

Excerpts from an  
interview on Jan. 21, 2016  
Patrick S. Regan

*Jointly hosted by members of the TUM School of Medicine and the Physics Department, the Phase-Contrast Computed Tomography Focus Group provides a compact illustration of traits that, in combination, set the TUM Institute for Advanced Study apart. The TUM-IAS promotes international networking and*



*facilitates all sorts of connections: between disciplines, between established scientists and the next generation, between basic and applied research, and between academic and industrial expertise. Furthermore, these are not joined serially like links in a chain, but rather like compounds and catalysts in a crucible. And while it is like comparable institutes around the world in insisting on scientific excellence and frontier topics, the TUM-IAS is more open than others to the pursuit of practical outcomes.*

*In this case, the research frontier and the eventual aim coincide in new methods and instrumentation for X-ray computed tomography – with an eye toward clinical applications, in service of patients and their doctors, as well as enabling basic biological research.*

*On their way to Garmisch-Partenkirchen for IMXP 2016 – the International Symposium on BioMedical Applications of X-Ray Phase-Contrast Imaging – seven members of this collaboration met in Garching to discuss their work with interviewer Patrick S. Regan (PSR): Professor of Biomedical Physics Franz Pfeiffer (FP) is a Carl von Linde Senior Fellow of the TUM-IAS and Host of the Focus Group. His Co-host is Professor of Radiology Ernst Rummeny (ER), based at the university hospital Klinikum rechts der Isar. PD Dr. Peter B. Noël (PBN) is affiliated with both the Chair for Biomedical Physics and the university hospital. The home institution of Dr. Kaye S. Morgan (KSM), a Hans Fischer Fellow of the TUM-IAS, is the School of Physics at Monash University in Australia. Dr. Thomas Koehler (TK), of the Philips Research Laboratories in Hamburg, is a Rudolf Diesel Industry Fellow. Both Regine Gradl (RG) and Wolfgang Noichl (WN) hold MSc degrees and are doctoral candidates in Biomedical Physics. (Gradl is completing her PhD with TUM-IAS support).*





Franz Pfeiffer

**PSR:** You're a diverse group with a lot of irons in the fire. To give an overview, what are the basic outlines of the group's common research program?

**FP:** We're focusing on several technology areas as well as a few specific clinical indications and applications. When we talk about X-ray imaging from a technology point of view, we are basically looking at three innovations, technological improvements that in themselves are research topics in our lab.

First is phase-contrast imaging, where the basic idea is that we exploit the wave nature of X-ray light instead of just using the absorption. Where we used to have only one information channel, now we have three. In addition to absorption we have a phase-imaging channel and a scattering or "dark-field" channel. These are still X-ray images, but they show slightly different interactions. The question then is: In which channel do you see what, in the best way? Second, we actually work with novel instrumentation, such as more brilliant X-ray sources, the highlight being the Munich Compact Light Source. Part of a joint TUM-LMU project called the Center for Advanced Laser Applications, this powerful new research tool is located right in this building, at IMETUM.

Finally, the C in computed tomography or CT has become increasingly important in the last ten years, with all the computational power that is available now. The third major technology focus for our group is novel algorithms to process the images we get.

**TK:** Ever since CT was introduced, we've been working on algorithms. After thirty years, there are really mature algorithms for attenuation images, well optimized. You learn over the years how imperfections in the system can be modeled, and how they can be treated in algorithms to produce very nice images.

