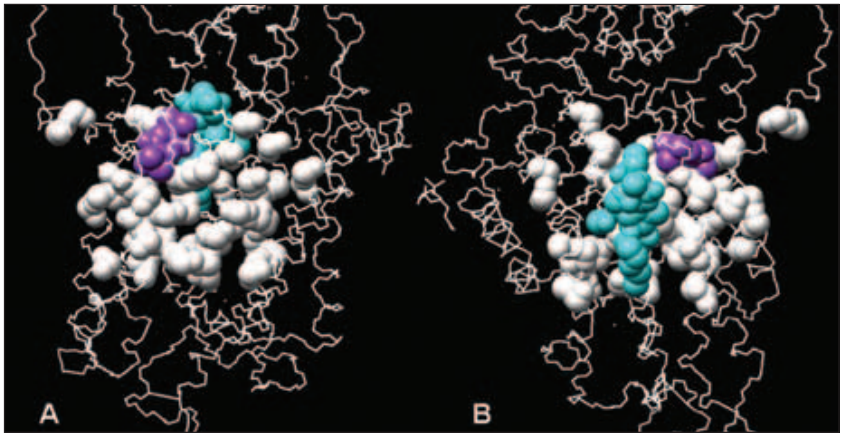
vast quantities of data that it has pushed the computational capacity to make sense of it all, and the Human Microbiome Project will produce an order of magnitude more data than that. The project aims to coordinate the results from all the different groups, producing a single, publicly-available dataset.

The researchers involved in the project say the most exciting part is that they simply don't know what they're going to find. "You have to expect that there will be very many ways microbes are impacting our health that we don't know and maybe can't imagine at this point," says **George Weinstock, PhD** of Washington University in St. Louis. "We're hopeful it will have an impact on the level of the human genome project."
—By Julie J. Rehmeyer



The algorithm created by Bourne and his colleagues identified a possible Tamoxifen binding site (white spheres) on a protein called SERCA that regulates calcium levels within muscle cells. They also found that two known inhibitors of SERCA bind to areas (shown in purple and blue) within the same zone. This suggests that a side effect of Tamoxifen could be inhibition of this protein, Courtesy of Philip Bourne.

Side Effects *in silico*

Many new drugs carry a risk that they will cause more problems than they cure. That's because a drug intended to bind one protein might also bind others. In an effort to address that problem, researchers have developed a new computational approach that can potentially predict the protein interactions that cause drug side effects. The new algorithm has already provided a possible explanation for some side effects caused by the widely-used anti-cancer drug Tamoxifen. The same approach may also help find new targets for commercially-available drugs.

Traditional drug discovery searches for possible drugs that can bind to a known receptor protein. "We're doing essentially the reverse of that," says **Philip Bourne, PhD**, professor of pharmacology at the University of California, San Diego and lead author of the work published in the November 2007 issue of *PLoS Computational Biology*. "We've already got something that binds to a receptor. The issue is that it doesn't necessarily bind only to that receptor."

To find out what else the compound is binding, Bourne and his colleagues start with a database of potential receptors—what they call the "druggable proteome." They then test whether the compound binds to one or more secondary sites in receptors other than the primary target. Previous attempts to predict such drug-protein interactions have met with limited success. But **Lei Xie, PhD**, a member of Bourne's team, developed a novel algorithm that considers the evolutionary relationship among potential binding sites and also allows the receptor proteins to bend and move.

Combining these new parameters with an analysis of the receptors' shapes and binding characteristics yielded a powerful search tool capable of discovering off-target proteins missed by previous algorithms. Bourne's team then looked at whether the known functions of those off-target proteins could provide a logical explanation for a drug's known side-effects.

Bourne's team applied their algorithm to a family of cancer drugs that includes Tamoxifen. Known as selective estrogen receptor modulators (SERMs), this clan of drugs often causes unwanted side effects such as heart disease and ocular degeneration, both of which involve a disruption in cells' calcium balance. So Bourne's team was not surprised when their algorithm found Tamoxifen could bind a protein that regulates calcium levels within muscle cells (Sarcoplastic Reticulum Calcium ion channel ATPase protein (SERCA)). Specifically, the algorithm predicted that Tamoxifen inhibits SERCA's action (by binding near natural inhibitors' binding sites).

Bourne hopes the algorithm will help identify potential side effects of new compounds before they reach clinical trials, saving enormous amounts of money and time. In addition, the algorithm could help researchers design drugs with fewer side effects and find new targets for already-approved drugs. Indeed, Bourne's group has already found that existing Parkinson's disease drugs may help treat extreme drug-resistant tuberculosis.

"The potential value is huge if one could do this reliably," says **Robert Stroud, PhD**, a professor of biophysics and biochemistry at the University of California, San Francisco. Stroud cautioned, however, that more examples of the algorithm's ability to successfully identify off-target proteins are necessary before any definite conclusions can be drawn.
—Matthew Busse, PhD □