Science AMA Series: I’m Albert Lau and I use supercomputers to simulate molecular machines in action, such as those in the brain. My research can help scientists understand how small molecules like neurotransmitters locate their targets. AMA!

Hi Reddit, my name is Albert Lau, and I’m a biophysics professor and computational and structural biologist at Johns Hopkins University School of Medicine. I am interested in studying how biologically relevant molecules interact and change shape in order to carry out their physiological functions. My lab has focused on studying proteins called glutamate receptors that help neurons in the brain communicate with each other and are necessary for learning and memory. We’ve been examining the details of how neurotransmitters, specifically glutamate, manage to bind to these receptors and what the energetic and dynamic consequences of this binding are. My team and I recently published a paper in Neuron that shows, in part using molecular mechanics simulations carried out on supercomputers, that flexible protein elements on the surface of the receptor accelerate the process of glutamate binding by grabbing glutamate and helping to guide it into its recessed binding pocket [http://dx.doi.org/10.1016/j.neuron.2017.11.024]. This discovery might assist the development of new therapies for neurological disorders and diseases associated with glutamate receptors, such as epilepsy, depression, and Alzheimer’s disease. Over the course of my training, I have been lucky to interact with and learn from extraordinary scientists in the fields of structural biology, computational biophysics, and neuroscience, and they have all influenced the research I pursue. I look forward to answering your questions at 1pm ET.

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While we can’t immediately translate our recent findings into current therapies, understanding the process by which small molecules or drugs bind to these class of receptors can help us learn how to engineer specificity into drugs. For example, we may know of a drug that binds to receptors that look very similar, but we need to target just one of them. So, if the process of binding is different for these receptors, we can explore how to make these drugs specific to each receptor.

As we learn more about the receptor binding process, we might find potential binding sites for drugs that are not obvious. The obvious binding site for these glutamate receptors is where the molecule settles into its binding pocket, but there may be a less obvious binding site along the binding pathway that may have high affinity for a drug.
What can you not do, as it pertains to simulating neurotransmitter interaction, with our current technological limitations that you wish you could?

adenovato

With current technology, there is a limit on the timescale that can be simulated if you are simulating individual atoms and molecules. The entire cycle of receptor activation and subsequent deactivation is on a timescale that’s currently too long to be simulated. Right now, we need to break the problem down into smaller pieces and focus on each one to answer a question on the biophysics of how these receptors work.

Can you give me a layman’s explanation for what your discovery is and means?

scienceaccount103040

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The question that motivated the study was: does a neurotransmitter diffuse direction into the binding site of a glutamate receptor to activate it or does the receptor somehow assist the neurotransmitter in binding to it? And we found that the latter was true: the glutamate molecule gets an “assist” from the receptor. The implication is that this assistance accelerates the rate at which the receptor responds to glutamate at a synapse.

How the software simulators look like? What are they lacking? How can an open source enthusiast interested in simulators can help your field?

jeanlucbernard

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Through the journal, we published a sample simulation from our study that shows the binding process: https://youtu.be/94SPOhhY8wg. The molecule highlighted in purple is the neurotransmitter glutamate, and the movie shows an example binding pathway that glutamate takes to find its way into the binding site. Along the path, it sticks to elements on the surface of the receptor, and these elements help guide the molecule into its binding pocket.

The simulation shows only the portion of the receptor that binds glutamate and not the entire receptor. We wanted to focus specifically on the binding site for glutamate, so we didn’t simulate the rest of the receptor. However, we’re currently working on simulating the rest of the receptor to expand the scope of our study.

Simulating these processes at a high level of detail can take an enormous amount of computing power, so we simplify the mathematical descriptors that go into the simulation. This means that we lose some degree of detail, but this is a trade-off that enable us to do these simulations on a biologically-relevant timescale.

Most of the code we use to do these simulations are already open source. There are research groups constantly working on improving the accuracy of these simulations.

How long, in decades or centuries, are we from being able to simulate an entire brain?

scincereader3455
You could simulate an entire brain, but not with these types of simulations. There are researchers looking at simulations of how entire organs function, such as the heart and brain, but the simulation itself does not replicate each molecule in the organ.

What does it mean for a neurotransmitter to bind to something?

sciencereader3455

A binding event is when the neurotransmitter has a stable association with a receptor, and this provides the energy required for the receptor to activate. In more simple terms, it’s how the body activates neurons. Almost all biological processes involve binding between molecules.

In this study, in addition to the stable binding of glutamate to its receptor, we also see more weaker associations between these two, and we found that they are also important to the receptor’s function.

Does your research include memory loss and/or brain damage from trauma or death, or is it only for degenerative diseases?

Boxisaurus-Wrex

Glutamate receptors are associated with all of these diseases and conditions. So, the more we learn about how glutamate receptors work, the closer we come to developing therapies tailored to each of them.