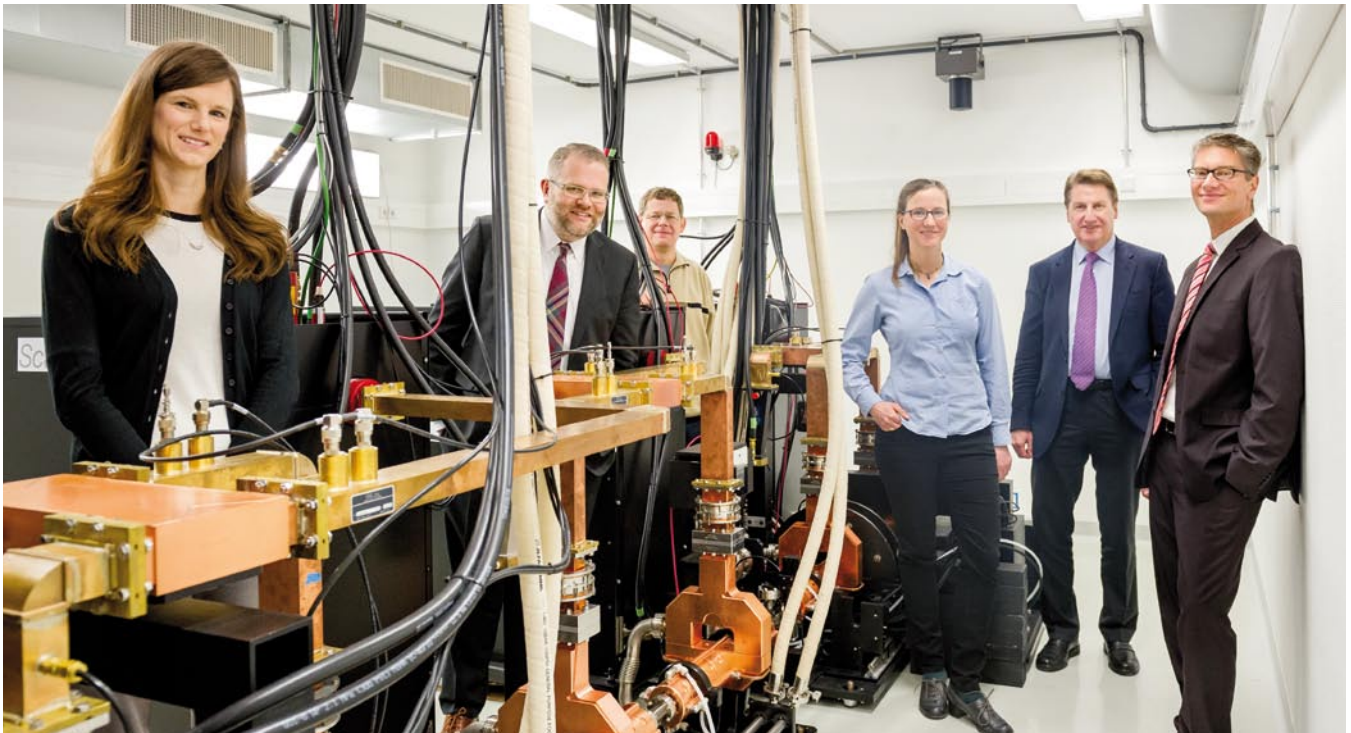
We'll have to do the same thing again with phase-contrast imaging. We're back on the learning curve. It may be clear from the physics point of view, but there are things you might want to neglect in order to make the algorithms faster. There are new imperfections in the system, which you might treat differently. Any time you modify your CT system, you have to model that in order to get good images.

**PBN:** As Thomas says, quite a lot of developments have already been done for absorption imaging. We try also to make the algorithms a lot more quick, a lot more efficient. Since phase-contrast has resulted in two other channels, you might also need different algorithms.

For instance, some algorithms you used before might only need a slight adjustment, but in other cases you need to think them through again from the very beginning. This is not only to make them quick, but maybe also to profit from the fact that those three channels are imaging the same thing and have something in common, something not in common – to take the quality in one of the images to remove artifacts from another imaging channel.

**TK:** The algorithmic research will be crucial to get to MRI-like images in the end, in the clinic, which is one of our aims. Here phase-contrast CT is competing with a very mature technology in terms of image quality, and this will be a challenge.

