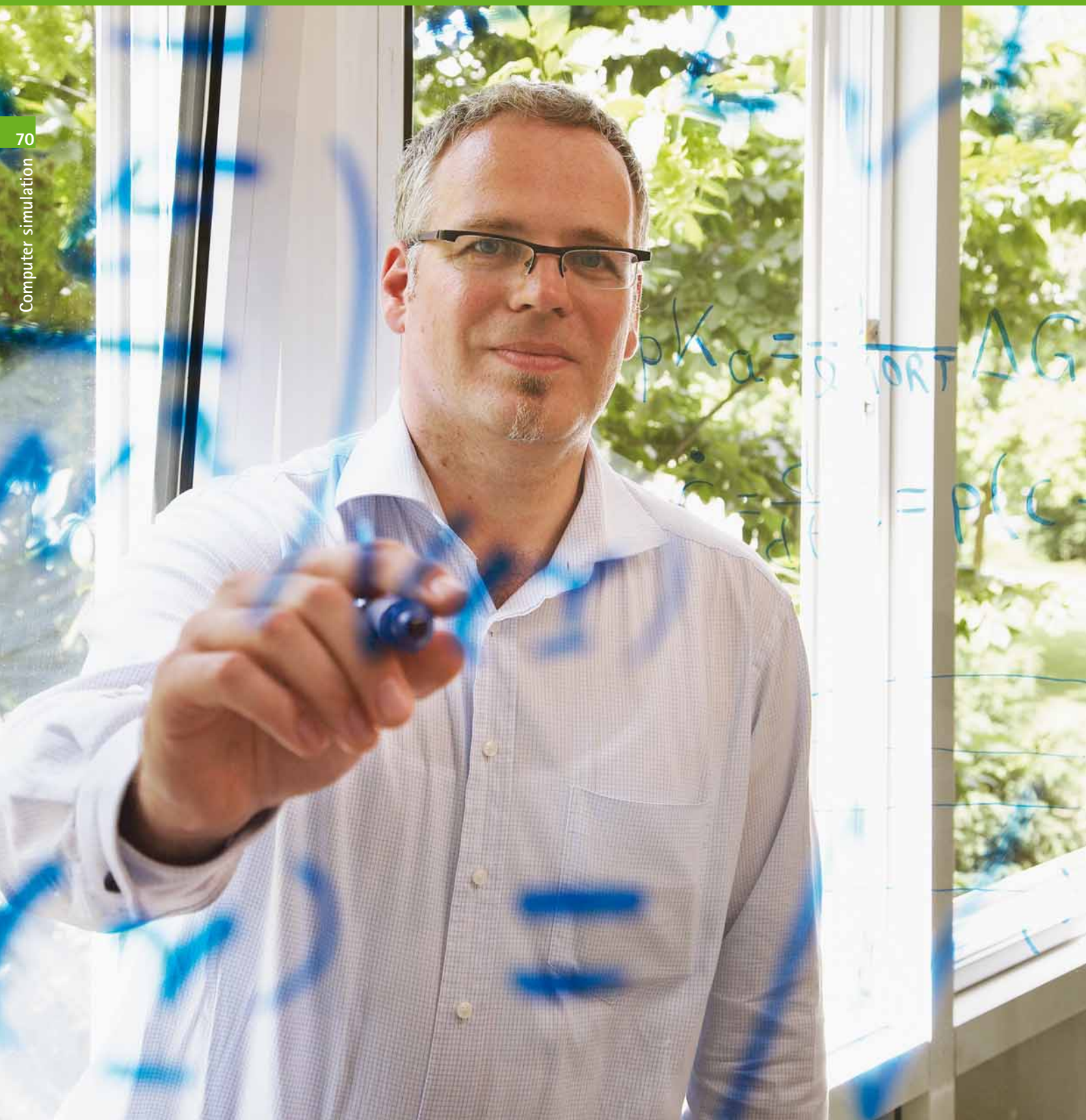


Computer simulation for effective pesticides

Aphid control with mathematics



Scientists need extensive chemical and biological knowledge to develop new pesticides, but computer simulation also helps with the design of optimum active substances. Physicists and quantum chemistry specialists at Bayer CropScience are using novel plant and insect models for more selective control of, for example, aphids and whiteflies in potato fields.

