Euler-Approach

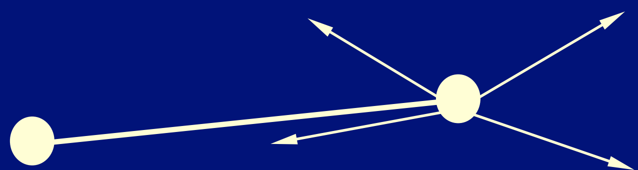
Fluiddynamics

- **Predictions of *convective* movement of a single particle from simulated velocity field:**

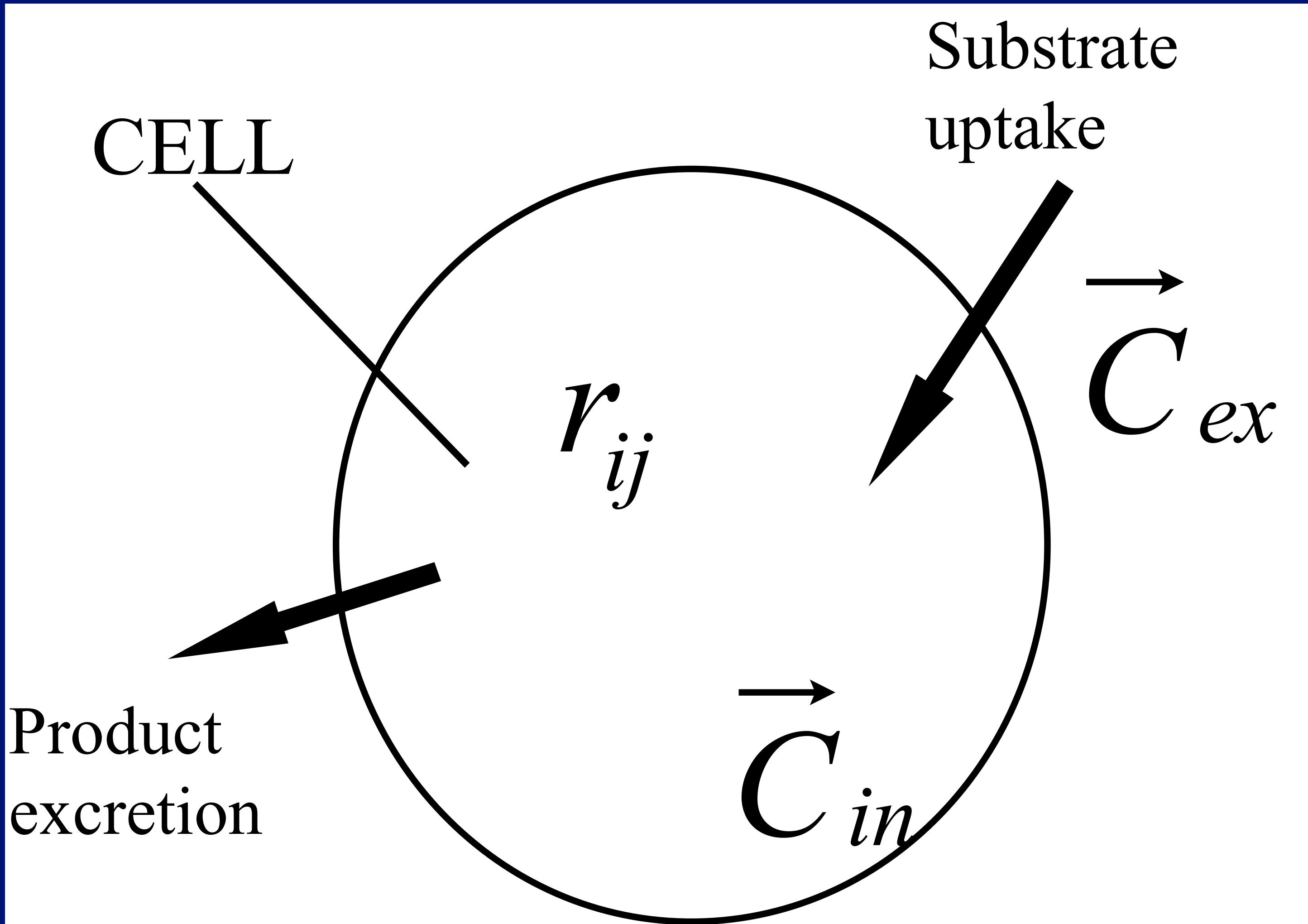
$$\frac{d\vec{x}}{dt} = \vec{V}$$

- **Superposition of random movement caused by turbulent Dispersion (SDE):**

$$\vec{x}(t+dt) = \nabla D_T dt + (2D_T dt)^{1/2}\vec{\xi}$$



ξ - Random number


Substrate
uptake
CELL
$\vec{C}_{ex}$
r_{ij}
Product
excretion
$\vec{C}_{in}$

- **Computation of intracellular state along the trajectory from integration of intracellular mass balance equations:**

$$\frac{d\vec{c}_{in}}{dt} = \sum_{n} r_{ij}\left[\vec{c}_{in}(t), \vec{c}_{ex}(\vec{x}, t)\right]$$

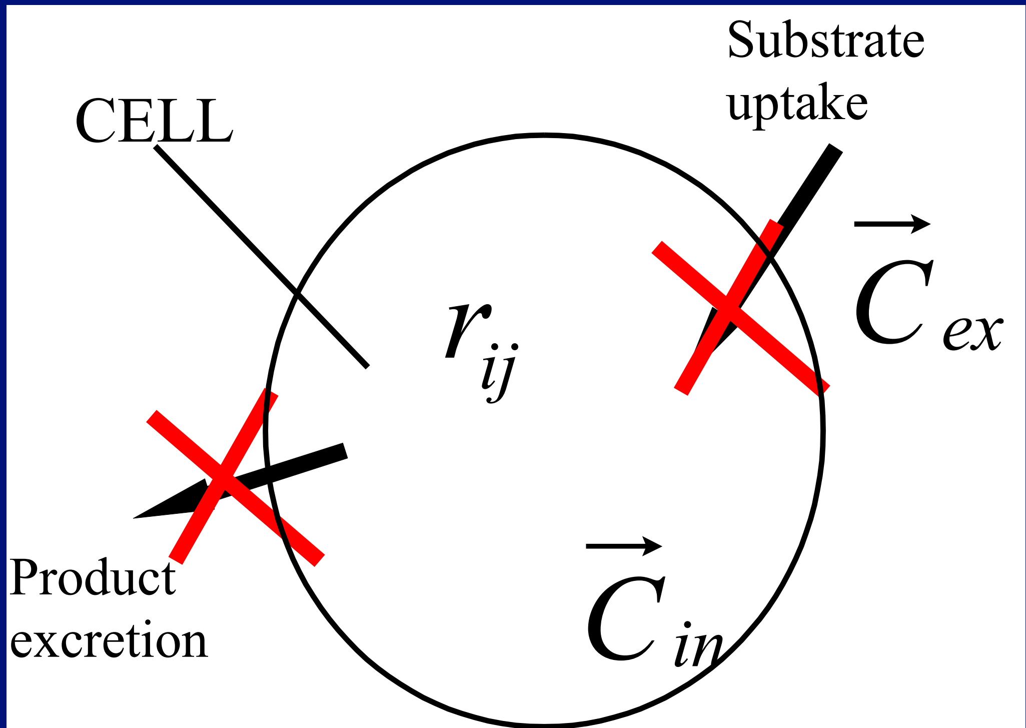
(substrate uptake and product excretion rates are included in r_{ij})

- **The individual exchange rates with the enviroment are taken into account within the Eulerian simulation of the extracellular state:**

$$\frac{\partial \vec{c}_{ex}}{\partial t} + \left(\vec{V}\nabla\right)\vec{c}_{ex} = \nabla\left(D_T \nabla \vec{c}_{ex}\right) + S_{exchange}\left(\vec{c}_{ex}, \vec{c}_{in}\right)$$

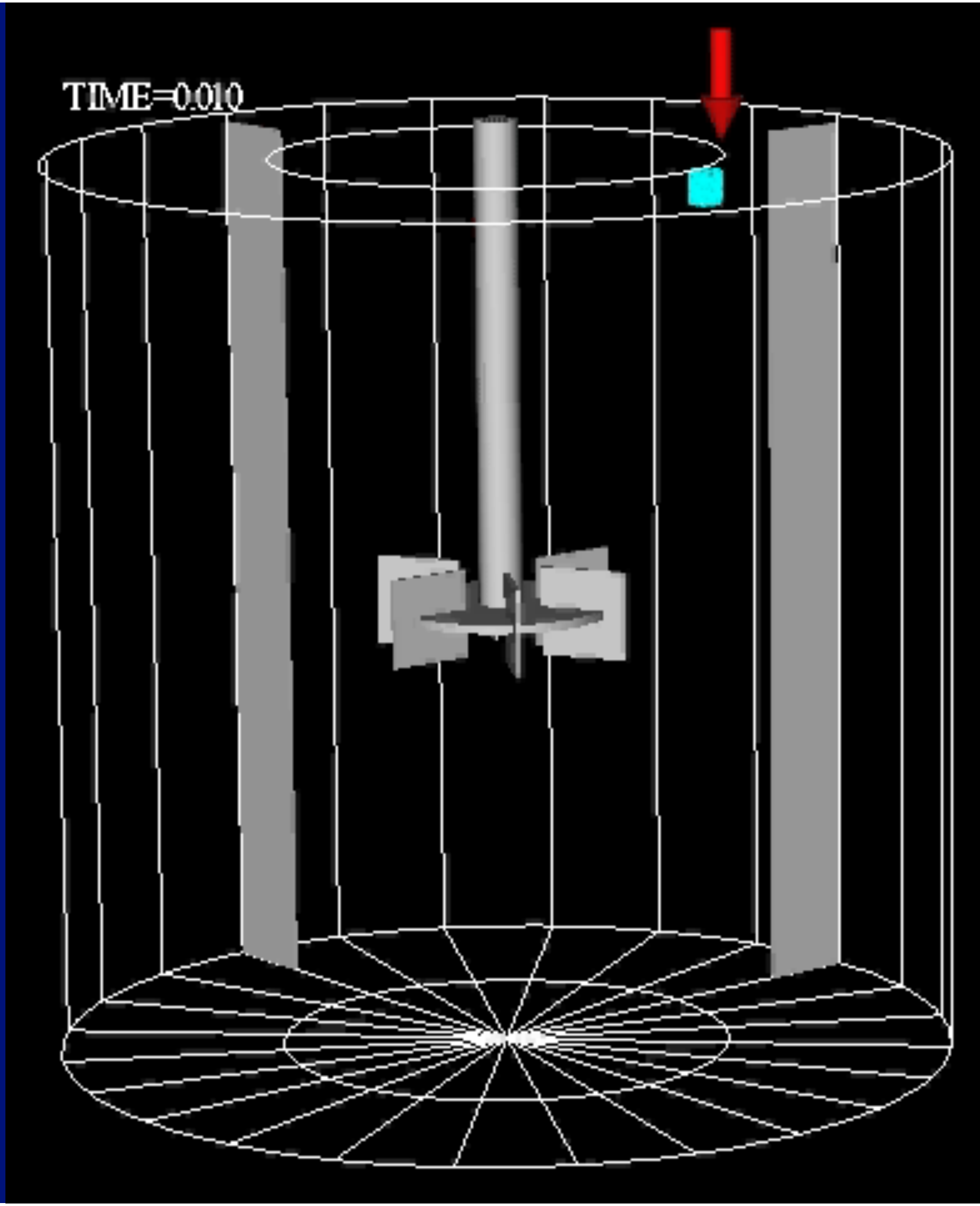
($\vec{V}$ and D_T again from CFD-simulations)

WITHOUT EXCHANGE (TRACER PARTICLE)



