

Software simulates drug absorption

through the body

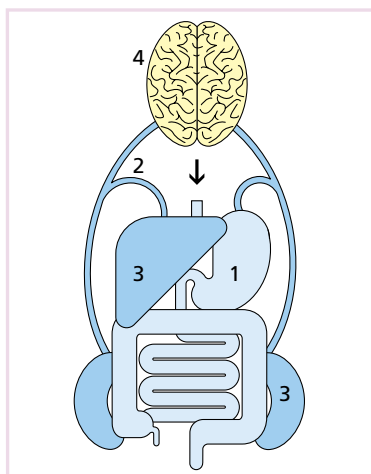
Virtual journey

Pharmacokinetics

Before a drug reaches its ultimate site of action in the body, it has to overcome a number of obstacles such as passage through the intestinal wall or through the liver. Until recently, the only way to identify the exact pathway was by means of lengthy experimentation. Two Bayer researchers have now developed a computer program that simulates the complex obstacle course encountered by an active substance as it passes through the bodies of humans and animals.

This "virtual reality" photomontage combines a computer simulation with real sequences of events in the human body.





Key issues in pharmacokinetics

- How much of the compound is absorbed and from where?
- How much remains in the bloodstream and for how long?
- How much is metabolized or excreted and when does this happen?
- How much reaches the target site and how quickly?

The pattern of distribution of a compound in the body can be worked out with the PK-Sim® software. This involves computer simulation of the properties of the body's most important organs: gastrointestinal tract (1), bloodstream (2), liver and kidneys (3) and brain (4).

Absorption

When the mouth closes with a tablet inside and a gulp of water sends the medicine on its journey through the body, it is mentally tracked by pharmacokineticists. These scientists are responsible for finding out what happens to a drug's active ingredient as it passes through the body. When and where does the active ingredient leave the digestive tract? When does it enter the bloodstream? How long does it remain there? And above all, what happens to it next? How much of the substance contained in a tablet actually reaches the site of action? How quickly?

Pharmacokineticists track the complex pathway followed by an active substance as it passes through the body. They establish how quickly a substance is metabolized, whether it lingers in the fatty tissue of organs and how readily it crosses the barriers between stomach and intestine and the blood vessels. This is an important task, as even the most impressive active substance, selected from thousands or even millions of other chemical compounds in screening tests by researchers and having the best performance in test-tube experiments, is no good at all as a medicine if it is broken down too rapidly in the body's incinerator, the liver. Indeed, between twenty and thirty percent of all newly identified candidates fall by the wayside during the subsequent drug development for this very reason.

Once identified, the prototypes of new active substances then undergo a

lengthy process of precision optimization. This is the task of biochemists. They modify the chemical structure, for instance, so that an even greater proportion of the substance reaches its site of action. The aim is to keep the dose required by patients as low as possible to minimize the risk of side effects. An important role is played by pharmacokineticists at this stage too. Their knowledge is crucial when it comes to testing a newly identified and optimized compound for the first time in clinical trials in humans. The more accurately the researchers can predict the appropriate dose in advance, the fewer such trials are required.

Detective work inside the bodies of humans and animals

Pharmacokinetic research plays a key role in the development of new drugs. Dr. Walter Schmitt and Dr. Stefan Willmann from the Department of Biophysics at Bayer Technology Services assist the pharmacokineticists in their work. In their laboratory, they too study the body's absorption of new compounds, their distribution to organs, their rate of metabolic breakdown and their excretion. They produce ADME (Absorption, Distribution, Metabolism and Excretion) reports for mouse, rat, dog and man. And yet the laboratory where Dr. Schmitt and Dr. Willmann work contains no animals and no human test subjects, no humming centrifuges and no bubbling water baths.

There is not even any testing of blood samples or dissection of organs. Their laboratory weighs a mere two kilograms and fits in any briefcase: it is a laptop.

