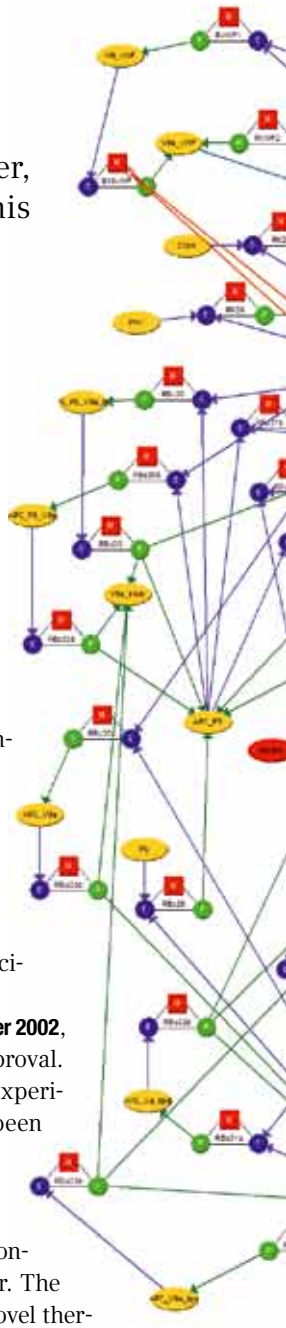
DRUG DEVELOPMENT

Let's Make a Model

With its Systems Biology & Computational Solutions global competence center, Bayer Technology Services helps customers better plan their clinical trials. This makes drug development more efficient – and patients stand to benefit as well.



Of course, it undoubtedly costs money to ask for support from the Systems Biology & Computational Solutions competence center at Bayer Technology Services. Then again, the work of these experts can also help save money – indeed, quite a lot of money. In some cases, customers can even be spared from needlessly spending hundreds of millions.

It is a simple fact that drug development is an expensive business. On average, pharmaceutical manufacturers have to fork out more than one billion US dollars for the development of product from the screening of a potential candidate compound to approval of the drug. Most of this expenditure is allotted to clinical trials, in which an active ingredient is tested on patients. The later in the development process it is discovered that the substance in question does not fulfill expectations, the more money is spent. In a worst-case scenario, the trials are concluded, but the drug then fails the application for approval.

This happened to a company that thought it had come up with a much-improved drug to treat hepatitis C. However, drug authorities in the United States and also in the European Union rejected the drug application in 2010. Their explanation was that a sufficient effect had not been proven.

Head of the competence center Dr. Jörg Lippert likes to cite this example because it demonstrates the value of his team's work. "With our capabilities today, we could have recognized in 2002 that this product might not have functioned as expected," he says, while pointing to a diagram with three green curves. All three start from the same point above left, but they slope down to the right to different degrees. Two lines – one dotted – drop similarly to the right, whereas the third is clearly beneath the other two.

