Spatio-Temporal Modelling of Biochemical Pathways: Introducing Cell++

John Parkinson
Molecular Structure and Function
Hospital for Sick Children
Department of Biochemistry
University of Toronto
Toronto
jparkin@sickkids.ca

Acknowledgements
Chris Sanford*
Matthew Yip
Carl White
Integrating ’omics data – modelling cellular processes

Cells are complex entities comprised of organized integrated biochemical pathways. Advances in recent technologies are beginning to generate the data to help us unravel their organization and dynamics.

- Lists of genes and gene products
- Relative abundance of transcripts / proteins
- Interactions between proteins
- Organization of biochemical pathways
- Localization of proteins in the cell
- Dynamics of proteins in the cell

Need for computational simulations
Cells are not homogenously mixed fluid filled bags

**Compartmentalization**
In addition to intracellular compartments such as nucleus, ER, golgi etc. The cytosol may be further subdivided into compartments by cytoskeletal elements which can impact the free diffusion of proteins.

**Molecular Crowding**
Up to 40% of the total volume is physically occupied by macromolecules. Crowding can reduce the rate of diffusion by factors up to 10. It can also affect the stabilisation of more compact structures such as protein complexes and their ability to perform coordinated functions.
Cell++: A temporal spatial modelling tool

A flexible 3D modelling environment, written in C++, for simulating cellular processes – 4 main elements:

**Cellular environments**
- Cubic 3D lattice
- Lattice sites user defined (membrane/nucleus etc.)

**Small molecule diffusion**
- ATP, Ca^{2+} etc.
- Concentrations defined at each lattice site
- Based on Euler method
- At each time step, a % of molecules move to adjacent sites

**Large molecule movement**
- Proteins
- Based on Brownian motion
- Off lattice random walks

**Molecular interactions**
- Signal transduction, enzyme catalysis, transporters
- Simulation specific rules
- Deterministic (metabolism)
- Probabilistic (signal transduction)

\[ P = f(\text{distance} \ (\bullet, \bullet^*)) \]
Modelling metabolic pathways: Glycolysis

- 500 nm cubic lattice
- Four enzyme species (1000 of each)
- Five metabolites
- Parameters obtained with reference to literature ($K_m$, $V_{max}$, diffusion coefficients)
- Different localization conditions
Spatial localisation can result in metabolic channelling

The different locales of the orange and green enzymes result in accumulation of green substrate

The low equilibrium coefficient of the blue enzyme results in a slower reaction and accumulation of blue and purple substrates

Co-localizing enolase \(\text{\textbullet}\) with phosphoglycerate mutase \(\text{\textbullet}\) allows the rapid removal of 2 phosphoglycerate \(\text{\textbullet}\) and production of phosphoenolpyruvate \(\text{\textbullet}\) ensuring the reaction proceeds rapidly from left to right
Future directions: Spatial localization as a means of controlling metabolic flux

Depending upon the localization of a key enzyme (e.g. through binding to another protein), a cell may be able to rapidly switch its metabolism between pathways.