Dynamic work

Computational and systems biologist **Dr Ivet Bahar** explains her laboratory's work towards understanding the dynamics of biomolecular and specifically neurosignalling systems

At the Bahar lab in the Computational and Systems Biology Department at the University of Pittsburgh, USA, you strive to understand the functions and mechanisms of biological systems at the molecular level. Could you provide an overview of your research?

The major focus in our lab is to investigate the 'dynamics' of biomolecular systems, and we would like to understand the motions of biomolecules not in isolation but in the context of their interactions in the cell – a molecular systems-level approach to biology, supported by physics and computational science-rooted theory and computations.

Can you outline the methodologies you employ to achieve these goals?

We use computational methods, along with fundamental concepts of physical science and engineering. Our lab introduced so-called 'elastic network models' for protein dynamics at a coarse-grained scale, which provide an extremely efficient framework to make predictions for intrinsically accessible, structure-encoded collective motions. Mapping biomolecular structures into an elastic network is an approximation; however, this allows us to analyse large, complex systems in their entirety, rather than having a detailed description of a small part of them. We lose resolution at the local scale for the sake of having a comprehensible view of motions at the global scale.

The National Center for Multiscale Modeling of Biological Systems (MMBioS) has recently been awarded a US $9.3 million grant from the National Institutes of Health (NIH) to develop computational tools to model and simulate biological systems. What are the main objectives of this initiative?

The MMBioS Center will develop tools to advance and facilitate cutting-edge research at the interface between high-performance computing technology and the life sciences. Our overarching biological goal is the predictive multiscale modelling of the spatiotemporal organisation and behaviour of neurosignalling systems.

We expect the advances made here to impact the research activities of a broad group of scientists, including molecular, structural, cell and systems biologists. They will also facilitate the translation of basic tools to biomedical and clinical research by establishing and disseminating a computational framework that integrates theory with experiment, and models with methods originating from different disciplines.

In what capacity are you involved with MMBioS?

I am Director of the MMBioS Center (or Principle Investigator of the NIH-funded award for establishing the Center). I work together with several leading scientists in the field, who lead the various components of MMBioS – such as biomedical technology and research development projects, or training and dissemination activities.

Which institutions are involved in the NIH-funded research conducted at the Center?

The MMBioS Center is a collaboration between four institutions: the University of Pittsburgh, Carnegie Mellon University, Pittsburgh Supercomputing Center and the Salk Institute for Biological Studies, San Diego. Investigators from these four institutions are currently developing advanced computational models, methods and tools for simulating and visualising signalling and regulation events at multiple levels, from molecular to cellular to tissue levels, in the brain and immune system synapses. In addition to these institutions, MMBioS activities involve collaborations with leading scientists conducting cutting-edge experiments in many other organisations, including the California Institute of Technology (Caltech), Bristol University, Allen Brain Institute, Howard Hughes Medical Institute, Harvard University, University of Texas at Austin, University of New Mexico and others.

To what extent has collaboration contributed to the advancement of your research? Why is there a disconnect between researchers and practitioners in the field?

Current research topics, especially in neurobiology, are too complex to be tackled by single-disciplinary studies. We need to bring together biologists, chemists, physicists, computer scientists and engineers, and the first challenge to address is building a common language. It usually takes one or two years for researchers specialised in different disciplines to start speaking the same language. There is even a lack of communication between researchers in the same field – computational biology, for example – when they tackle problems at different scales. Molecular-, cellular-, tissue- and organ-level researchers are all focused on different things.

An immediate advantage of biomedical technology and research centres such as MMBioS is that they provide an environment that promotes dialogue between researchers who are highly specialised in their own fields. Such individuals could definitely benefit from the input of colleagues exploring the same type of problems from a different angle – using different methods, theories or concepts. An even more important endeavour is to shape our computational studies so as to respond to the needs of experimentalists or provide novel hypotheses that can be experimentally tested.