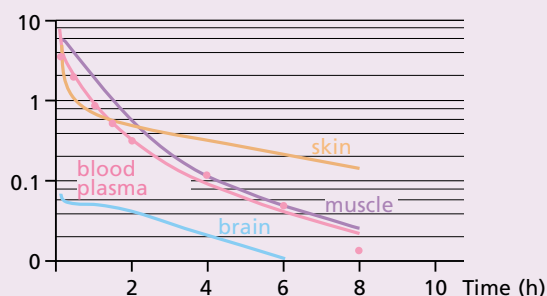
For these two biophysicists, the detective work involved in finding out what happens to different chemical compounds inside the bodies of humans and animals is taken care of by the computer program "PK-Sim®" (Pharmacokinetics Simulation). "PK-Sim® is the first whole-body ADME simulation that encompasses all the processes determining the fate of active substances in the body," says Dr. Willmann proudly. He and Dr. Schmitt are the program's spiritual fathers. They developed and

Distribution

Simulated breakdown

The PK-Sim® software calculates how a particular compound is distributed and metabolized in the body after ingestion. The concentrations of a compound in the skin, the muscles, the blood plasma and the brain are indicated by lines in the diagram. The dots show the levels actually measured in the plasma.

Concentration (mg/l)



Transport helpers sought urgently

Whether or not a substance can penetrate cell membranes depends largely on its fat solubility. This is a passive process based purely on physical and chemical conditions. In membranes, however, active as well as passive processes play a role. Special membrane transporters convey desired compounds in increased quantities into the cell, while other transporters carry increased amounts of unwanted compounds out of

the cell. Active transport processes are of particular interest to drug developers. Once the researchers have a more precise understanding of what is happening, the substances can be chemically modified in such a way that they make even better use of the processes or, conversely, actually bypass them. The simulation program PK-Sim® helps to determine the membrane transporters' every move.

Metabolism

successfully tested it and were initially the only people who knew how to use it. It soon emerged, however, that PK-Sim® was more than just the plaything of two biophysicists. Other drug researchers were also interested in clarifying ADME issues with the aid of the simulation system. It was at this point that it was decided to give the program a universally comprehensible and easy-to-use user interface. Development of this interface, which was undertaken by Bayer's computer scientists, was labor-intensive and correspondingly very costly. It therefore seemed a good idea to make the software available externally to other companies, research institutes and academe-

mic establishments as well so as to recoup the development costs. Now the work is complete and PK-Sim® is available to other interested parties outside Bayer.

Computer simulation of 15 different organs

Although the program is still new, it has already solved a number of intricate problems. For example, one test substance – let's call it "substance X" – exhibited excellent results in test-tube experiments. A promising candidate, therefore, for a new drug, it might be assumed. In the mouse, however, substance X was an inexplicable fail-

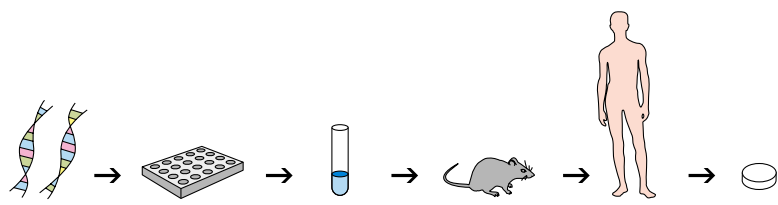
ure. Dr. Schmitt and Dr. Willmann keyed specific parameters into their simulation program: fat solubility, protein binding, molecular weight and clearance (rate of metabolism and elimination in liver and kidney). These data for over 10,000 compounds already exist in a database. Only clearance is difficult to predict. This therefore has to be measured by determining the concentration of substance X in blood plasma.

In addition to these five parameters, PK-Sim® also requires data on the individual organs and parts of the body that are to be simulated: liver, heart, brain, bone, fat, etc. Approximately 15 different organs are described in this way in terms of blood flow rate, volume, fat content, protein content and blood vessel surface area. This is also how PK-Sim® distinguishes between mouse, rat, dog and human, as the bodies of each of these species are very different.

In the case of substance X, PK-Sim® found out straight away that the reason why it had no effect in the mouse was because the dose was too low. With the extremely rapid turnover of blood cells in the mouse, the active ingredient had disappeared from the blood before the necessary plasma concentrations could be attained. At the same time, PK-Sim® also predicted that the same dosage (adjusted to body weight) would be sufficient in the markedly larger rat. This was confirmed subsequently in the experiments. For its developers, experiences like these

The data fed into the software is collected by robot sensors in Wuppertal and Monheim.





