# Titanium implant **bioactivity**

**Professor Dr Walter Langel** is analysing the mechanical and surface properties of titanium implants using molecular modelling in efforts to reduce the number of implant rejections that currently take place

### What is the background to your study, and could you outline what you aim to achieve?

Medical implants made from titanium (Ti) are widely used because of their excellent mechanical properties, but this material is not as hydrophilic in practice as simple surface chemistry would suggest. This is significant, because bacteria related to inflammatory processes tend to deposit on hydrophobic surfaces. These microbes can cause inflammation, and Ti implants have a significant rate of complications and even revisions.

On an atomistic scale, my project models the growth of biomolecule layers on realistic implant surfaces, as well as the complicated interface between Ti metal and human cells. The aim is to help shift activity on the surface of the metal from bacteria to bone growth.

### Could you explain the potential benefits of using Ti implants?

Many people will require a medical implant of some sort during their lifetime to replace a hip, knee or tooth. For many applications, metals are superior to ceramics or polymers as they have better mechanical properties. Ti implants remain preferable compared with artificial bone materials. As a result, we carry out fundamental studies on Ti biocompatibility that go beyond trial-and-error experiments.

### What exactly is molecular modelling?

Molecular modelling is a simulation technique. Atoms and molecules are defined as objects, which the computer keeps in its memory as the initial state, and the rules affecting how these objects behave are stored in the computer as a program. The structure is then processed over a long time – days or even weeks – and the result is analysed, usually using methods developed by the researcher. Molecular modelling is often used as a computer experiment connected to laboratory experiments.

### How do you foresee your work developing? Do you have any related projects on the horizon?

It would be sensible to include the surfaces of practical alloys, such as the famous TiAl6V4, in our calculations. This alloy contains aluminium and vanadium which could influence the surface chemistry. Parallel to that, only small fragments of the biopolymers have been handled so far – this is not sufficient. It is akin to describing the properties of a long unit using pieces measuring a few micrometres in length. Another very ambitious aim would be to add a small part of the cell membrane and its link to the titanium oxide into our simulations.

These efforts towards larger and more complex systems are necessary if we want to combine theory with our recent experiments in the field of quartz crystal microbalance. There, the adsorption and viscosity of a liquid is measured by damping the mechanical vibrations of quartz. As you may know if you own a watch, a clean piece of quartz vibrates almost perfectly. However, placing a droplet of liquid on the quartz downshifts the frequency and dampens the vibration. This can be achieved by applying a biological solution to a Ti film on a quartz disc.

## Collab map

**Professor Dr Erich Knözinger**, who first worked in Siegen and then in Vienna, helped to pique Langel's interest in metal oxides and their surface hydroxylation

**Dr Susan Köppen**, who now works with Professor Dr Lucio Colombi Ciacchi in Bremen, was involved in the development of models for TiO2 and biopolymers as well as algorithms for energy evaluation

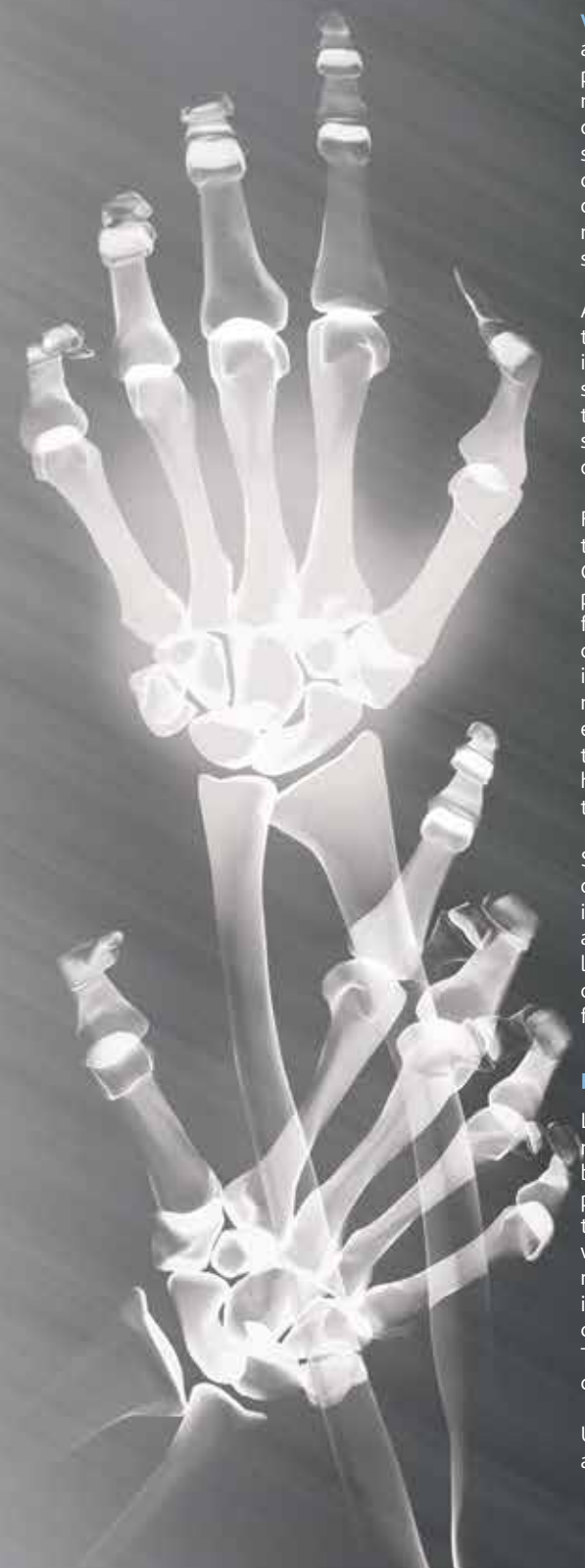
In cooperation with **Professor Dr Christof Wöll** in Karlsruhe, Langel studied the adsorption of alcohols on $TiO_2$

