SWISS NATIONAL CENTRE OF COMPETENCE IN RESEARCH

KIDNEY
CONTROL OF HOMEOSTASIS

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Kidney—Control of Homeostasis is a Swiss research initiative, headquartered at University of Zurich, which brings together leading specialists in experimental and clinical nephrology and physiology from the universities of Bern, Fribourg, Geneva, Lausanne, and Zurich, and corresponding university hospitals.

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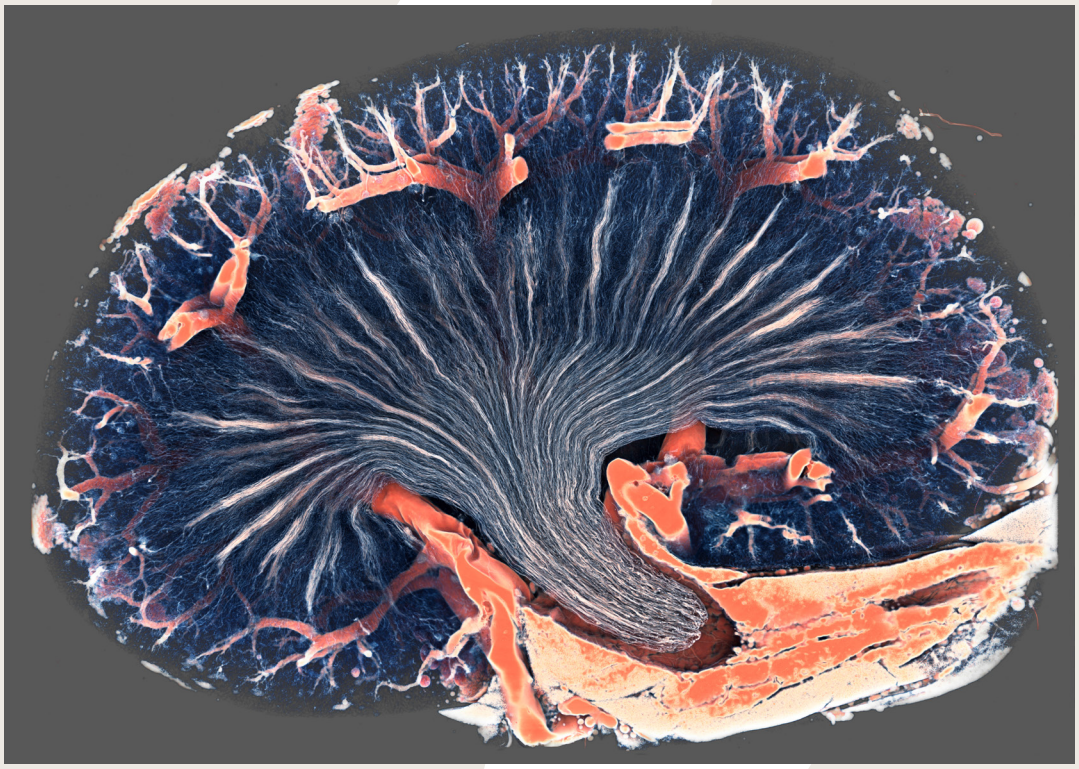
THE VIRTUAL KIDNEY



The idea of virtual organs - digital representations of organ physiology—promises nearly boundless research opportunities by means of virtual experiments. Imagine investigating kidney function without worrying about ethics committees, long breeding times, or compliance of test subjects. Imagine studying the effect of gene mutations by the stroke of a button. How far away are we from replacing in vivo models by in silico representations? And how will such models change the role of kidney researchers?

The field of computational physiology has its beginnings in the 1950s, with the first in silico models addressing macroscopic physical phenomena. The cardiovascular system lent itself particularly well to such modeling, leading to a head start compared to other systems that is still evident today. Therefore, it is not surprising that the most famous early model including elements of kidney function was established by Arthur Guyton and co-workers to investigate the regulation of blood pressure and cardiac output. The model, built on a combination of basic physical principles and empirical data, was instrumental in demonstrating the role of the kidney in the long-term control of blood pressure.

