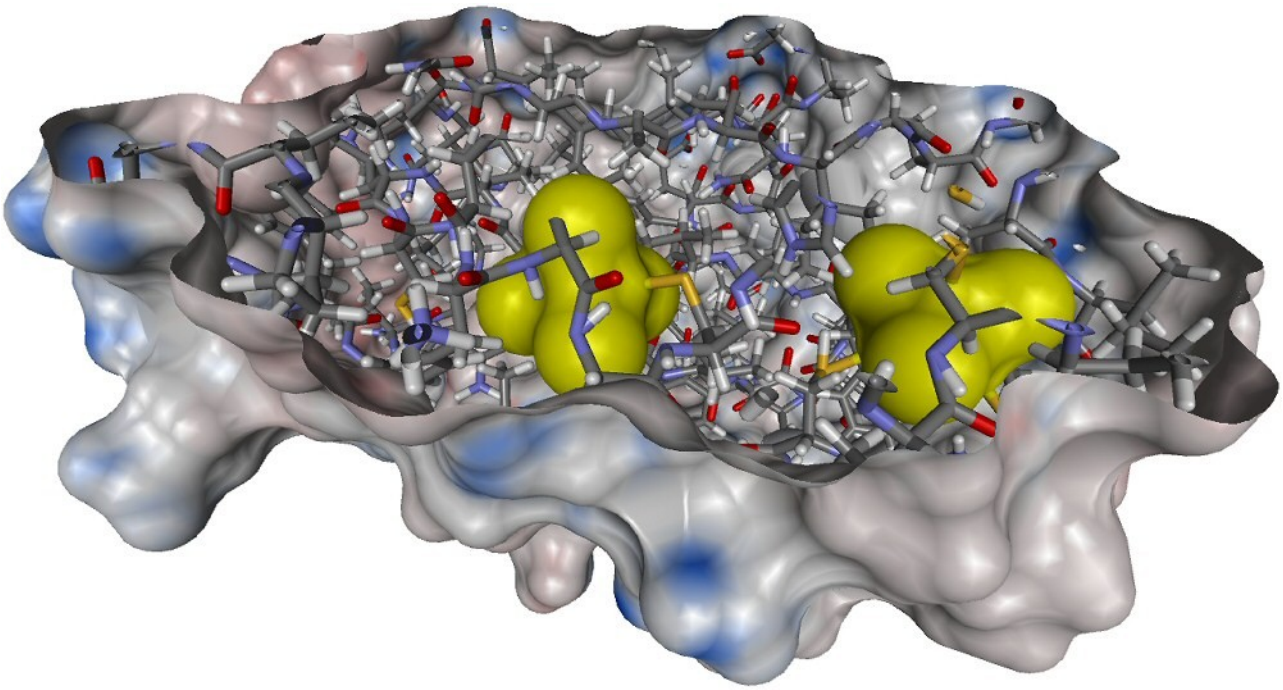
Healthcare industry BW

Computer-assisted drug design

Bioinformaticians from Tübingen have developed the "BALL" software platform that accelerates and simplifies the search for active agents. Computer modelling and simulation enables the assessment of molecule modifications and the optimisation of their function accordingly.



The BALL software can combine different presentations. The Figure shows the surface (solvent-excluded surface, SES) of a molecule, combined with a sphere-rod model and the van der Waals model. A clipping plane was used to get a better look at the two ligands.

Researchers at the Centre for Bioinformatics Tübingen (ZBIT) deal with a broad range of different active agents. The majority of these are pharmaceutically active substances that are used in human medicine, but some of them are also required in veterinary medicine and plant protection. Selective herbicides that specifically combat undesired species in plant cultures are an example of substances of great commercial interest in the field of agriculture. In general, these active agents have in common that they fit like a key into a lock, i.e. target structure, due to their specific molecular structure; they interact with the target structure and induce a desired effect.

Prof. Dr. Oliver Kohlbacher is the head of a ZBIT work group that focuses primarily on computer-assisted drug design. He explains the process: "Out target structure is generally a protein structure that we derive from experimental data. This is our lock whose structure is difficult to change. That is why we are looking for small molecules that fit into these locks like keys. Initially, we carry out a database search, looking for molecules that are already on the market. In order to optimise suitable candidates, we then assess how we can modify these molecules. This leads to derivatives whose function and effect we simulate with the computer."