Moving targets

A laboratory at the University of Pittsburgh in Pennsylvania, USA, has been working towards a more complete understanding of biomolecular dynamics, with the intention of helping drug developers target neurological conditions

IN THE STUDY of biomolecular systems, there has been a steady shift over the last few decades away from sequence towards structure and the networks of interactions within the cell. As scientists attempted to understand the function of certain systems, they looked first to the sequence of the human genome. In doing so, they essentially discovered that this immense 'alphabet' of one-dimensional data provides very little information applicable to the actual mechanisms of biomolecular function and dysfunction, even when disease genes are specifically identified. When it comes to developing new ways to combat disease, sequencing information alone does not help. This realisation has prompted researchers to explore the structure of biomolecules and how structure dictates function.

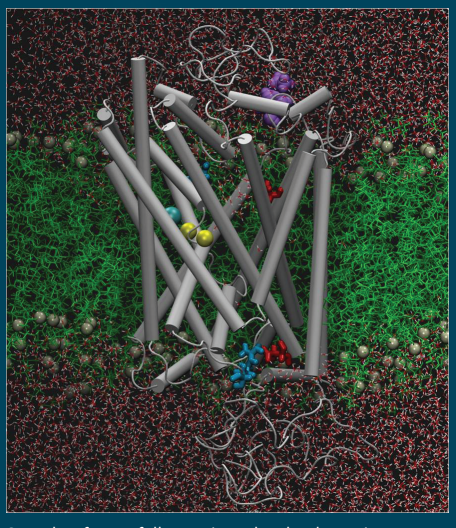
The problem is that a biomolecule is not a static structure but a dynamic one, defined in many ways by its movement, interaction with other biomolecules and ability to alter its shape. So, in the same way that a photograph cannot convey much about the functions performed by a car, the static structure of a biomolecule is not a particularly good indicator of its function. However, structural information is a good starting point for determining the machinery of biomolecules, which subsequently may help scientists design more effective intervention methods.

A MAMMOTH TASK

Gaining an understanding of biomolecular systems at this level is hugely complex and involves investigation via a number of routes. The challenge is that molecules do not function in isolation. They form assemblies and networks of interactions that come together to perform cellular functions. Understanding molecular events in the cellular context requires detailed analysis across a range of scales involving countless moving components.

Visualising and simulating biomolecular interactions across these levels in a way that is feasible and comprehensible is a task that requires significant planning in itself, as well as considerable expertise and access to extensive resources. Predicting the collective mechanisms of biomolecular function is a priceless goal, but attaining it could prove very expensive.

One laboratory at the University of Pittsburgh in Pennsylvania, USA, however, has proven that it is up to the task. Led by Dr Ivet Bahar, John K Vries Chair in Computational & Systems Biology, this team's ultimate aim is to develop useful models of biomolecular interactions based on structure-encoded dynamics, on the premise that such tools will be essential to a greater understanding of biological systems and enhanced opportunities for rational



Snapshot from a full-atomic molecular dynamics simulation of a dopamine transporter (grey cylinders) embedded in a lipid bilayer (green) and water molecules (red/grey) on both the extracellular and intracellular regions. (Courtesy of Dr M H Cheng).

COMPUTATIONAL AND SYSTEMS BIOLOGY: NATIONAL CENTER FOR MULTISCALE MODELING OF BIOLOGICAL SYSTEMS (MMBIOS)

OBJECTIVES

To investigate the dynamic behaviour of biomolecular systems in order to understand the motions of biomolecules in the context of their interactions within the cell, through the construction of comprehensible models and methods for simulations and *in silico* visualisation of biomolecular interactions at multiple levels.

KEY COLLABORATORS

MMBioS Center Leadership: **Dr Robert Murphy**, Lane Professor and Director of Computational Biology, Carnegie Mellon University • **Dr Terry Sejnowski**, Professor and Head, Computational Neurobiology Laboratory, Salk Institute for Biological Studies • **Dr James Faeder**, Associate Professor of Computational and Systems Biology, University of Pittsburgh • **Dr Ralph Roskies**, Scientific Director, Pittsburgh Supercomputing Center • **Dr Markus Dittrich**, Director of Biomedical Applications Group, Pittsburgh Supercomputing Center

Bahar lab members: **Dr Tim Lezon** • **Dr Indira Shrivastava** • **Dr Ahmet Bakan** • **Dr Mary H Cheng** • **Dr Ignacio General** • **Dr Filippo Pullara** • **Dr Mert Gur** • **Dr Bing Liu** • **Murat Can Cobanoglu** • **Chang Liu** • **Cihan Kaya** • **Feizhuo Kaitlyn Hu** • **Wenzhi Mao**

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DR IVET BAHAR is currently leading the MMBioS Center, in addition to conducting NIH-funded projects on biomolecular systems dynamics and drug discovery.