SIMULATION OF TRACER EXPERIMENTS

MIXING CHARACTERISTICS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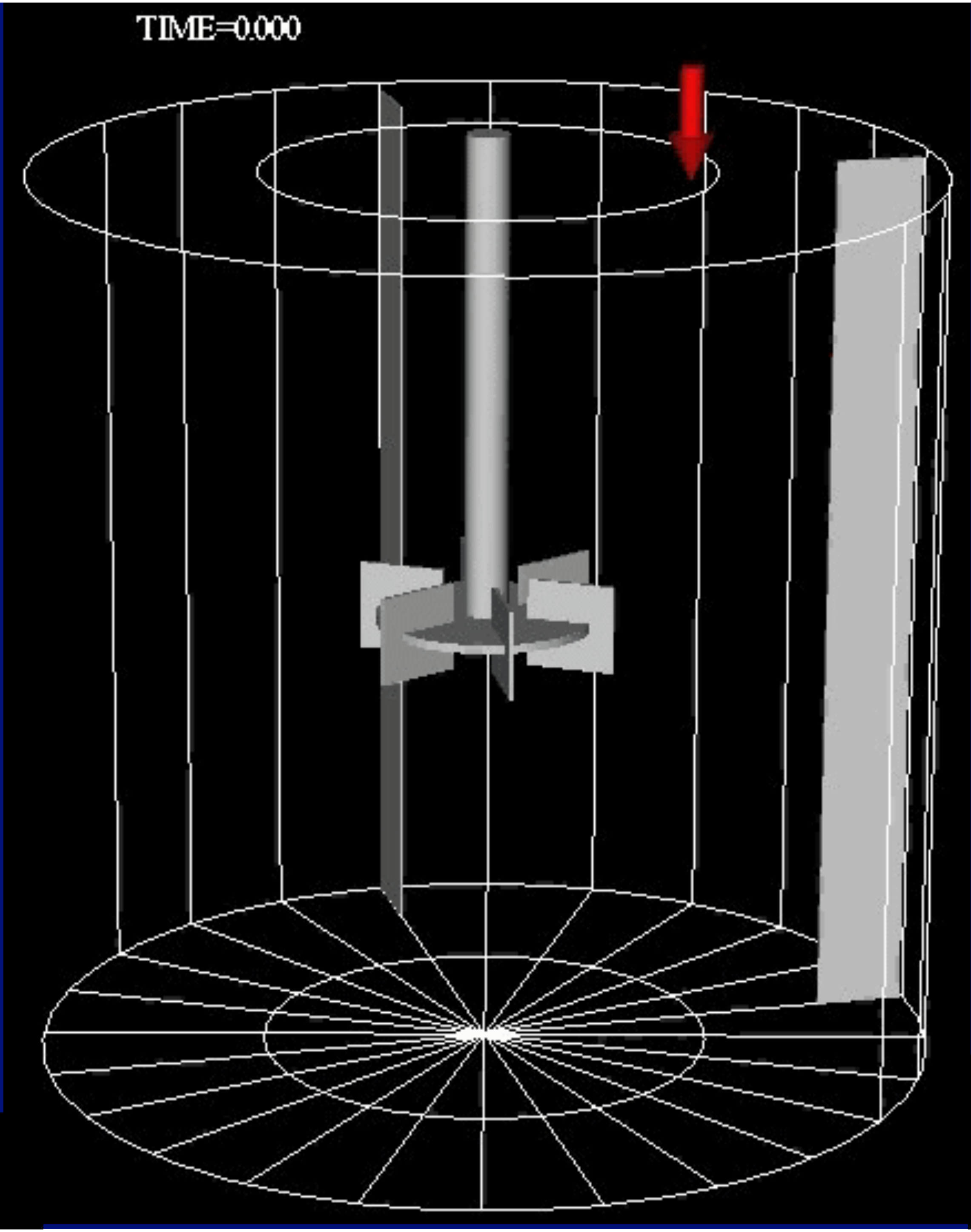
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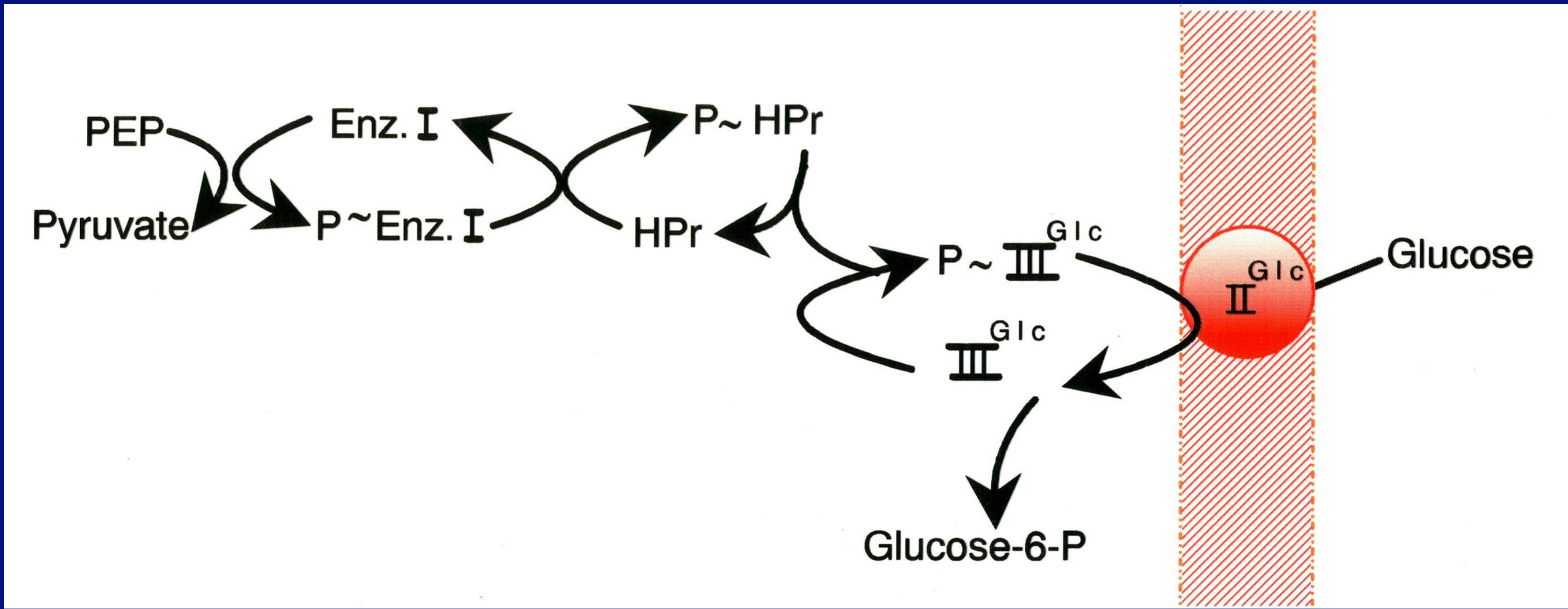
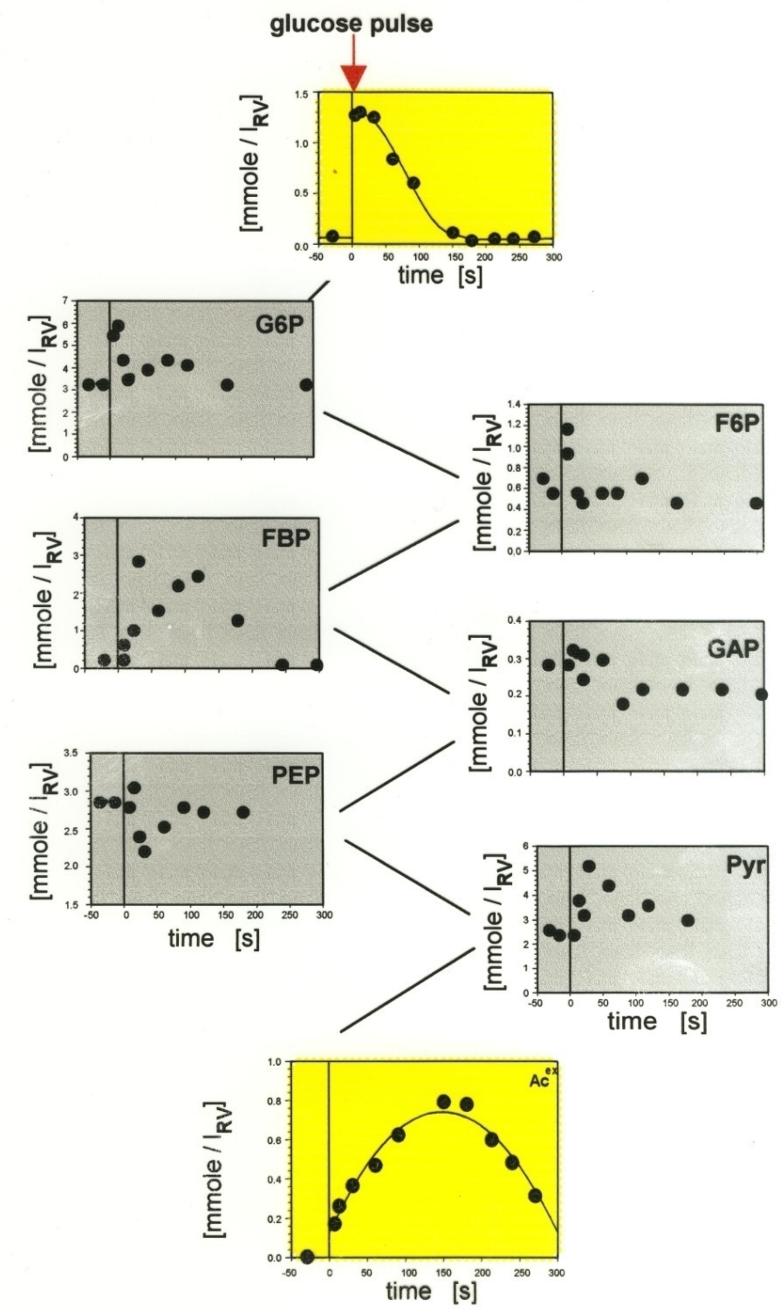
Glucose uptake into *Escherichia coli*:

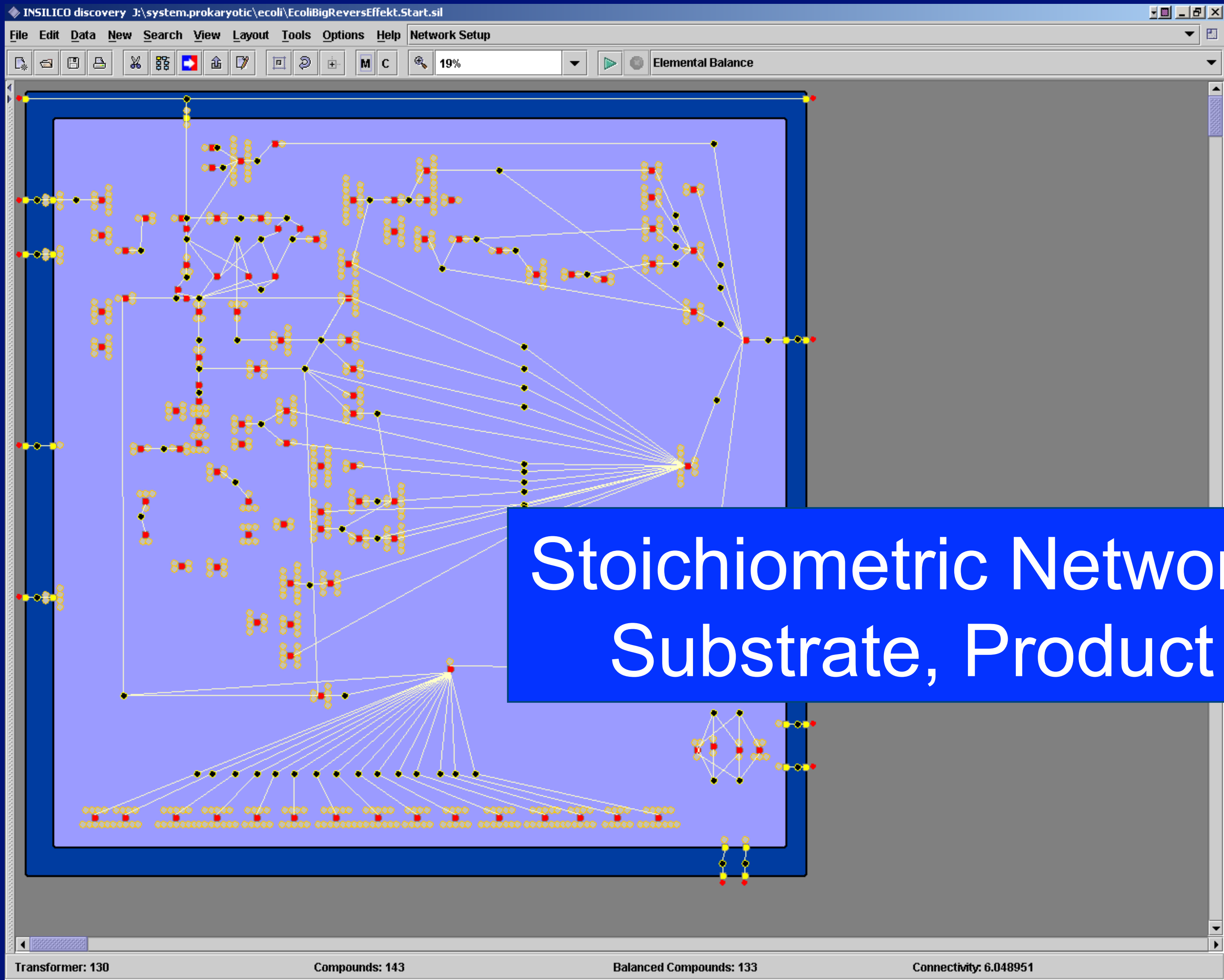
Traveling along the lifelines of single cells


