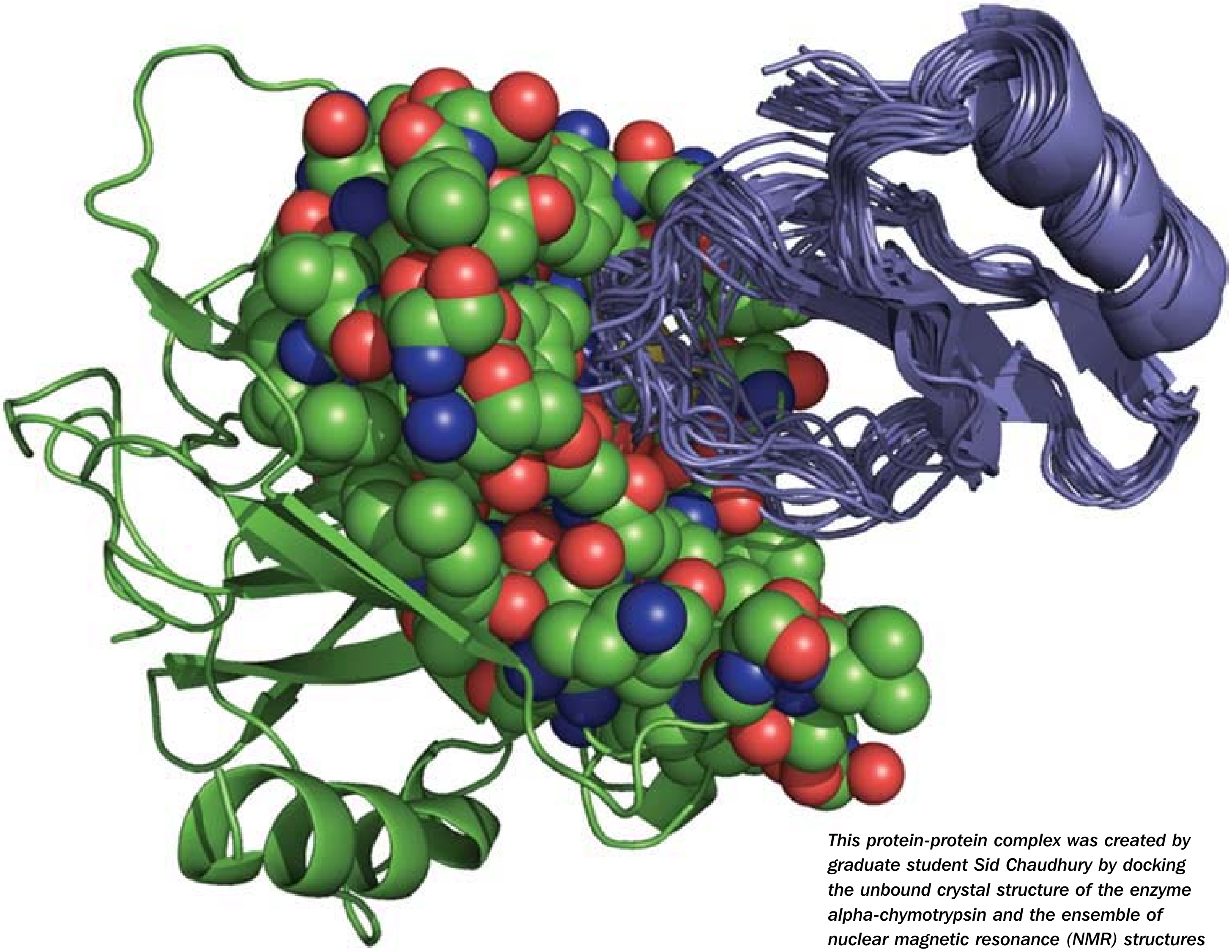

This protein-protein complex was created by graduate student Sid Chaudhury by docking the unbound crystal structure of the enzyme alpha-chymotrypsin and the ensemble of nuclear magnetic resonance (NMR) structures of the inhibitor eglin-C. Using PyRosetta, students learn to fold, dock, and design proteins.

Final Exam

In the new course Design of Biological Molecules and Systems, undergraduates learn to design and build proteins. Or at least they get to try.

The course, split into two seven-week sessions, is co-taught by assistant professor Jeff Gray and associate professor Marc Ostermeier, both of Chemical and Biomolecular Engineering. “In my half of the course,” says Gray, “students apply rational thought and physics to the design of a protein, using computational methods to read and manipulate 3-D structures.” Making it all possible is PyRosetta, a computer program Gray helped to develop that marries a programming language called Python with Rosetta, the leading research tool for protein structure prediction and design.

Fundamentally, a protein’s function is dictated by its structure (or shape), which is determined by its gene sequence. “Structure is interesting to engineers because it’s like driving a car and then opening up the engine and seeing how it works,” says Gray. By using computer models to adjust and tweak the model’s sequence and shape, students change its theoretical function.

However, since a protein is a complicated system of thousands of atoms, the calculations the students must perform often become inexact. “Many forces are very carefully balanced by nature and because calculating them can be tricky, we end up having to approximate things like the effect of water or the electrostatic energy,” says Gray. That complexity often prevents the students from designing a protein that could survive in real life, so, halfway through the semester, Ostermeier takes over with a different method. Their new mission: to learn how proteins evolve and function in real cells.

“My approach is quantitative and rational, while Marc’s is more experimental by trial and error,” Gray says. “However,” he adds with a laugh, “his usually works and mine doesn’t.”

“We use evolution as our design tool,” Ostermeier says. “You put a protein into a scenario such that if it doesn’t do what you want it to, it doesn’t survive the process. It’s survival of the fittest.” Through readings and lectures, the students learn about such experimental methods and techniques that, essentially, take an approach opposite to Gray’s: by forcing a protein to evolve function and later determining its sequence and shape. By the semester’s end, the students know how to design proteins theoretically in Gray’s lab and, in Ostermeier’s, the methods and techniques that can be used to build them through experimentation.

“Ultimately, if engineers could build proteins that perform specific tasks,” Gray says, “they could potentially do things like make better drugs, make proteins that destroy agents in biological weapons, build biosensors that detect environmental contaminants, or make better enzymes for biofuels. The applications could be incredible.”

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