New and Notable

Using Models to Design New Bioinspired Materials

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Molecular simulation is a quickly evolving research area and is increasingly being recognized as a tool for studying biological processes that are relevant in the real world. Molecular models can help researchers understand biological phenomena and predict novel properties of systems made of assemblies of biological macromolecules.

Typically, such models are defined in terms of physical interactions between microscopic entities, most often atoms, and the purpose of the simulation is to determine the macroscopic properties of complex systems comprising a large number of such microscopic components (see Robertson et al. (1) and Guy et al. (2) for the most recent applications of molecular simulation published in *Biophysical Journal*). However, such a bottom-up approach is not suitable for the exploration of systems that are large enough to truly represent macroscopic biological objects over the (long) timescales on which their behavior is most interesting. One such system is the protein fibronectin, a multidomain glycoprotein that connects cells with collagen fibers, allowing cells to move through the extracellular matrix.

In an article published in this issue, Peleg et al. (3) use fibronectin as an inspiration to model a minimalistic virtual material with very special properties. One can dissect these properties by performing a large number of computer simulations that, given the simplicity of the model, can be performed in minutes or hours on a desktop computer.

The fibronectin domains have a peculiarity: when force is applied to fibronectin, some of the domains expose binding sites that are normally inaccessible and are therefore called cryptic (hidden) sites. Such a force-induced modulation of the properties of individual fibronectins is itself remarkable, and atomistic molecular simulations have contributed to their discovery and investigation (4). Despite its simplicity, the model proposed by Peleg et al. captures several important features of fibronectin: 1), the opening of single domains under force is due to the breaking of noncovalent bonds, and the repeats reversibly refold when relaxed; 2), the opened repeat exposes a cryptic site that can specifically bind to neighboring chains; and 3), noncryptic sites (i.e., those that do not need application of force to be activated) are also present. When fibronectin molecules are stacked together to form fibers, the mechanical properties of such fibers are rich, depending on the relative strength of interactions, on their mutual arrangement, and on the direction of the force. The approach is perfectly suited to answer a number of "what if" questions.

Could the design principles used by Peleg et al. be practically used to create biologically inspired materials with unique properties? Indeed, this prospect looks very promising. Although man-made polymers can be tough and resilient, and have memory, among other properties, it remains a challenge to make polymers that can adapt their properties in response to an external stimulus. The model presented here has the merit of showing how such adaptive properties can emerge from the relatively simple properties of fibronectin-inspired domains. This is not the first attempt to design bioinspired materials with adaptive properties. In fact, materials with interesting, highly nonlinear stress-strain curves have been realized in practice (5–7) with the use of synthetic analogs of biological systems, such as the protein titin.

The work by Peleg et al. is important mainly because it provides a rational tool that is generalizable to other systems and can predict emergent mechanical properties of materials made of basic protein components. It also provides insight into how the design of fibronectin might regulate its many mechanical functions and be exploited as a mechanochemical signal transducer by cells that stretch extracellular matrix fibrils.

Recent experimental results showed that mechanical forces, and particularly the small forces experienced in vivo, modify the free-energy surface of a protein in a complex way. Substates that would not be populated in the absence of a force, or would not be crossed if the protein were subject to a larger force that caused its unfolding, may become metastable (8). This is a general property of proteins that holds promise for the development of protein-based materials with a very broad range of properties, including some that may not yet be foreseen.

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