PEP
Pyruvate
Enz. I
P~Enz. I
P~ HPr
HPr
P ~ III Glc
III Glc
II Glc
Glucose
Glucose-6-P

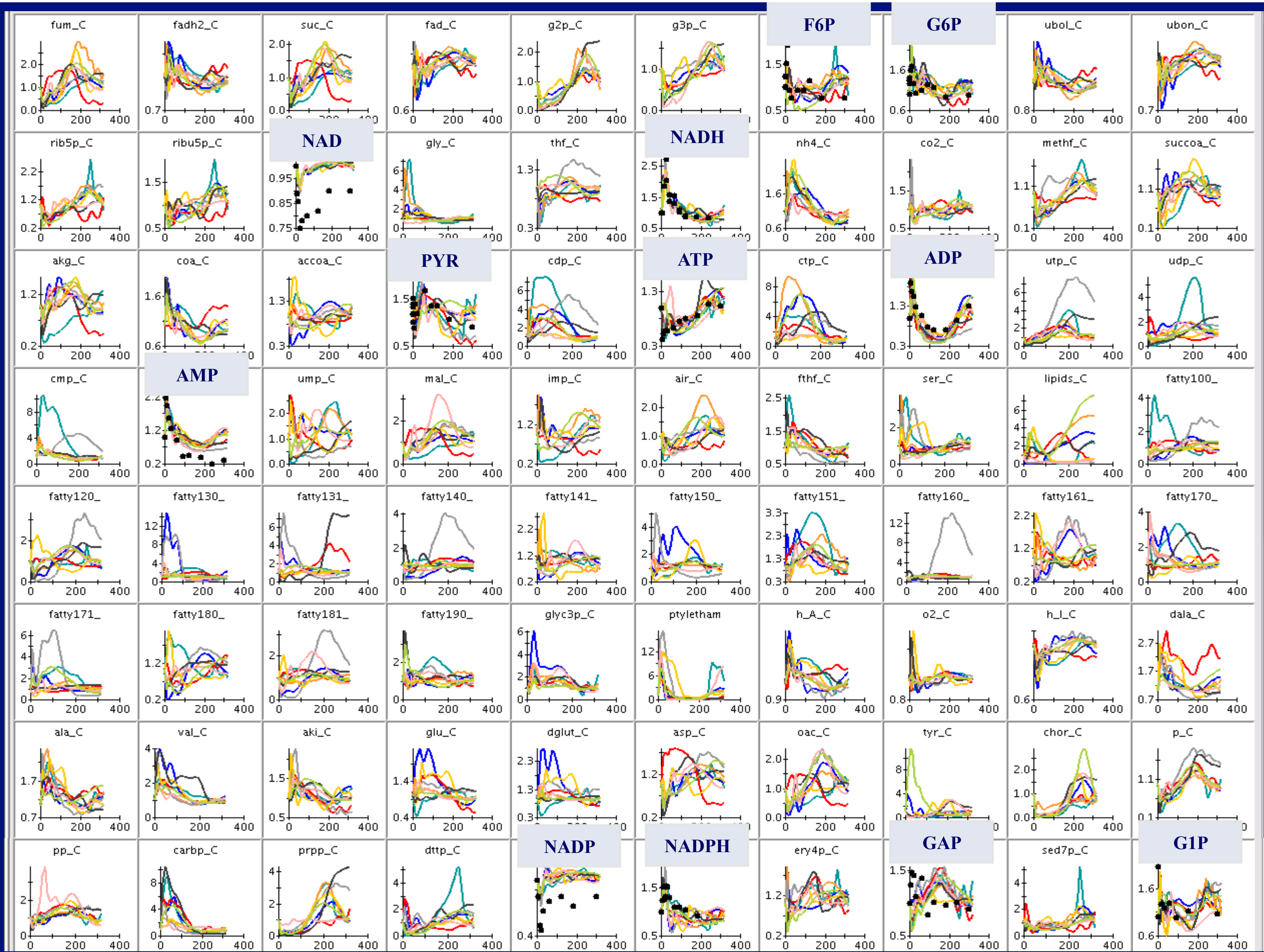
STIMULUS-RESPONSE METHODOLOGY



Stoichiometric Network: Substrate, Product

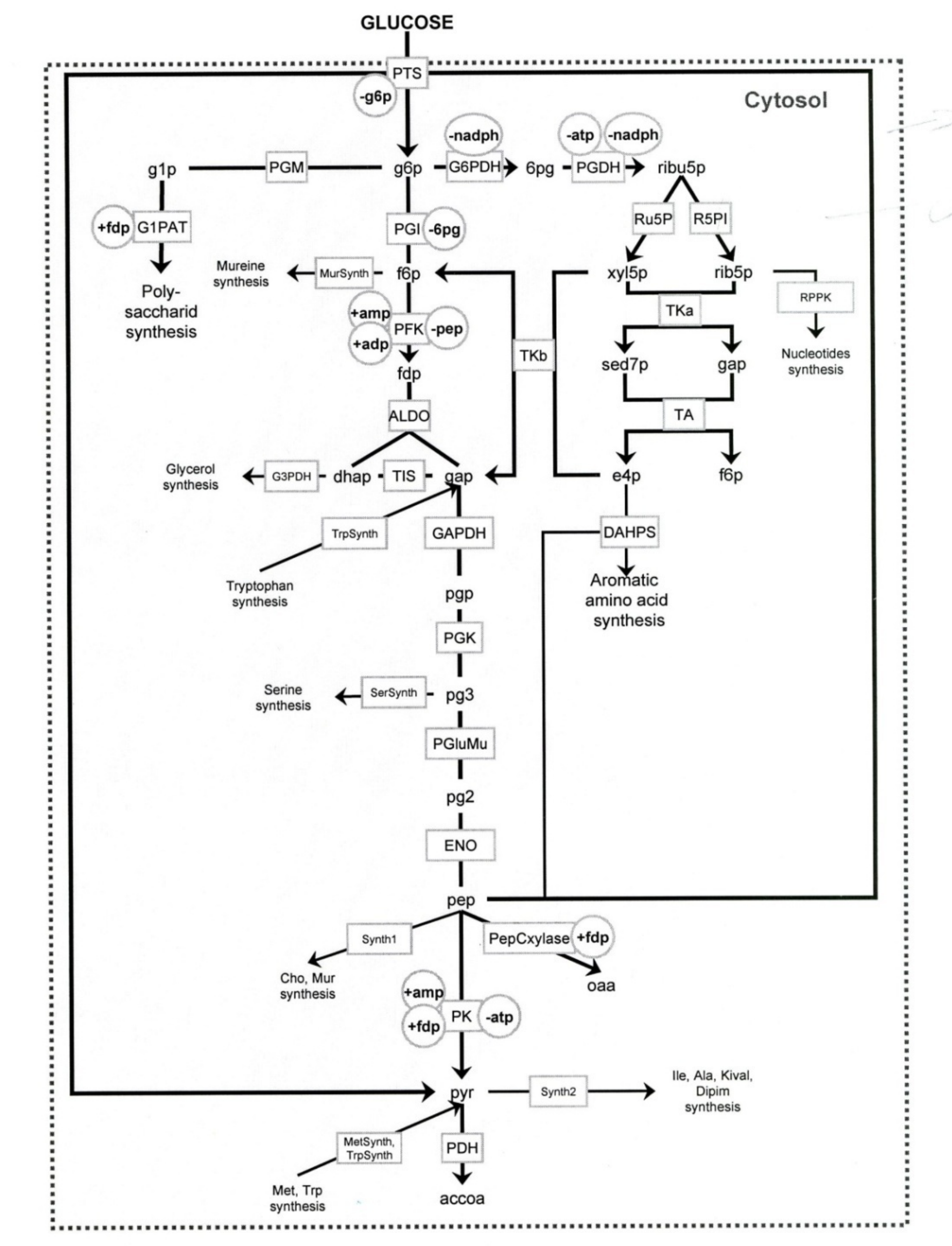


Escherichia coli



Escherichia coli

Reuss, Aguielera-Vazquez, Mauch (2007). Topics Current Genetics



Chassagnole, Noissomit-Rizzi, Schmid, Mauch, Reuss (2002) Biotechnol. Bioeng.79, 53-73