**PSR:** Ernst, how do you view the potential advantages from the medical point of view?



Kaye S. Morgan, Peter B. Noël, Thomas Koehler, Regine Gradl, Ernst Rummeny, Franz Pfeiffer

**ER:** With conventional CT, you see dense structures like the bone very nicely, and with MRI you see the soft tissue. Now with phase-contrast, we have the potential to get both with one system. I think of this as the MRI-zation of CT. Maybe when we have the technology in our hands, we will be able to do soft tissue diagnosis, finding small soft tissue tumors as well as bone diseases. In a small animal, we have shown that it works. Does it also work in humans? We'll see.

That's one potential advantage. We may also find we can reduce patients' exposure to X-rays. The technological goal in CT was first to make it faster and faster. It is now 200, 300, even 600 slices with one rotation, depending on the vendor. The other concern is how you keep the radiation dose down. We already have different technologies to keep the doses low, but this could be another.

I'm a clinical radiologist, and my goal is precisely this, to see what we can take from the technical part to the clinical part, to the translational part. That means when the machine comes to the hospital and a little bit before. I say little bit before because we are a technical university and thus have the opportunity to work closely together, even though our hospital is

downtown. There is a lot of exchange back and forth between doctors and Franz's group, and we hope at some point to put a phase-contrast X-ray system into the hospital and do the first clinical trials, here in Munich.

Before that, we need a company. Franz cannot be the company to build the machine and distribute it all over the world. But if we find a company to build the system, then we may have two, three, or four prototypes, and even do research internationally.

**PSR:** Clearly it must help to have someone from industry on the team from the start. Thomas, how would you describe your role?

**TK:** I'm a physicist with a background of working on algorithms for computed tomography. In the Focus Group, my role is supporting or pushing this from the industrial side, into the clinic. There's some really cool stuff already in the fundamental physics, in developing the technology, in showing that there is some benefit to be expected, and even setting up a small animal scanner. But once you come to a clinical environment, it's an order of magnitude bigger effort to set up a machine.



Kaye S. Morgan

And that's a point where it's good to have a company on board, to support the development, to point to certain boundary conditions that you have to comply with.

**FP:** A good reality check.

**PBN:** It brings us back from our dreams to the real world sometimes.

**PSR:** And Kaye, what brings you here from down under?

**KSM:** Besides the group itself, one of the attractions is the Munich Compact Light Source. The physics group I was working with in Australia was also doing phase-contrast X-ray imaging. I'm particularly looking at applying the technique as a medical research tool. In parallel to clinical imaging, you can use this kind of imaging to better understand the body, how treatments work, and that kind of thing. But most of my research to date has been done using synchrotron X-ray sources. There's some limit to how much time you can access there, so we're now looking at doing the same kind of research using the Munich Compact Light Source, which is much more accessible.

**RG:** It's really useful that we have this instrument. It's similar to a synchrotron, which is normally a building with a circumference of five to eight hundred meters, shared by many scientists. And now we have something that can produce similar radiation yet fits nicely inside a lab. That is really amazing. We don't have to write proposals to get access for a couple of days in the year – we can use it every day. It's also very interesting because it's a prototype, and you want to improve it.

**PSR:** So the instrument becomes part of the research?

**RG:** Exactly.

**PSR:** What's the difference between the big systems and the small ones? Can you do the same things with the Munich Compact Light Source that you could do with a synchrotron?

**KSM:** The MuCLS is filling in a big gap in that it is far more capable than an off-the-shelf lab source but on the other hand far less expensive than a billion-euro synchrotron facility. The synchrotron produces really bright light, so you can take a high-speed X-ray movie. Until now, most of the sources that could fit in labs



weren't bright enough to do that, since you had to have quite a long exposure. But the CLS is much brighter than, say, a spinning anode X-ray source, and also it's very coherent – that is, much closer to a single wavelength and uniform phase. That's one of the qualities that make for very good phase-contrast X-ray imaging.

It's the only one in the world, so we're lucky to have it here. There are two different end stations where you can take images, and there are many different setups available. There are quite a few people working on different potential applications.