In theory, fundamental principles of physics could be used to model kidney function by starting at the atomic level and calculating the interactions of atoms in a process known as atomistic molecular dynamics simulation. In practice, while even a smartphone is powerful enough to solve the corresponding equations for the short-term interaction of a few atoms, not even all of the computers on our planet combined could calculate the entirety of molecular interactions in a

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The ultimate goal of computational kidney models is to someday enable personalized therapies for patients with kidney disease. Current models seek to elucidate fundamental mechanisms and signaling cascades, to investigate the impact of gain- or loss-of-function mutations, to provide an integrated understanding of multi-level systems, and to predict the impact of drugs and other therapeutic interventions. To these ends, modelers require large amounts of well-designed experimental and clinical data, and the increasing availability of RNA-Seq, proteomics and metabolomics data should accelerate their efforts. More importantly, modelers must work in close collaboration with experimentalists and clinicians, who play essential roles in identifying key gaps in knowledge, guiding the choice of hypotheses to be tested, and critically assessing model limitations – all of which are indispensable to broaden the relevance and impact of in silico explorations. Modelers have long sought multidisciplinary advice, but until recently few "on the other side" were convinced of the utility of renal computational physiopathology. This gap is dwindling, however, thanks in part to the omics revolution. Expanding awareness of the ability of models to explain how disease-related structural changes affect renal function, or to dissect the complex effects of drug therapies, to cite a few examples, has created more and more converts. Increasing recognition of the power of combining experimental and computational approaches can only bode well for the successful development of targeted treatments for kidney disease.

renal cell using this approach, let alone in an organ. Therefore, molecular dynamics simulations are used for small systems, for example to study the functional movement of membrane transporters.

As long as we lack the computer power to expand atomistic modeling to the organ level, we cannot produce a one-to-one virtual representation of the kidney. This means that, in the foreseeable future, there will not be one universal virtual kidney, but a number of them, each made for a specific set of research questions. This will be familiar to those using transgenic animals in their research: While it would be ideal to have a universal mouse model in which the expression of any gene can be controlled at will for any application, in reality, it is the research question that determines which mouse model is required.

The same goes for virtual kidney models. One family of models derives its principles and mathematical formulations from empirical data, to study, for example, tubular transport. Empirically derived kinetics of individual transporters can be linked to capture transporter interactions and net transport at the cellular level. Typically, the renal anatomy is not considered explicitly in a geometrically accurate manner, but rather simplified to functional compartments such as intracellular spaces, interstitium, or tubular and vascular lumina. This approach has been applied to study solute transport along nephrons, tubuloglomerular feedback, as well as oxygen transport and consumption. An attractive feature of these virtual systems is the possibility to modulate the activity of each transporter individually allowing for highly specific virtual knock-out experiments. For example, Layton, Vallon and Edwards developed a model of solute transport, accounting, among other factors, for glucose and sodium cotransport along a superficial nephron of a rat kidney to study the effects of diabetes and SGLT2 inhibition on sodium reabsorption and renal oxygen consumption.

Another family of models builds on fundamental laws of physics at the macroscopic level. A typical example are simulations of fluid dynamics, be it of renal blood flow or of the flow of primary urine through nephrons. When the rheology of the fluid, the geometry of its conduit and the driving forces are known, equations representing mass and momentum conservation can be used to calculate velocity and pressure at any given location in an artery or tubule. This is relevant, for example, for calculating the shear forces that mechanosensors of the proximal tubular epithelium are exposed to. When also the properties of solutes of interest are available, their distribution in the fluid can be predicted by additionally considering the advection-diffusion equation. One application is in the interpretation of tracer studies: Do the physical mechanisms taken into account in the model suffice to explain the experimentally observed tracer distribution, or is there a clear discrepancy, suggesting that other mechanisms, such as a yet unknown active transporter, must be at play?

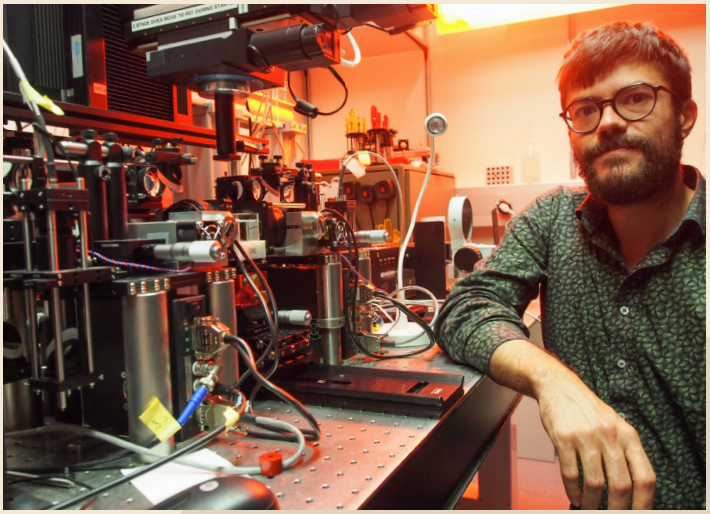
Members of the two families of models can also be merged to expand their scopes of application. For instance, to investigate the fate of oxygen in the kidney, the transport of oxygen with blood, its dissociation from hemoglobin, diffusion through tissue, as well as the chemical reactions involved in oxygen consumption must be considered. While blood flow and diffusion can be captured by physical models, the chemical steps are described empirically, including with the well-known oxygen–hemoglobin dissociation curve. We have used such a hybrid model to assess the plausibility of pre-glomerular arterial-to-venous oxygen shunting.