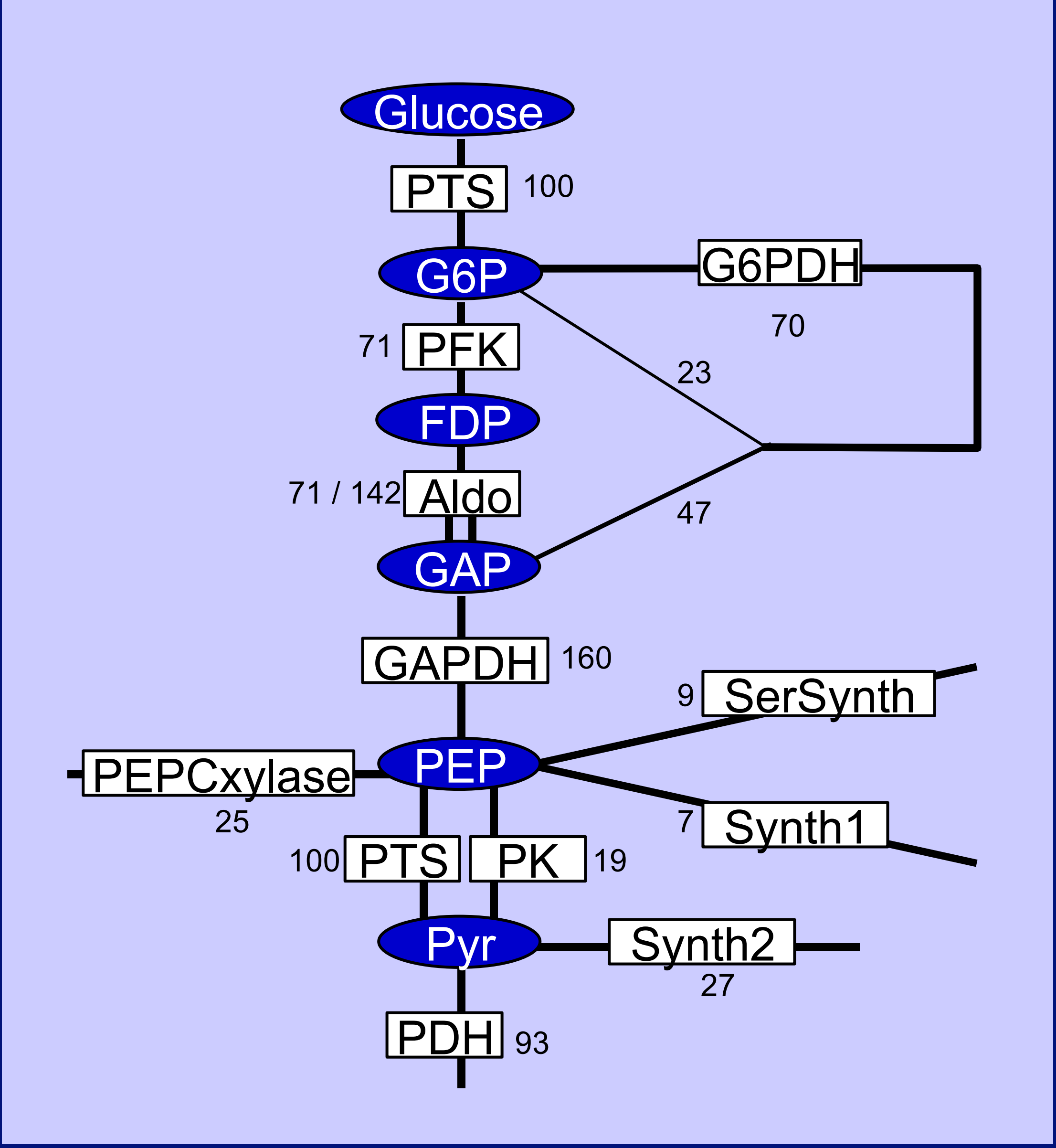
Bridging scales

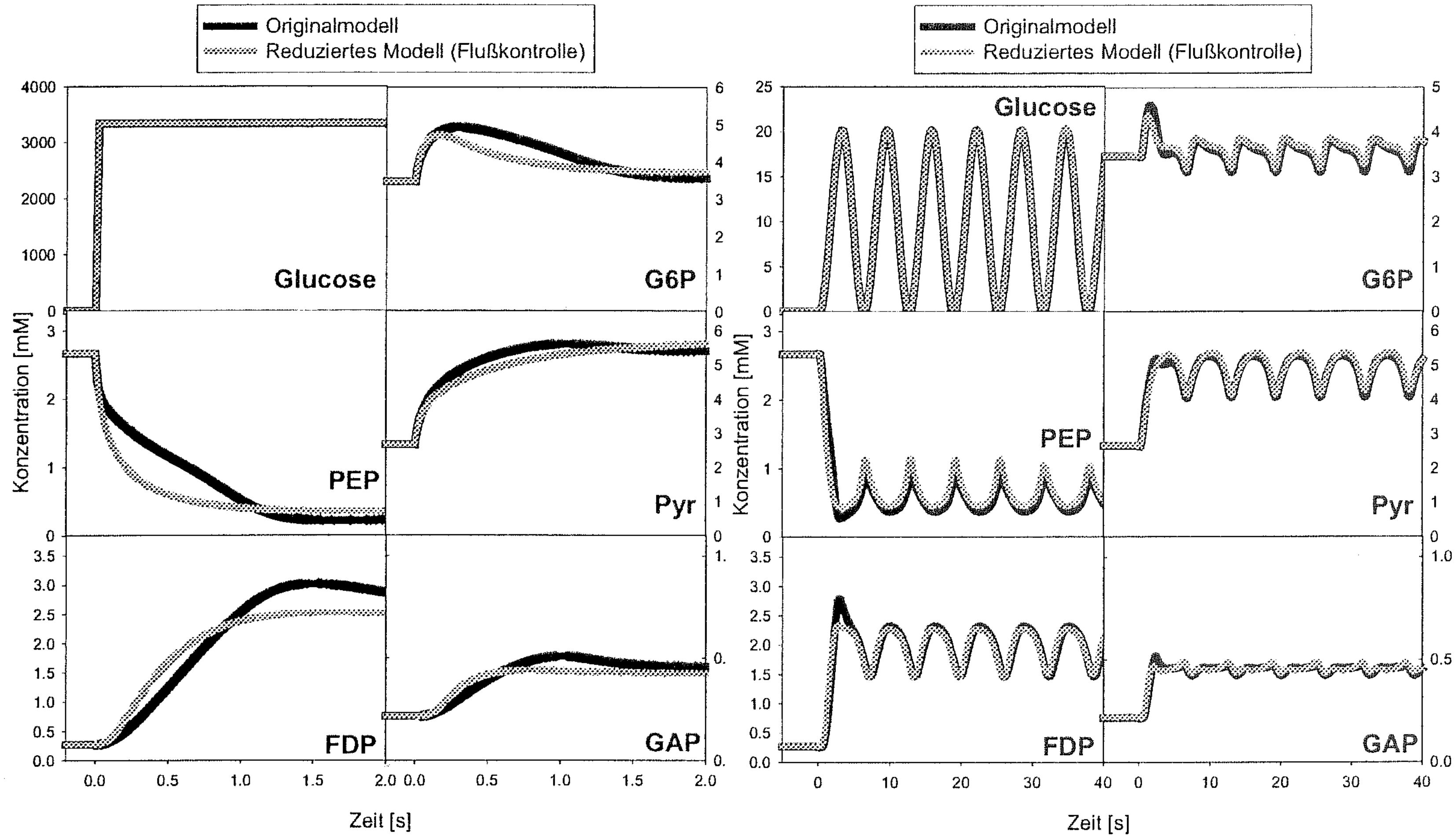
Model reduction

Flux control coefficients

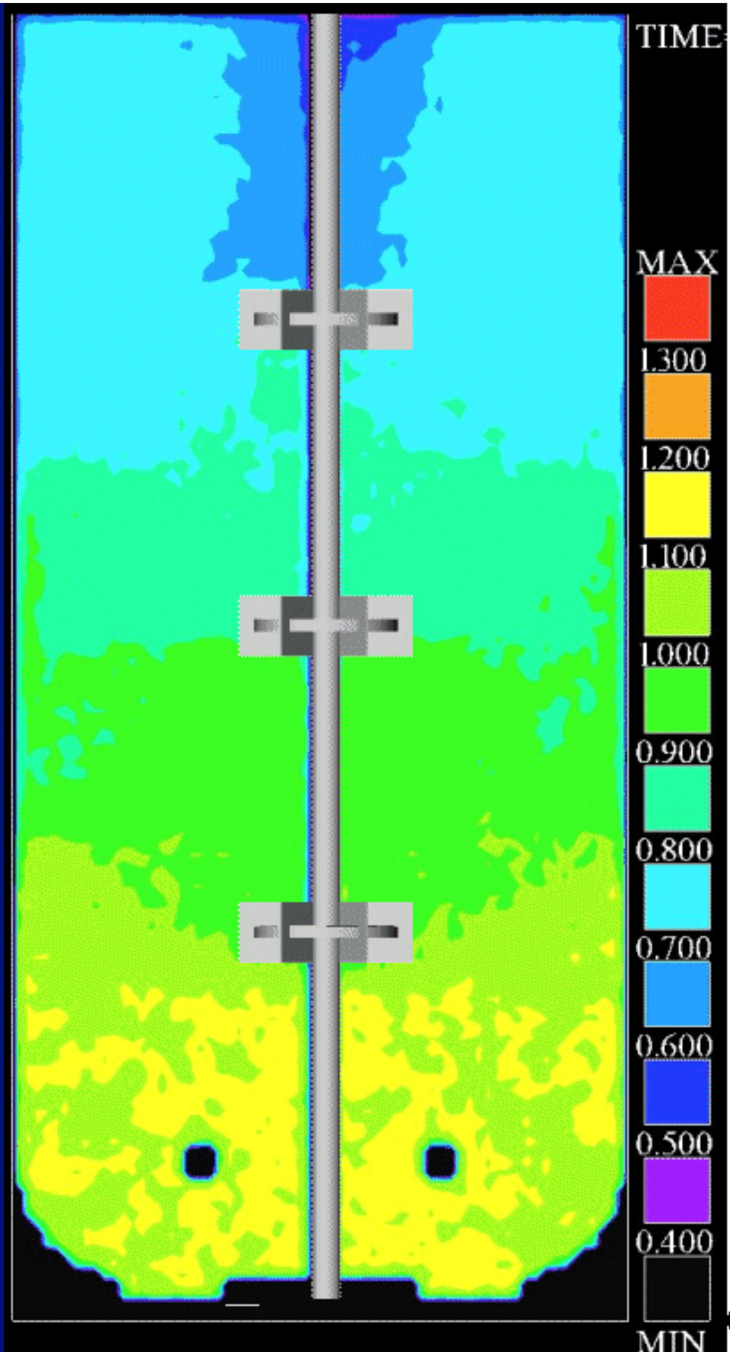
$$C^J = \frac{E}{J}\frac{dJ}{dE} = \frac{d \ln J}{d \ln E}$$

Glucose uptake system (*E.coli*: PTS)

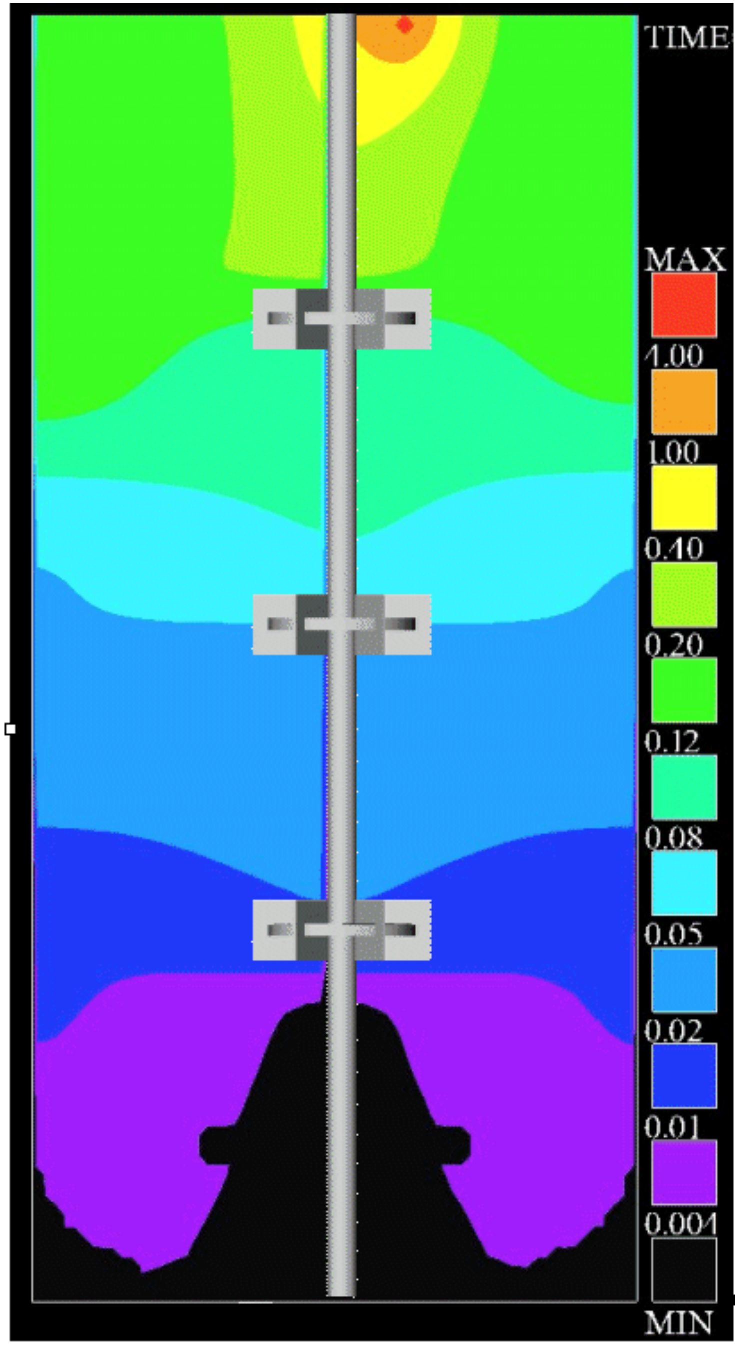




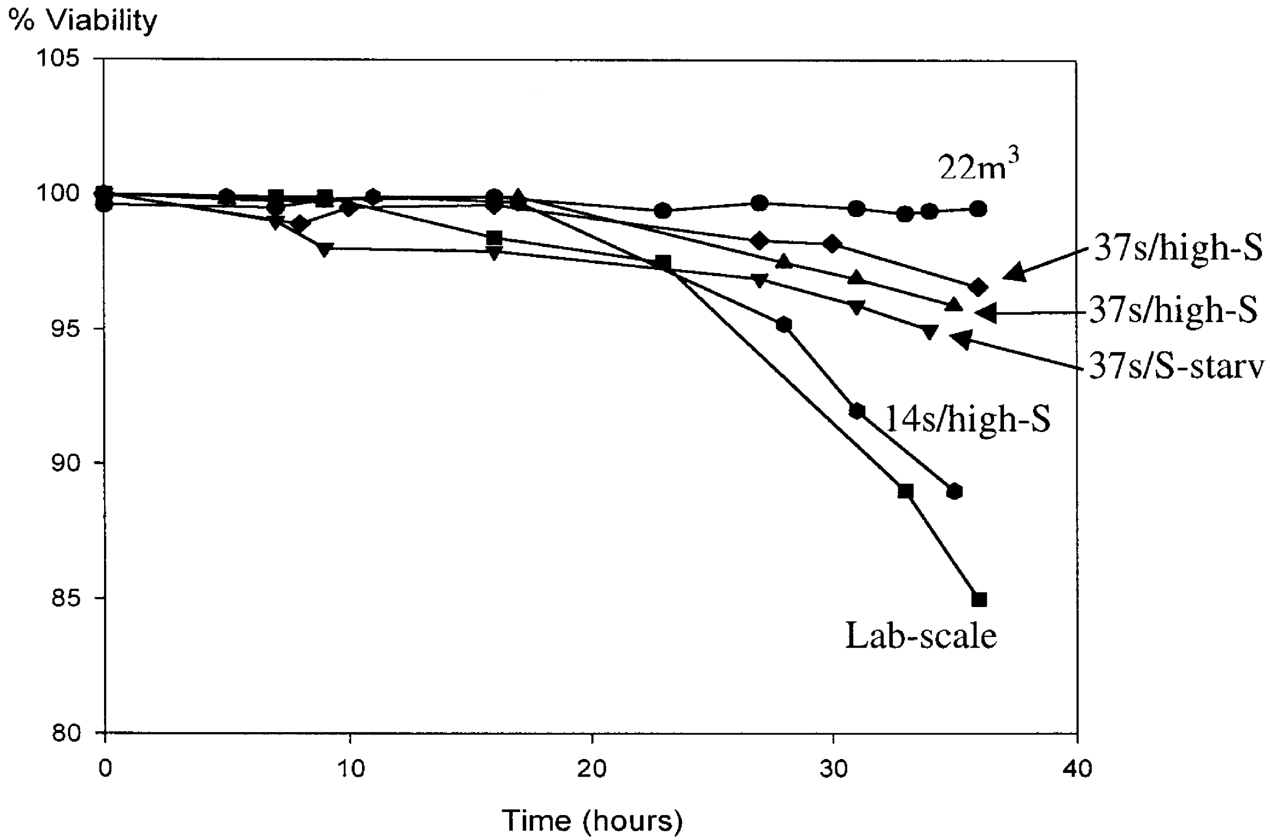
Originalmodell
Reduziertes Modell (Flußkontrolle)
Glucose
G6P
PEP
Pyr
FDP
GAP
Konzentration [mM]
Zeit [s]
Originalmodell
Reduziertes Modell (Flußkontrolle)
Glucose
G6P
PEP
Pyr
FDP
GAP
Konzentration [mM]
Zeit [s]