**Professor Dr Gianfranco Pacchioni** from the University of Milan-Bicocca collaborated with Langel et al. to model the electron structure of Ti metal and its influence on the structure of the oxide

**Professor Dr Ursula van Rienen** in Rostock works on continuum models for water in cell adsorption and, together with Langel, has explored the limits of these on small-length scales

# Molecular models for titanium implants

Simulation is not just for computer games, according to researchers at the **Universität Greifswald** in Germany. The team is using the technique to view the oxide surfaces of titanium implants in a bid to reduce the risk of infection and promote bone growth



**WHILE VARIOUS TYPES** of medical implant are available, titanium (Ti) has always been a popular choice. This is primarily because it is non-toxic, unlike other metals such as cobalt containing steel, and also because it is less susceptible than other materials to erosion caused by friction. However, while Ti is more compatible with the human body than other metals, polymers or ceramics, Ti implants are still sometimes rejected.

A high number of knee and hip operations take place each year, with several 100,000 in Germany alone. Although only a relatively small percentage have to be repeated due to implant rejection, this causes additional suffering for the patients and adds to the cost of the procedure.

For this reason, Professor Dr Walter Langel from the Institut für Biochemie at the Universität Greifswald has been looking into ways of preventing implant contamination so that fewer rejections occur in the future. Langel comments: "From its mechanical properties, Ti implants will remain preferable to artificial bone materials and the implant technique might even survive recent approaches such as growing tissue by 3D printing and stem cells". Therefore, he believes it is of critical importance to unravel the fundamentals of Ti biocompatibility.

Studies show that implants can become contaminated by bacteria while the procedure is underway. This bacteria settles on the surface area between the tissue and the implant, leading to inflammation. Not only does this cause pain, but it can also prevent successful fusion between the implant and the bone.

## FORCE FIELD MODEL FOR TI DIOXIDES

Langel and his team are using molecular modelling to investigate how integration and bone growth can be promoted while also preventing bacterial growth on the surface of the metal: "Ti passivates extremely rapidly when exposed to air and becomes chemically resistant; more so than aluminium foil used in the kitchen," he explains. "The oxide determines the properties of the Ti surface. This means that only oxide surfaces had to be considered in our simulation."

Using molecular mechanics, the researchers assembled models comprised of small spheres with atomic masses connected to each other by springs, mimicking chemical bonding. Electrical charges on the atoms were then applied to establish an effective force field, which allowed the team to analyse various proteins in water. "If these molecules are kept at a normal temperature, say 20-40°C, they rattle around and hit one other," explains Langel. "This is known from Brownian motion, where small particles tremble under the microscope in a solution. Using this 'molecular dynamics' process, the different molecules find the right mutual positions."

The computerised model is then captured on a digital film so that the images can be manipulated and analysed. However, while this is an effective way to see what happens to the molecules, the process is extremely time-consuming. A Hollywood film comprises around 130,000 images, which are shown at a rate of 24 frames per second – often it takes a year to produce around 90 minutes of film. However, in molecular dynamics, which is digitally 'filming' fast-moving atoms, millions of images can only scan small fractions of seconds. "Each frame corresponds to a time step of 1 femtosecond rather than 1/24 seconds, and is produced in less than 0.1 seconds," Langel elucidates. "A typical 'movie' lasts up to 100 nanoseconds, and comprises 100 million frames; one thousand times more than you see during a trip to the cinema."