It should be evident now that the first question asked in the introduction needs to be rephrased: How far have we come in using in vivo and in silico models synergistically? Given the astounding progress in computer technology over the last decades, the expectations may be high. However, unless we are considering the ultimate virtual kidney built on atomistic modeling, the main bottleneck is not computer power, but the schism between experimental and computational kidney research. This answers the second question: Computational models will not replace experimental kidney research anytime soon, but those scientists who can design and integrate experimental studies and computational models will be best positioned to make groundbreaking contributions to renal research.

Vartan Kurtcuoglu is an Associate Professor of Computational and Experimental Physiology at the Institute of Physiology of the University of Zurich. His research focuses on the study of fluid flow and associated solute transport processes in the kidney, the brain and the cardiovascular system.

Diane de Zélicourt is a junior group leader within the Interface Group at the Institute of Physiology of the University of Zurich, with a long standing interest in computational physiology and fluid mechanics applied to cardiac and renal pathologies.

TRAINING MACHINES TO PHENOTYPE FROGS



Dr Thomas Naert is a post-doctoral researcher at the Lienkamp Lab in the University of Zurich's Institute of Anatomy. His work recently earned him a prestigious fellowship under the Marie Skłodowska-Curie Actions programme. Combining his interests in the technological and the natural, Dr. Naert's research investigates how CRISPR and machine-learning-based tools can be used to model congenital kidney diseases in Xenopus tropicalis.
We sat down with him to ask him about his work.

THANK YOU FOR TAKING THE TIME TO SPEAK WITH US! I KNOW YOU ARE WORKING WITH XENOPUS AT SOEREN LIENKAMP'S LAB IN ZURICH. WHAT LED YOU TO THIS GROUP?

I moved to Zurich in February 2020 (just in time for the start of the pandemic!), after finishing my PhD in developmental biology at Ghent University in Belgium. I did my Masters and PhD working with frogs, so I was really looking for another Xenopus lab, ideally one that was quite tech-driven. For me personally it's always been a bit more about the technology; that's why I previously worked with CRISPR/Cas9, back when it was new. Soeren Lienkamp's lab is very technologically driven.

WHAT IS THE CURRENT FOCUS OF YOUR RESEARCH?

Currently I'm working on applying machine learning to disease modelling in frogs, mostly with a focus on polycystic kidney disease. We start by using CRISPR/Cas9 to create tadpole models with polycystic kidneys. That part goes very quickly; it only takes 4-5 days for the cysts to appear. Then we put some dyes into the embryos, and use the MesoSPIM open-source light-sheet microscopes to get 3D scans of the kidneys.
The MesoSPIM was developed here in Zurich by the Helmchen Group at the HIFO in Zurich. It's like an MRI, but instead of using resonance, it uses lasers. It allows us to very quickly get 3D scans of an entire embryo. The problem is, the image files are huge – about 16GB per animal, so manual analysis would basically be impossible. That's where deep learning comes in.

SO YOU GET ALL THIS RAW IMAGE DATA, AND INSTEAD OF ANALYSING IT MANUALLY, YOU USE DEEP LEARNING TO FIND PATTERNS IN IT?

Exactly. The machine does most of the work now. We have set up a platform by training the algorithms with the end goal to create some kind of standardized platform where we can investigate different conditions, drug tests, etc. Before CRISPR/Cas9, it used to take years of work to make animal models, but now it's relatively simple. Making an animal model is not really an issue anymore, so now the question becomes: How do you get meaningful information from it? What we are doing now is training deep learning algorithms to automate that phenotyping process. This has the added benefit of eliminated researcher bias.

TRAINING SOFTWARE SOUNDS LIKE A COMPLICATED FEAT.

I'm a biologist by training. Until 1.5 years ago I had never written a single line of code. But the nice thing about deep learning is that, the more sophisticated the program gets, the less human intervention is needed. We still need to do some manual annotation here and there, but it doesn't require a computer science background. Up until a few years ago, you might have needed a computer science degree just to work with these neural networks, but now I think most people can learn it with very little effort. And that will become more and more important as datasets in science keep getting bigger and bigger.

WHAT MAKES FROGS AN IDEAL MODEL FOR THIS KIND OF WORK?