	Determine target	Screen substances	Seek active substance	Optimize active substance	Test active substance	Medicine
Virtual	-	-	passive processes	active processes	first-in-man dose, individuality	
Real	genome	high-throughput screening	in vitro experiment	in vivo experiment	clinical study	

How PK-Sim® can help

At several stages in the drug development process, from target identification in human genetic material through to the finished product that is ready for introduction onto the market, the pharmacokinetics program PK-Sim® can provide useful information on passive transport processes during compound selection and active transport processes during compound optimization as well as initial human dosages and intrapersonal differences at the clinical trials stage.

are impressive proof of the reliability of PK-Sim®.

If substance X clears all the hurdles in its path to clinical testing in humans, the simulation program can again help the researchers to answer another key question: what is a reasonable dose for the first use in humans? Extrapolating this "first-in-man dose" from prior experiments in rats or dogs to human body weight would be far too simplistic. If, on the other hand, the dose were to be set low to be on the safe side, that would mean more trials and higher development costs. At this point, the calculations performed by PK-Sim® can provide a realistic prediction of the correct initial dose.

Simulation reduces the need for trials in humans

PK-Sim® can also perform tests to predict whether a substance will be absorbed from the gastrointestinal tract or whether it needs to be injected directly into the veins. The simulation also provides valuable insight into whether the intestinal wall is readily penetrated by the substance or represents a huge obstacle to its progress, as well as into the effect of taking the substance on a full stomach or of the differences in metabolic rates which vary considerably from individual to individual.

If PK-Sim® continues to enjoy such success, simulation could herald a new era in pharmacokinetics. Just as simulator training for some time has sup-

plemented practical flying experience for pilots and safety designers in the automotive industry now initially simulate their crash tests on a computer to save countless tons of scrap metal, computer projections could similarly become a quick, flexible and economical tool for determining the effect of compounds in a key area of pharmaceutical research. As in the case of other applications for simulations, however, they can only ever supplement actual trials in humans and animals (albeit perhaps also reducing them in number or opening up new possibilities), and can never replace them completely.

"It's incredible that the pharmaceutical industry didn't make more of an effort to create effective tools for simulation of pharmacokinetics a long time ago," says Dr. Schmitt. "No plane, no car and no electronic circuit could be developed nowadays without using state-of-the-art simulations".

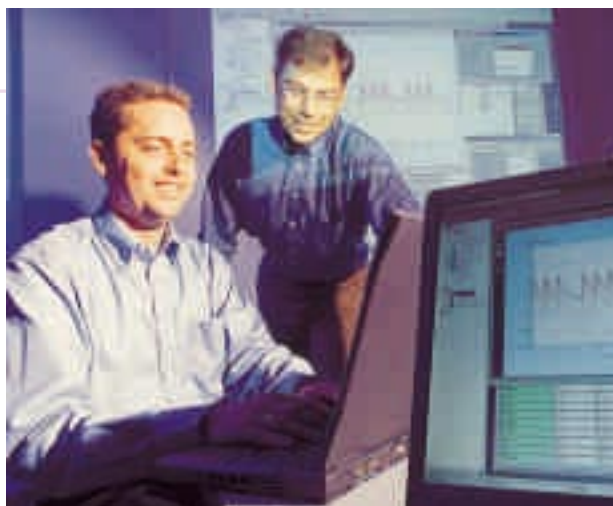
The predictions of the computer simulation are already working so well in

humans and animals that PK-Sim® is opening up whole new horizons. If a target for an active substance is identified in the genetic material of sufferers from a particular disease, a chemical database can then be searched for compounds that might seek out this target on the basis of their structure and binding properties. PK-Sim® can then be used to simulate what happens to these compounds inside the body.

Other computer programs could in future handle toxicological and formulating issues in a similar way. This would allow far-reaching conclusions on the importance of a target and on compounds from the chemical library to be drawn at a very early stage in drug development. As a result, the virtual journey through the body would continue to open up attractive new targets.

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Visit this website for further information on pharmacokinetic simulation.



The "body detectives", Walter Schmitt (right) and Stefan Willmann, track medicines on their virtual journey through the body.

Excretion

www