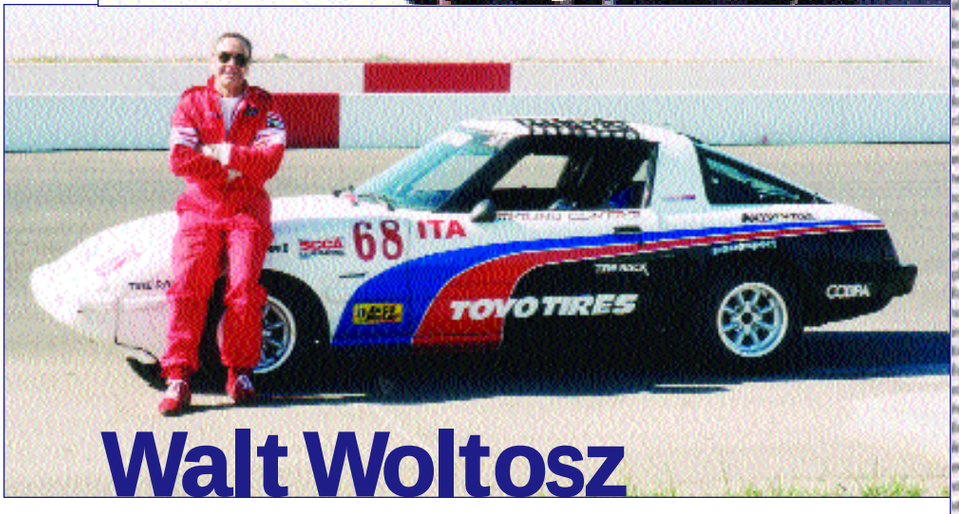
BY KIM RIBBINK

Quantum Leap



Walt Woltosz

is using his experience with simulation software in the aerospace industry to try to transform the way pharmaceutical companies approach data gathering and research, and he's proving that **it just might take a rocket scientist to get the industry on track**.

WHAT DOES THE PHARMACEUTICAL INDUSTRY HAVE IN COMMON WITH AEROSPACE? According to Walt Woltosz, chairman and CEO of integrated science at software company Simulations Plus Inc., a lot more than many people in either industry might realize. "It's just amazing how two totally different fields — solid propellant rockets and pharmaceutical science — can have so much in common in terms of the processes involved," Mr. Woltosz says.

Mr. Woltosz, an aerospace engineer by training, would know, having spent many years grappling with, and solving, numerous puzzles involved in designing solid rocket motors and propellants. For the past six years, Mr. Woltosz has been developing simulation tools to help the pharmaceutical industry overcome the abundant difficulties it faces in discovering and researching molecules for therapeutic value.

"Simulation and modeling is probably the most powerful tool available for integrating the knowledge gained through experiments and for researchers to find out what their data are trying to tell them," Mr. Woltosz says. "The aerospace industry learned more than 30 years ago how to apply modeling and simulation tools to deal with problems; the pharmaceutical industry is just now recognizing this potential."

Fitting the pieces

Without simulation and modeling tools, the sheer size of the problem that pharmaceutical companies face in investigating molecules is incomprehensible, Mr. Woltosz says.

"The number of potential drug-like molecules has been estimated as somewhere around 10 to the 62nd power," Mr. Woltosz says. "If we investigated one new molecule every nanosecond, we would be able to do about 10 to the power of 22 molecules in a million years, so we'd need 10 to the power of 40 million years to do them all. The numbers are so large that we can't even begin to comprehend them. It's like looking for a needle in a million haystacks."

The solution to such colossal problems lies in accelerating, rather than reducing, attrition, Mr. Woltosz explains.

"Projects will fail — almost every single project that is ongoing today in every single pharmaceutical company will fail," he says. "It's a sad fact, but that's how it works. The faster we can make those projects fail, the sooner we stop wasting resources on them and move on to another project that might not fail."

When it comes to testing premises and ideas, simulation software can provide quick and cost-efficient alternatives to the wet lab approach.

"Modern pharmaceutical simulation and modeling software gives project teams greater insight into what is happening with their compounds and allows them to rapidly conduct 'what if' studies in the computer instead of in the lab or in the field," the aerospace engineer turned pharma solutions leader says. "For example, studies might look at what if the liver blood flow rate was faster or slower, or body weight was higher or lower. It's a lot faster and cheaper to fail in the computer than in a lab or in the field."

