



## The Silicon Cell

### Mathematical / computational challenges

#### Modelling / Analysis

- control analysis (networks, cell cycle models)
- model reduction into functional modules (modular control analysis, combinatorial optimization, choice of metric definition)
- modelling dynamic structures
  - DNA supercoiling
  - aggregates (protein, chromatin)
  - membranes (growing cell, cell division)

#### Numerics

- time integration aspects
  - stiff ODE/DDE solvers
  - split-methods
- data sensitivity parameter estimation
- spatial aspects
  - (stochastic) PDEs on adaptive grids with dynamically changing boundaries/interfaces
  - particle-based methods
- coupling of the above
- dynamical systems
- model reduction

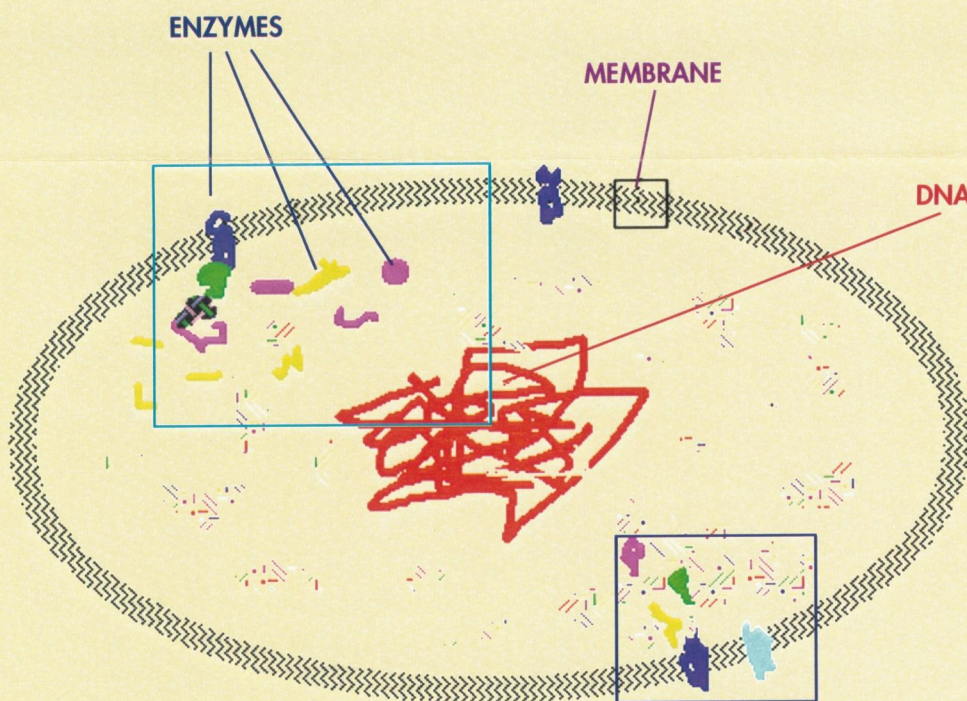
**Spatial Effects in Chemical Pathways**  
 "Standard" kinetic models metabolic pathways:  
 Homogeneous distribution of components → system of ODEs  
 But:  
 Components membrane bound in cytosol  
 E.g., glucose uptake

Continuum hypothesis (# molecules  $O(10000)$ )  
 $\frac{dc}{dt} = \mathbf{R}(c) + \mathbf{V} \cdot (\nabla \cdot (\mathbf{D}(c, \mathbf{a}) \nabla c))$   $\mathbf{D}(c) = \mathbf{J}$  (flux, 0 for most species)

Steady-state simulations  
 Questions:  
 - Membrane flux  
 - Rate limiting/control  
 - Gradients

Read data important

Metabolic Control Analysis (Kholodenko, Westerhoff, Palmiter)  
 well-stirred:  $\sum c_i' = 1$   
 with diffusion:  $\sum c_i' + \sum c_i'' = 1$



**Membrane simulation**

Modeling / simulation:  
 - growing membrane  
 - cell division

Mesoscopic model: Gaussian chains  
 Beads: Head, Tail, Solvent  
 Dynamic mean-field density functional theory  
 Energy minimization (see, e.g., Fraaije et al. 1997)

$$\frac{\partial \rho_i(\mathbf{r}, t)}{\partial t} = \sum_j \nabla_j \cdot \mathbf{A}_{ij}(\rho) \nabla_j \rho_j + \mathbf{a}_i \quad i, j = \{H, T, S\}$$

$\rho_i$ : density  
 $\mathbf{A}$ : kinetic coefficients  
 $\mu_i = \mu_i^{int}(\rho) + U_i(\rho)$ : intrinsic chemical potentials  
 $\mu_i^{int}$ : free energy interchain reactions  
 $U_i$ : external potential field  
 $\mathbf{a}_i$ : stochastic term

**Modelling spatial structures**

- Macroscopic continuum hypothesis, PDEs
- Microscopic Molecular Dynamics / Monte Carlo
- Mesoscopic 'averaging over molecules'

Structures:  
 - aggregates of membrane  
 - DNA → protein  
 - DNA supercoiling

pro LB  
 - particle character (suspension in fluid)  
 - boundary conditions for complex geometry  
 - scalable parallel

pro PDE  
 - no restriction to Cartesian grid  
 - computationally more flexible  
 - less memory requirements  
 - cheaper (steady-state comp.)

#### Software

- large scale computations
- coupling PDE-based and particle-based codes
- systematic data access
- model validation / calibration
- reduction into functional modules (algorithmic + human steering)
- software management
- visualization / Virtual Reality
- HPCN / Grid computing

**Visualization / Virtual Reality**

Chromatin decondensation and essential protein dynamics in virtual reality  
 Robert van Lier, CWI, URL: www.cwi.nl/~robert