Living Matter in Crash Test: How Biomolecules Respond to Mechanical Forces

Max Planck-CAS Research Group on Protein Mechanics and Evolution

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Dr. Frauke Gräter (first right front row) with her team of the Group on Protein Mechanics and Evolution at the CAS-MPG Partner Institute for Computational Biology at a group outing in 2009.

credit: Photos by courtesy of Dr. Frauke Gräter

The Group on Protein Mechanics and Evolution at the CAS-MPG Partner Institute for Computational Biology, Shanghai, was established in January 2007 and headed by Dr. Frauke Gräter. The Klaus Tschira Lab has continued the efforts of this former Independent Junior Research Group, since Dr. Gräter took up a position at the Heidelberg Institute of Theoretical Studies (HITS) in Heidelberg, Germany, in 2009. In 2014, Dr. Gräter was appointed full professor for Molecular Biomechanics at the Interdisciplinary Center for Scientific Computing at Heidelberg University.

Reported by Group Leader Dr. Frauke Gräter

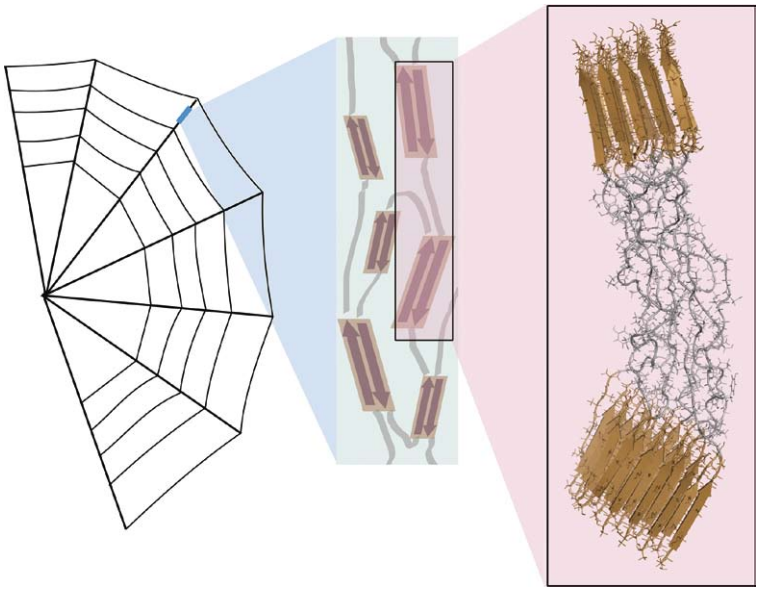

Figure 1: Spider silk webs are made from intricately designed fibers showing a hierarchical structure all the way from the fibers (left) to the atomistic scale (right).

OVERVIEW

The Protein Mechanics and Evolution Group asks how nature has been designed to respond to and generate the mechanical force. The force is a physical concept dating back to antiquity and defined centuries ago by Newton. It has more recently emerged also as a critical quantity in biology. This is very neatly reflected by the role it plays in our five senses. While sight, taste, and smell are based on photochemical or other biochemical processes, both hearing and touch are based on mechanical stimuli. The impact of mechanical forces on living organisms is also operative at the level of individual cells. Applying a tensile force to a cell within a muscle tissue or plated on a stretchable substrate in a laboratory results in measurable alterations to that cell's mobility, shape, proliferation, and function.

More recently, the impact of forces on biological systems has even been identified in single molecules. Stretching a protein or a smaller molecule can alter its structure and biochemical reactivity. Molecules can "sense" forces, and this enables nature to alter cellular processes and signaling pathways by mechanical stimuli. The work of the Protein Mechanics and Evolution Group (now the Klaus Tschria Laboratory) is designed to elucidate the interaction between the mechanical force and the structure and function of biomolecules. The group uses and develops a number of simulation techniques to study how complex structures such as proteins, protein complexes, or protein-based materials respond to external forces and thus in their turn exert an influence on a biological cell or organism.

Problems such as the deformation or failure of materials like concrete or steel under mechanical load are routinely analyzed by computer simulations, *e.g.* in the field of material engineering. Biological structures are so much more challenging to deal with using the computer, because they show an intricate structure on each spatial dimension, from the molecular scale of single proteins to the macroscopic scale of the resulting material, such as muscles, bones, or silk. Here, computational techniques including the force distribution analysis (FDA) developed in Gräter's lab as well as molecular dynamics and other more coarse-grained techniques are utilized. Here, two aspects of this work will be described, first multi-scale simulations to investigate the mechanics of silk fibers, and secondly, coarse-grained simulations to understand protein unfolding and refolding under stretching forces.

MAJOR RESEARCH THEMES

Bottom-up modeling of biomaterials: silk

As one focus of the Protein Mechanics and Evolution Group, Dr. Gräter and co-workers have been intensively involved in the investigation of two biological materials, namely silk fibers spun by spiders and nacre. In both cases, it has become evident that the molecular scale structures, such as the very periodic arrangement of hydrogen bonds in silk, or of ionic interactions in aragonite crystals of nacre, are crucial for the toughness of these materials. To connect the molecular structure to the mechanics of the material, we combined molecular dynamics simulations with finite element methods, in collaboration with mechanical engineers at Stuttgart University.