Most significantly, Mr. Woltosz says, simulation software can help companies make the most efficient use of the data they gather from research. This is particularly relevant in trying to understand what causes a drug to behave differently depending on the size of the dose.

"Molecules now are bigger, they're more lipophilic, they don't dissolve as well, and they're more complicated in terms of metabolism," he explains. "When researchers start dosing molecules in an animal — rat, or dog, or even human — they get some behaviors that they don't quite understand. The question is what is it that causes a drug at a dose of 10 milligrams to behave one way but at 50 milligrams it behaves in a different way and at 100 milligrams it behaves differently again? That's where simulation tools are ideal, because it may be that the molecule is saturating some kind of transporter in the stomach, or it may be a protein binding issue, or it may be a metabolism issue. There really isn't any other way that I can imagine where researchers can tie it all together and look for ways to fit a model that explains all the doses at the same time with the same model. If researchers can fit exactly the same model to all doses and the model explains all the data well, then it may be possible to hone in on the mechanism that's causing the drug candidate to behave differently from dose to dose."

Many pharma companies are embracing sim-

Simulating Predictions for Success

Simulations Plus Inc. develops Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) neural net and simulation software for the pharmaceutical and biotechnology industries. Its software allows pharmaceutical scientists to predict certain key potential drug dynamics, such as absorption, *in silico*, thereby reducing the risk of multi-million dollar clinical-trial failures and speeding up the time to market of effective new medications.

The company has two tools for the pharma industry: GastroPlus, which is a simulation program, and QMPRPlus, which is a collection of neural network models to predict properties of new molecules from their structures.

GASTROPLUS

GastroPlus is a computer program for Windows platforms that simulates absorption and pharmacokinetics for orally dosed drugs. The underlying model is the Advanced Compartmental Absorption and Transit (ACAT) model — an extension of work originally done by Gordon Amidon and Lawrence Yu.

QMPRPLUS

QMPRPlus is an advanced computer program that enables pharmaceutical researchers to rapidly estimate a number of ADME properties of new chemical entities (NCEs) from their molecular structure. These predictions can be further used as inputs for GastroPlus to calculate fraction absorbed or used internally by a powerful screening filter called J-Alert. Estimates are quickly and easily produced interactively or in batch, by simply inputting the structures of the molecule. The program accepts inputs in SMILES strings (2D predictive models only).

2D or 3D molecular structures can be imported from ISIS databases in SDF, RDF, or MOL formats. QMPRPlus automatically uses the appropriate 2D or 3D predictive models for these inputs.

ulation and modeling tools and software, and recognize the role they can play in eliminating hugely expensive clinical-trial failures and in bringing medications to market more rapidly.

Where the industry has dragged its heels is in taking a multi-disciplinary approach to problem solving, Mr. Woltosz says. If the industry is going to make best use of the expensive data it collects through modeling and simulation, there will need to be greater coordination between groups, he continues.

"We have about 19 of the top 20 pharmaceutical companies in the world, but while all use simulations software in different departments, I've yet to see a single company that uses it completely across the board," he says. "At one company, the formulation groups will be very strong users, but the pharmacokinetics groups aren't. Then at another company, the formulations groups aren't using the tool at all and the pharmacokinetics groups are using it intensively."

Certainly, pharmaceutical companies have moved forward in leaps and bounds in terms of simulation adoption and inter-departmental communication since Mr. Woltosz first entered the arena.

"I remember being at a meeting at Novartis in Basel, Switzerland, about five years ago. They told me it was the first time they'd ever had a meeting where the formulation people, the pharmacokinetics people, and the discovery people were together in the same room for this type of meeting," he says.

Nevertheless, a greater degree of organizational change at the pharma level is required if maximum benefit is to be realized from simulation and modeling tools.

"Managers need to identify those researchers in their organization who can think in a multi-disciplinary way to achieve maximum payoff from these new tools and give them the training and tools to do their jobs," Mr. Woltosz says.