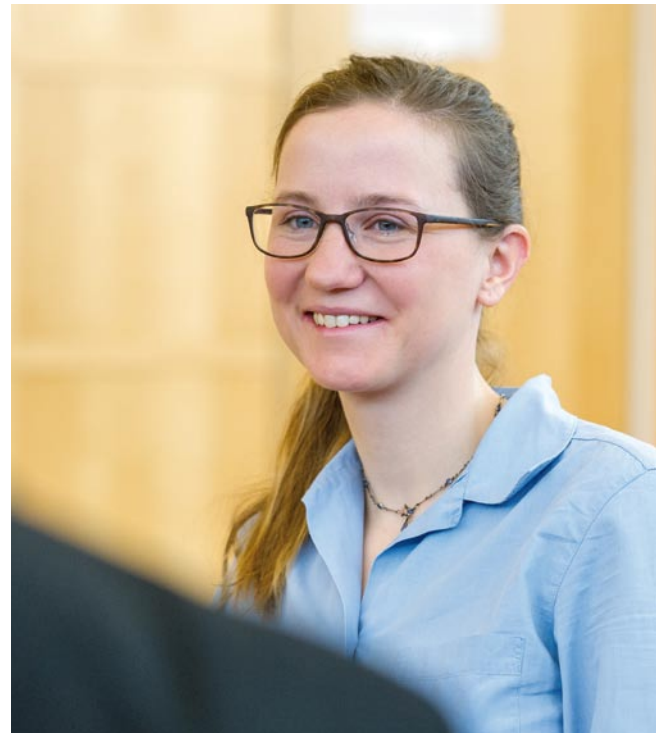
**PSR:** And what are you doing with it?

**KSM:** Some of the work we've been doing is imaging the airway surface. A lot of previous work that's looked at this on the micron scale has been using either a tissue culture or a piece of tissue in a dish, which is not quite as realistic as when the tissue is inside the body. Using this X-ray phase-contrast imaging, we can look at the airway surface *in vivo*. We can see how the liquid layer on the surface changes in response to treatments, and we can see how particles move along that liquid layer as they're inhaled.

**PSR:** What other kinds of biological questions become accessible with phase-contrast imaging?

**FP:** There are questions that go along with the clinical applications, such as how a certain state in the body changes as a disease progresses. If you take for example the liver, it's probably interesting to look at the chemical composition and how different diseases change that. This is information you would not always have from a clinical radiology picture but would still be worth investigating to know more about the reasons for disease – chemical, biological, or structural reasons – on a scale that is usually not accessible in the clinic.

Another example would be bone research. In the clinic you can look at bones from a certain length scale, or you have a resolution on the order of half a millimeter. But in the research lab, we can complement that by looking at small pieces of bone with a



Regine Gradl

micron resolution, so we get more information about why and how the structure changes on a different level. And maybe that leads back eventually to clinically relevant information that will add to our understanding of why a disease progresses this way or that way.

**ER:** Think about osteoporosis, a disease of the bone structure that affects everyone at a certain age. Why is this happening? Why is the structure changing? When is the bone breaking? All these things have to be evaluated for prevention, to protect people from that. Then there are new strategies in treating osteoporosis with drugs. Are they helping? Are they changing the bone structure?

Now you can take pieces of bone and examine them with high resolution. With the Munich Compact Light Source you can even go into molecular structures. You can see the molecules. What that means is that clinical questions inspire experiments that then feed back into medicine. That's the interface where these various disciplines meet, the basis of the whole collaboration.

**PSR:** This seems like a very special environment for you doctoral candidates, Wolfgang and Regine. Is that the way you see it?



Thomas Koehler

**WN:** I did my master's degree in condensed matter physics. What I find really interesting about this applied research in physics for medical imaging is that it's so close to applications. So there is some chance that you will see how your work is used by someone. And I like the challenge of developing algorithms for computed tomography. Nowadays computers are so fast, and for most purposes you can just write a quick script and it will happen instantly. Here the data is still big, and the algorithms can be very complicated, and it's still interesting to leverage the most recent technology. The algorithms are in a way somewhat slow, and you have to push the limits. I find that really tempting.

