

BY KATHARINE MILLER

In the (Protein) Loop

In the gaps between the tight coils and flattened sheets that comprise most protein structures, flexible loops wave and bend. When crystallized, these loops can appear fuzzy in an electron density map—like moving objects captured in a still photograph. Often, loops may have an important role in a protein’s function, but because they are so mobile, their structure and dynamics can be hard to study.

To better understand how protein loops move, Simbios researchers have created LoopTK, a toolkit that samples and visualizes many conformations of a loop, and provides various algorithms to manipulate and analyze loop structures. “We want to find answers that are distributed over all the motion space,” says **Jean-Claude Latombe, PhD**, a roboticist and professor of computer science at Stanford University whose team developed the software. LoopTK is now available for download on the SimTK.org web site.

Latombe and his colleagues set out to place protein loops so that they correctly connect up with the protein’s coils and sheets while avoiding atomic clashes in the loop and between the loop and the rest of the protein. “Solving both constraints simultaneously is the hard part,” says Latombe. “That’s what we do with LoopTK. And we can do it very fast. We can sample many conformations very quickly.”

LoopTK relies on two techniques: seed sampling and deformation sampling. The seed sampling algorithm starts with nothing but the amino acid sequence of the protein. It then tries to place the loop in the full range of possible solutions. When several correct placements are found, the deformation sampling algorithm is used to deform the loop slightly without breaking the ends and without creating collisions among the atoms. “The two techniques are very complementary,” says Latombe. “One gives you a global picture of the entire molecule in space, and the



The Latombe group’s seed sampling algorithm successfully defines the motion space for loops surrounded by empty space (as shown here) as well as for loops that are more constrained by the surrounding protein structure (not shown). In this picture, the red dots show the positions of the middle C atom of the loop in many sampled conformations, but for clarity only a small number of these conformations are displayed in their entirety. Courtesy, Jean-Claude Latombe and Peggy Yao.

other allows you to explore specific regions of the motion space in more detail.”

Latombe’s group is working with others on two applications of LoopTK. With the part of the Joint Center for Structural Genomics located at the Stanford Linear Accelerator Center, they are interpreting fuzzy electron density maps created from X-ray crystallography. “One would like to know the full range of loop conformations that could fit into this fuzziness,” says Latombe. The resulting loop positions could then be submitted to the Protein Data Bank. “Biologists need to be aware of the flexibility of the loop and the uncertainty in the conformation,” says Latombe. LoopTK can provide a sense of which conformations are more likely—a characterization of the distribution of possible conformations.

In a second project, LoopTK is being used for functional homology research. **Russ Altman, PhD**, chair of Stanford’s bioengineering department, and his group are trying to extract structural knowledge based on partial knowledge about a protein’s function. For example, if a protein X is known to bind to protein Y, LoopTK might help to infer possible conformations of the loop that are consistent with such binding.

“There might be dozens or more applications for this tool,” says Latombe. “What we hope is that by putting it on the web site other people will explore those possibilities.” □

DETAILS

LoopTK, a C++ based object-oriented toolkit, models the kinematics of a protein chain and provides methods to explore its motion space. In LoopTK, a protein chain is modeled as a robot manipulator with bonds acting as links and the dihedral degree of freedoms acting as joints.

LoopTK is now available for download at <https://simtk.org/home/looptk>. An application programming interface (API) lets users embed LoopTK in their application software.

LoopTK will be presented at the 7th Workshop on Algorithms in Bioinformatics in Philadelphia on September 8-9, 2007. (<http://www.wabi07.org/>)

