



Lincoln's Inn Fields

Biomolecular Modelling

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In this laboratory we are motivated by fundamental and challenging problems in both structural and systems biology; in particular, how macromolecules interact at the atomic level to facilitate higher order cellular events. Much of the work involves applying the principles of physics to design novel computer-based algorithms. Output from these algorithms can usually be displayed along a time course, indicating, for example, how macromolecules diffuse and interact in the cytosol and how cells migrate in various morphogen gradients. These simulations are proving to be important in helping to interpret experimental data and suggest further experiments to probe complex molecular pathways. Outlined below are a few macromolecular systems currently under investigation.

Exploring the dynamics of chromosome structural maintenance proteins by elastic networks

The study of structure-function relationships for biological macromolecules, and the complexes they form, is crucial to our understanding of cellular activities. However, the dynamics and the functioning mechanism for many protein complexes are still not clear. Therefore, computational

techniques that take account of available structural and biochemical information, are necessary to elucidate how bio-molecules work together. Coarse-grained elastic network models, that use a mathematical technique called normal mode analysis, are computationally efficient models for determining the collective dynamics of macromolecules in the cell. Here, crystal structures of the macromolecules can be modelled at lower than atomic resolution, enabling us to simulate macromolecular dynamics on much longer time courses than with classical molecular dynamics approaches. The elastic network models are currently being used to explore the dynamics of the supramolecular complexes of cohesin and condensin; chromosome structure maintenance proteins that play important roles during cell division. The molecules are similar in structure yet different in function; cohesin is responsible for holding two sister chromatids together during cell division whilst condensin facilitates promotion of mitotic chromosome condensation by reorganising chromosomes into their compact shape. All insight derived from the dynamic interplay between these proteins and the chromosomes they affect will be tested by further experimentation in collaboration with Frank Uhlmann (Chromosome Segregation Laboratory). The work should greatly enhance our understanding of sister chromatids cohesion and chromosome condensation processes at the molecular level.

Simulating protein-protein interactions in signal transduction pathways

Atomic-level simulations of protein-protein interactions usually only consider two proteins at a time. However, this is unrealistic as *in vivo* bimolecular interactions take place in an environment where there are many proteins interacting simultaneously (Figure 1). We are developing a computer simulation package (BioSimz) that uses a simulation technique called Brownian Dynamics. Using our program we can study how signal transduction proteins, such as Ras and GAP, interact at the atomic-level in the crowded protein environment of the cytosol. One of the key questions we are

trying to answer is: does an overcrowded environment facilitate the interaction between the relatively low concentrations of signal transduction proteins or inhibit such interactions? Moreover, for mutations within these proteins, how do the protein network dynamics of interaction change?

Our computer simulations indicate that molecular crowding cannot be ignored if we are to understand the full consequences of signalling strengths and how they are modulated in tumourigenesis.

Multiscale modelling of cell motility

Cell migration is an essential component in many biological processes including metastasis in cancer. Recent studies suggest that, depending on the cell type and environmental conditions, the mechanisms of cellular morphology and motility can vary significantly. Understanding these variations is important since inhibiting metastasis is as essential as minimising tumour growth for efficient treatment of cancer. In our current multiscale computer model of cell motility, the primary focus is on amoeboid type cell motility of metastasising tumour cells in the extracellular matrix (ECM). Both the extracellular conditions (e.g. ECM density) and intrinsic cell properties (e.g. relative distribution of contractile and blebbing regions of the cell membrane) are being investigated. In collaboration with Erik Sahai (Tumour Cell Biology Laboratory), experimental data on cell morphology during motion is being utilised in both the construction and validation of the computational model. At a later stage, the model will be extended to include mesenchymal types of cell motility, and according to availability of kinetic and qualitative data on proteins involved in regulation of the modelled process, protein interaction networks will also be implemented.