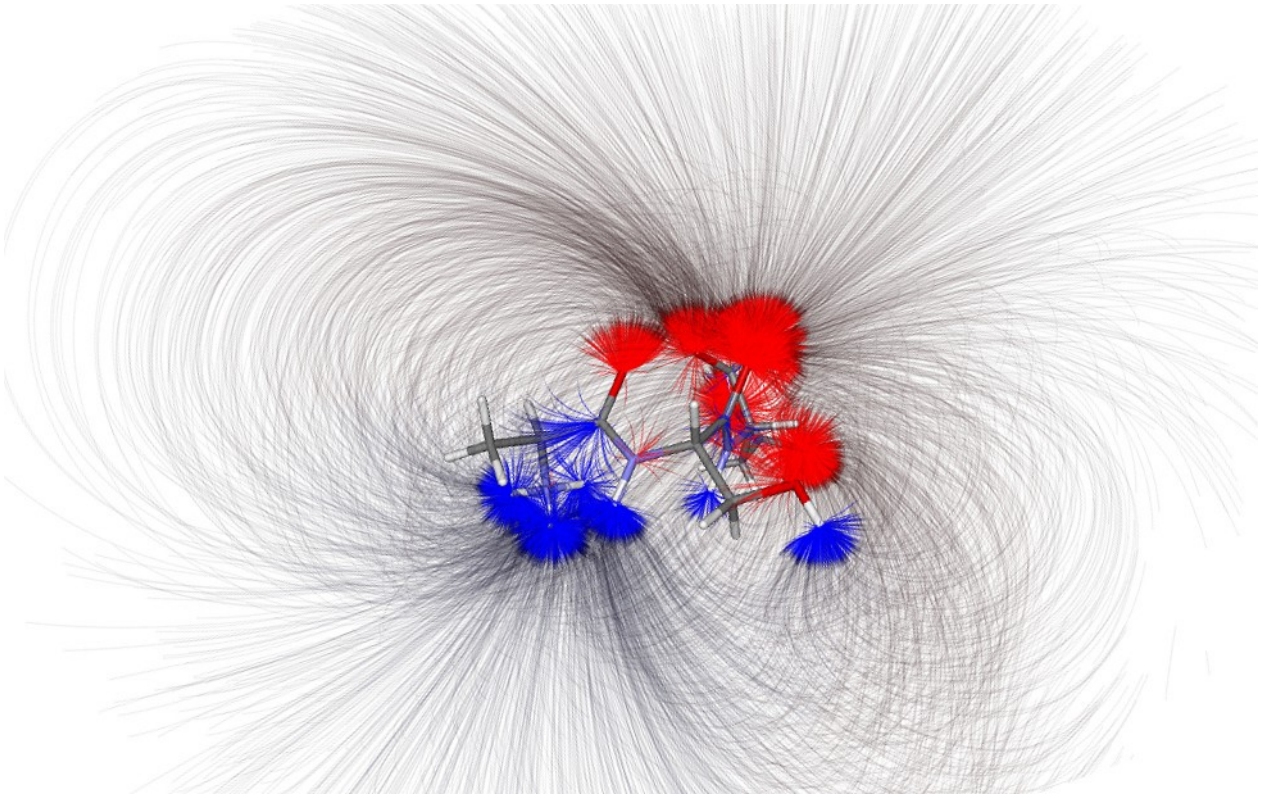
Experiments have the last word

A typical scenario involves the selection of around 50 molecules from around 100,000. These 50 molecules are highly likely those with the sought-after effect. "It just so happens that we have to talk with medical chemistry experts or structural biologists in order to be able to limit the number to two to 25 candidates that can be effectively synthesised and handled," said Kohlbacher. Some important parameters can be tested directly with the BALL software package in whose development Kohlbacher was decisively involved. The software package contains methods that enable the testing of the molecules' biocompatibility. Structures that stand all the tests will subsequently be validated experimentally, which is something that is usually done by the group's cooperation partners who are looking for a specific molecule for their research activities.

The bioinformaticians led by Kohlbacher are not only focused on the possibilities of direct application. In the field of basic research, the scientists develop molecular probes for use as research reagents and hope to use these probes to elucidate the biological mechanisms of action. "We do this, for example, when we want to understand the processes of a signalling cascade," said Kohlbacher.

Excellent structural data of the target structure are essential

The greatest obstacle in the search for active agents is the quality of the data about the target structures. "Out input data are derived from excellent crystal structures or NMR structures. If these are not available, we need to use homology models. The uncertainties associated with these homology models make the search for active agents rather difficult," said Kohlbacher. In addition, the mechanisms of action are also influenced by the molecular environment. However, it is



Screenshot from the "Ball" version 1.2: It brings support for calculation and visualisation of field lines e.g. for electrostatic potentials, also with custom colorisation

difficult to comprehensively model biological systems due to their high complexity. "Despite all the progress that has been made, we are unfortunately not yet able to answer the questions on when the structures are found, for example in the ER or in the Golgi apparatus, or when they are found between the cell organelles," added Kohlbacher.

Networked structures are the future of small molecule searches

However, the quantity of data is increasing worldwide with every hour that passes, so that modelling and simulation are improving and becoming more accurate. At the same time, bioinformaticians are working hard to improve their methods and the methods' accuracy. This in turn increases the search hit rate for small molecules with the sought-after optimal effect. However, the computers have to be able to process such a huge amount of data, something that is not always easy. The challenge lies in the processing of data as well as in the clear presentation of the results.

Kohlbacher believes that high-performance computing enables non-IT experts to use the software more efficiently. "We want to combine our applications with high-performance and grid computing, so that the systems can also be used by 'normal' users. This is the only way to establish a web-based service for the search for small molecules, for example." Kohlbacher's vision is a service that allows users to indicate the 100,000 molecules they want to screen. The data will then be available after two days.

Small molecules seen in a Second Life environment

Kohlbacher knows from his teaching activities that clear presentations are necessary, especially with regard to complex molecules. In Tübingen, second-semester biochemistry students are given the possibility to deal with computer modelling. "I repeatedly experience how much the students learn on an intuitively understandable level if they see an interactive 3D model of the molecule on the screen, where they can zoom in and out," said Kohlbacher. The molecules become 'graspable' in the truest sense of the word when a 3D printer prints a plastic model of the molecule.

In cooperation with their partners from the University of Saarbrücken, Kohlbacher's team is going even a step further – into the virtual world of Second Life. "At first sight, this seems to be a playful activity, but it nevertheless has a serious background. Built into the Second Life software is a three-dimensional modelling tool that enables several users from anywhere in the world to interactively immerse into 3D structures," said Kohlbacher who knows from his own experience just how difficult it is to talk about structures with colleagues at the other end of the world. The Second Life environment creates a cooperative space where the participants can engage in constructive discussions. If, for example, a Japanese group of researchers provides a molecule structure for which another group of researchers would like to develop ligands, the researchers can comfortably look at the three-dimensional structure online and test it. "This is our contribution to interactive collaboration. At the moment, the Second Life environment is not yet optimal, but has huge potential that can be further exploited in future," said Kohlbacher.

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