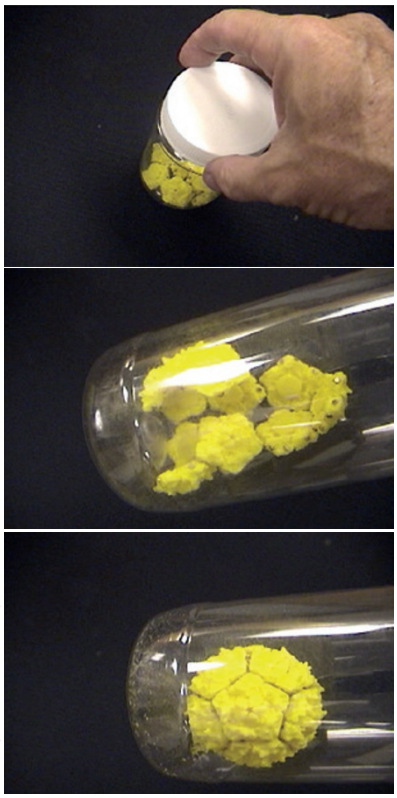
Self-assembly gets physical

Interacting with 3D-printed molecular models helps students to grasp insightful concepts on the kinetics and thermodynamics of molecular self-assembly, as **Arthur J. Olson** explains.

I was trained in X-ray crystallography at a time prior to interactive 3D computer graphics. When the first atomically resolved structure of a viral capsid was published in 1977, I had to build a model out of brass parts representing individual atomic components so that I could visualize the various protein subunits. The process took months and required physically measuring the position of each atom in the finished model. By the end of the 1970s interactive computer graphics systems were becoming commercially available, and the practice of building physical biomolecular models was subsequently abandoned. Although the computer-based representation had numerous advantages, some of the characteristics of the physical models were lost during the transition. Physical models can convey spatial relationships and mechanisms in ways that images alone cannot: they engage perceptual and cognitive processes that go beyond the visual and bring a sense of reality and natural interaction into the process of exploration and understanding.

Recently, the development of 3D printing has enabled the automated production of complex shapes, such as protein structures, directly from the computer model without the inordinate time and effort that were previously needed. With the aim to bring back the advantages of physical molecular models, I began to explore the use of 3D-printed models in creating representations of various biomolecular structures and processes. In one example, I printed out the assembly units of the poliovirus, whose structure had been solved by X-ray crystallography. With 12 identical pentagon-shaped assembly units I could build the complete spherical poliovirus capsid. The edges of each assembly unit are equipped with cylindrical insets accommodating small magnets. The polar complementarity of the magnetic interactions at the edges is analogous to the electrostatic complementarity in the natural molecular structure. The shape and polar complementarity of the assembly units, as well as the icosahedral symmetry of the complete viral capsid, makes the manual assembly both easy and physically satisfying. On a whim, I decided to put the 12 individual units into a closed plastic container and shake them to see if they would self-assemble — which to my delight they did in short order.



© 2005, ARTHUR J. OLSON, THE SCRIPPS RESEARCH INSTITUTE

Interacting with this physical model reveals a number of fundamental characteristics of the self-assembly process. First, ordered structures can happen through random collisions, where the kinetic energy input must be within a specific 'temperature' range (that is, not too little or too much shaking of the container). Second, sub-assemblies that have a larger number of assembly units are more stable at a given temperature (intensity of shaking) than those with only a few elements, illustrating the concept of positive cooperativity in natural assemblies. And third, the interactions between assembly units must be able to form and break apart to avoid potential misassembly, illustrating the error correction of off-target structures in the natural world.

Of course, poliovirus self-assembles through electrostatic and not magnetic interactions and the detailed mechanism is vastly different at the nanoscale than at the macroscale. Nevertheless, several of the fundamental characteristics of the assembly process are shared.

With regard to the timescale, the main reason that this particular human-scale demonstration works well is due to the symmetry of the individual units and the final structure. There are 10^{15} ways in which the 12 pentameric units can come together to form the complete icosahedral capsid. With so many ways to reach the final structure, the assembly can occur in a reasonably short time (usually less than a minute). (Self-assembly by shaking 12 differently shaped macro-sized pieces into a fully assembled unique structure could take millions of years.)

Participants of all ages (from 3 years old and upwards) have played with this virus model, and experienced the phenomenon of self-assembly first hand. It has been used in both high school and undergraduate classrooms to teach different aspects of self-assembly, from the simple observation of order from chaos, to its relationship to strength of shaking, to insights on entropy and other thermodynamic concepts. A formal educational study has been published on the use of the model involving undergraduate students in Sweden (G. E. Host, C. Larsson, A. Olson and L. E. Tibell, *CBE Life Sci. Edu.* **12,** 471–482; 2013). As expressed in the students' written reports, those that were taught using this physical model developed a higher degree of understanding that included more conceptual facets of the self-assembly process than students that were taught using graphical representations.

The self-assembling virus model is one of several models we have designed and 3D printed to interactively demonstrate biomolecular structures and mechanisms. Among these are models of protein polypeptide folding and DNA structure and topology. In conjunction with educational researchers from WestEd in California, we are now testing these models with high school teachers and students. We are also creating apps for mobile platforms to augment the interactivity of these models using computer graphics and computation. ❐

ARTHUR J. OLSON is in the Department of Integrative Structural and Computational Biology at The Scripps Research Institute, La Jolla, 92037 California, USA.
e-mail: olson@scripps.edu

© 2015 Macmillan Publishers Limited. All rights reserved