Pep/Pyr

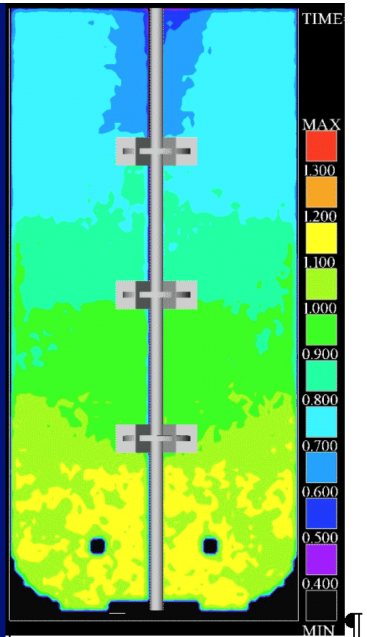


Glucose (Segregated)

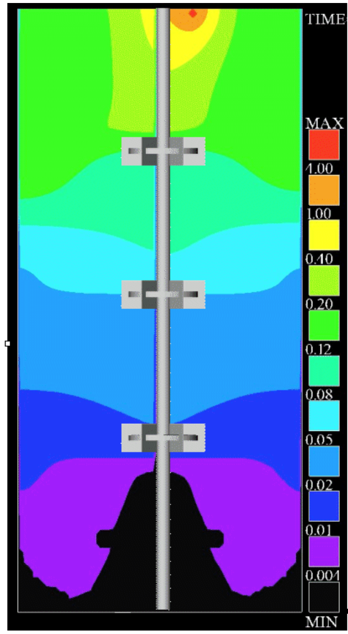


E. coli viability (flow cytometry) in lab-scale, at 22 m^3-scale and in a scale-down reactor with 14-37 sec passages through a glucose starvation or glucose excess (oxygen limitation) zone

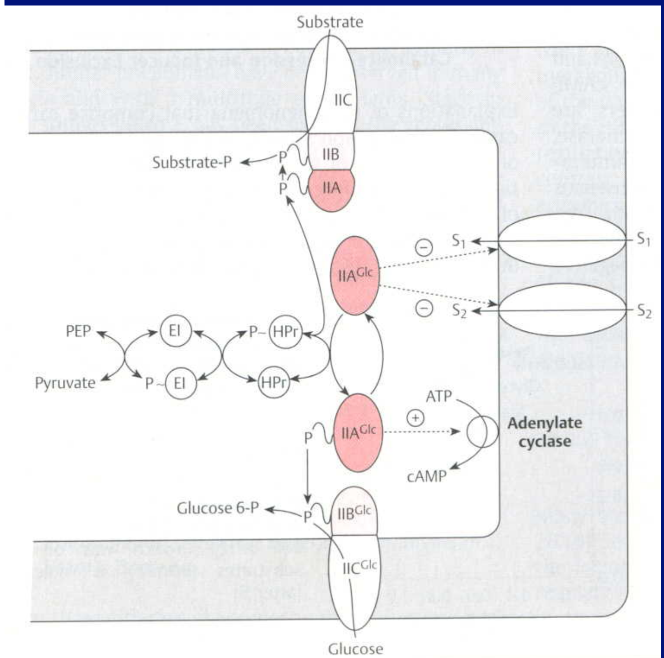
Hewitt et al. 1999

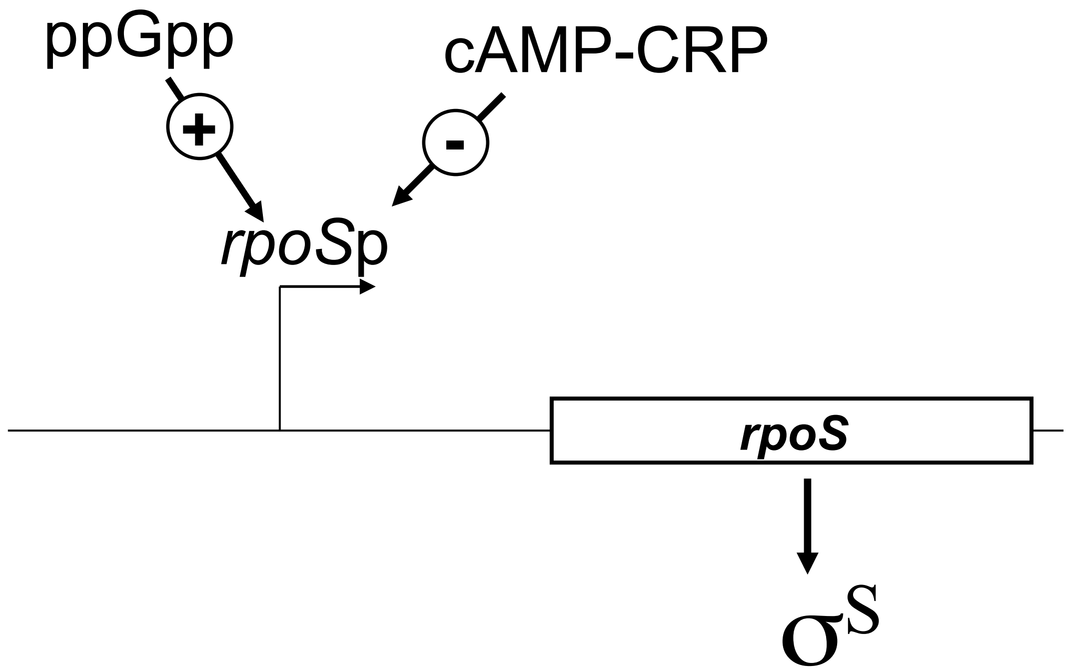


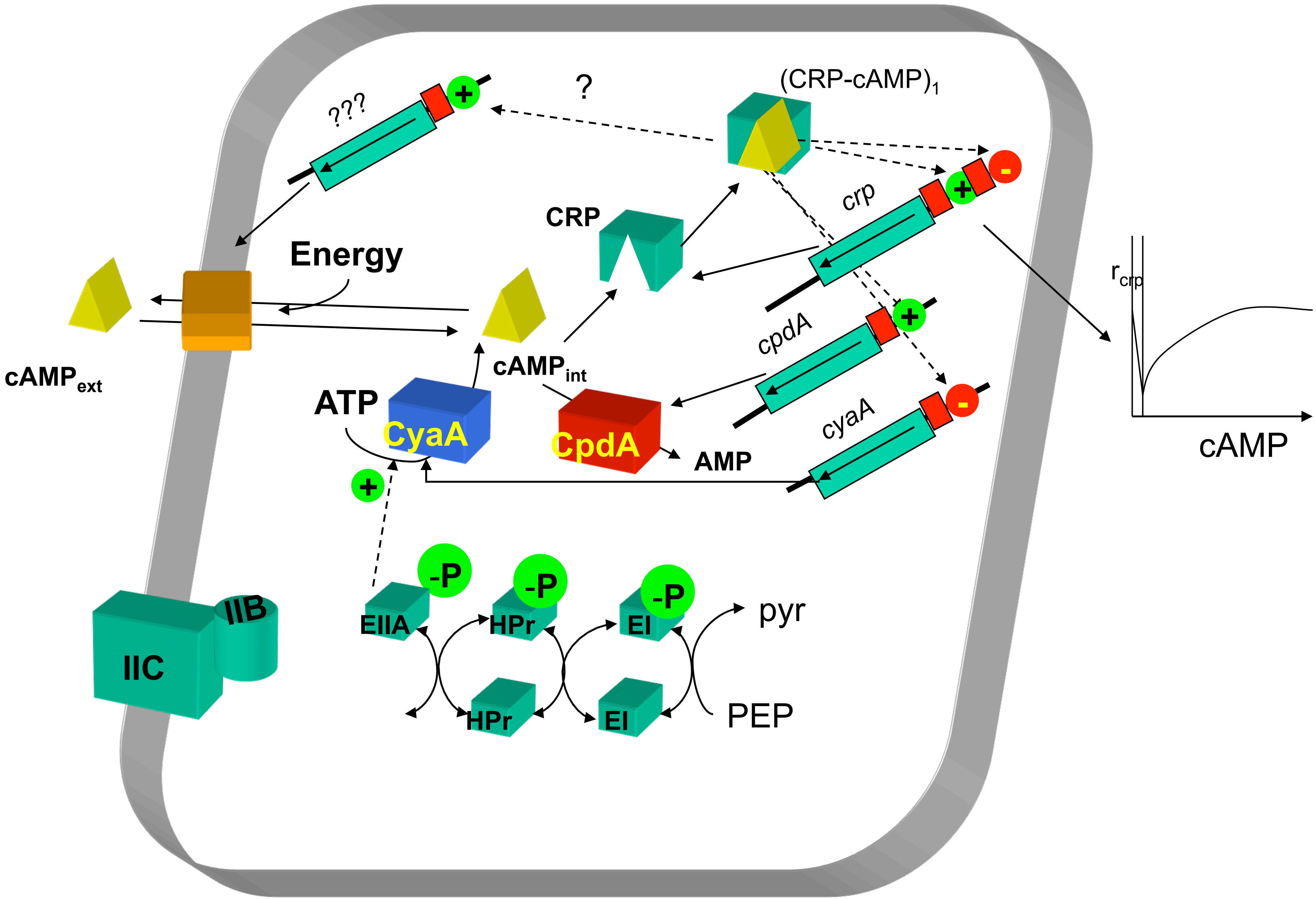
Pep/Pyr



Glucose (Segregated)