**RG:** My research focuses mainly on the physics, working with the Munich Compact Light Source and trying to improve the imaging. We would like to do some lung imaging, and also investigate some new treatments for lung diseases, and here we get together with the medical part. I feel we're doing something important. You want to improve medicine, and you want to help people.

**TK:** I think that goes for all of us. Of course my motivation also has something to do with the fact that my employer earns money selling medical equipment.



Wolfgang Noichl

It's good to have innovations that could position us to create great products. But there's also the level of personal motivation, and as Wolfgang and Regine said, it's really cool to work in an environment where the outcome of your work could do something good for people. Having that in combination with great science is wonderful.

**PSR:** Taking stock of where the Focus Group has come so far and looking ahead, are there findings or milestones you would want to highlight?

**FP:** There were three nice demonstration papers showing proof of principle and the first imaging applications for the Munich Compact Light Source. There are by-products of these experiments that may have biologically or clinically interesting implications. For example, we looked at mice and found that we can tell the difference between brown and white fat. In terms of algorithms, there was also a paper on iterative CT for phase-contrast imaging. We worked a long time on that, with several students. Also, a small-animal CT proof-of-principle system has now been installed at Klinikum rechts der Isar. Planning is under way for the first biomedical studies in close connection to the clinics –



Ernst Rummeny and Patrick S. Regan

to look at various disease models in mice. I'm very excited about having such a direct connection to the clinics.

**ER:** We already learned a lot last year about the three channels. With phase contrast you see the bone and you see the soft tissue. Now with the dark field, we see certain structures in the bone better than with phase contrast alone. In fact, all air-containing tissues will have different contrast in the dark field, so we have the feeling we could do lung imaging.

**FP:** That brings up the most basic clinical questions: Where exactly would this technology be most beneficial? Which disease could you diagnose or treat better if you had this technology in the clinic? We can't yet answer these questions in a clinical setting because the machine is not there yet. But a big effort of this collaboration is to do pre-clinical experiments with what we have here – to look at small samples of bone or liver or brain to help determine where this technology would eventually be most helpful, and where it would be better than what's already available.

**PSR:** It may be a long way to commercialization of this technology, but you seem to be moving pretty quickly. How do you straddle the line between university-based research and the prospect of influencing the whole medical imaging industry?

**TK:** There's a master research agreement that was negotiated between the university, the hospital, and Philips. The intellectual property is split among the parties. The whole idea with patents is that you can disclose what you've invented while protecting the initial investment. But this is by no means proprietary research or product development.

**PBN:** The business case, for Philips or any other company, will come from what Franz and Ernst were discussing earlier – whether there is a business case based on osteoporosis, or some other applications.

**FP:** The main point is that the product cannot be envisioned tomorrow. There is still a big jump to take before anyone is going to embark on a multimillion-euro product development. What we're doing is the preparatory work for clinical indications, technology development, and algorithmics – all of this is research and will be published.



50 **ER:** All the companies are looking at us, and at the literature. TUM and Philips are not the only ones doing phase-contrast imaging. There are different concepts. At MIT they do it differently. We think we are better. We have a feeling we are in the lead, but it's always good to have competition in science.

**PSR:** How does the TUM-IAS Focus Group relate to your separate, larger research environments?

**PBN:** Only this framework makes it possible to set up such groups, with excellent people from different fields.

**FP:** This interdisciplinary effect is absolutely unique.

**TK:** Personal contact is a very important thing, if you want to get creativity in a room and create new ideas. I'm here on a regular basis, and I'm of course connected to colleagues back in Hamburg. They are also part of the team in a sense, even though they are not so often here. It's really good that we have the framework but can also connect other people.

**PSR:** So behind each of you, there may be ten, twenty, or fifty more people involved in some way?

**FP:** That's the point. With all our individual networks, we are able to bring in, or drag in, or tap into resources as needed. But I would say it's more a one-way street. We are not, with this Focus Group, answering questions for other researchers – because it really is focused!



Peter B. Noël