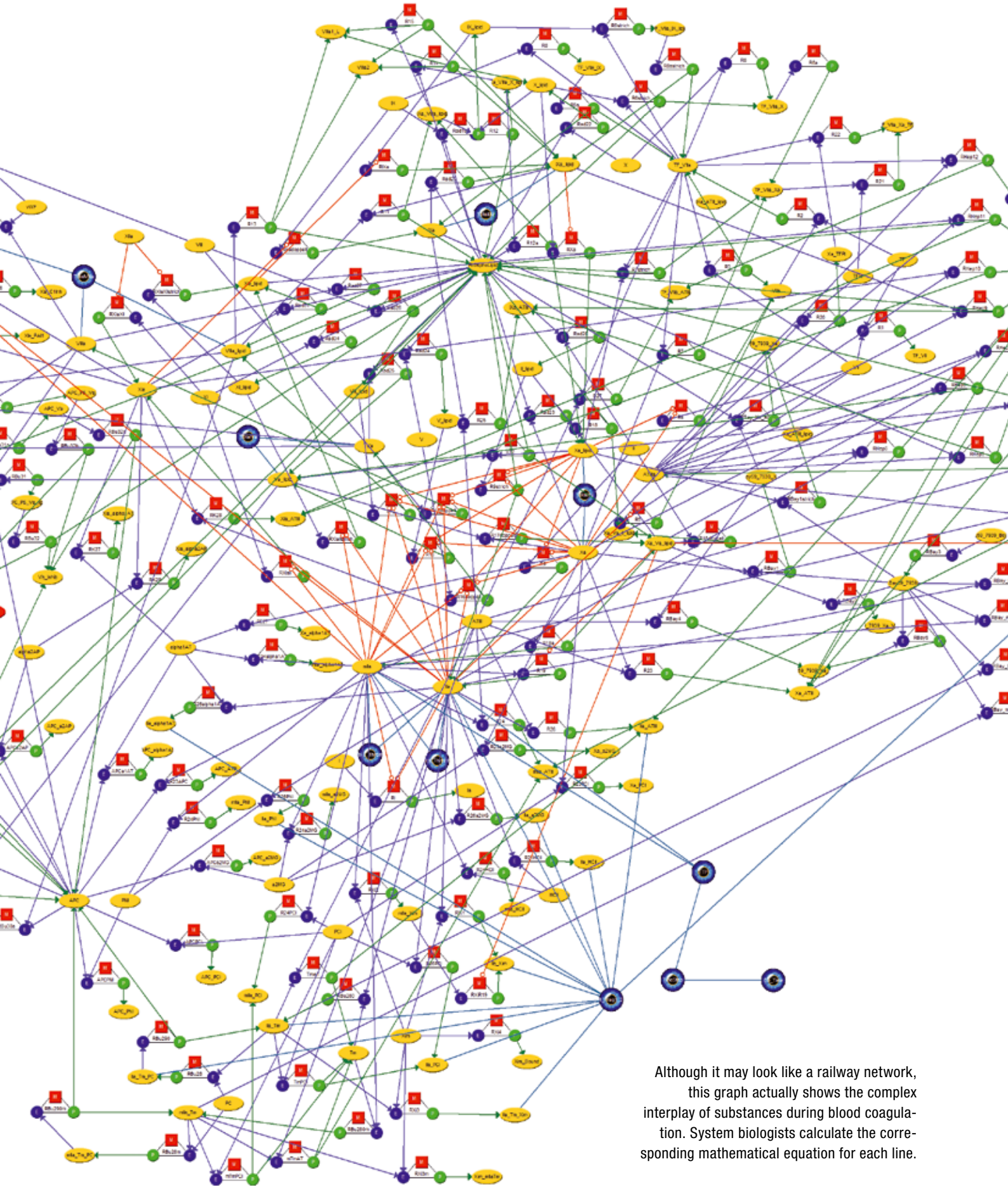
The curves show the level of concentration of the assumed anti-hepatitis substance in monkey's blood – at the time of the injection to the left and then to the right in the hours thereafter. The upper curve is based on the actual measured data in 2002; the two remaining ones stem from the computers of Lippert's work group.

And this is where you have to listen very carefully. "The lower curve is what our model determined for the case that the active ingredient interacted in the same way as precursors with its target structure," he explains. "However, if we disregard this interaction in the model, the dotted curve arises as a result – in other words, the one that comes very close to the experimental data."

So, Lippert is saying the following: In the actual animal experiment, the concentration of the active ingredient in the blood only remains this high because it is not performing as expected. But exactly that would probably be necessary for it to show the anticipated efficacy.

The compound went through all the clinical trials after 2002, only to ultimately fail the application for approval. Eight (costly) years passed after the monkey experiments – a failure that perhaps could have been avoided, if only the researchers had had a decent computer model back in 2002. Indeed, one like Lippert's workgroup can now provide.