Simulating cell-cell interactions during angiogenesis

In collaboration with Holger Gerhardt (Vascular Biology Laboratory) we have developed a novel three-dimensional agent-based multiscale model 'the memAgent model' to investigate the dynamics of tip cell selection by Notch-Dll4 lateral inhibition in normal and pathological angiogenesis (blood vessel formation). The model predicts tip cell selection failure in pathological angiogenesis. We now believe this to be due to a synchronous oscillation of Dll4 in high VEGF environments. Modelling also highlights a more important role for filopodia and shape changes in selection than previously thought.

Ongoing research into the later stages of angiogenesis, utilising a novel inclusion of membrane physics into the model in the form of springs between agents, has revealed unexpected insights into the robustness of tip/stalk cell patterning. The model predicts that cell fates will flip upon anastomosis and that junction size, between cells, contributes to the robustness of the system in pathological environments by naturally regulating Dll4/Notch binding between neighbouring cells.

The model has highlighted a possible new avenue for normalising tip selection in pathologically high VEGF environments, via partial inhibition of the actin pathway alone. This is shown to reduce filopodia, which in turn reduces surface area and junction size through reduced migrational stretching. These reductions lead to lower Dll4 production and presentation at junctions, which helps stabilise selection in high VEGF environments.

Publications listed on page 121

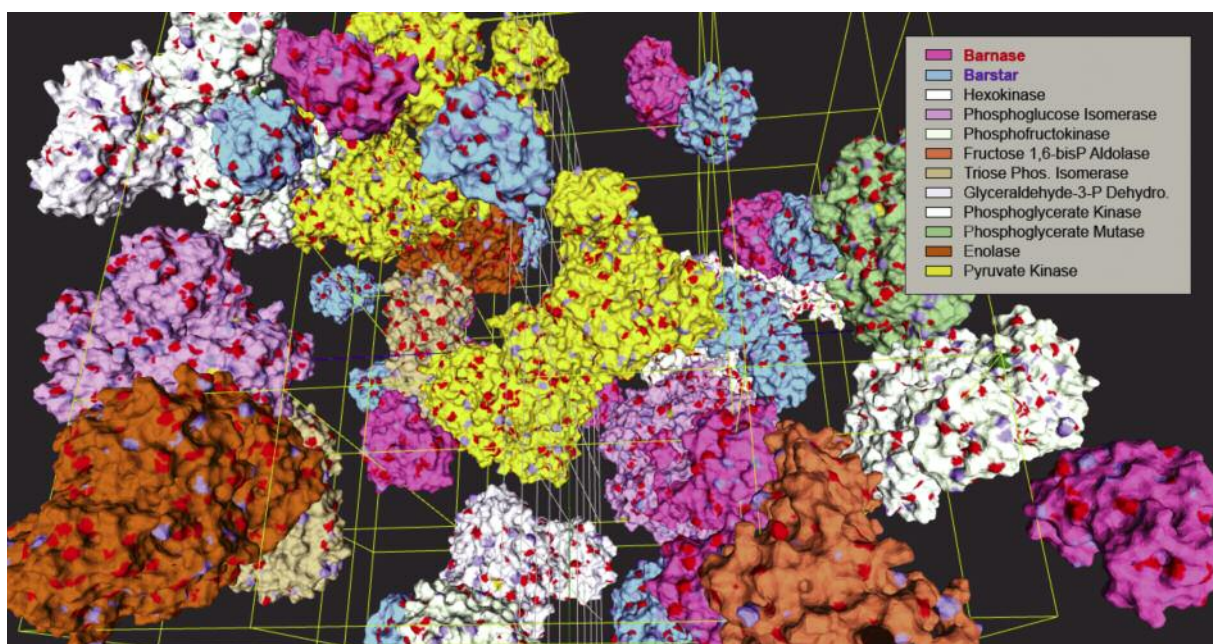


Figure 1. Snapshot from our simulation program, BioSimz, of Barnase (endonuclease) and Barnstar (endonuclease inhibitor) in a crowded cellular environment.