The plants which Dr. Walter Schmitt has been growing in recent years are rectangular. They consist of small green boxes full of numbers and black lines and need neither water nor sunlight. Nor do his potato and vegetable plants take root in the soil in the greenhouse but rather on the hard disk of a computer at Bayer CropScience in Monheim – as mathematical models. Schmitt is a physicist, specializing in reducing the complexity of nature to simple mathematical formulae, rules and software.

In addition to plant models, his virtual equipment store includes other models which calculate the breakdown of chemical compounds in the soil or even their transport through a caterpillar's gut. The computer simulations provide information on how well a substance accumulates in different parts of plants or in the bodies of insects. Experts can draw conclusions from this as to how effective their molecule is – or even at which point the transport chain grinds to a halt, if the experiment has failed. Schmitt also calculates whether an active substance will remain stable in moist soil and not even penetrate the plant. The most important parameter here is the size of the molecule, because compounds that are too large generally cannot penetrate the cell membranes of plants at all. The Bayer scientist has developed tools which can reduce the

time spent on experiments, measurements or growing trials or do away with them altogether. Usually this is in connection with new pesticides – herbicides, insecticides or fungicides which his chemistry colleagues are developing.

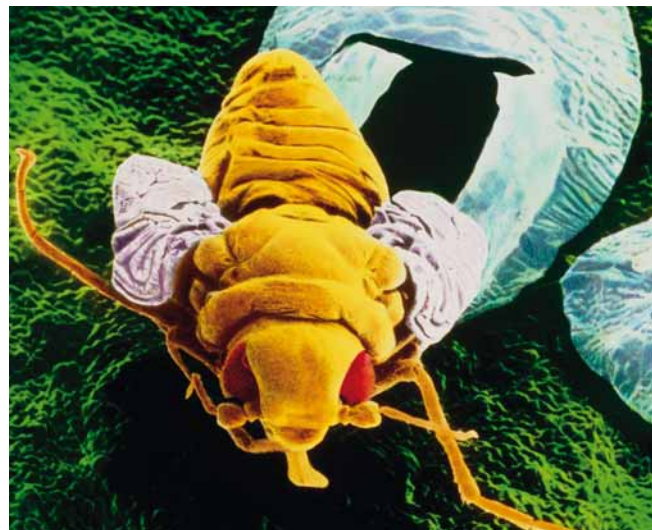
Finding the optimum path for the active ingredient

