Parallel Session

Cell and Intra-Cell Dynamics I

THE FBLM-FEM: FROM CELL-CELL ADHESION TO THE CLUSTER OF CELLS AND CELL MONOLAYERS

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Keywords: Tissue formation, Cell motility, Lamellipodium, Actin filaments.

The lamellipodium is a thin, sheet-like structure that is found in the propagating front of fast moving cells like fibroblasts, keratocytes, cancer cells, and more. It is a dense network of linear biopolymers of the protein actin, termed actin-filaments. These actin-filaments are highly dynamic structures that participate in a plethora of processes such as polymerization, nucleation, capping, fragmentation, and more.

These processes are important for the structure and functionality of the lamellipodium and the motility of the cell. They are, to a large extent, affected by the extracellular environment; for example, the chemical landscape in which the cell of resides and the local composition and architecture of the Extracellular Matrix (ECM), lead to biased motility responses of the cell. When in proximity to each other, they develop cell-cell adhesion via specialized transmembrane proteins of the *cadherin* family. Collectively, they coagulate to clusters of cells that eventually merge to form cell monolayers.

We model these phenomena using the Filament Based Lamellipodium Model (FBLM); an anisotropic, two-phase, two-dimensional, continuum model that describes the dynamics the lamellipodium at the level of actin-filaments and their interactions. The model distinguishes between two families (phases) of filaments and includes the interactions between them, as well as between the network of the filaments and the extracellular environment. The FBLM was first proposed in [1] and later extended in [2, 4, 5]. The FBLM is endowed with a problem specific Finite Element Method (FEM) that we have previously developed in [3].

In this talk we present the basic components of the FBLM and the FEM and focus on a series of simulations reproducing fundamental components of the motility of the cells, such us chemotaxis, haptotaxis, interaction with the environment [3, 4]. We also present our new findings with respect to cell-cell collision and adhesion, as well as the formation of clusters of cells and cell monolayers [5]. To confront the increased computational needs of the monolayer, we have developed a parallel version of our numerical method which we also address in this talk.

References

[1] D. Oelz, C. Schmeiser. How do cells move? in Cell mechanics: from single scale-based models to multiscale modeling, Chapman and Hall, 1, (2010), 1–10.

[2] A. Manhart, D. Oelz, C. Schmeiser, N. Sfakianakis, An extended Filament Based Lamellipodium: Model produces various moving cell shapes in the presence of chemotactic signals. J. Theor. Biol., 382 (2015) 244–258.

[3] A. Manhart, D. Oelz, C. Schmeiser, N. Sfakianakis. Numerical treatment of the filament based lamellipodium model (FBLM) (2016) in Modelling Cellular Systems.

[4] N. Sfakianakis, A. Brunk, (2017) *Stability, convergence, and sensitivity analysis of the FBLM and the corresponding FEM*, (in review)

[5] N. Sfakianakis, D. Peurichard, C. Schmeiser, and A. Brunk *The FBLM-FEM: from cell-cell adhesion to cluster formation*, (in preparation)

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Cell and Intra-Cell Dynamics I

MODELLING CELL SHAPE AND MIGRATION: A PHASE-FIELD APPROACH

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Keywords: Mechanobiology, Cell motility, Phase-field model.

One of the most fundamental abilities required for the sustainability of life is active cell migration. The movement of a cell is an extremely complex process, involving a coordination of mechanical forces with biochemical regulatory pathways and environmental cues. Cell migration plays a key role in several biological processes in complex organisms, from morphogenesis to leukocytes seeking pathogens in the blood stream. In this work we use a phase-field model in 3D to describe endothelial cells. We explore how parameters such as adhesion, fibre density and internal force balance can affect their morphology and migration. We look into cell shape and movement in two different computational setups: a) micro-patterned fibronectin surfaces, and; b) three-dimensional complex fibre network. For the first case, preliminary results show that the surface pattern is the main responsible for the shape geometry, affecting directly the way a cell exerts force and migrates. The adhesion strength reinforces the cell deformation, allowing an increase of the adhered area. In the fibre network we study the effect of spatial restriction on cell migration strategies and on the regulation of the cell's morphology. We quantified the migration and compared our results with experimental data and with coarse-grained dissipative molecular dynamics simulations.

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THE EVOLUTION OF SYMMETRIC AND ASYMMETRIC PROTEIN BINDING INTERFACES

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Keywords: Evolution, Protein.

Although many quantitative studies on protein interface binding strengths have been conducted in recent years, with evolutionary arguments put forth on the greater-than-expected prevalence of symmetric interfaces, the actual evolutionary history is difficult to reconstruct [1]. An abstract protein assembly model can offer strong analytic capabilities while allowing robust and featureful evolutionary dynamics, and hence allow the evolution of protein interface binding properties like strength and symmetry to be probed in greater detail.

Modelling a protein interface to consist of I residues, each with a binary value, the interaction strength between two interfaces can calculated as their Hamming ("edit") distance. With mutations and fitness proportional selection providing a framework for evolving a population, the binding interactions can be tracked over time and compared to analytic expectations.

While the evolved interfaces are nuanced with respect to certain simulation parameters like the binding threshold "temperature", the general behaviour shows a clear divergence from randomly distributed residues, matching observations in existing literature. Additionally, with complete information on evolutionary history, the increases in structural complexity can be time ordered, offering further insight into the observed distribution of naturally-occurring proteins.