Above all, knowing how all the pieces of the research puzzle fit together is crucial in working out how to balance the competing factors in a drug molecule or pharmaceutical formulation, such as potency versus solubility. This requires a balancing act, or optimization that is necessary when designing any product — be it a pharmaceutical product, a space shuttle, or a car.

"Back when I was doing my aerospace work I had jokingly created a rule called Woltosz's first rule of optimization and that was if any part of a system is not optimum then the whole system is not," Mr. Woltosz explains. "With race cars, for example, if a team were to use the biggest engine in the world, but the car had little skinny tires, the driver would burn the rubber off those tires and never go anywhere. If there were huge tires and a little tiny engine that wouldn't work well either. There are all these compromises that have to be made to create an optimum balance between all the properties. The same is true in pharmaceuticals."

Again, that comes back to the need for a multi-disciplinary approach to research. "The person who works on metabolism can't work in isolation from those who work on solubility, or potency, and so on," he continues.

And therein lies the challenge for an industry that for years has taken a silo approach to much of what it does.

"The first group of scientists would design molecules and pass them onto one group to run lab experiments and another group would run a different set of tests," Mr. Woltosz says. "This information would all be fed to another manager, who had multi-disciplinary responsibility, but who didn't participate directly in any of the groups supporting the project.

"In the aerospace industry, every company has a group of generalists," he says. "These generalists have a good working knowledge of each of the interacting disciplines involved in making, say, a rocket motor — propellant chemistry, structural analysis, heat transfer, nozzle

A Model of Inspiration

IN AN EXCLUSIVE INTERVIEW WITH PHARMAVOICE, WALT WOLTOSZ, CHAIRMAN AND CEO OF SIMULATIONS PLUS INC., TALKS ABOUT THE CHALLENGES FACING THE PHARMACEUTICAL INDUSTRY AND THE JOY OF DESIGNING A PRODUCT THAT CHANGES PEOPLE'S LIVES.

WALT WOLTOSZ

WHAT LESSONS CAN THE PHARMACEUTICAL INDUSTRY LEARN FROM AEROSPACE AS IT LOOKS FOR WAYS TO ENHANCE ITS RESEARCH AND DEVELOPMENT EFFORTS?

The difference between aerospace and the pharmaceutical industry is that in aerospace something is designed, then manufactured. In the pharmaceutical industry, first we make something and then we test it to see if it's a good design. In aerospace, most of the R&D money that is spent results in a product. In the pharmaceutical industry, the vast majority of R&D money that is spent results in failures. In aerospace, once there is a product it usually makes money. In the pharmaceutical industry, according to some statistics, only 1 of 23 products ever makes enough money to cover its development costs. One big difference is that aerospace designs have been tested, failed, and redesigned millions of times on the computer before anything is made. But the pharma world hasn't been doing that. Its failures have been in the lab and in the field where it's very expensive to fail. That paradigm needs to change. Companies need to shift as much of that early development process as possible into the virtual environment, into the computer. And the tools are becom-

design, flight dynamics, and so on. Their job is to come up with a design that is not final, not perfect in every detail, but close enough that they know the requirements can be met with the approach they develop. Later, project teams refine the design and fill in the details. I believe pharmaceutical companies that adopt such an approach will avoid the parochialism that seems to result when one factor, usually potency, is favored over all others. It's all about balance."

Journey into Healthcare

For Mr. Woltosz his entry into life sciences has been long and has required patience, perseverance, and above all an unswerving belief in the value of the technology to bring life-saving therapies to market.

The journey began 21 years ago when Mr. Woltosz and his wife set up Words+, which is now a subsidiary company of Simulations Plus. That was when Mr. Woltosz first began to look into the huge potential simulation software held for life sciences, in this case as a tool for the handicapped.

"My wife and I started Words+ to develop computers for the handicapped," he explains. "What led us into that business was that my wife's mother had Lou Gehrig's disease. Words+ designs computers to help people who are not able to talk or to write without assistance."

Some years later, a Michigan-based physicist phoned Mr. Woltosz to ask him about his experience with ALS patients and to find out whether he might be able to help an English physicist with the condition, who had lost the use of speech after a tracheotomy procedure.

Simulation and modeling is probably the most powerful tool available for integrating the knowledge gained through experiments and for researchers to find out what the data are trying to tell them.