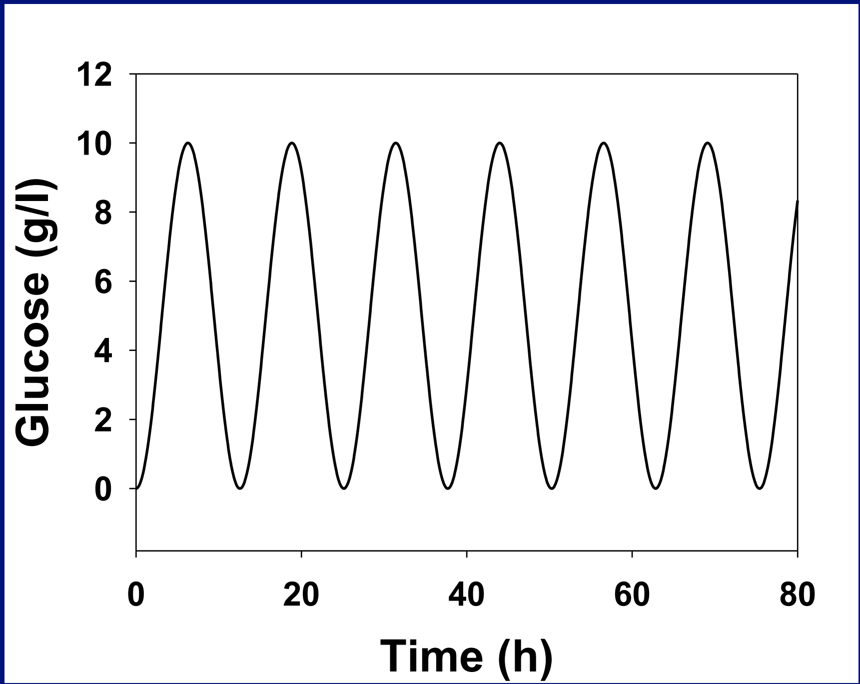


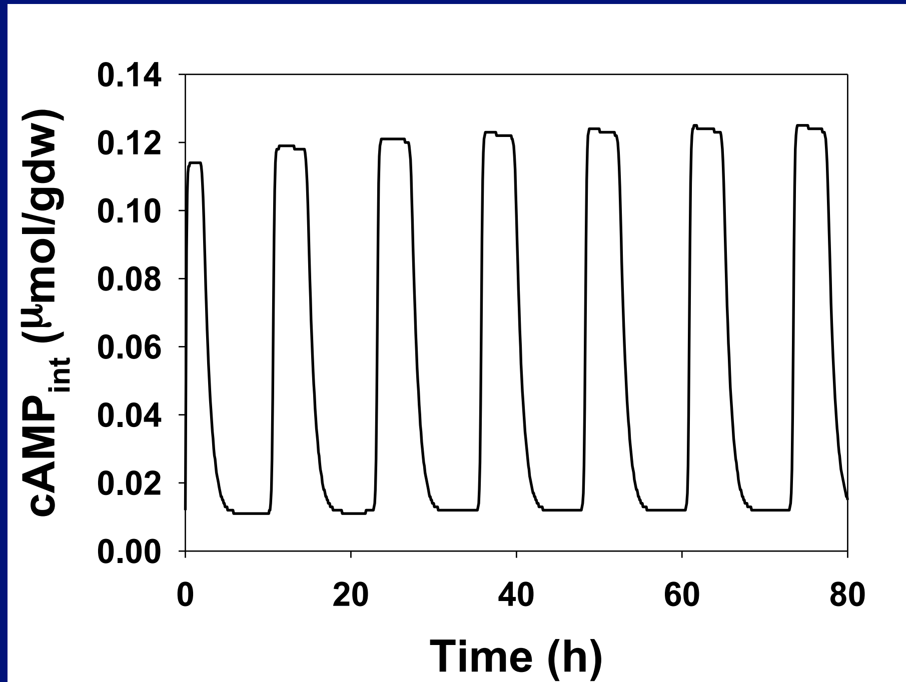




???
?
(CRP-cAMP)1
crp
CRP
Energy
cAMPext
cAMPint
cpdA
ATP
CyaA
CpdA
AMP
cyaA
rcrp
cAMP
-P
EIIA
HPr
EI
pyr
PEP
IIC
IIB

