



Molecular modeling helps to optimize active ingredients

## Hunting molecules in 3D

**Looking for active ingredients for new medicines is a process of constant selection. Researchers must identify the most effective combinations out of millions of potential substances. Molecular modeling is an effective way of doing this.**

It makes a harmonious picture: The Bayer HealthCare Pharmaceuticals Division research campus, located in the countryside outside Wuppertal, is populated by people like Dr. Alexander Hillisch. With his open, friendly expression and his youthful appearance, he fits in very well in this place, where 1,300 people just like him are searching for new active substances in a relaxed yet focused atmosphere.

Nevertheless, Dr. Hillisch is a rarity here on the campus: although he heads one of the eight medical and chemical departments, he doesn't have his own laboratory, and although he is a qual-

ified pharmaceutical scientist with years of research experience, he doesn't synthesize new compounds. His "laboratory" is his desk, and his "test tube" the computer. Dr. Hillisch is the head of the Computational Chemistry department. To put it simply, he designs molecules on the computer screen and changes them until they fit the target perfectly. What Dr. Hillisch does is give chemists in other departments ideas for finding and optimizing new substances.

Dr. Hillisch has only been with Bayer since December 2003. His department is currently being built up, and should



Virtual chemistry:  
Bayer researchers Dr. Kai Thede, Dr. Alex Jensen, Dr. Peter Nell and Dr. Alexander Hillisch (left to right) view the projection of a three-dimensional protein structure on the wall of their 3D room wearing special glasses.

comprise nine members by the end of the year. Most of them will be investigating queries from chemists in projects aimed at finding new active substances. The others will be preparing new programs for use or “feeding” the computers. This is an important task, because the computer is to the modeler what the microscope is to the cytologist: the computer translates two-dimensional molecular formulas into spatial structures – with shiny surfaces or wire frames that can be zoomed in, reflected, rotated, detached, attached or marked. A pair of special glasses adds extra spatial

depth, making the molecule really seem to stand out from the monitor.

#### **Molecules match up their bumps and hollows**

This makes the structures visible, but surely nanospace, with its electron clouds and peculiar elementary particles, has its own laws? Then what is the use of playing with models of molecules as if they were as big as LEGO® bricks? The answer is quite simple: because – simplifying things considerably – molecules really do act like plastic bricks: where there is a hollow

point in the molecule, a bump will fit into it. And, consequently, the closer two substances fit together with their bumps and hollows, the more strongly they will react together in reality. Computational chemistry makes use of these findings.

As members of the Pharmaceuticals Division of Bayer HealthCare, Dr. Hillisch and his colleagues, help to find and optimize active substances which can then be further developed into medicines. They are working both with the substances themselves and with the molecules that the substances attack, known as targets. These tar-



Protein architects:  
Dr. Alexander Hillisch (left) and Dr. Kai Thede discuss a 3D molecular structure on the screen.

gets are usually proteins, such as enzymes used in human metabolic processes. Dr. Hillisch is the head of a virtual “dating agency” for molecules, so to speak.

#### Chemists make virtual models of the 3D structure of proteins

Before Dr. Hillisch and his colleagues can get started, the biologists need to identify a promising target and some potential candidate substances. Bayer’s collaboration with Millennium has yielded 470 of these targets, for instance. For his part of the job, Dr. Hillisch first obtains the structural formulae of the target and the potential active substances. Bayer has recently set up a sophisticated database linking biological data with chemical structures. The much larger and more complex target protein is usually more of a

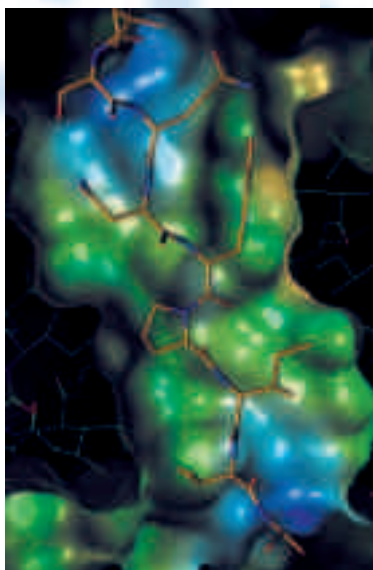
problem. The structures of around 7,400 different proteins have already been identified around the world, including some of interest to Bayer, but there is no 3D structure for two thirds of the Bayer targets as yet. If the target in question is one of them, the experts in Bayer’s Enabling Technologies department will identify its structure. For proteins, this can prove a tedious process, and success is not guaranteed. The first step – crystallizing the protein – only works sometimes, even if it is carried out with experience and an expert touch. If it is successful, the crystals are investigated in a particle accelerator, such as the German Electron Synchrotron (DESY) in Hamburg, using X-ray radiation to reveal the protein structure. If crystallization fails, the experts from Computational Chemistry can sometimes model, and thus predict, the structure of the targets.