That English physicist was Stephen Hawking. Mr. Hawking has been using Words+'s equipment ever since, and the two men have maintained a close connection over the years.

"The first time I received a long-distance telephone call using a voice synthesizer that was from Stephen, it was quite a thrill," Mr. Woltosz says.

Ever eager to take his problem-solving skills further, Mr. Woltosz came up with the idea of simulating lab experiments for students with severe physical disabilities so they could set up and run their own experiments.

"The experiments would be virtual experiments — computer simulations that would look and behave as much as possible like the real thing," he says.

Mr. Woltosz submitted a grant proposal to the National Science Foundation and the project was awarded a $51,000 SBIR grant, followed by a $300,000 Phase II grant.

Still Mr. Woltosz felt the potential for simulation could be taken further in healthcare, and he began looking for ways to link his discoveries with what the pharmaceutical industry was doing in the lab. Through his daughter, who was working for Syntex Pharmaceuticals at the time, he obtained the name of a scientist who was doing simple simulation in the GI tract.

"I contacted him and we put together a business plan that didn't go anywhere in 1991," he recalls. "But in 1996 it caught the interest of an underwriter, and we were able to do an IPO and raise $5 million to get going."

Today, Mr. Woltosz oversees Simulations Plus, a thriving company that works with many of the world's top pharmaceutical companies.

Simulations Plus develops drug discovery and simulation software. Its ADME absorption simulation and neural net structure-to-property prediction software is licensed to pharmaceutical and biotechnology companies worldwide to assist in conducting drug research and development. ADME stands for absorption, distribution, metabolism, and excretion.

The tools include GastroPlus, which simulates the dissolution and absorption of a drug in the human gastrointestinal tract, and

ing available. We have a long way to go, I won't begin to tell you that we can design drugs on the computer, but in 100 years I bet we will be.

ARE THERE RISKS FOR THE PHARMACEUTICAL INDUSTRY IN ADOPTING SIMULATION SOFTWARE TO GATHER AND PROCESS DATA?

To me the risks are zero. Simulation software is the kind of tool where researchers can quickly and inexpensively investigate hundreds of options. Once there is a small amount of experimental data, there is a foundation to build a good model for the molecule being investigated. So whether drugs are being dosed in rat, dog, or human, researchers can leverage the knowledge they gain from those few experiments into a wider range through simulation and modeling. This depends on making sure the tools are applied properly, by ensuring that the people who use the tools get the proper training and have the skills and motivation to use them.

WHO ARE SOME OF THE PEOPLE WHOSE LIVES HAVE BEEN CHANGED THANKS TO THE SOFTWARE TOOLS YOU'VE HELPED TO DESIGN?

Clearly, Stephen Hawking is the ultimate example, but there are thousands of others. One example was a young boy I worked with about 15 years ago. I had been at Purdue University giving a seminar and the organizers asked if I'd mind seeing some of the kids they had been working with.

One was an 8-year-old boy who had severe disabilities and only had peripheral vision. They had not been able to find a way to help him communicate. We had a system at the time that used picture symbols. This little boy couldn't use a keyboard or a mouse, so we had him use a paddle switch. I put a picture of a boy on the screen and programmed the voice synthesizer to say "Hi, my name is Scott." He quickly understood that hitting the switch caused this message to be spoken. Then we split the screen with two images, and the second said, "I am 8 years old." Within a minute or two he'd figured out how to choose the image he wanted. From there we went to three pictures, then two rows of three, and within 30 minutes we had him doing row-column scanning of the six pictures. He later learned to read, he finished high school, he's moved on and is using much more sophisticated software now. But his story always gives me goosebumps, because we were able to totally change his life.

QMPRPlus, a computer program that enables pharmaceutical researchers to estimate ADME properties, such as permeability, solubility, lipophilicity, and diffusivity, of new chemical entities from their molecular structure.

By using such simulation and modeling tools to assess how molecules will be absorbed in the body, researchers are able to eliminate poor compounds quickly, thereby refining their search efforts and streamlining R&D costs.

