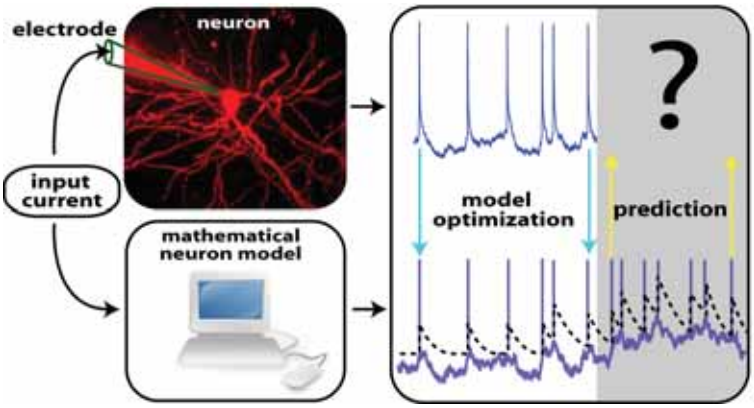


To set up one of the challenges for the neuron modeling competition, an artificial current was injected into a live neuron (upper left) and the resulting electrical activity was recorded for 60 seconds (blue trace, top right). Competitors used data from the first 38 seconds of the recording to fine-tune the parameters of a mathematical neuron model receiving an identical current injection (purple trace, lower right). Model performance was measured by the percentage of spikes correctly predicted in the final 22 seconds of the recording. Graphic courtesy of Richard Naud.

Contestants had to predict the precise timing of electrical spikes in individual neurons from different parts of the brain. Since different neurons can respond differently to the same signal, competitors used the first 38 seconds of data from a neuron to adjust their model parameters to better fit that neuron. They used the freshly tuned model to predict spikes in the subsequent 22 seconds of data. Shinomoto's winning model predicted 59.6 percent and 81.6 percent, respectively, of the spikes from two different neurons.

Electrical activity in a real neuron spikes when its membrane potential passes a set threshold value. Shinomoto's model neuron has an adapting threshold that increases immediately after a spike and decays exponentially to its initial value. The decay is modulated by two time constants of 10 ms and 200 ms, chosen to reflect the timing of ion currents in the neuron membrane.

The competition will evolve with the field, Gerstner says. Computational neuroscientists will soon draw on an emerging body of molecular knowledge to improve their models, says **Erik De Schutter, PhD**, a professor of computational neuroscience at the Okinawa Institute of Science and Technology. Advanced molecular techniques should reveal the physical structures and electrical properties of neurons in much greater detail than is currently known. These data may help modelers account for the effects of variations in temperature and chemical conditions and in the physical structures of the neurons.

"Neuron modeling is still a work in progress," De Schutter says. "It's much more difficult than we thought."

—By Sandra M. Chung

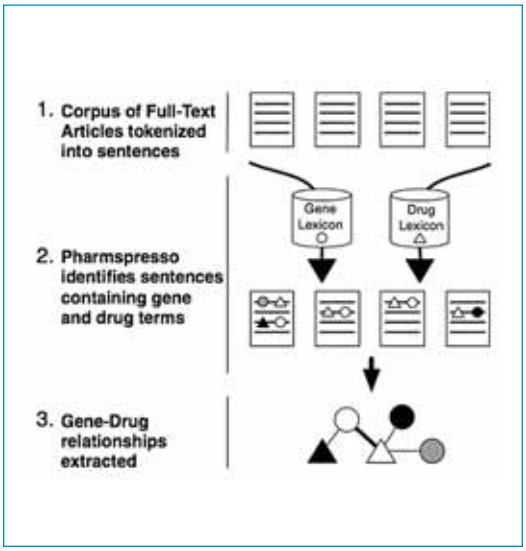
Trawling for Drug-Gene Relationships

When a drug saves one person but makes another ill, a bitter lesson in genetic differences often follows. With many such lessons already under our collective belts, researchers are using existing knowledge to predict additional drug-gene relationships as a way to forestall future calamities. A new software program can trawl published papers for gene-drug relationships, plug those relationships into known genetic networks, and predict which genes are likely to affect a patient's response to a drug.

"Our contribution is using text mining and taking decades of research and folding that in to inform the prediction," says **Yael Garten**, biomedical informatics PhD candidate in the lab of **Russ B. Altman, MD, PhD**, at Stanford University and a lead author of the work. "We showed that this is as good as and sometimes even better than manual curation," in which scientists painstakingly enter published drug-gene interactions into a database. Garten will present the team's research January 2010 at the Pacific Symposium on Biocomputing in Hawaii.

The previous version of the algorithm, designed by Altman and others, relied more heavily on manual labor. Called PGxPipeline, it employed a database of gene-drug relationships manually compiled from scientific articles by a team of scientists at Stanford Medical School. PGxPipeline wove these relationships into an orderly web, along with a database of gene-gene interactions and other data, to predict how strongly each of 12,460 genes affects response to a specific drug.

The team has now cut PGxPipeline loose from the manually created drug-gene database, automatically mining the information from published papers. This faster, cheaper method will inform the drug-gene rankings with constant updates from new literature. The manual-curation- and text-mining-based



The text-mining-based version of PGxPipeline automatically dissects journal articles into component sentences and marks where a drug or a gene is mentioned. Reading the sentence syntax and vocabulary, it tracks the interactions between drugs and genes. A network/web of interactions is established (bottom), in which the thickness of each edge corresponds to the number of articles that support the interaction. The web of relationships is later enhanced using a database of gene-gene interactions and other information. Image reprinted from Garten, Y., Tatonetti, N., & Altman, R., Improving the prediction of pharmacogenes using text-derived drug-gene relationships, Pacific Symposium on Biocomputing, Hawaii, January 2010.

versions of PGxPipeline predicted with similar accuracy a test set of 682 drug-gene interactions. And the text-mining-based version was slightly better at identifying genes that play the largest roles in response to a specific drug.

