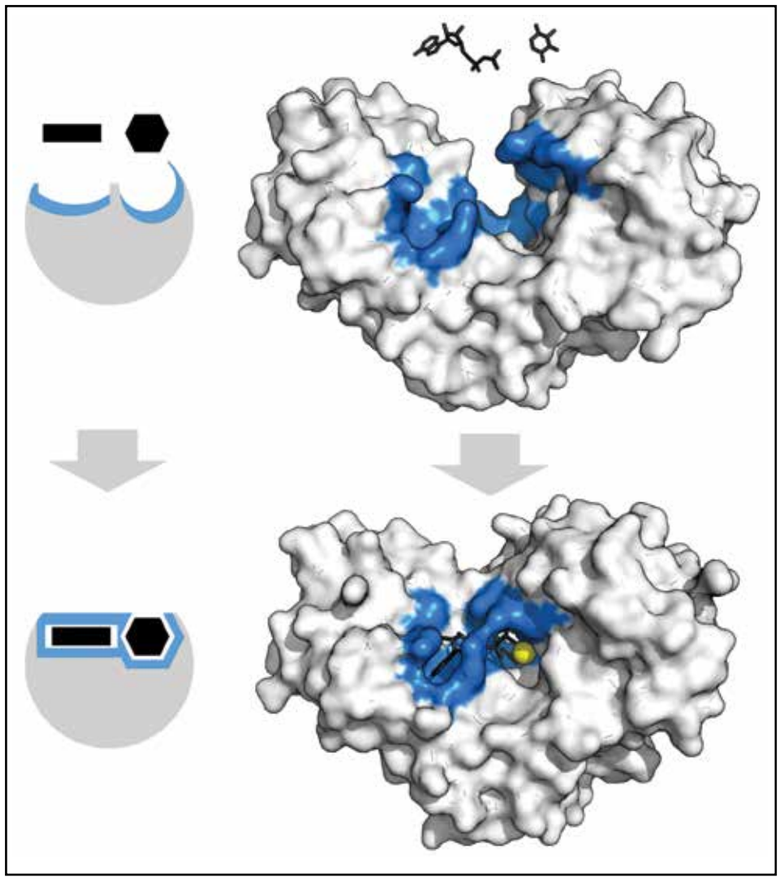

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About ARCHER

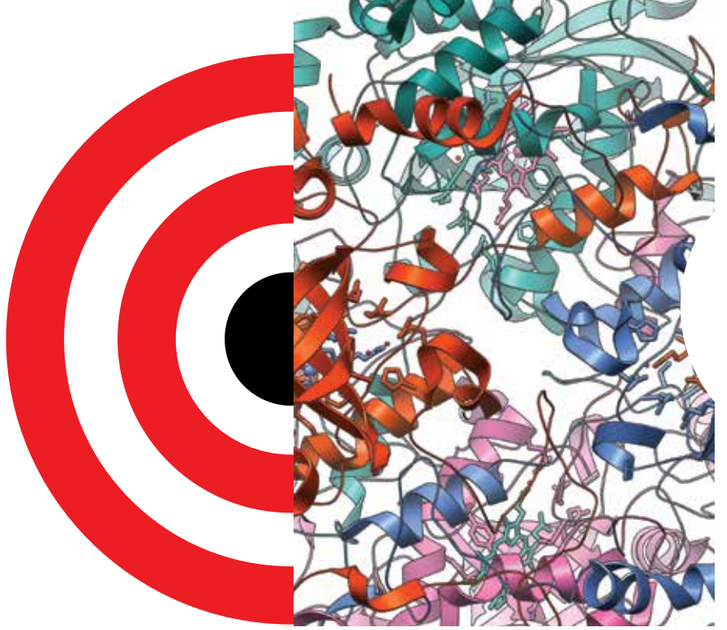
ARCHER is the UK National Supercomputing Service. The service is provided to the UK research community by EPSRC, UoE HPCx Ltd and its subcontractors: EPCC and STFC's Daresbury Laboratory, and by Cray Inc. The Computational Science and Engineering (CSE) partners provide expertise to support the UK research community in the use of ARCHER. The ARCHER CSE partners are EPSRC and EPCC at the University of Edinburgh.

The eCSE Programme

The Embedded CSE (eCSE) programme provides funding to the ARCHER user community to develop software in a sustainable manner to run on ARCHER. Funding enables the employment of a researcher or code developer to work specifically on the relevant software to enable new features or improve the performance of the code.

The Case Study Series

This case study has been produced as part of the ARCHER CSE service, supported by EPSRC research grant number EP/N006321/1.



EXPLOITING THE SHAPE-SHIFTING PROPERTIES OF PROTEINS TO DESIGN NEW DRUGS

Drug design is one of the most promising sectors of scientific research today. As we learn more about how our cells function and how invading pathogens infect us, we discover new ways to fight disease. From designing much-needed new antibiotics, to curing previously incurable diseases, drug discovery has the potential to significantly improve human health.

However, designing new drugs from scratch is very difficult. To take a potential drug from the lab to market takes many years and hundreds of millions of pounds.

