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Innovative computational approach helps design proteins for cancer treatment

The computational design of new proteins for biomedical or other applications involves long computing times on powerful servers. A joint team of researchers from the Max Planck Institute for Biology Tübingen and the University Hospital Tübingen has now developed and tested a new computational method to greatly speed up the necessary energy calculations. Their framework, now published in the journal Cell Reports Methods, allows for a precise and efficient design of functional proteins. Evidencing the usefulness of their findings, the researchers developed two classes of proteins which can be deployed in cancer diagnostics and treatment.

Proteins are essential for life: while some provide structural integrity to our skin and bones, others regulate the metabolism or recognize and neutralize viruses – to name just a few of their manifold tasks. This is why developing protein molecules with a specific purpose has the potential to revolutionize biomedicine.

To design a protein with a desired function, researchers need to pick its desired overall structure first, since the shape determines how the protein can interact with other molecules. The challenge is to find a stable configuration of building blocks that can form the target structure: organic molecules called amino acids, strung together in long chains, make up every protein. The interaction of the amino acids and of all their single atoms is what gives the protein its three-dimensional shape and hence its function.

Drastic reduction of computational cost

Since the sequence of amino acids in a protein determines its overall shape, even a small change – a single substitution of an amino acid, for instance – can markedly stabilize or destabilize the desired structure.

"For designing a stable protein, you have to calculate and compare the energy of myriads of amino acid sequences for a given target structure," explains Mohammad ElGamacy, research group leader at the University Hospital Tübingen. "These estimates constitute the computational bottleneck of the protein design process."
ElGamacy and his collaborators now developed a new computational method which not only accelerates the energy computations by orders of magnitude, but also opens room for profound improvements in accuracy. The researchers were the first to apply tensorization, a computational method heavily used in graphics rendering and computer games, to the protein design problem. Instead of calculating interaction energies for every pair of atoms that are close to each other, they pre-evaluated and stored most of the interaction information for an amino acid's atoms in 3-dimensional grids. These grids can then be used to calculate interaction energies on the fly.

"We are especially happy that speeding up the energy calculations was possible without relying on machine learning," says Kateryna Maksymenko, who is first author of the study and a researcher at the Department of Protein Evolution of the Max Planck Institute for Biology Tübingen. "Our energy calculations are simply based on physics. Thus, we can always retrace why and how the software reached its conclusions, which would be impossible with deep learning algorithms."

Clinical applications in cancer diagnostics and therapy

The researchers demonstrated the usefulness of their new framework by designing two different classes of proteins and testing them in collaboration with researchers from the University Hospital Tübingen and the Werner Siemens Imaging Center. The first one of these inventions blocks the communication of the epidermal growth factor receptor, a protein regulating growth and diversification of cells, which plays a central role in several cancer types.

The second protein the team successfully developed and tested is also suitable for direct clinical application. "A remarkable feature of our design is its potential dual action in cancer diagnostics and therapy," Maksymenko highlights. "The new protein binds to copper-64, which means that we can track it with radioimaging. But it can also transport the radioisotope copper-67,

which kills the cancer cells."
Importantly, the protein can bind to 13 copper ions simultaneously, which constitutes a previously unachieved packaging density and therefore makes the molecule especially valuable for high-quality imaging.
The team plans to further develop their new invention to fuse the copper binders with other therapeutically relevant proteins and study their biodistribution. They are confident their computational approach will assist many scientists in achieving their protein design tasks.

Publication:

Maksymenko K, Maurer A, Aghaallaei N, Barry C, Borbarán-Bravo N, Ullrich T, Dijkstra TMH, Hernandez Alvarez B, Müller P, Lupas AN, Skokowa J, ElGamacy M: The design of functional proteins using tensorized energy calculations. Cell Reports Methods 3, August 28, 2023.

Press release

28-Aug-2023
Source: Max Planck Institute for Biology Tübingen

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