



## COMPUTING IN BIOLOGICAL TIME

### The Design of an Anticocaine Molecule

By Pam Frost Gorder

**W**E MEASURE OUR LIVES IN YEARS, PLAN OUR ACTIVITIES ACCORDING TO CIRCADIAN RHYTHMS, AND GAUGE OUR HEALTH BY COUNTING BREATHS AND HEARTBEATS.

Yet, our bodies' most natural timescale is only a fraction of a second. The cellular processes that keep us alive occur so fast that scientists often can't directly observe them, but computer simulations fill that gap amazingly well—considering that a single biochemical reaction that lasts only a billionth of a second might require an entire day to simulate on a supercomputer.

At the molecular level, life already moves fast. In search of a better anticocaine medication, scientists at the University of Kentucky used computer simulations to create a “souped-up” version of the human enzyme that breaks down the drug even faster.

#### How to Block a Blocker

When chemist Chang-Guo Zhan at the University of Kentucky considered how to design a drug to treat an overdose, he thought about cocaine antibodies—large molecules that bind one-on-one with cocaine molecules to pull them from the bloodstream. But cocaine is hard to counteract because it blocks the brain's natural cleanup of the feel-good chemical dopamine, and blocking a chemical blocker is difficult.

“The problem is that a cocaine antibody is a very big molecule,” Zhan says, “so the concentration of the cocaine molecules will always be much higher than the available antibody. You just can't have enough antibody available.”

The body manufactures an enzyme called butyrylcholinesterase (BChE) to break down cocaine in the bloodstream, but it doesn't work fast enough to stop an overdose, which can cause a fatal heart attack or stop a person from breathing by shutting down the central nervous system. Zhan and his University of Kentucky colleagues decided to enhance the enzyme's activity by using a supercomputer running software called Amber (Assisted Model Building

with Energy Refinement; <http://amber.scripps.edu/>) to shape the molecule. In the November 2005 issue of the *Proceedings of the National Academy of Sciences* (“Computational Redesign of Human Butyrylcholinesterase for Anticocaine Medication,” vol. 102, no. 46, pp. 16656–16661), they reported a new BChE molecule that works 450 times faster.

#### Molecules Moving in Amber

Understanding how biological molecules work requires an understanding of their structures and how they change as spaghetti-like protein branches fold and unfold to bind to other molecules. Although visualizing this ultrafast process of molecular dynamics requires powerful computers, the science is firmly rooted in 17th century Newtonian mechanics.

Protein chains tend to form the most energy-efficient structure for a particular function by minimizing a configuration's potential energy. Amber, which was first developed at the University of California, San Francisco, more than 25 years ago, simulates how BChE normally works: the enzyme binds with a cocaine molecule to form one stable chemical complex and then rotates the cocaine molecule to form a second chemical complex before tearing the cocaine molecule apart.

What made his strategy unique, Zhan says, is that most computational modeling focuses on simulating molecules' stable states. Instead, he and his colleagues focused on the transition state between two stable structures, which turned out to be the slowest step in the process. They wanted to speed it up by lowering the energy required to make it happen. That meant changing the molecule's structure so that it would naturally follow a new, faster procedure. Of the hundreds of amino acids in the molecule, they zeroed in on four and replaced them. Simulations suggested that the new and improved BChE would work 450 times faster—and when the scientists tested their new molecule in the lab, it performed exactly as they'd hoped.

David Case, a molecular biologist at the Scripps Research Institute and one of Amber's original creators, praised the strategy for its simplicity. The changes Zhan and his colleagues made shortened the distance between key atoms responsible for the hydrogen bonds that enable the reaction.

“They didn’t try to directly see if one mutant was faster than another, but looked at things that were known to correlate well with stabilizing that transition state, and therefore speed up the reaction. So in that sense, it’s a very straightforward simulation,” Case says. “I think it’s a very nice analysis.”

Joel Stiles, director of the Center for Quantitative Biological Simulation at Carnegie Mellon University, says he found Zhan’s results encouraging because he frequently studies acetylcholinesterase, a relative of BChE. Acetylcholinesterase cleans up the naturally occurring neurotransmitter acetylcholine, which carries instructions from the brain to muscle cells. In other laboratories, molecular dynamics simulations of acetylcholinesterase have led to the development of drugs to treat Alzheimer’s disease.

