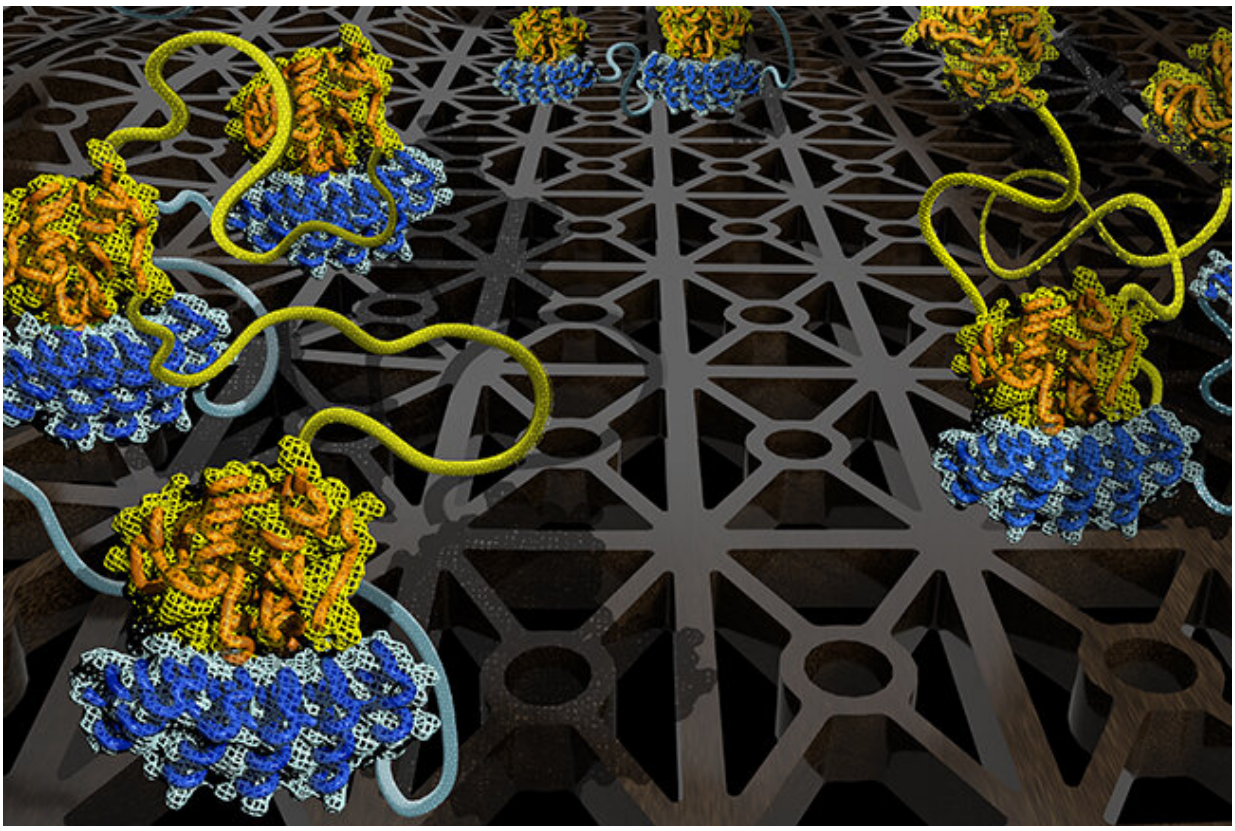
# Breakthrough study on molecular interactions could improve development of new medicines

January 3 2020



This illustration highlights a small sampling of the 78 unique binding configurations that arise when molecule chains with three binding sites interact. The research team developed a computational model that can predict how key parameters can be “dialed up” or “dialed down” to control how such molecules with more than one binding site interact with one another. This should accelerate biological research and discovery of new medicines. Credit: Errington et al.,

A first-of-its-kind study on molecular interactions by biomedical engineers in the University of Minnesota's College of Science and Engineering will make it easier and more efficient for scientists to develop new medicines and other therapies for diseases such as cancer, HIV and autoimmune diseases.

The study resulted in a mathematical framework that simulates the effects of the key parameters that control interactions between molecules that have multiple binding sites, as is the case for many medicines. Researchers plan to use this computational model to develop a web-based app that other researchers can use to speed the development of new therapies for diseases.

The research is published in the *Proceedings of the National Academy of Sciences* (*PNAS*), one of the world's most-cited and comprehensive multidisciplinary scientific journals.

"The big advance with this study is that usually researchers use a trial-and-error experimental method in the lab for studying these kinds of molecular interactions, but here we developed a mathematical model where we know the parameters so we can make accurate predictions using a computer," said Casim Sarkar, a University of Minnesota biomedical engineering associate professor and senior author of the study. "This computational model will make research much more efficient and could accelerate the creation of new therapies for many kinds of diseases."

The research team studied three main parameters of molecular interactions—binding strength of each site, rigidity of the linkages

between the sites, and the size of the linkage arrays. They looked at how these three parameters can be "dialed up" or "dialed down" to control how molecule chains with two or three binding sites interact with one another. The team then confirmed their model predictions in lab experiments.

"At a fundamental level, many diseases can be traced to a molecule not binding correctly," said Wesley Errington, a University of Minnesota biomedical engineering postdoctoral researcher and lead author of the study. "By understanding how we can manipulate these 'dials' that control molecular behavior, we have developed a new programming language that can be used to predict how molecules will bind."

The need for a mathematical framework to decode this programming language is highlighted by the researchers' finding that, even when the interacting molecule chains have just three binding sites each, there are a total of 78 unique binding configurations, most of which cannot be experimentally observed. By dialing the parameters in this new mathematical model, researchers can quickly understand how these different binding configurations are affected, and tune them for a wide range of biological and medical applications.

"We think we've hit on rules that are fundamental to all molecules, such as proteins, DNA, and medicines, and can be scaled up for more complex interactions," said Errington "It's really a molecular signature that we can use to study and to engineer molecular systems. The sky is the limit with this approach."

**More information:** Wesley J. Errington et al, Mechanisms of noncanonical binding dynamics in multivalent protein–protein interactions, *Proceedings of the National Academy of Sciences* (2019). DOI: 10.1073/pnas.1902909116

Provided by University of Minnesota