AuPS/ASB Meeting - Adelaide 2010

Symposium: Fundamentals of Biophysics - development of mathematical and computational methods

Tuesday 30th November 2010 - Broughton Room - 14:30

Chair: John Gehman

Erythrocyte shape, metabolism and membrane transport – computations

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Our aim in modelling cellular responses to chemical and physical perturbations is to gain insights into underlying structural, transport, and metabolic mechanisms. Such models can enable predictions of cell behaviour under conditions that are not experimentally accessible; or the models can be added to others thus building up the complexity of the model to describe highly-nonlinear cellular phenomena such as metabolic and structural oscillations. The cellular system under study has been the human erythrocyte. Data on cell shape on the minute-to-hour time scale have been obtained with NMR-diffusion spectroscopy and differential interference contrast (DIC) light microscopy; on the sub-second time scale fast image capture of membrane 'flickering' has been carried out with DIC microscopy. Data processing and modelling of cell shape-changes and membrane flickering have been carried out by using Mathematica. A drive to understand the "link" between the rate of transmembrane pumping of Na^+ *via* the Na,K-ATPase, and the rate of glycolysis has used multinuclear NMR spectroscopy. Again modelling of the system has been set up in Mathematica. The next challenge is fitting multi-parameter models to real experimental data. For this we are using a Monte Carlo Markov chain (MCMC) approach.

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Fast acquisition of multidimensional NMR experiments by maximum entropy reconstruction of non-uniformly sampled data

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(Introduced by John Gehman)

The discrete Fourier transform (DFT) played a seminal role in the development of modern nuclear magnetic resonance (NMR) spectroscopy. Nevertheless it has a number of well-known limitations. Chief among them is the difficulty of obtaining high-resolution spectral estimates from short time records, because the ability to resolve signals with closely-spaced frequencies is largely determined by the longest evolution time sampled.

The ability to obtain accurate, high-resolution spectral estimates from short data records is critical in many applications of NMR spectroscopy because the available sampling time is limited, for example due to sample instability or simply due to constraints on available instrument time. In practice the latter is mainly encountered in multidimensional NMR experiments where the data collection time is directly proportional to the number of data samples collected in the indirect time dimensions (indirect time dimensions correspond to time delays between RF pulses; real time is referred to as the acquisition dimension). Furthermore, at very high magnetic field, the competition between the goals of short data collection time and high resolution becomes more severe as the bandwidth spanned by the nuclear resonances increases linearly with field strength, necessitating a decrease in the time between samples in order to avoid aliasing.

Non-Fourier methods of spectrum analysis provide an avenue to high-resolution spectral estimates from short data records. Over the past three decades a host of non-Fourier methods of spectrum analysis have been developed, including maximum entropy, maximum likelihood and Bayesian methods, the filter diagonalization method, G-matrix Fourier transform, back projection reconstruction, and multidimensional decomposition. These methods span a continuum of assumptions about the nature of the signal, and restrictions (or lack thereof) on the characteristics of the data sampling. MaxEnt reconstruction lies at the extreme of making few assumptions about the signal, and furthermore can be applied to data collected in essentially arbitrary fashion (non-uniform sampling, NUS).

Extensive use of synthetic and experimental, non-uniformly sampled data in 2-4 dimensions, processed using MaxEnt has enabled us to both theoretically and practically evaluate the pros and cons of this method. The results suggest the method to be resilient to false positives and robust in situations of poor signal to noise, with the consequence of producing non-linear reconstructions.

Toward the virtual heart: graphics processor accelerated interactive simulations of cardiac function

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Heart disease is the leading cause of death in the developed world. Despite this, our understanding of the mechanisms of cardiac dysfunction, particularly acute disorders related to the electrical system of the heart is limited. Our goal is to create a realistic virtual model of the heart to develop insight into this clinically important problem.

Using the multiscale modelling approach, we began at the molecular level with mathematical descriptions of the ion channels, pumps and buffers present in every heart cell. Integration of these subcellular components reproduces the cardiac action potential waveform the basic unit of cardiac electricity at the single cell level. From this building block we can extend our simulations to simple strings (1D), sheets (2D) and wedges (3D) of cells and even include descriptions of the overall architecture, anatomical detail and tissue heterogeneity necessary to simulate realistic hearts. At each level of complexity we have endeavored to gather appropriate experimental data to validate the model.

The computational complexity of the virtual heart has been prohibitive until very recently. However, the continued development of massive parallelisation using graphics processor technology has allowed us to compute the electrical activity of over several thousand cells concurrently. This has made the virtual heart a much more realistic and achievable goal.

Vesicle docking and delivery: Life in the TIRF zone

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Cells traffic membrane-embedded proteins to the plasma membrane *via* a variety of mechanisms. One of these is the docking and fusing of vesicles with the plasma membrane. Even this mechanism, however can happen *via* several modalities.

Given the live-cell imaging techniques using total internal reflection (TIRF) microscopy (in which the first ~200nm of the cell surface is observed using fluorescent markers attached to the molecules), it is now becoming possible to view the dynamics of these processes, albeit that in some systems the vesicles are below the resolution of the system.

In order to systematically extract these delivery events from other background traffic, we need robust, quantitative descriptions of the dynamics. These can then be employed in automated detection systems to analyse the system under a variety of perturbations.

Such an automated detection system has been developed within the Diabetes & Obesity Group at the Garvan Institute of Medical Research. The proteins of interest in this case are the glucose transporters GLUT4, which are highly insulin-responsive. These may be brought to the plasma membrane *via* methods including the full fusion of the vesicles, and also *via* a process termed “Kiss-and-Run”, whereby a pore connection is made between the vesicle and plasma membrane allowing diffusion of the GLUT4 proteins across the boundary. The vesicle does not, however, become fully integrated, but, after a period, detaches from the plasma membrane. Thus, the amount of GLUT4 delivered depends on the amount of time the “Kiss” persists, and also on the physical dimensions of the vesicle and pore connection.

The model for this process can also be used to explore the possibilities of differential diffusion rates of the molecules in the vesicle and the plasma membrane. In the case of GLUT4 vesicles in adipocytes, the analysis of TIRF imagery is further exacerbated by the fact that the ~80nm diameter vesicles are well below the microscope resolution. Advances in the understanding of these processes are still, however, being made, with the use of mathematical modelling and sophisticated image analysis techniques. Current work is exploring the modelling and imaging of the “Kiss-and-Run” delivery process, and the insights this may additionally give us into the diffusion characteristics of the membranes.