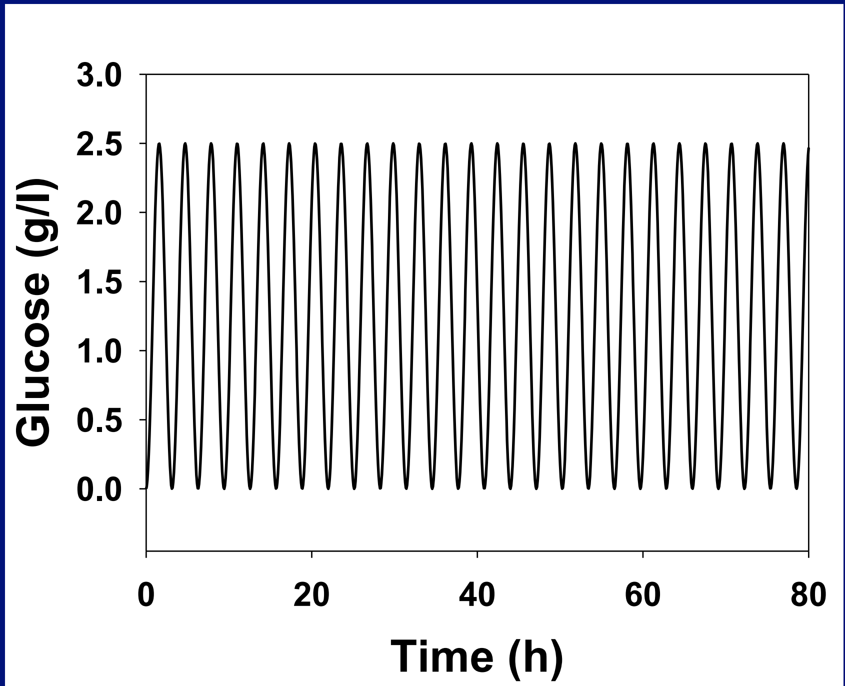
Low frequency

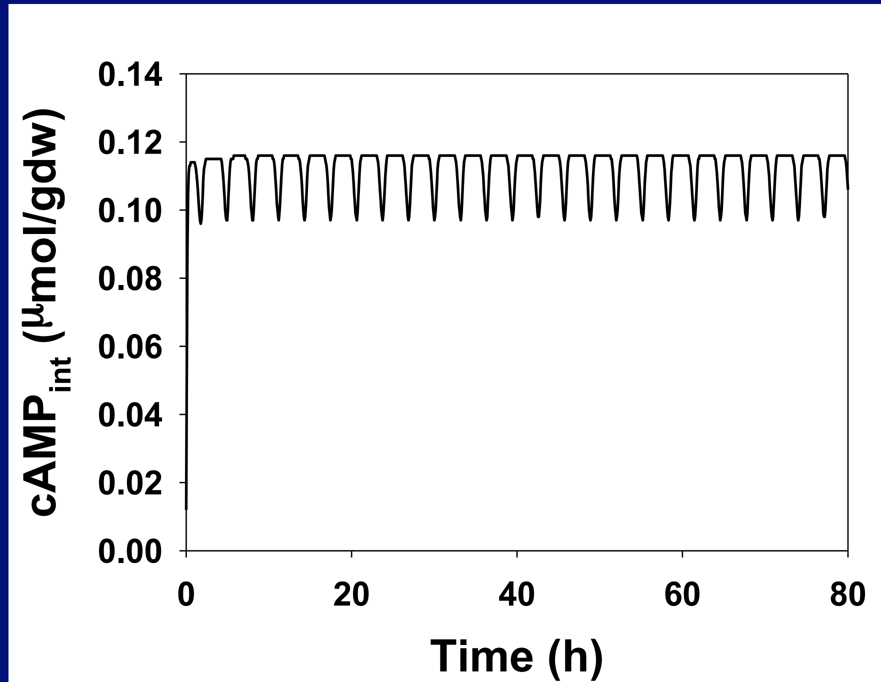




Sevilla, Reuss: to be published

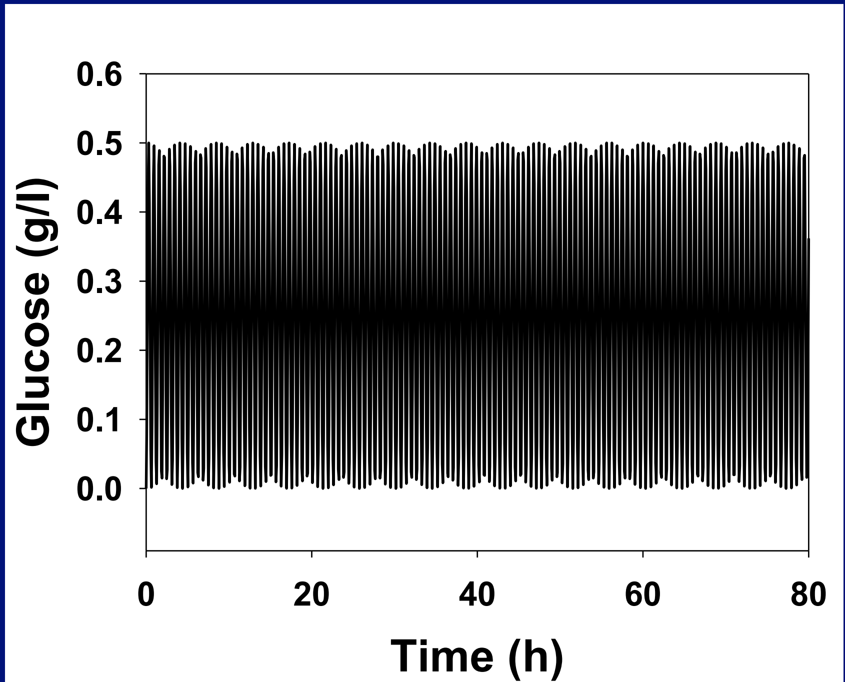
Medium frequency

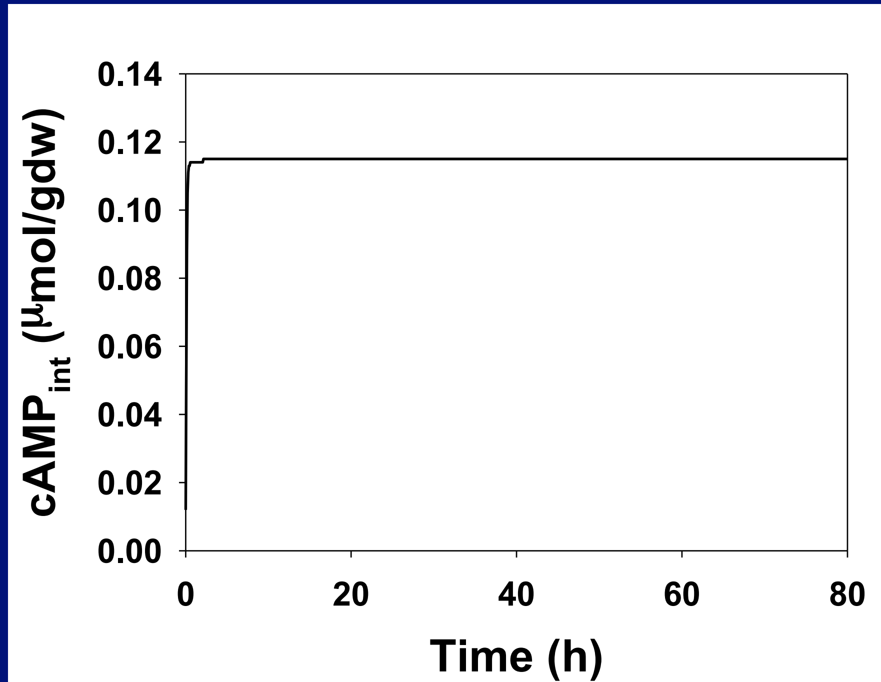




Sevilla, Reuss: to be published

High frequency

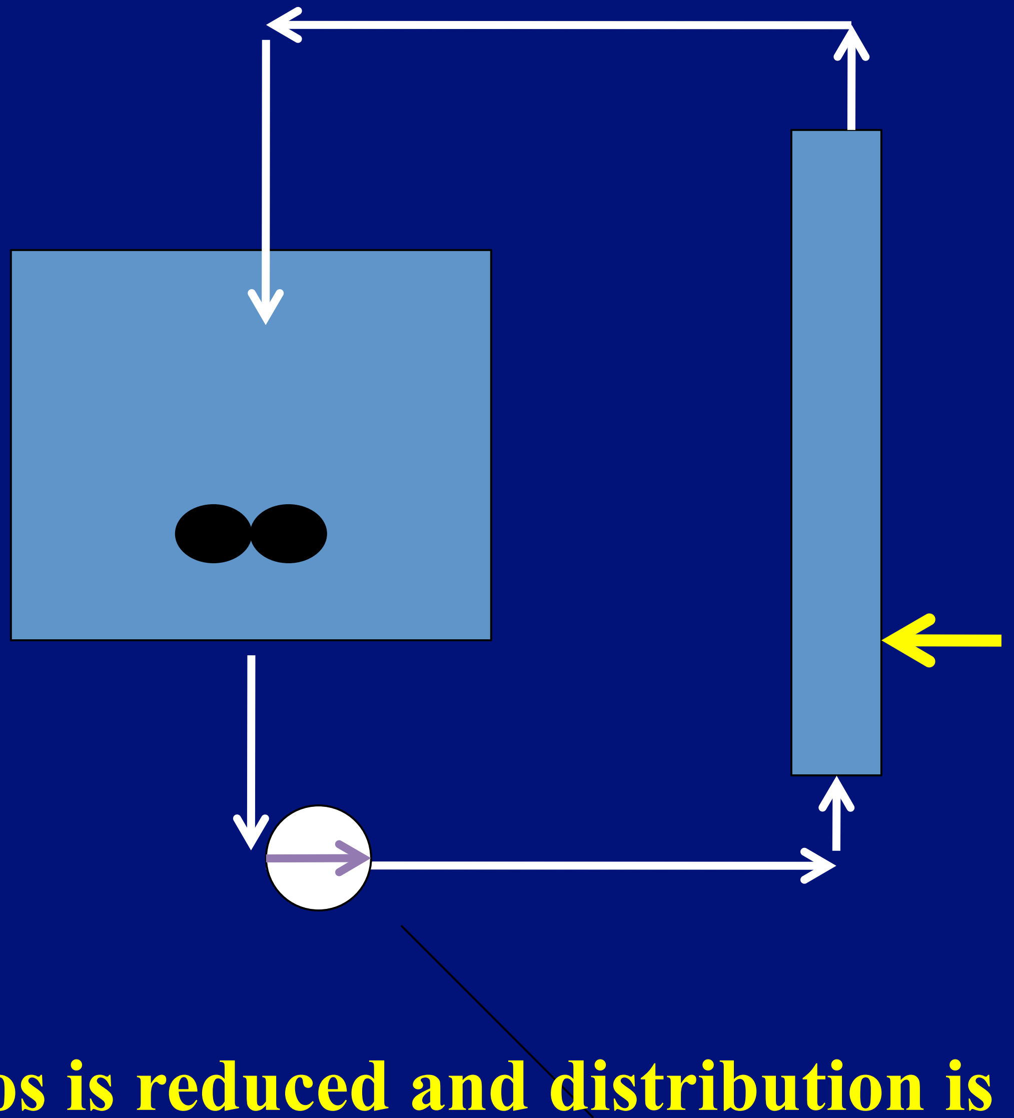




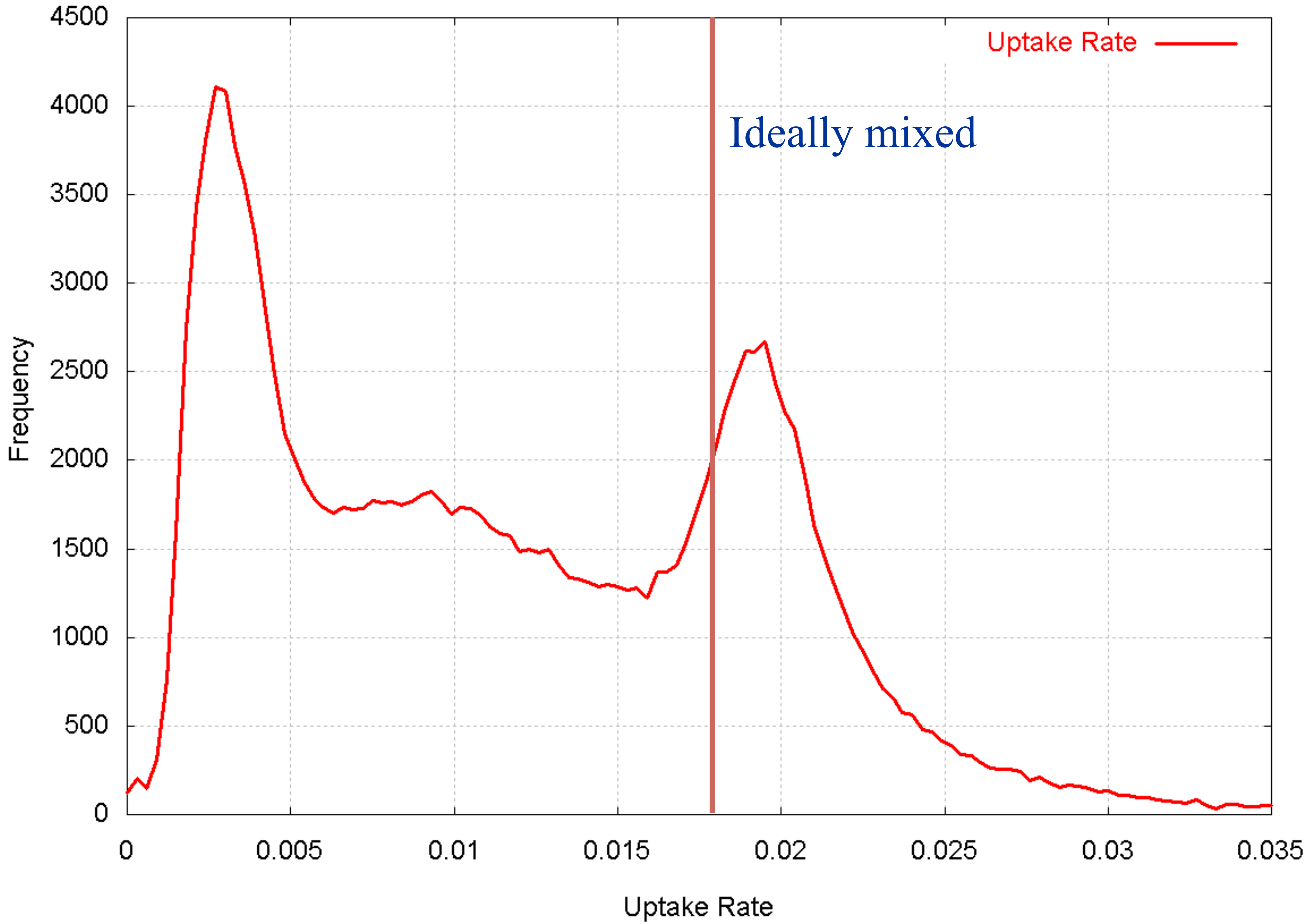
Sevilla, Reuss: to be published

Delvigne, F., Boxus, M., Ingels, S., Thonart, P (2009)
Microb. Cell Factories 8: 1-17 prpoS:GFP reporter gene

Delvigne, F., Boxus, M., Ingels, S., Thonart, P (2009)
Microb. Cell Factories 8: 1-17 prpoS:GFP reporter gene



expression of rpos is reduced and distribution is bimodal



Uptake Rate
Ideally mixed
Frequency
Uptake Rate
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
0.005
0.01
0.015
0.02
0.025
0.03
0.035

CONCLUSIONS

- Formidable challenges stand in the way of progress in multiscale modelling and simulation research. These challenges involve resolving open problems associated with simulation methods, appropriate quantitative data, model validation and verification and vizualization.

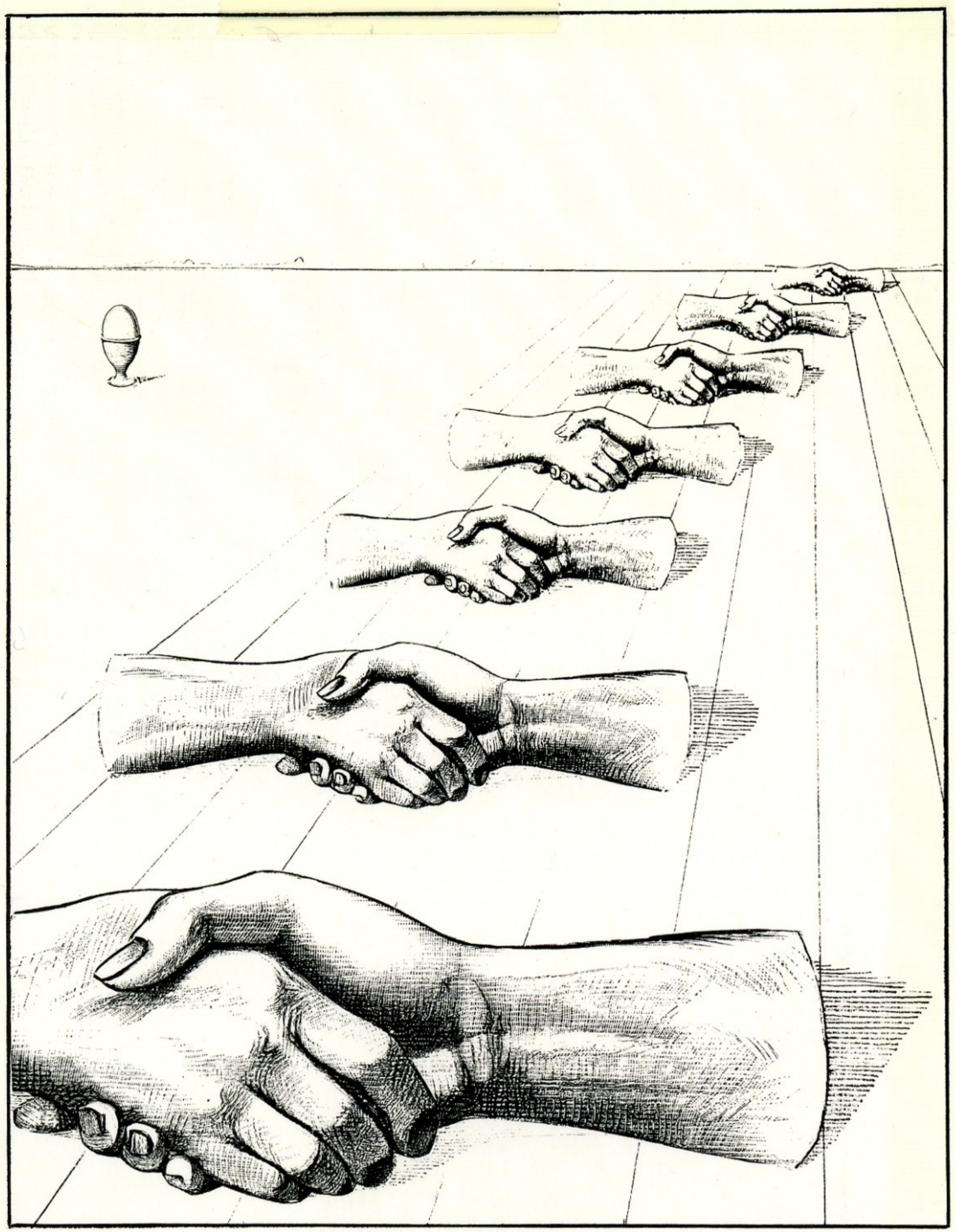
- Sustained research in multiscale modeling with lasting impact on bioprocess technology requires long term strategic planning. Progress in the field will require the creation of multisdisciplionary teams that works together.

- Significantly, one of the challenges is cross disciplinary education to improve interdisciplinary communication between biologists, bioinformatitions, computer scientists, mathematicians ,physicists and engineers.