MMBioS
An NIH Biomedical Technology Research Center

PITTSBURGH SUPERCOMPUTING CENTER
SALK INSTITUTE FOR BIOLOGICAL STUDIES

drug development. Recently, funding from the National Institutes of Health (NIH) has allowed the group to launch a new initiative – the National Center for Multiscale Modeling of Biological Systems (MMBioS) – in collaboration with renowned partners, and with Bahar as the Principal Investigator. The goal of this project is to develop advanced computational tools for tackling complex neurobiological problems.

A CENTRE FOR NEUROSIGNALLING

The Bahar lab was the first to demonstrate that elastic network models could be adopted to obtain a unique, analytical solution for the structure-encoded dynamics of each protein near its equilibrium state. These models have since provided widely used frameworks for analysing biomolecular systems behaviour, the idea being to envision the biomolecule as a set of particles or nodes interconnected by a web of elastic strings.

By using this model, studies have revealed an important and previously unknown property of protein dynamics. It turns out that when a protein undergoes structural changes to accomplish its function, these changes are usually in line with the easiest modes of motion associated with their structure. This fact is perhaps unsurprising in that evolution would presumably have selected proteins for functionality of movement, but it does provide proof of principle for the network modelling approach.

In collaboration with colleagues at the NIH National Institute of Mental Health and the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge, UK, the Bahar lab has been investigating the dynamics of glutamate transporters and receptors involved in synaptic signalling, in an effort to discover the molecular mechanisms of information transfer in the central nervous system. Now, with the creation of MMBioS, the team has the opportunity to take their research even further. Their work will be integrated with those of colleagues in her department as well as leading computational biologists at Carnegie Mellon University, Pittsburgh Supercomputing Center and the Salk Institute for Biological Studies. Computations will be driven by experimental studies performed by new collaborators, opening the way to an exchange of data that Bahar characterises as a dialogue: "We envision a two-way flow of information: from experiments to computations and vice versa until the observations of the former converge with the predictions of the latter".

IMPORTANT IMPACT

In terms of impact, Bahar hopes that the computational technology developed by MMBioS will eventually constitute a framework that will enable the development of new treatments for neurobiological disorders. Psychiatric disorders such as autism, depression and schizophrenia affect almost half of Americans at some point in their lives, but the molecular mechanisms of (dys)function are yet to be understood, and currently administered drugs tend to treat symptoms rather than causes. It is clear that there is a need to examine the system from multiple perspectives, not only the dynamics of individual targets but also their coupled interactions in the cellular environment and integration of multiple synaptic signals. The research being undertaken at MMBioS could help bridge molecular events, cellular dynamics and brain functions, and help identify specific molecules that alter or regulate signalling events if targeted by drugs.

The advances made at MMBioS will not only have an impact on health, but within the scientific community as well. The team behind it hope that the creation, distribution and wide usage of advanced methods and software capable of encompassing complex systems dynamics at multiple scales will boost quantitative research in neuro-, molecular, systems and cell biology.

MMBioS: key targets

NIH recently awarded a grant of US $9.3 million for the development of a new centre that will facilitate the development of novel computational tools for systems biology: MMBioS. The main objectives of this ambitious project come under three categories.

TECHNOLOGICAL OBJECTIVES

The overarching technological goal is to develop computational tools and software to facilitate and advance cutting-edge research in neurobiology. An essential aspect of the developed tools will be their ability to provide an accurate representation of the structures and dynamics of biological systems at multiple levels, from molecules to synapses and organelles, and their adaptability to a broad range of systems and events:

BIOLOGICAL OBJECTIVES

The focus on signalling and regulation at synapses (including both chemical synapses in the central nervous system and T-cell synapses) will generate new data on the mechanisms of interactions between several pharmacological targets near the synapse, and thus provide guidance for discovering more potent modulators of function.

TRAINING AND DISSEMINATION OBJECTIVES

The project's objectives call for several workshops to promote the broad usage of the new computational technology developed by MMBioS researchers. The success of this technology will be defined by how effectively it can be used by the broader community.