Stanford and Google team up to simulate key drug receptor

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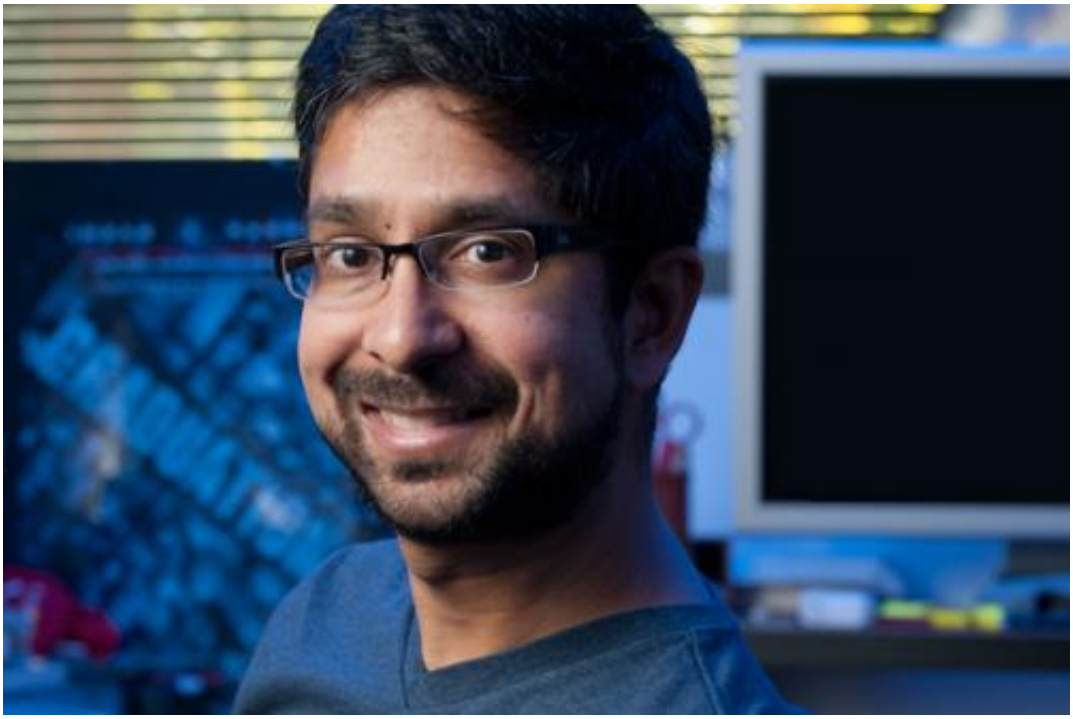

Chemistry Professor Vijay Pande and colleagues tapped Google's cloud computing system to simulate thousands of actions at the atomic level. Credit: L.A. Cicero

(Phys.org) —Roughly 40 percent of all medications act on cells' G protein-coupled receptors (GPCRs). One of these receptors, beta 2 adrenergic receptor site (B2AR), naturally transforms between two base configurations; knowing the precise location of each of approximately 4,000 atoms is crucial for ensuring a snug fit between it and the drug.

Now, researchers at Stanford and Google have conducted an unprecedented, atom-scale simulation of the receptor site's transformation, a feat that could have significant impact on drug design.

This is the first scientific project to be completed using Google Exacycle's cloud computing platform, which allows scientists to crunch big data on Google's servers during periods of low network demand.

The study was published online in *Nature Chemistry* on Dec. 15.

As a type of GPCR, the B2AR is a molecule that sits within the membrane of most cells. Various molecules in the body interact with the receptor's exterior, like two hands shaking, to trigger an action inside the cell.

"GPCRs are the gateway between the outside of the cell and the inside," said co-author Vijay Pande, a professor of chemistry and, by courtesy, of structural biology and computer science at Stanford. "They're so important for biology, and they're a natural, existing signaling pathway for drugs to tap into."

Roughly half of all known drugs – including pharmaceuticals as well as natural molecules such as caffeine – target some GPCR, and many new medications are being designed with these receptor sites in mind. The 2012 Nobel Prize in Chemistry was co-awarded to Brian Kobilka, a professor at the Stanford University School of Medicine, for his role in discovering and understanding GPCRs.