In fact, the reason why Lippert's team is concerned with this subject at all is due to Pfizer. The pharmaceutical company was working on a novel therapy for the treatment of hepatitis C. Their experts approached Lippert's team and provided additional data. The computer model was further developed and allowed for predictions to be made of outcomes in humans even before clinical trials were run. "The model provided us with a new tool to predict the attributes of novel molecules at a very early stage of our drug discovery program, and it helped us select clinical candidates and design our first clinical trials," recalls Dr. Piet van der Graaf, Senior Director Pharmacometrics and Research Fellow in the Department of Pharmacokinetics, Dynamics and



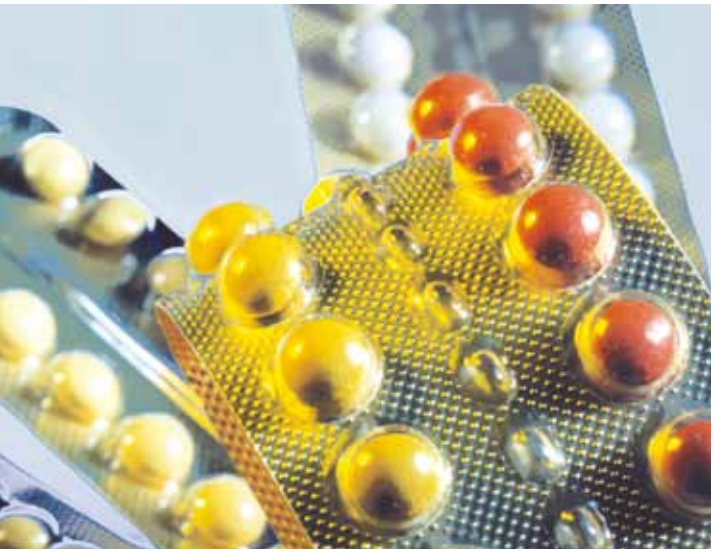
Although it may look like a railway network, this graph actually shows the complex interplay of substances during blood coagulation. System biologists calculate the corresponding mathematical equation for each line.

"The model provided by Bayer Technology Services helped us select clinical candidates, design the first clinical studies and ultimately make specific investment decisions."

Dr. Piet van der Graaf, Pfizer

Metabolism at Pfizer. "It really increased our confidence in the approach and helped us make investment decisions. In addition, the model gave us new insights into the biological mechanism that generated hypothesis for new experiments and potentially new approaches."

Clearly, it is no easy task to get a computer to reliably describe the behavior of compounds in an organism. For physicist Lippert it is "clearly defined, factually based, hard scientific work." And, ultimately, it is a question of the available data. After all, everything is subject to certain rules, and they can be expressed



Help in calculating how much active ingredient per tablet

mathematically – with a bit of effort. The more bodily processes are recorded in this way, the more precise the assertions of the models deduced from them are going to be. And this is exactly what Systems Biology is attempting to do. Although it is formally a sub-discipline of biology, this particular competence center at Bayer Technology Services is nevertheless a collecting tank for scientists and engineers of all disciplines. And one thing is clear: The good two dozen colleagues on Lippert's team have no difficulties dealing with mathematical formulas or biological, physiological and pharmacological relationships.

Just how complex this study can be becomes clear in the process of blood coagulation. The relational network of the participating substances is comparable to a national railroad network, in which each train station represents a substance and each connection a concrete biochemical process.

The requisite expertise of the competence center has grown steadily since its beginnings more than 10 years ago. At first the focus was on basic questions of pharmacokinetics. How quickly is a substance absorbed in the blood or in individual organs? How is it broken down in the body? How is it eliminated via the kidneys? And so on. With PK-Sim, Bayer Technology Services has been marketing a software platform that perfectly simulates (= Sim) such pharmacokinetic processes (= PK) for eight years now. The respective contracting client usually supplies the substance-specific data that are important for accurate modeling, such as a compound's solubility in water or fat or the speed of degradation in contact with different liver enzymes. In addition to the software, Bayer Technology Services also offers the actual modeling – both for the human organism and also for all the established animal models used in drug development, whether for mice, rats or monkeys. The spectrum even includes farm animals, such as cattle, which has proven helpful in the development of veterinary products.