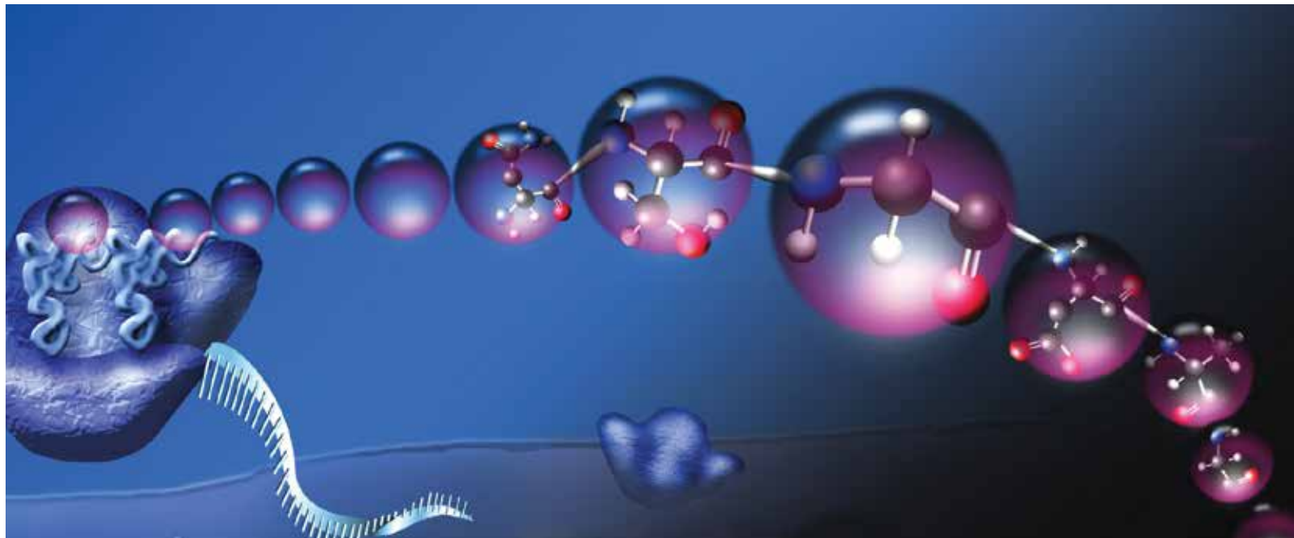
Most drugs target proteins. Proteins are the building blocks of all forms of life, performing many of our essential functions. A single human cell contains between one and three billion protein molecules at any one time. Most diseases are linked to proteins either functioning incorrectly - such as in cancer - or foreign proteins from pathogens.

Because they are so abundant and essential, proteins make excellent drug targets. Drugs can be designed to target a specific protein, to interrupt a specific cell function.

For a drug to be effective, it needs to stick strongly to its intended protein. But for a drug to be safe, it needs to stick only to that protein, and not to the many healthy proteins that are also present. Proteins come in lots of unique shapes so, in theory, researchers could just find the drug that matches one single protein.

In practice, however, it's not this simple. Proteins are not static; they can change their shape dramatically in response to their environment. This makes it difficult to reliably predict how the drug molecule will interact with the protein.

If we could understand how proteins change shape over time, it could help us design new strategies to discover new drugs.



Looking for protein shapes

One group at the University of Edinburgh has used ARCHER to model the mechanisms governing the ability of proteins to reshape over time. This will allow them to develop new computational tools for better drug design. Proteins are large and complex molecules, so carrying out realistic simulations is difficult. Using ARCHER is key for this research, as lots of computational power is needed.

Protein molecules are formed by folding - different parts of the protein chain stick together to create the final structure. This means that even small proteins have a huge number of potential shapes. To simulate the protein interactions correctly, each potential shape needs to be checked and tested. ARCHER is essential to simulating all of these protein shapes in a reasonable timeframe. The researchers developed an algorithm, JEDI, which evaluates different protein shapes. The JEDI algorithm scores protein structures on their ability to bind small molecules. This allows researchers to only focus on shapes that are most likely to bind with the drug.

When the drug target is different from other healthy proteins, the aim is to develop molecules that attach strongly to their target. In these cases, only a small number of protein shapes need to be considered. Focusing on the wrong protein model can result in a waste of valuable time and resources. The JEDI algorithm can help here by ensuring that only the shapes most likely to bind to the drug are tested.

In other cases, differences between proteins are subtle. In a pool of similar proteins, only some may be unhealthy, so a drug needs to target just these while leaving the healthy proteins alone. What is key in this case is that two proteins that appear to be identical may sometimes adopt different shapes due to small chemical differences. However, these small changes are very difficult to characterize as they are rare and short-lived. Molecular dynamic simulations provide a way to compute the structure of these transient states. This information can then be used to design molecules that target shapes unique to the intended protein target.