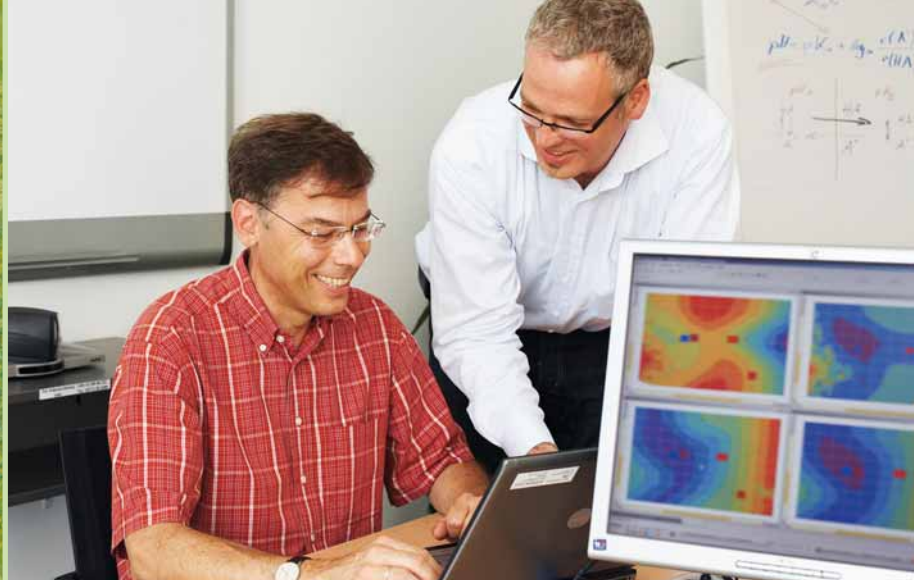
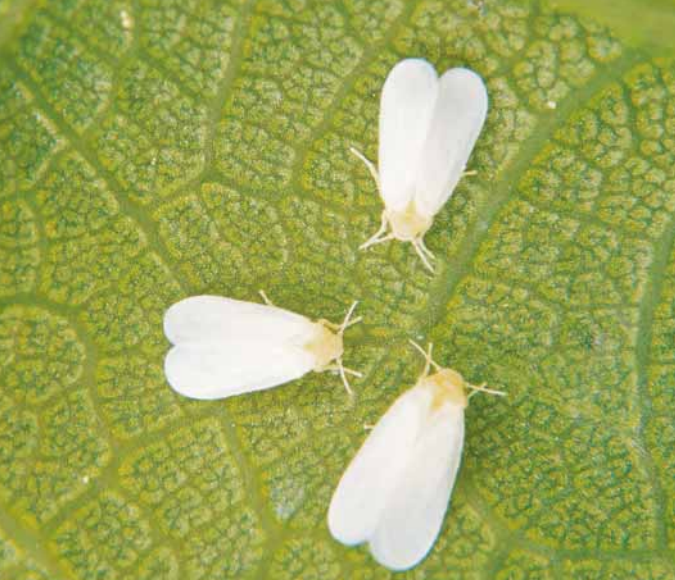
Nowadays, modern pesticides such as insecticides control voracious pests very selectively. "The active substances are only intended to affect harmful insects, not beneficial ones," says Schmitt. Yet the development of new and improved active substances takes a great deal of instinctive feeling: although chemists know exactly which classes of substances are suitable for certain insects, even very minor changes to a molecule, for example to a side chain, can radically alter the effect of a substance and render a promising candidate completely ineffective.

Schmitt's simulation program often comes into play when a new and promising substance fails at the experimental stage and aphids, for example, continue to crawl around merrily. In such cases, chemists cannot usually crack the problem merely by putting on their thinking caps; after all, the active substance's way from the spray droplet

on the leaf into the cells of the sucking insect is a long and complex one. After it has been sprayed, the substance penetrates the plant via the leaves or roots. This is where the first hurdle has to be overcome: the outer protective coverings of the plant such as the waxy layer (cuticle) on the leaf or the epidermis on the root. Once inside the plant, other barriers await. The active substance has to pass through cells and transport channels in which pH levels vary. These conditions can alter the substance or even render it useless. Finally, the active substance must be designed in such a way that it collects where insects suck or eat – for example on the stems of fresh leaves. If it finally makes it to the pest's gut, however, there is yet another bath of different acids waiting for it. Schmitt has managed to reduce this odyssey to a simplified mathematical form which nonetheless closely resembles reality. To achieve this, he had to design a program that was small and quick enough to generate results within minutes but which neverthe-

Math specialist: Dr. Michael Edmund Beck, Head of Scientific Computation at Bayer CropScience in Monheim, drafts algorithms on the glass wall for computer programs (large photo) with which he can simulate active ingredient uptake in pests such as the whitefly (photo, right).





Target and hunters: combating the whitefly (photo, left) is the mission that physicist Dr. Walter Schmitt (right photo, left to right) and quantum chemist Dr. Michael Edmund Beck have set themselves. They use special software to simulate the uptake and transport of various chemical compounds against pests.

less provides reliable information. The software needs only around 30 to 40 equations and a handful of molecular parameters. In the model, all the stages that the active substance has to pass are shown as small, brightly colored boxes.