Dr. Hillisch enters the structural formulae of the target and the potential hits into his computer, and it determines how well the binding partners of the compound fit together. Lengthy calculations are required to do this. To avoid waiting months for the result, Dr. Hillisch’s workgroup has a Linux cluster operating in the basement, with 200 processors operating in parallel. The room has to be rigorously cooled to prevent the “superbrain” from overheating. A close fit between target and active substance is an important parameter in identifying the most promising hits, but it is not the only one. The ultimate goal, after all, is to develop a medicine. And what use is a compound that binds really well to the target but is impossible to take as a tablet – either because it will not dissolve in the stomach, is not absorbed by the gastrointestinal tract, or is actually toxic?

Dr. Hillisch has his own experts whom he can ask about absorption, toxicity and distribution, and they work closely with their colleagues from the various experimental areas. Explains computational chemist Professor Tim Clark of the University of Erlangen, Germany: “It is only in the last 10 years that the hardware has become powerful enough to start to tackle problems as complex as this. Investigating toxicity, for example, involves thinking about all the possible causes of a toxicity reaction. For this we need to be familiar with every part of the human body and all its metabolic processes. That is the biggest challenge.”

Hardware expert Felix Uellendahl in the server room of the Bayer Pharmaceutical Research Center with the Linux machines in water-cooled cabinets.





Computer model: Using powerful computers and special software, Bayer researchers develop new active substances. Protein structures like these help with the design of the compounds.



Interview with Professor Tim Clark, Erlangen

## “Virtual chemistry makes searching more efficient”

**What can virtual chemistry do?** *research spoke to Tim Clark, editor of the Journal of Molecular Modeling, professor at the University of Erlangen and Bayer cooperation partner.*

### Are today's computers powerful enough for virtual chemistry?

I did my first calculation on the institute's own computer over 20 years ago. It took about 40 minutes to produce a result. Today, exactly the same calculation takes half a second on my laptop. That shows how much computing power has increased in recent years. But it still isn't enough. We still can't simulate the changes in the conformation of proteins – that is, conformational switching – which help biological processes to take place and are thus extremely important. Computers are a thousand times too slow to do this.

### Ten years or so ago, researchers moved around the 3D world using special tools, such as data gloves. Why have these become obsolete?

Tools like these are not much use to chemists, and they don't use them very often. Even as students, chemists are taught to see things and think three-dimensionally, while biologists are not.

### What has virtual chemistry got to offer the traditional science?

It shows the direction research is going in and should make laboratory work much more efficient. It is particularly useful for identifying lead compounds and can help us to start thinking in the right direction before we start testing a substance library.

### Will it replace traditional chemistry altogether?

No, definitely not. There are a great many questions which are just too complex. And no one is going to swallow a compound just because a computer says it isn't toxic.

### Researchers play on-screen with molecules and 3D glasses

When the computational chemists have reached a verdict about the future prospects of the hits, it is the chemists' turn. “It's an interactive process,” says Dr. Hillisch, describing the selection procedure. When a promising compound has been developed in the laboratory, the next question is: can this compound be improved – i.e. bound more closely to the target protein?

At this point, Dr. Hillisch goes back to his office and “plays around”. He brings the target and the most likely compound up on the screen, puts on his 3D glasses and aligns the compound with the target. Then he tries to modify the binding partners, or “ligands”, by means of minute chemical changes, so that the gaps which existed before are filled in. “We're an ideas machine”, says Dr. Hillisch. He goes back to the synthetic chemists with his suggestions, and they add in new ideas and practical considerations: can the proposed compound actually be synthesized? Might slightly different structures be easier and faster to create? The Computational Chemistry department has its own 3D room for discussions like this. An image of the molecule measuring seven meters by four can be projected on to the wall, and up to 18 people can study it simultaneously in 3D. “We discuss new ideas for improving the compounds with our colleagues from the biology and synthetic chemistry departments,” says Dr. Hillisch.

This procedure, combining synthetic and

computational chemistry, really works. Dr. Hillisch and his colleagues have recently heard that their information has really led to improved molecules. With something like that, the word quickly gets around among the experts. Dr. Hillisch certainly can't complain that he doesn't have enough to do: the pile of inquiries on his desk brings him straight back from the virtual world of the molecule into the real world of the research campus.

[www.mpibpc.mpg.de/abteilungen/index\\_en.html](http://www.mpibpc.mpg.de/abteilungen/index_en.html)

At this site, under the heading “Computational Biomolecular Dynamics”, visit the “Image/Movie Gallery” page to view an aquaporin molecular animation.