Garten hopes to use the revised PGxPipeline to parse all relevant scientific literature for drug-gene relationships. Better predictions will save researchers time in deciding which of the possible interactions to test in the lab and eventually influence how doctors prescribe drugs, she maintains.

"There is an emerging trend in bioinformatics to combine information from curated databases with information extracted from text," says **Tom Rindflesch, PhD**, principal investigator for the semantic knowledge representation project at the National Institutes of Health in Bethesda, Maryland. "This is an excellent example."

—By Olga Kuchment, PhD

Scientific Discovery Through Video Games

When it comes to folding proteins, even modern supercomputers don't always get things exactly right. Enter FoldIt, an online video game that harnesses the human brain's natural pattern-recognition abilities to tweak computer oversights. Since its release in May 2008, FoldIt has captivated a core group of several thousand dedicated players. Contestants manipulate three-dimensional protein chains into the best configuration they can find, exposing effective and previously unknown algorithms. In recent months, the puzzles have focused on medical applications. For example, a puzzle released in October called "Finding Home" asks players to bind a potential gene therapy tool—a homing endonuclease—to DNA. In another, called "Pack the Holes and Fight Cancer," gamers will help design a protein that could activate a new kind of cancer drug.

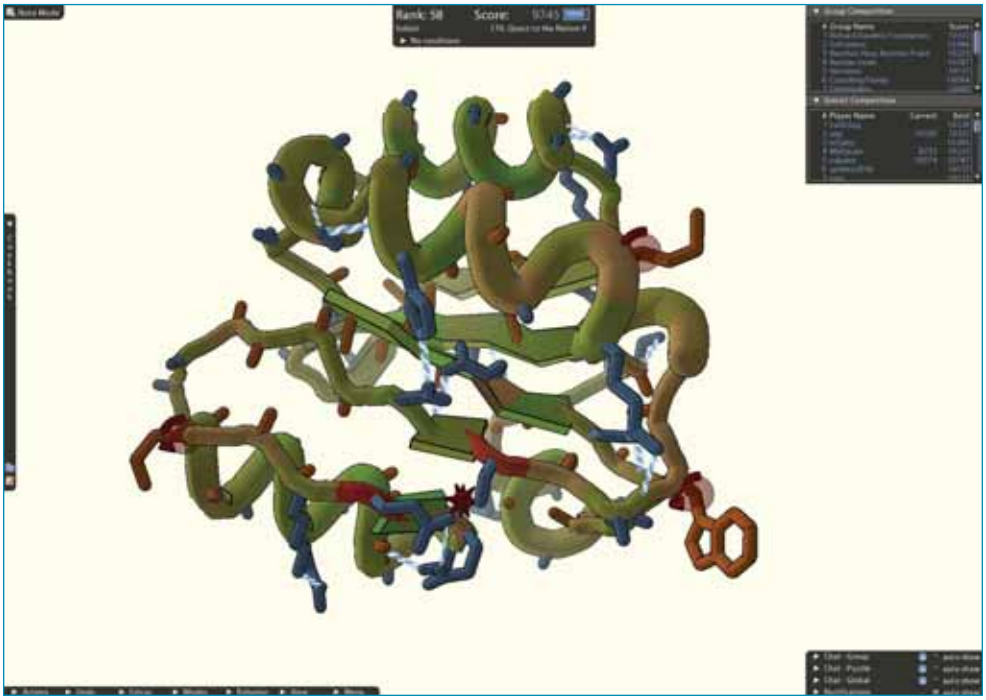
"The players, most of whom are non-experts, have sort of become protein scientists," says **Adrien Treuille, PhD**, assistant professor of computer science at Carnegie Mellon University. Treuille helped create FoldIt with a team at the University of Washington led by graduate student **Seth Cooper**, computer scientist **Zoran Popović, PhD**, and biochemist **David Baker, PhD**.

Researchers often must correct obvious errors in computer-folded proteins. FoldIt was developed to allow amateurs to spot and fix these computer inaccuracies. Players rack up points by pulling, wiggling, and tweaking a polypeptide sequence into the most chemically and physically accurate orientation. Most gameplay has concentrated on uncovering new folding algorithms, but FoldIt's current focus is producing player-designed proteins that can interact with particular biological targets, such as a small DNA strand. The game's creators recently released a puzzle asking players to generate a better design for human fibronectin, a protein used to mimic antibodies. One player modified fibronectin's peptide chain in a way that may turn out to be more stable than the original. Chemists at the University of Southern California are currently fabricating the novel structure for testing.

"FoldIt is a seminal and important project," says **David P. Anderson, PhD**, research scientist at the University of California, Berkeley Space Sciences Laboratory who created an online astronomy volunteer project called Stardust@home. But he encourages the team to focus more on hard scientific data in the future. "I hope they are able to quantify what they've actually done," he says.

Despite such concerns, Treuille thinks other researchers might imitate FoldIt's approach to computational analysis. "Everywhere you look in science there's labor that could use many people," he says. Treuille believes that similar projects could draw on the power of crowds while entertaining and educating the public.

—By Adam Mann □



A team at the University of Washington designed the online game FoldIt to improve protein-folding algorithms. Players maneuver polypeptide chains, such as this 2HSH sequence, into their lowest energy configuration to get the highest score. Image courtesy of Seth Cooper at the University of Washington.