Personally, I really like how quickly you can do experiments. Xenopus spawns a large number of embryos, and in some cases, you can get kidney disease modelling results within weeks. And since amphibian animal models have external development, it's easy to look at early development with frogs. Early development has always interested me, that's one reason I used to work on childhood cancers.
And CRISPR/Cas9 has made everything even easier. If you tell me a gene to investigate, I can get it done in 2 weeks – with a mouse it could take up to a year. We think that's a really nice baseline. Clinical genomics has changed a lot in the last 10 years, but it's still not feasible to make mouse models for everything. Frogs and Zebrafish can be used as an intermediate model: You can look at certain genes and eventually narrow it down before moving to a higher model, like mice. We can do this very fast now, and the more automated this becomes, the more genes we can screen.

WHERE DO YOU SEE THIS TECHNOLOGY BEING USED IN THE FUTURE?

The deep learning platform we are currently setting up, and the work we are doing, is being distributed free of license. We want it to be used as widely as possible.

LASTLY, WHAT DO YOU LIKE TO DO WHEN YOU'RE NOT IN THE LAB?

I'm a post-doc, so I'm in the lab a lot! But when I'm not in the lab, I like to be outdoors; I really enjoy climbing and hiking. That must be one of the reasons I chose to come to Switzerland. You just have to drive an hour and a half from Zurich, and you're already in the mountains!

NCCR SAYS "HELLO, KIDNEY!" AT SCIENTIFICA 2021

Soeren Lienkamp explains to a young visitor how tadpoles contribute to kidney research.

The NCCR was pleased to participate in this year's Scientifica event, which was held at campuses across Zurich on September 4—5, under the theme "Synthetic, Naturally". Over 25'000 visitors attended the event. The NCCR hosted an interactive information booth where the public could get up close and personal with the kidney – both in its digital and natural forms.
Visitors were given a chance to experience a "virtual kidney", a 3D model of the kidney's major blood vessels as shown through virtual reality goggles. A dish of live Xenopus tadpoles, viewed under a microscope, was particularly popular among the youngest attendees. Visitors could also take a peek at their own kidneys in real time using ultrasound, which was offered on location. The information booth was complemented by a short talk from Soeren Lienkamp on the various roles kidneys play in our bodies. The talk was followed by a lively Q&A session.

The Lichthof at University of Zurich, Irchel, was abuzz with visitors throughout the weekend.

Many thanks to Soeren Lienkamp, Vartan Kurtcuoglu, Andrew Hall, and their excellent teams for volunteering their time and expertise!

ZURICH KIDNEY CENTRE TO LAUNCH AT UNIVERSITY OF ZURICH

ZKC
Zurich Kidney Center

The provisional logo of the upcoming Center of Competence

A new centre of competence in kidney research is set to open in 2022. The Zurich Kidney Centre (ZKC), based out of the University of Zurich, will maintain and build upon the network and collaborations established under the NCCR Kidney.CH, which will complete its 12-year run at the end of 2022. The new centre will provide a platform for continued and new co-operations between basic and clinical scientists to foster new innovations in kidney research. Members and associates will be invited to participate in symposia and will have access to continuing education programmes. The ZKC will also publish regular newsletters highlighting the research of its members, along with other communication and public outreach activities.
The Zurich Kidney Center is slated to officially launch on August 01, 2022, in a joint 2-day event alongside the closing of the NCCR Kidney.CH. The event will include a series of public lectures at Zurich's Volkshochschule, as well as a symposium and a closing celebration.

#NCCRWOMEN CAMPAIGN CELEBRATES WOMEN IN RESEARCH

To celebrate the 50th anniversary of women obtaining the right to vote in Switzerland, the 22 active NCCRs have joined forces in an online video campaign, with the aim of showing how women occupy a central place in research in almost all scientific fields.
From Women's Day on March 8th, to the 50th anniversary of the women's first vote in Switzerland October 31st, female researchers from across the country are showing viewers who they are, what they do and why they are doing it. The video series is targeted at women and girls of school and undergraduate age, and show what day-to-day life as a scientist is like. Each NCCR has the task of hosting for one week, during which they publish a series of videos featuring researchers from different scientific disciplines.
The NCCR Kidney.CH was proud to host during the first week of April 2021. We spoke to esteemed NCCR scientists Murielle Bochud, Ruxandra Bachmann-Gagescu, Sophie de Seigneux, and Uyen Huynh-Do.
Follow this exciting campaign under #NCCRWomen on Twitter, YouTube, and Instagram.

#NCCRWomen
Women in Swiss Research

EVENTS

"BENCH 2 BIZ" WORKSHOP
15—29 November, 2021
Virtual

53RD ANNUAL MEETING OF THE SWISS SOCIETY OF NEPHROLOGY
09—10 December, 2021
Congress Centre Kursaal
Interlaken, Switzerland

11TH KIDNEY.CH RETREAT 2022
27–28 January, 2022
Centre Löwenberg
Murten, Switzerland

LS2 ANNUAL MEETING 2022
17—18 February, 2022
(Satellite 16 February 2022)
University of Geneva,
Switzerland

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