References

[1] Levy, Emmanuel D and Teichmann, Sarah A. *Structural, evolutionary, and assembly principles of protein oligomerization*. Progress in molecular biology and translational science, pg 25-51, Elsevier. 2013

Parallel Session

Cell and Intra-Cell Dynamics I

TOPOLOGICAL ANALYSIS OF PENICILLIN-BINDING PROTEINS

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Keywords: Topology, Fatgraph, Structural biology, Antibiotics, Methicillin-resistant Staphylococcus aureus, MRSA.

Prediction of the mutation of antibiotics- or antiviral drug- binding proteins is an urgent need since it would be a remedy for a pandemic. Broad picture of my research is to construct a protein structure library with possible mutations of bacteria or virus that would have drug resistance in order to design drugs before or as soon as pandemic happens.

To achieve the goal, we focus on a topological method called "Fatgraph models of proteins [1]". Fatgraph models of proteins are topological two-manifold with boundary components (surface) which have one to one correspondence with three-dimensional protein structures listed on Protein Data Bank (PDB) [2] with only a few exceptions. The traits of each surface for each protein are described by the following invariants; Euler characteristics, number of boundary components, and genus. Fatgraph is also called ribbon graph and has already proven their utility in theoretical physics including string theory [3].

Objects of the study are penicillin-binding proteins (PBP). Penicillin is a group of beta-lactam antibiotics (BLAs) which shares the core structure, and it has been developed to cope with drug resistance caused by mutation, quality of life for patients and so on. PBP is a group of proteins that have the affinity for penicillin. Methicillin is one of the BLAs and methicillin-resistant Staphylococcus aureus (MRSA) strains are responsible for most hospital-onset bacterial infections. MRSA strains are resistant to most BLAs as a result of the biosynthesis of a penicillin-binding protein with low affinity for BLAs, called PBP2a, PBP2' or MecA. [4]

In this research, we constructed Fatgraph models of PBPs and investigated the traits of the complexes of the surfaces based on PDB especially focusing on MecA. Then, we topologically examined the transformations of the fatgraphs of the proteins due to the changes of of protein sequences or existence of ligands. Novelty of this research is that this is the first report on the relationship between transformation of fatgraph models of the proteins and similarity of the protein sequences.

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References

[1] R. C. Penner, et al., (2010). *Fatgraph models of proteins*. Communications on Pure and Applied Mathematics. Volume 63, Issue 10, 1249-1297.

[2] H.M. Berman, et al. (2000),*The Protein Data Bank*. Nucleic Acids Research, 28: 235-242. http://www.rcsb.org/

[3] R. C. Penner, (2016). *Moduli spaces and macromolecules*. Bull. Amer. Math. Soc. 53, 217-268.

[4] A. Marrero, (2006).*Unbound and Acylated Structures of the Mecr1 Extracellular Antibiotic-Sensor Domain Provide Insights Into the Signal-Transduction System that Triggers Methicillin Resistance*. J.Mol.Biol. 361: 506

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SCORING, ANALYSIS AND RANKING OF PROTEIN-PROTEIN DOCKING MODELS BY QASDOM SERVER ON THE EXAMPLE OF NEF-CALNEXIN INTERACTION

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Keywords: Protein-protein docking, QASDOM server, Interaction sites prediction, Models scoring and ranking.

In molecular biology, bioinformatics and drug design, there is often a need to predict interaction of protein with another protein or ligand. We proposed an approach to protein-ligand interaction prediction based on the principle of simultaneous use of several docking programs. The advantage of this approach is that the resulting models represent interactions modelled by different, unrelated methods and therefore it is more reliable than using a single server.

Evaluation and comparison by experts of all models obtained through different servers takes a long time and is not suitable for large volumes of data generated by this approach. To address this problem we have developed a meta-server QASDOM Server (Quality ASsessment of Docking Models) for automatic processing and analysis of the docking models data [1]. The server is a simple and efficient tool for real-time simultaneous analysis, scoring and ranking of datasets of receptor-ligand models built by global docking techniques. This meta-server is designed for users who need to analyze large datasets of docking models, built by different algorithms and prediction tools, in order to estimate the probability of specific residues and clusters of residues being involved in the process of receptor-ligand recognition, to rank the models by quality criteria, and to select the best model. The server allows visualizing residues forming interaction sites in the receptor and ligand sequence, and displays three-dimensional model structures of the receptor-ligand complexes.

It was shown that the HIV protein Nef impairs cholesterol efflux mediated by the cholesterol transporter ATP-Binding Cassette A1 (ABCA1), leading to lipid accumulation in macrophages and their conversion into the 'foam' cells [3]. We have modelled Nef - calnexin interaction and obtained reciprocal binding sites in calnexin and Nef structures, and predicted small molecule compounds that can potentially inhibit this interaction [2]. These new findings provide a platform for searching for new therapeutic agents to treat HIV-associated co-morbidities.

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References

[1] Anashkina, A.A., Kravatsky, Yu.V., Kuznetsov, E.N., Makarov, A.A., Adzhubei, A.A. (2018). *Meta-server for automatic analysis, scoring and ranking of docking models.* Bioinformatics 34(2), 297–299.

[2] Hunegnaw, R., Vassylyeva, M., Dubrovsky, L., Pushkarsky, T., Sviridov, D., Anashkina, A. A., et al. (2016). *Interaction between HIV-1 Nef and calnexin: from modeling to small molecule inhibitors reversing HIV-induced lipid accumulation.* Arteriosclerosis, thrombosis and vascular biology 36(9), 1758.

[3] Mujawar, Z., Rose, H., Morrow, M.P., Pushkarsky, T., Dubrovsky, L., Mukhamedova, N., et al. (2006). *Human immunodeficiency virus impairs reverse cholesterol transport from macrophages.* PLoS Biology 4:e365.