Acknowledgements

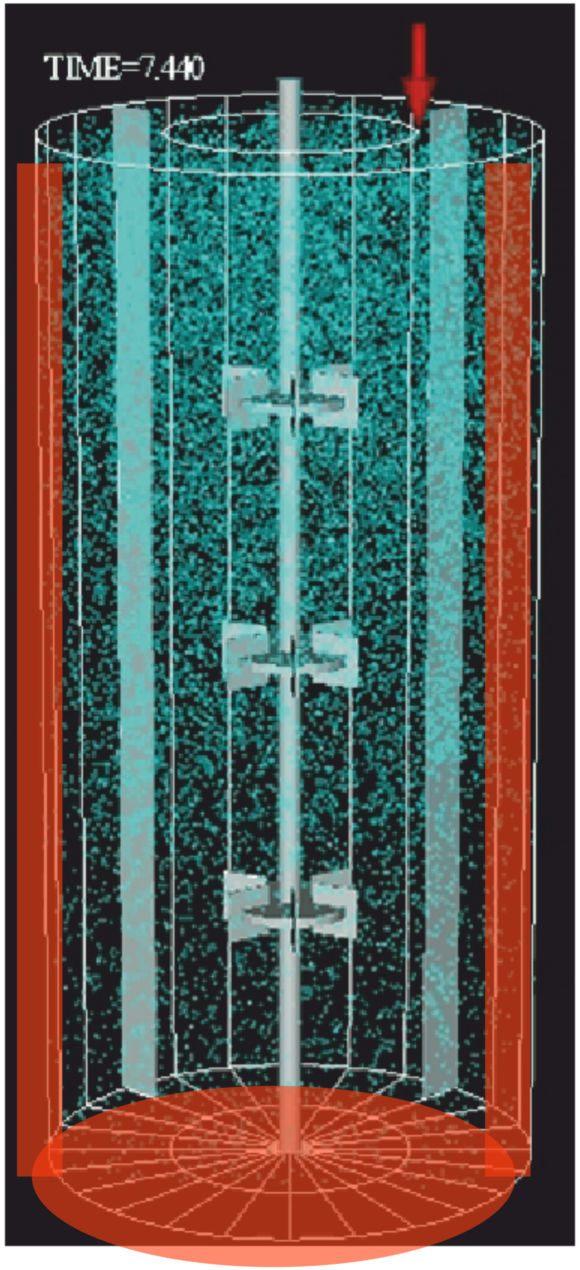
Alexej Lapin
Joachim Schmid
Klaus Mauch

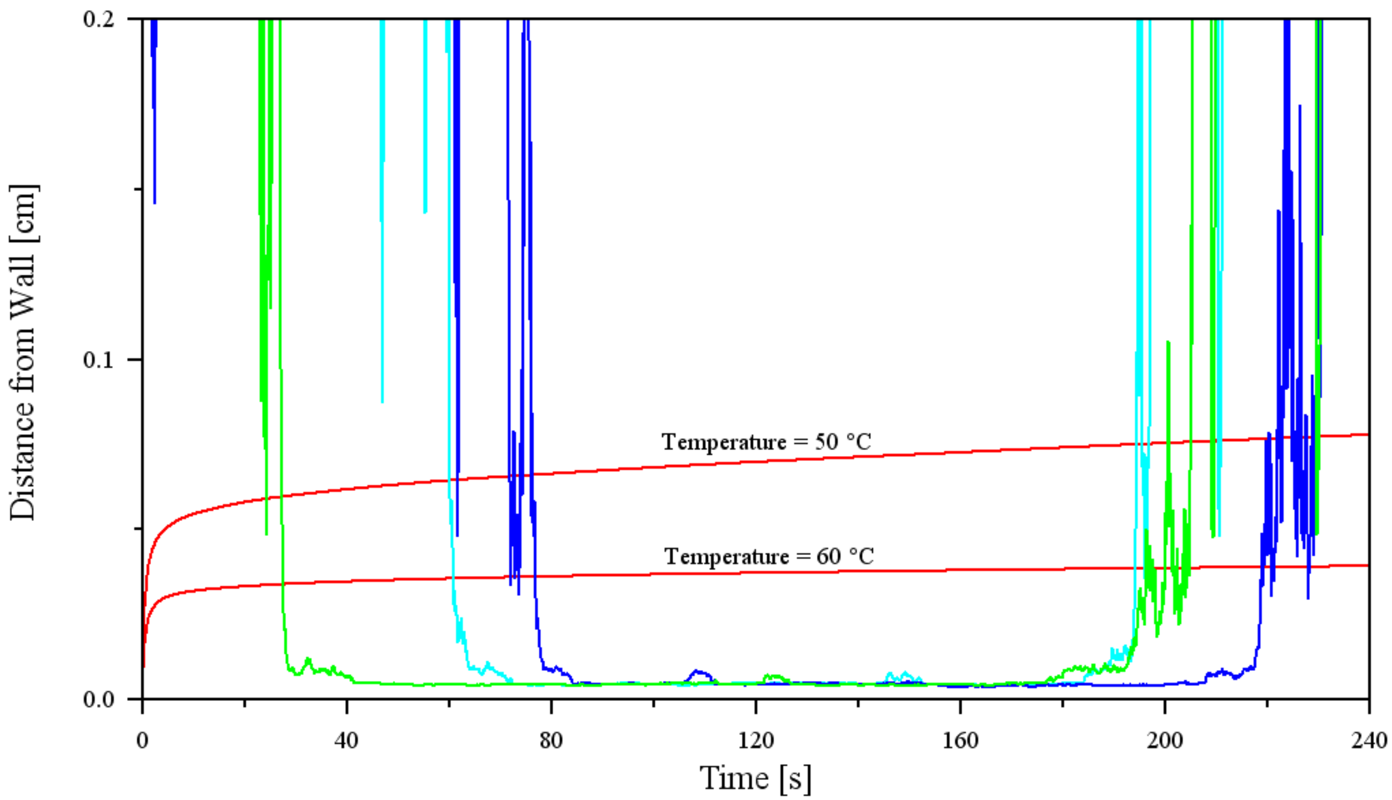
Funding: German Science Foundation (DFG)



MAX ERNST (1891-1976)

$37 \rightarrow 42^0 C$



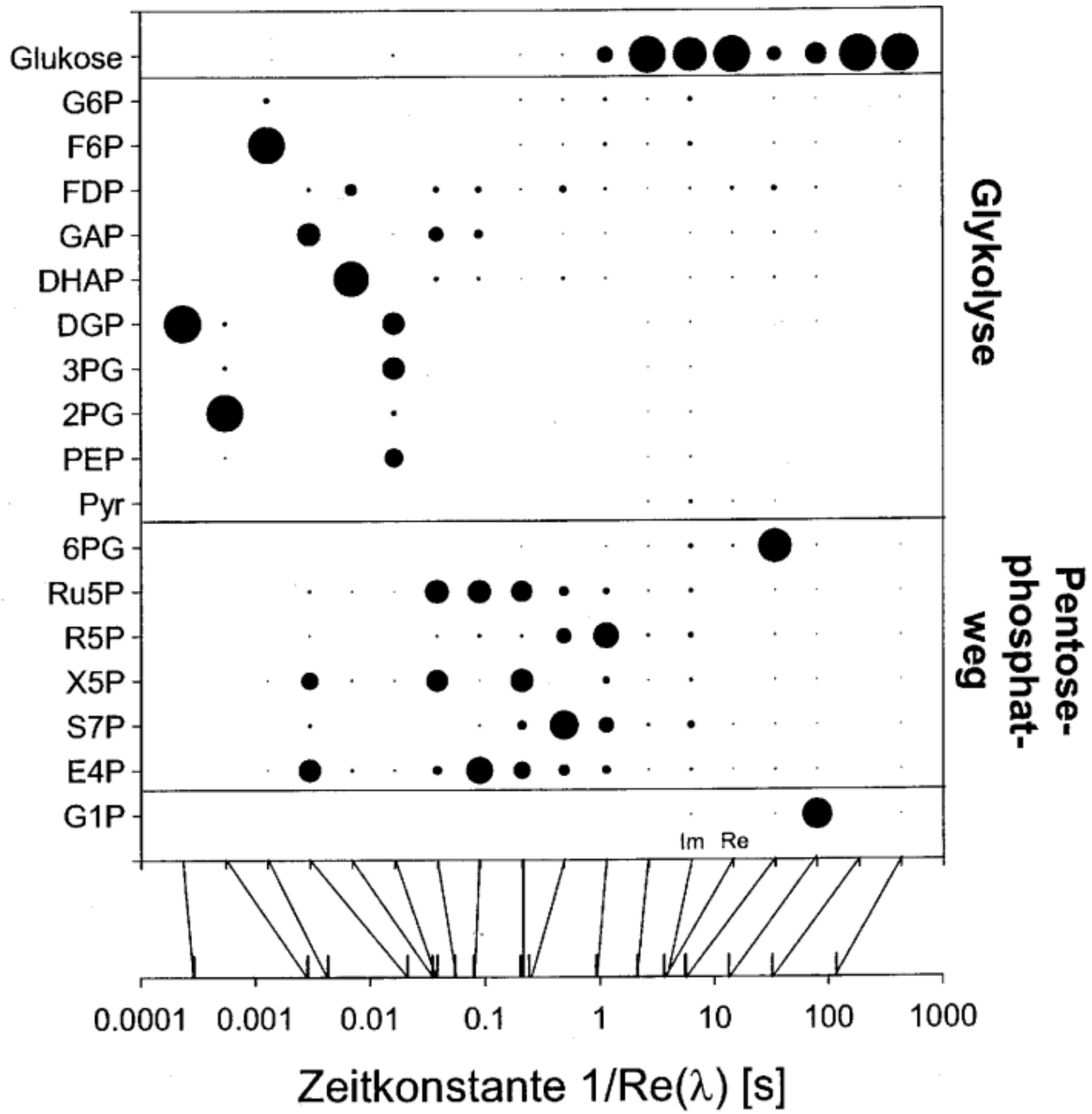


0.2
0.1
0.0
Distance from Wall [cm]
0
40
80
120
160
200
240
Time [s]
Temperature = 50 °C
Temperature = 60 °C

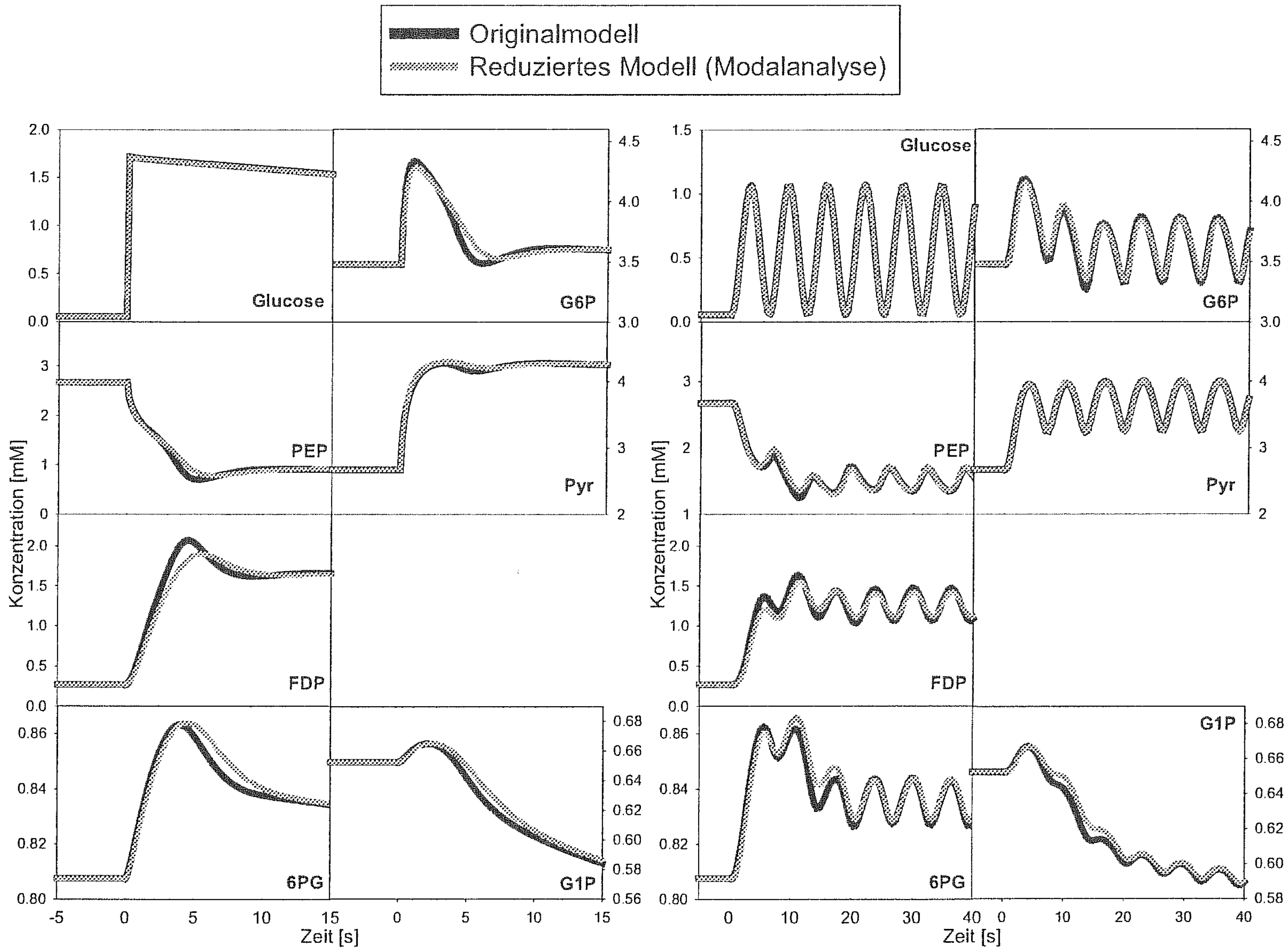
Modal Analysis:

$$c_i\left(t\right) = \overline{c}_i + \delta c_i\left(t\right)$$

$$\tau_i = \frac{1}{\left|\mathrm{Re}\left(\lambda_i\right)\right|} \qquad i = 1,\ldots,n$$



Glukose
G6P
F6P
FDP
GAP
DHAP
DGP
3PG
2PG
PEP
Pyr
6PG
Ru5P
R5P
X5P
S7P
E4P
G1P
Glykolyse
Pentose-
phosphat-
weg
Im
Re
0.0001
0.001
0.01
0.1
1
10
100
1000
Zeitkonstante 1/Re(λ) [s]



Originalmodell
Reduziertes Modell (Modalanalyse)
Glucose
G6P
PEP
Pyr
FDP
6PG
G1P
Konzentration [mM]
Zeit [s]