How such computer simulations help us to better understand the uptake and transport of chemical compounds can be shown by a newly developed class of insecticides: the ketoenols. One of these insecticides is currently marketed under the name Movento®. Its effect is particularly targeted at sucking insects such as aphids, whitefly and scale insects and vine pests and so provides protection for potato and vegetable crops, for example. The pests ingest the active substance with the sap. It therefore has to penetrate the plant cells via the leaves in the first instance. Movento® is a weak acid which can only penetrate the cuticle and the cell membranes of the leaf with difficulty. The molecule therefore initially has a sort of camouflage, a small side group. The plant's waxy layer then allows the active substance to penetrate and reach the plants' lifeline – their transport pathways. There are two different types of these: the phloem and the xylem. In the xylem, water and minerals are transported from the roots, as if by an express lift, up to the tip of the plant. The xylem flow is also what causes droplets from

freshly cut branches. Things are a lot steadier in the phloem, on the other hand. In this transport system, the sugars and nutrients created in the fully developed leaves by photosynthesis not only flow down to the roots but also into the young leaves – and so directly into the sucking insects' larder.

Harmful leaf-sucking insects as computer models

So, anyone wishing to target aphids precisely would do well to smuggle the active substance into the phloem. This is exactly what happens with Movento®. Once inside the plant, the molecule drops its mask: the camouflaging side branch is chemically cleaved off and the substance changes back into a weak acid which concentrates in the phloem flow. Thus, the active ingredient is directed precisely to the insects' suckers. It then passes through the aphid's gut and into the whole body, where it blocks lipid metabolism. Movento® is the first insecticide ever to be transported throughout the whole plant in the phloem vessels. Using his models, Schmitt was able to find out what properties are needed to make this transport possible. He could then give chemists advice on how the active substance needed to be varied so that this would be possible.

The example shows how complex the search for an ideal active substance is, but also how precisely and effectively

modern insecticides work. "Years ago, kilograms of active substance had to be applied to a hectare of agricultural land," says Schmitt. "Nowadays, a few grams are usually enough." Schmitt's expertise is required, for example, when a substance has already been synthesized in the laboratory and is causing problems at the subsequent experimental stage. His colleague in Monheim, Dr. Michael Edmund Beck, on the other hand, is often involved at the developmental stage of new substances before they have actually been produced.

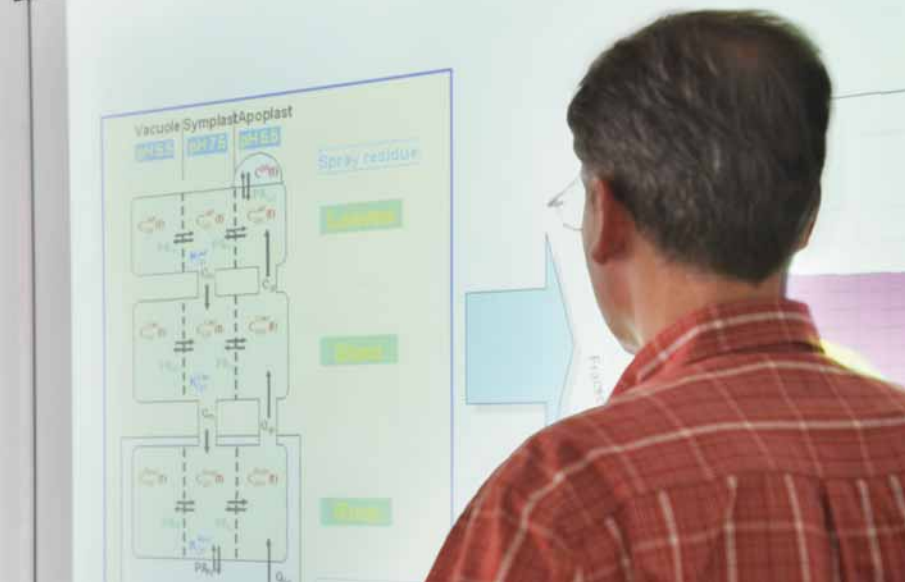
Quantum chemistry is also used in crop protection