The most frequent inquiry from customers involves determining the proper dose of a new active ingredient for trials with animals or humans. Of course, it is possible to approximate the optimal dose experimentally, but with theoretical preliminary work one can often substantially reduce the efforts involved. Clearly, this is also beneficial for the well being of the patients who do not need to be given over an extended period of time doses of substances that have no therapeutic value or are higher than the required amount.

A project with Bayer HealthCare illustrates how useful the work of systems biologists can really be. The company is currently testing its approved anticoagulant rivaroxaban for a further indication called acute coronary syndrome. Several thousand patients have already participated in the phase II clinical trials; for the phase III trial currently underway it is a five-figure number – at an enormous expense. For this reason it is absolutely crucial that such trials are very precisely planned and carried out within a medically acceptable dose range. "Even though we performed the phase II trial with several different doses, it should still be clear beforehand in which range the optimal dose is to be expected," says Dr. Rolf Burghaus, Head of Modeling & Simulation in the Clinical Pharmacology Department of Bayer HealthCare. The models produced by Bayer Technology Services allow not only prognoses about this range, but also about the most promising dose. "By the end of our study, the exact dose already favored by the model actually turned out to be the optimal one," Burghaus reports.

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Child-Oriented Medicine

What dose should be used to treat young children and adolescents? For a long time, physicians had to answer this question on the basis of vague assessments. They then prescribed, for example, half a tablet in cases where adults took a whole one.

Today, national health authorities demand that pharmaceutical manufacturers investigate the proper dose for children already during the development process of a new active ingredient. They are also required to carry out the appropriate clinical trials. This is no easy task and can even be precarious for ethical reasons. Depending on the age of the patient in question, the liver, for example, can react in a totally different way. Incorrect assumptions can quickly lead to over- or under-dosing – neither of which would be in the interest of an under-age trial participant.

It is not at all easy to determine the optimal drug dose for children.

"With our models we help ensure that a proper dose is administered in such trials right from the beginning," says Dr. Jörg Lippert, Head of Systems Biology at Bayer Technology Services. Some results may at first surprise an outsider. For instance, one case showed that at a certain phase of preschool age, an antibiotic should be administered in a higher dose per kilogram of body weight than with adults. The reason: At this age the liver constitutes a relatively high share of total body weight. In other phases and with different active ingredients, the influence of the liver can be exactly the opposite.

Bayer Technology Services," Burghaus acknowledges. He, like Lippert, is a physicist and particularly pleased about the collaboration that succeeded in establishing a standard process for pediatric development – i.e. for the planning of studies with under-age patients. "Using our models, we can give specific recommendations for the treatment of children based on the data from studies with adults," Lippert explains (see box).

Just as it is possible for the systems biologists to draw conclusions about children, they are also able to use pharmacokinetics for certain ethnic groups or genetic changes. Lippert sees something very special about the service of his competence center in that his people are, in principle, able to expand the existing basic model – at will and at any time.

Viewed in this light, modeling the hepatitis C treatment was also a special commission. The active ingredient was specifically modified in order to circumvent the degradation mechanism. This aspect had to be depicted appropriately in the model, too.

There is also a "human factor" in the work of a systems biologist. In one particular case, for example, Lippert's team worked out a new risk assessment for codeine, which is used in some countries for pain treatment after giving birth by Cesarean section. Using a computer model, the Bayer team showed that, due to their genetic makeup, more women than previously thought convert codeine to morphine extremely quickly. This in turn could overexert the morphine degradation capacity of the newborn babies who ingest the substance with the mother's milk. In fact, deaths of such babies had already been reported. The only solution was a genetic test prior to therapy or to forego codeine treatment in the first place.

In Lippert's opinion, the ideal case would be if such considerations occurred before drug approval. "Approaches using systems biology should be incorporated into the development of every active compound – right from the beginning."