Not only is this a long and complex procedure, but it can also prove off-putting to prospective researchers because it tends to sound like a very mathematical process. This does not always appeal to biochemists, who are required to master both the mathematical and physical aspects of the simulation. However, Langel makes the point that basic video games rely on a similar system of mathematics, and that this does not seem to put gamers off; moreover, students who take on the task tend to find that they are in demand when they come to apply for other jobs.

## DIFFERENT SURFACE STRUCTURES

Once the model was developed, the first issue the team was confronted with was the complexity of affixing a biomolecule to a chemically inert implant. According to Langel, adhering organic material to metal is an intricate process: "Only a thin film is adsorbed

## BIOACTIVITY OF TITANIUM IMPLANTS AND MOLECULAR MODELS FOR THEIR SURFACES

### OBJECTIVES

- To demonstrate that present molecular dynamics enables analysis of complex biochemical systems such as the interface between medical implants and the incorporating tissue
- To clarify the nature of hydrophobic layers which favour inflammatory complications
- To understand energetics and sequence specificity of biomolecules which stick on the implant and form the basis for cell growths

### KEY COLLABORATORS

**Professor Dr Lucio Colombi Ciacchi**; **Dr Susan Köppen**, Universität Bremen

**Professor Dr Gianfranco Pacchioni**, University of Milan-Bicocca

**Professor Dr Ursula van Rienen**, Universität Rostock

**Professor Dr Christof Wöll**, KIT Karlsruhe

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### CONTACT

**Professor Dr Walter Langel**

Institute of Biochemistry
Biophysical Chemistry
Felix-Hausdorff Strasse 4
D-17487 Greifswald
Germany

**T** +49 3834 86 4423
**E** langel@uni-greifswald.de

**www.mnf.uni-greifswald.de/institute/institut-fuer-biochemie/biophysikalische-chemie/forschung.html**

WALTER LANGEL is a Professor in Biophysical Chemistry at Greifswald University, Germany. He began his studies in gas phase kinetics and laser spectroscopy and has a Diploma in Physics (1976) and a PhD in Physical Chemistry (1980). After neutron scattering experiments and habilitation (1990) he turned to molecular dynamics during a Heisenberg fellowship (1991-1996). He worked with Professor Michele Parrinello at IBM Zurich in 1992-93.

and may have variable composition, and this film must be the basis for bone cell growth".

Using rutile and anatase, which can easily be cut to produce a range of surface structures, the team was able to come up with a model that initially focused on rigid atoms, but later evolved into a more flexible structure. This model allowed the researchers to explore any interaction between the water droplets and to measure the contact angles. "Our calculations indicated that an implant with pure oxidation and hydroxylation would have a very hydrophilic surface and small water droplets would spread all over. Only by 'waxing' the surface with a thin film of hydrophobic molecules were we able to obtain reasonable droplet shapes and contact angles," Langel explains.

The initial aim was to look at the differences between single amino acids, which revealed that changes in the side chains were more significant than Langel had previously realised. Following this, phosphate and calcium ions – which play an important role in bone formation – were added to the mix so that the team started with peptides consisting of 12 amino acids and can now analyse collagen fragments measuring 40 nm. Polysaccharide layers were later simulated, as saccharides play an important part in producing the protective film between the implant and the biological solution.

"By making calculations on the electronic structures, we found that even very thin oxide layers on the metal might be crystalline, but have different surface structures exposed to the solution," Langel reveals. "As known from the experiment, larger surfaces show very fine roughness. We showed that this makes it more difficult for biomolecules to adapt to the surface structure."

### PREVENTING CONTAMINATION

The experiments also crucially showed that contamination often occurs because airborne alcohol – typically used in hospital disinfectants – can add a carbon layer to implants that have been exposed to the air, whether or not they have been cleaned or handled with gloves. "The hydrophobic properties we observed were purely due to hydrocarbon coverage," elucidates Langel. "This contamination is not included in standard models of passivation layers, but we showed experimentally that the small quantity of alcohol in ambient air is sufficient to create such a carbon layer."

The only way to prevent contamination is to apply a protective film to the implant, which prevents this carbon layer from forming. This can be done by applying bactericide substances; by using hydrophilic peptides to prevent the adsorption of hydrophobic hydrocarbons; or by depositing hydrophilic, nitrogen-containing organic layers onto the surface of the implant. When such actions are taken, this will move Langel's work from the field of theory to praxis.

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