Beck specializes in quantum chemistry and is also a computer modeler. He calculates what are known as the physicochemical properties of molecules or searches in databases for interesting substances. He helps to reduce the enormous supply of potential active substance molecules, separating the wheat from the chaff. In cases of doubt, his computer is quicker than his colleagues in the laboratory. One of his digital tools is called Quantitative-Structure-Activity-Relation, or QSAR for short. This mouthful describes the quantitative relationship, for example, between a chemical, biological or physical characteristic of a molecule and its chemical structure. Thus the different features of a molecule can be used to



Acceleration of development

Professor Matthias Rarey is Managing Director of the Bioinformatics Center at Hamburg University. *research* talked to the computer scientist about the importance of bioinformatics to research



Theoretical crop protection: the "blueprint" of the software simulating a substance's transport path inside a plant is just as complex as the structure of an active ingredient for an effective crop protection agent. Biophysicist Dr. Walter Schmitt keeps an eye on the big picture.

calculate what characteristics it is likely to have and how it works.

Experienced chemists are able to find such structure-activity relations even without the help of QSAR programs, but computer models provide valuable additional information. Scientists can use this method, for example, to discover molecular characteristics which could not be discovered in an experiment, or only at great expense. Above all, models can be used to calculate characteristics of molecules which have not yet even been synthesized and only exist in the imagination of chemists. This was the case with the ketoenols. To calculate their acidic strength, known as the pKa value, Beck had to create his own QSAR process.

Ketoenols have protons which happily wander around the molecule and can be located at quite different sites. Their position, however, determines aspects such as how pronounced the acid character of the molecule is – and hence its tendency to migrate into the phloem. Initially, Beck tried to calculate the proton movement using conven-

tional programs, but whichever ketoenol variants he fed into the software, the simulations always produced almost identical pKa values – which did not correspond with what was observed experimentally. He then tackled the subject from a quantum chemistry perspective and carried out very detailed calculations for each molecule variant on which positions of the protons in the molecule are favorable from an energy perspective and are therefore more likely to occur. Finally, Beck was able to provide the chemists with valuable advice on how molecules need to be constructed in order to achieve the optimum phloem-pKa value.

The quantum chemistry specialist knows, however, that a model alone cannot help a great deal. "The knowledge of the whole project team is always needed to ask the right questions and to feed the computer appropriately," says Beck. However, the computer really has been shown to provide valuable help. "And at any rate it's certainly better than relying on chance", he says with a wink.

What disciplines, apart from crop protection research, also benefit from bioinformatics mathematical models?

Bioinformatics helps in the development of a large number of products, from medicines and pesticides to enzymes for detergents which dissolve fat and dirt on clothing even at low temperatures. The greatest area of application is pharmaceutical research, however. Recently, bioinformatics has been used in all areas of modern life sciences, including what is known as "white biotechnology", which produces chemicals with the help of bacteria, amongst other things – for example biocatalysts which accelerate chemical reactions.


How reliable are mathematical models?

Bioinformatics and computer processes function by learning from experimental data and deriving rules from these. They are therefore only ever as good as the database itself. How reliable the models are also depends on the characteristics under consideration. Fundamental characteristics of a molecule such as its acidic strength can be predicted more successfully than its behavior in a biological system. Computer modeling can reduce the development time for a substance considerably, thus saving costs. However, fundamentally unknown processes which are not understood cannot be modeled with computers. For example, it is extremely difficult to design models to predict the effect of a molecule on the whole body. In reality, a minor change to the molecule can completely change the effect of a substance. A toxic substance can suddenly become non-toxic, or vice versa.

What will biomathematics be able to do in future?

In some areas we may be able to make such reliable predictions in future that the experimental work can be kept to a minimum, but we will not be able to do without experiments completely for at least the next 30 years. To use a pesticide or a medicinal product straight from the computer on the field or in a patient will remain a pipe dream for a long time to come.

www.ndsu.nodak.edu/qsar_soc/index.htm

 *The Cheminformatics and QSAR Society provides more information on this subject.*