Silk fibers constitute an intriguing class of natural materials. Through a flawless assembly of strong and soft building blocks, they exhibit astonishing mechanical properties. Even today,

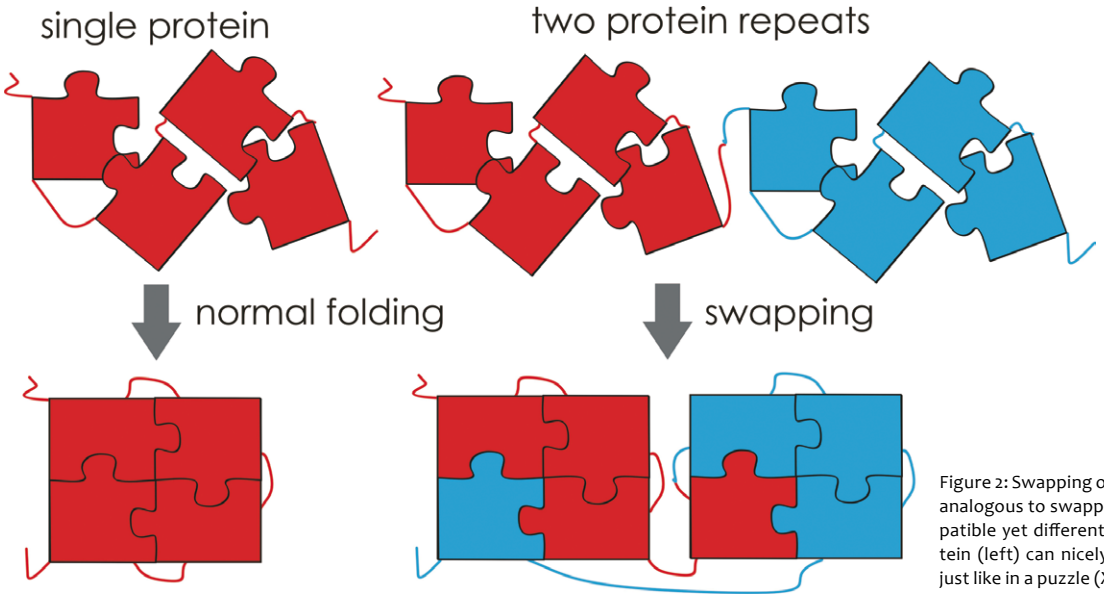

Figure 2: Swapping of places during protein folding is analogous to swapping puzzle pieces between compatible yet different puzzles. A single ubiquitin protein (left) can nicely fold into its favored structure just like in a puzzle (Xia, F. *et al*, *PNAS*, 2011).

natural silk fibers outperform their artificial counterparts in terms of mechanical performance, which originates from the nano-scale morphology of silk building blocks. But how do these constituents contribute to the silk fiber mechanics? Dr. Gräter's aim is to understand the origins of the mechanical properties of spider silk fibers and further predict their mechanical properties under different structural variations by using a bottom-up computational approach. Her approach bridges two discrete methods and scales: atomistic molecular dynamics (MD) simulations for individual building blocks, and finite element (FE) simulations for a comprehensive fiber model on the continuum scale. It thereby combines the accuracy of atomistic models with the practicality of continuum models in order to predict the macroscopic properties of spider silk fibers that are the results of molecular interactions.

The multi-scale simulations revealed that nature makes a balanced trade-off between elasticity, strength, and toughness in spider silk fibers by choosing a moderate crystallinity level of 10-25%. Interestingly, a significantly higher toughness can be achieved in fibers with lamellar structures at 40% crystallinity, which can be pursued in artificial fiber design.

With a tremendous decrease in the computational cost (up to 6 orders of magnitude when compared to the atomistic models) the approach is also applicable to similar semi-crystalline systems such as biological or non-biological block copolymers. The approach can be utilized not only for understanding, but also for the design and prediction of new composite systems.

When proteins swap places

Mechanical forces can unfold single proteins, being within a fiber like silk or in individual molecules. Proteins take up very well defined three-dimensional structures which are the crucial determinants for their functional role in biological cells, and which can be destroyed under the action of a tensile force. A certain set of proteins shows a repeat pattern, in which a specific three-dimensional structure is repeated over and over again, forming a shape reminiscent of pearls on a chain. The hypothesis of Dr. Gräter and co-workers to reconcile a set of recent force-induced folding and structural experiments of poly-proteins was a very simple, and thus very likely, swapping of places of fragments between adjacent repeats. Let us consider each repeat as a separate jigsaw puzzle (Figure 2), and each segment as a piece in the jigsaw. We can now play the following game. Because the shapes of the pieces of the different jigsaw puzzles are the same, they can swap places: The red puzzle piece of one jigsaw can swap with the same puzzle piece of the blue jigsaw adjacent to it.

The joint experimental and theoretical results suggest that swapping could be a very common phenomenon in nature. Indeed, it is feasible to speculate that swapping is involved in many cases of protein aggregation into fibrils, again under the influence of mechanical tension. More experimental and theoretical evidence is needed to reveal the role of proteins' "swapping places" in the fascinating dynamics of biological matter.

Dr. Gräter's group is involved in an international network of research groups with the joint aim to understand mechanics of biological systems at diverse scales. Among others, experimental and theoretical collaborators include Dr. Philip Hogg in Sydney, Dr. Dave Thirumalai in Maryland, USA, Dr. Gustavo-Caetano-Anolles from the University of Illinois at Urbana-Champaign, Dr. Daniel Lietha in Madrid, Dr. MA Yurong based in Beijing, and others. Even though Dr. Gräter's research group (now Klaus Tschira Lab) at the Partner Institute for Computational Biology will come to an end in 2014, the strong scientific ties to Shanghai and China will by any means be kept alive. ◂