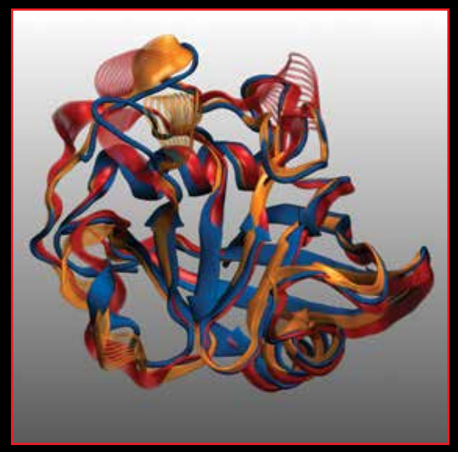


FIGURE 1: Proteins change their shape over time and in response to their environment.

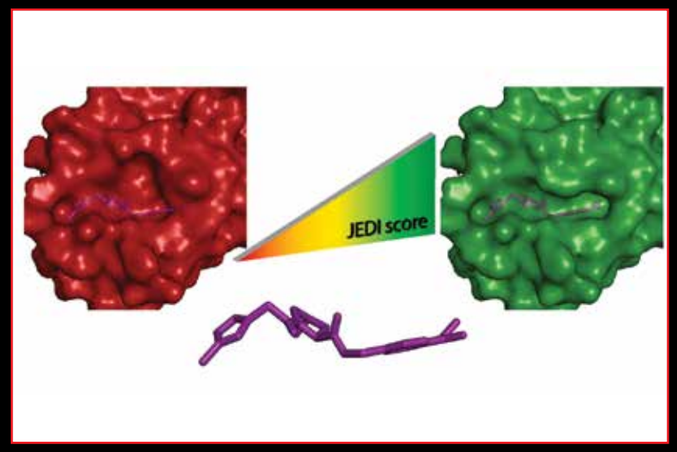


FIGURE 2: The JEDI code helps to distinguish protein shapes that can bind drugs of those that cannot.

Cyclophilin Inhibitors: from the computer to the test tube

One of the major classes of protein that this research has focused on is the cyclophilin family. Cyclophilins are extremely common proteins throughout our bodies that regulate many biological functions. Any problems with a cyclophilin protein will therefore have a huge impact on the person. These proteins are involved in diseases such as arthritis, cancer, HIV progression, and organ transplant rejection.

The research group in this experiment have been investigating cyclophilins for several years. Because cyclophilins are so abundant, there is a lot of interest in drugs that target them. However, the active part of cyclophilin is almost identical across the whole class of proteins. This makes very difficult to find drugs that will only attack unhealthy proteins.

The researchers used ARCHER to build a computer model of cyclophilin A, the most abundant cyclophilin. This was used to study how cyclophilin adopts different shapes over time. Having computed a number of shapes, the researchers next designed a range of experiments to validate the computations. Once validated, the structural information was used to design a new generation of cyclophilin A inhibitors. The new inhibitors were then synthesised and biologically verified. The current stage is to test the new inhibitors to see if they are able to target unhealthy proteins while leaving the healthy ones alone.

Using ARCHER was instrumental to the researchers' efforts. It allowed them to test many shapes in a reasonable time, and carry out tests that could not be done experimentally. Using computation, they were able to adopt a highly multidisciplinary approach, with scientists and computation experts involved. The results of this experiment may be transformative to the development of future medicines.

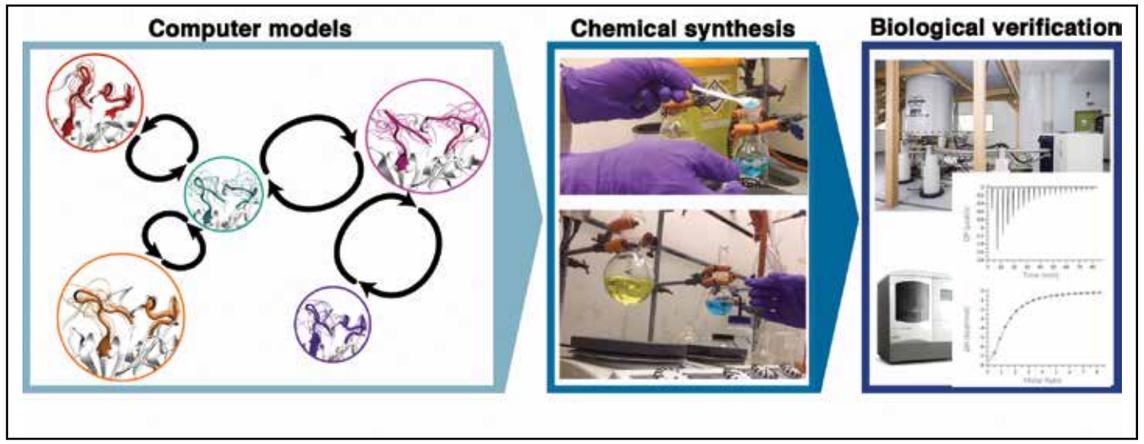


FIGURE 3: The research group has combined computer models, chemistry and biological evaluation to develop a new generation of cyclophilin A inhibitors.