Airborne Solutions

When it comes to solving puzzles for pharmaceutical companies, what Mr. Woltosz brings to the table is an ability to look at the big picture and offer an outside perspective to the process. Puzzle solving comes naturally to Mr. Woltosz. Early in his career, he was part of a team developing a computer program to optimize the flight of the space shuttle from launch pad to orbit.

"We discovered, quite by accident, that the most efficient way to fly the shuttle to orbit was upside down," he explains. "By rolling the shuttle over and on its back and flying it upside down, it was possible to get about 20% more payload to orbit."

Simulation and modeling were new when Mr. Woltosz began his aerospace career. "We pioneered a number of methods, including automatic design optimization of rocket motors and missile flight trajectories in the early to mid-1970s. Today's computers are so much faster, and the knowledge base has expanded so much, that the aerospace industry today doesn't make anything until it has been thoroughly tested through computer simulation and modeling."

Many of the modeling approaches Mr. Woltosz and his colleagues used to solve the space shuttle issue have relevance to the pharmaceutical industry today.

To demonstrate the intricacy involved in biological formulations, Mr. Woltosz compares the calculations required for the space shuttle program with the calculations required to simulate the dissolution and absorption of a drug in the human GI tract.

"A block diagram of our GastroPlus program would be virtually identical to a block diagram of the space shuttle program," he notes. "The space shuttle program involved about two dozen equations that were integrated for the equivalent of 10 minutes or so of real time, the typical amount of time for a launch. In the GastroPlus program, there are about 90 equations typically integrated for 24 hours. We have four times as many equations over a 150-times longer period. We are addressing a problem that is about 600 times more complex in terms of the number of calculations that need to be made than the space shuttle program."

Despite the variability of biological systems, Mr. Woltosz says by using simulation software it is possible to predict many complex situations with useful accuracy, which helps researchers to make better project decisions.

The opportunities for the pharmaceutical industry in using simulation software are as unlimited as they have been in the aerospace and automotive industries, Mr. Woltosz says.

"From small subsystem models to full-blown integrated system models, the potential for application of simulation and modeling technology is enormous," he says. "On the modeling side, the power of artificial neural networks to predict how new molecules are likely to behave is becoming widespread. For example, Simulations Plus is just about to release a new tool that automates the process of generating a high-quality model based on an ensemble of artificial neural networks in as little as a single day, a process that would have taken two to three months just last year." ❖

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Launching a Career in Healthcare

WALT WOLTOSZ — RESUME

1996-PRESENT. Chairman and CEO, Simulations Plus Inc., Lancaster, Calif.

1983–PRESENT. President, Words+ Inc., Sunnyvale, Calif., and Lancaster, Calif. Words+ produces communication aids for people with severe disabilities

1979-1983. Manager, engineering computing, Chemical Systems Division/United Technologies Corp., Sunnyvale, Calif.

1976-1979. Project manager, Air Force Rocket Propulsion Laboratory, Edwards AFB, Calif.

1975-1976. Senior engineer, Thiokol Corporation/Huntsville Division, Huntsville, Ala.

1974-1975. President, PSW Associates, Huntsville, Ala.

1973-1974. Senior research scientist, URS/Matrix Company, Huntsville, Ala.

1973. Engineer, Sperry Space Support Division, Huntsville, Ala.

1972-1973. General manager, Karex Corp., Huntsville, Ala.

1971-1972. Engineer, Northrop Services, Inc., Huntsville, Ala.

1970-1971. Electronics engineer, Federal Aviation Administration, Atlanta

1969-1970. Graduate research and teaching assistant, Auburn University, Auburn, Ala.

1963-1968. Launch missile systems analyst, USAF

EDUCATION AND TRAINING:

1977. M.S. Aerospace Engineering, Auburn University

1976. M. Admin.Science, University of Alabama in Huntsville

1970. Transistor Electronics, F.A.A. Academy

1969. B.A. Aerospace Engineering, Auburn University

1963-1964. Air Launch Missile Systems Analyst, USAF

AWARDS:

1977. USAF AFSC Technical Achievement Award

1977. Sustained Superior Performance Award (USAF)

1970. National Science Foundation Graduate Fellowship

1963. New York State Regents Scholarship

Tau Beta Pi — National engineering honorary society

Sigma Gamma Tau — National aerospace engineering honorary society