Traditionally, maps that detail each atom of GPCR, and other receptors, are created through a technique called X-ray crystallography. The technique is industry standard, but it can only visualize a molecule in its resting state; receptors naturally change configurations, and their intermediate forms might also have medical potential.

When developing a drug, scientists will often run a computer program, known as a docking program, that predicts how well the atomic structure of a proposed drug will fit into the known receptor.

In the case of GPCRs, for example, the X-ray crystallography techniques have detailed teceptors' "on" and "off" configurations; many medications have been specifically designed to fit into these sites. Scientists expect, however, that other fruitful configurations exist. Many drugs engage with GPCR sites, even though computational models suggest that they don't fit either of the two defined reaction site configurations.

Computer simulations of a GPCR's shape as it morphs from "on" to "off" could create a thicker catalog of reaction site profiles, Pande said, and provide scientists a better jumping-off point for computational drug design and more discoveries.

A cloud-based attack

To simulate the GPCR alternatives at the same atom-level accuracy of X-ray crystallography, however, would take too long using traditional computing methods.

"The computational burden of a model that is faithful to atomic details is very high," Pande said. "A very fast computer processor can compute a billionth of a second of this reaction in one computer day. So if you want to simulate a full reaction on a millisecond time scale, it's going to take millions of days."

Instead, Pande and his colleagues tapped the power of Google's Exacycle cloud computing system, which harnesses a distributed network of computers to process data in parallel.

The B2AR simulation consists of almost 60,000 atoms. Each Exacycle

system simulated tens of thousands of random trajectories that these atoms could take as the protein shifted its shape, generating about 250,000 molecular structures per simulated system.

The researchers then wrote algorithms to identify the most consistently generated configurations and to sift through that group for the states that are the most likely to actually exist given real-world constraints.

In total, the researchers simulated 2.5 milliseconds – a virtual eternity in chemical reaction time, the authors said – of the receptor shifting from "on" to "off," capturing every viable configuration of atoms in between. These intermediate structures can then be experimentally confirmed, Pande said, but even before that happens, they can guide more efficient drug design. In particular, the authors have shown that different classes of drugs are preferred by different intermediate GPCR states.

"There is some tension right now between doing this type of work with specialized hardware or with general commodity hardware, as we have done," Pande said. "Cloud resources are much more accessible to the general scientific community, and I think that we've shown here that, with the right method and algorithms, you can do the same quality of work."

The next "ridiculous" challenge

The work grew out of a key project from Simbios, the NIH Center for Biomedical Computation at Stanford, a decade-old collaboration between a broad group of bioengineering, chemistry, biology and computer science faculty from Stanford and the Stanford School of Medicine.

"This work really represents a capstone to the molecular types of calculations that a diverse group of people can tackle, and it's a challenge

that I thought was really pushing the limits," Pande said. "Ten years ago I would have said this is ridiculous; even five years ago it felt a little bit out of reach.

"But we brought together people who are really at the top of their game, and being around people like that really pushes you to be the best that you can."

Asked to project the next insane step in this research, something that might take another 10 years to unfold, Pande said he'd really like to develop similar atomistic simulations of processes at the scale of an entire cell.

A key challenge of battling a disease like cancer, he said, is that the tumor cells are using normal proteins to conduct abnormal processes. Deciphering how the cells and proteins behave (or, rather, misbehave) at the molecular scale, he said, could help scientists design drugs that target specific molecular pathways to battle cancer.

"We will need to push the boundaries of both computers and algorithms," Pande said, " but the conceptual steps are there."

More information: "Cloud-based simulations on Google Exacycle reveal ligand modulation of GPCR activation pathways." Kai J. Kohlhoff, Diwakar Shukla, Morgan Lawrenz, Gregory R. Bowman, David E. Konerding, Dan Belov, Russ B. Altman, Vijay S. Pande.*Nature Chemistry* 6, 15–21 (2014). DOI: 10.1038/nchem.1821

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