SimbiosNews

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Putting Exacycles and Markov State Models to Work on GPCRs

Despite being well-studied, much remains unknown about the dynamics of G-protein coupled receptors (GPCRs), molecules that are prominent drug targets. Recent work published in the journal *Nature Chemistry* breaks new ground in both our understanding of GPCRs and in methodologies for simulating such molecules. Using Google Exacycle and Markov State Models, the study by Google research scientist **Kai Kohlhoff, PhD**, and Simbios collaborators **Vijay Pande, PhD**, and **Diwakar Shukla, PhD**, achieved an unprecedented and insightful millisecond simulation of the GPCR beta-2 adrenergic receptor (β_2AR).

"The impact of this paper is not just that we matched what others found experimentally," says Kohlhoff. "We've gone beyond that and shown the activation mechanism of a GPCR."

The achievement was made possible by combining Google hardware with software from Simbios researchers. Normally, simulating a millisecond of a reaction involving a large molecule like β_2AR would require millions of days on a fast computer or access to a specialized resource such as Anton, the supercomputer designed specifically for molecular dynamics (MD) simulations. But the collaboration with Kohlhoff, a previous Simbios postdoctoral fellow, offered a different solution: tens of thousands of shorter independent simulations of β_2AR on Google Exacycle, a cloud computing infrastructure that transforms Google's spare computing cycles into what is known as an "embarrassingly parallel" system, where there is minimal communication between individual computers. The resulting simulations were then assembled into a single model using Markov State Models (MSMs) to capture 2.15 ms of β_2AR dynamics.

"Cloud resources are much more accessible to the general scientific community [than specialized hardware], and I think that we've shown here that, with the right method and algorithms, you can do the same quality of work," Pande said in an interview with the Stanford News Service.

For its part, Google is pleased with its investment. This study was the first to participate in the Google Exacycle for Visiting Faculty program. "It has shown that the cloud can be used as a new research tool and is worth the time to investigate," says Kohlhoff.

With Google Exacycle, the team generated many trajectories first, exploring them later for insights—a shift from the conventional approach of setting up a simulation to prove a predefined hypothesis. "Traditional simulations are often very narrowly defined and might miss important information," says Kohlhoff. "Our approach is better suited for exploratory research with a lower risk of introducing human bias from the start."

Google's data center, courtesy of Kai Kohlhoff, Google.

From all that data, they generated the first molecular-level description of GPCR activation pathways and identified a large number of previously unknown states that could help in the design of more selective drugs, potentially causing fewer side effects.

"We only have a few structures capturing the inactive and active states of GPCRs because it is very challenging to crystallize them," says Shukla. "However, as we've shown with this study, with computer simulations, we can even identify infrequently visited intermediate states. That's one big scientific plus."

Kohlhoff has high hopes for the study. Beyond the impact for GPCR research, Kohlhoff says, "We hope this study gets other people to rethink the way they do science." □

DETAILS

To learn more, read the full publication: Kohlhoff, KJ, *et al.*, "Cloud-based simulations on Google Exacycle reveal ligand modulation of GPCR activation pathways," 2014, *Nature Chemistry*, 6:15-21. The MSMBuilder software used to produce the Markov State Models is available at http://simtk.org/home/msmbuilder, and links to the resulting GPCR simulation results will be accessible through https://simtk.org/home/natchemgpcrdata.

Simbios (http://simbios.stanford.edu) is the National Center for Physics-Based Simulation of Biological Structures at Stanford.