### Initiate Force Field

Chemists refer to the equations that describe molecular dynamics as force fields. They treat the molecules’ atoms, and the bonds that hold them together, like balls and springs; based on the potential energy of different structures, chemists can solve Newton’s force equations for the molecules’ tiny movements. In Amber, just like any situation in classical dynamics, you must have a starting point and move forward in time, Case says. The starting position is either the molecule’s natural “wild-type” structure or a mutant structure. The only way to make a molecule move in a particular way is to change its structure and observe what happens, he says. “You change an amino acid, and Amber shows you the spontaneous results of that—what you get is what you get.”

Scientists don’t even get to choose the timescale that’s best for simulating a reaction—that’s determined by how fast the forces change inside the molecules. Bonds vibrate back and forth like springs, Case says, “and to follow that, you need to model several time steps for every vibrational period. A femtosecond [one quadrillionth of a second] time step is pretty universal, and it’s determined by the types of forces that are present in organic molecules.”

To go to longer timescales, Stiles says, scientists must approximate the structure as a modified ball-and-spring model in which amino acid groups are treated as if they were single particles. He and his colleagues at the Salk Institute for Biological Studies carried the concept even further by developing the MCell (Monte Carlo cell) and Dreamm (Design, Render, and Animate MCell Models; [www.mcell.psc.edu/](http://www.mcell.psc.edu/)) applications, which reduce entire molecules to single points in space to simulate pieces of biological cells. “We don’t pay explicit attention to the molecular structure, and because of that, we’re able to push the timescales out to mi-

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croseconds, milliseconds, and in some situations, whole seconds of simulation time," Stiles says.

Zhan and his team prepare their input files on an SGI workstation, where simulating one BChE transition state—a process that completes in one nanosecond (billionth of a second) in real life—takes two to three weeks. Then they try out the simulation on their 34-processor IBM Linux cluster to make sure the code is ready to run on the University of Kentucky's Center for Computational Sciences' Hewlett-Packard supercomputer (a Superdome with 256 shared-memory processors). There, simulating the one-nanosecond transition state takes a little less than a day.

Zhan confesses that he could have easily used a different program, such as Charmm (Chemistry at Harvard Macromolecular Mechanics; www.charmm.org/) or Namd (Nanoscale Molecular Dynamics; www.ks.uiuc.edu/Research/namd/), to simulate his mutant enzyme. In the end, however, he chose Amber because of its popularity for protein simulations. As Case and his colleagues wrote in a recent issue of the *Journal of Computational Chemistry* ("The Amber Biometrical Simulation Programs," vol. 26, no. 16, 2005, pp. 1668–1688), the Amber force fields are among the most widely used for biomolecular simulations.

## Closer to Reality

Case began working with Amber in the late 1970s, while attempting to design an artificial substitute for whole blood by modeling how the hemoglobin molecule binds with oxygen in red blood cells. He revisits the problem every 10 years or so in the hope of discovering a new way of thinking about it. The next time he does, molecular dynamics will yield more realistic force-field descriptions.


"Those force fields will be more computationally expensive than the ones of today because they'll contain more complicated mathematical terms, and they'll take into account the environment around each atom," he says. "That's the direction where things are going."

According to Stiles, one of computational biology's major challenges is to develop methods to do what he calls true multiscale simulations. "In other words, finding ways to couple simulations at molecular levels to simulations using the methods that we employ [at the subcellular level] and then going beyond that to even larger timescales," he says. "Right now, we have a lot of tools that are very capable, but are very focused at particular levels of space and time. So trying to bridge those scales is the big challenge now."

Although scientists are making great strides with molecular dynamics, no newly designed molecule is ready for clinical use.

Case used his artificial blood research as an example. “We’ve designed some pretty good hemoglobin mutations, but how do you deliver them in the body and keep them from being degraded? Artificial blood, just like this cocaine advance, has many steps ahead of it before it can be used clinically.”

**Z**han is busy scaling up production of his cocaine enzyme for animal testing. He hopes that it will eventually be made into a drug that not only saves people from cocaine overdoses but also lingers in the body to immediately destroy any cocaine the person takes for weeks afterward. With that goal in mind, he’s working on enhancing the enzyme’s thermal stability so that it will survive longer in the blood. Zhan knows that the social issues surrounding drug abuse are very complex. He wonders whether cocaine addicts will want to use his enzyme if it eliminates the high they crave, for example, and doctors will have to figure out how to use the enzyme as part of a treatment program.

In the meantime, his lab is using the same computational techniques to design drugs to enhance memory and to treat anxiety disorders. 

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