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Episode 99: Click on the Kidneys: Virtual organs in your medical future

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VOICEOVER
Welcome to Up Close, the research, opinion and analysis podcast from the University of Melbourne, Australia.

SHANE HUNTINGTON
I?m Shane Huntington. Thanks for joining us. The virtual physiological human project, involving research groups from around the world is set to revolutionise healthcare by building a virtual human. Tomorrow?s researchers and clinicians will be able to use virtual models of different body parts to predict how an individual will respond to particular treatment or disease. It is an endeavour that combines the most advanced physiological and biomedical knowledge with sophisticated mathematical modelling and computer simulation.
At the forefront of this powerful vision is Professor Peter Harris from the Department of Physiology at the University of Melbourne, Australia. Professor Harris is responsible for developing the virtual human?s kidneys. He is part of a team of around 80 physiologists, computer scientists, software engineers, mathematicians and visualisation experts from Australia, France, Denmark and the United States. Professor Harris joins us on Up Close today to tell us more about the thrilling possibilities offered by the creation of a virtual human. Welcome to Up Close, Peter.

PETER HARRIS
Thank you very much, Shane.

SHANE HUNTINGTON
Now, why don?t we start with just talking a bit about the motivation for developing a computer model of parts of the human body. Why do we want to do this?

PETER HARRIS
Well, there are a number of reasons for it. This is an idea, which has been going back for many years; in fact, since just after the Second World War when

engineering solutions were being applied to the human body. And the fact is that you can?t do experiments on human beings that you can do in a computer model, so that?s a really very good reason.
The other is that it?s common to do animal experiments as part of the process for developing new treatments. Again, the number of experiments that you would need to do to test the efficiency or efficacy or safety of a drug are absolutely enormous. Computer models can help you to reduce that.

SHANE HUNTINGTON
Peter, in other areas of biology, I guess, simpler systems are used to replicate parts of the human body and condition, such as, as you mentioned, the mouse model. Is that how you start with this sort of computer modelling?

PETER HARRIS
Yes, you start with a basic understanding of physics and chemistry and you put together a model, by which I mean a set of equations, which describe the behaviour of an individual cell or a rather simple system. How do molecules get from one side of a membrane to the other, for example. Then you work out and say, well, that?s supposing that the cell has a membrane all round it. How do things get in and out of a cell? How do they then get between cells and then how is that controlled in the body?
It begins with that abstract process and then it validates that against the results from animal experiments and then validates against, well, what happens in a human being?

SHANE HUNTINGTON
Peter, I understand that for this particular work, you have a specific programming language that you use. Some of our listeners will be aware of HTML, C++, perhaps Fortran, but you use something called Systems Biology Markup Language. Can you describe how that?s different and why you need it?

PETER HARRIS
Well, Systems Biology Markup Language or Cell Markup Language are rather high level descriptors of the process. Underneath that, there could well be routines and sub-routines written in a whole variety of languages. In fact, many of the original equations describing what happens in the body are still written in Fortran because it took 30 years to write them and they can contain hundreds of nested differential equations.
And it was an interesting discussion, whether in a worldwide integrated approach to this, should we re-write all those earlier programs in whatever is today?s favourite language? Or should we try to avoid that problem and try to develop a super-structure, if you like, of systems markup languages, which could then call those sub-routines and put them in. That?s the approach that?s been taken with a standardisation protocol, which is a very, very important part of the project.

SHANE HUNTINGTON
Tell us a bit about that. What?s the purpose of the standardisation protocol?

PETER HARRIS
It?s to enable people around the world to get access to other peoples? models. We are assuming it?s a very hard ask to re-write those models, but I would still like to run them, either on my computer and my desktop, or in an institutional computer, or in fact in a supercomputer network around the world. I can call those through an interface, which can in fact be a web interface, which may use HTML and I can have access to the inputs and outputs of that model without having to own the model in my own laboratory.

SHANE HUNTINGTON
With regards to the modelling that?s been done so far, are there examples of biological functions that have already been accurately modelled?

PETER HARRIS
I like the word accurate there. I think that?s very interesting because on the other side of that coin is the word complete. We can be as accurate as possible; that is, we can validate a model against experimental findings, against the data from human treatment of patients or against the physical models. They?re only accurate as far as we understand it, and what we do know is that there are many, many parts of the body that we actually don?t even know the existence of yet because we don?t know what all the genetic code is actually producing.
But as far as we can determine a process or a chemical exists in the body, we can describe its functions. Then we can be as accurate as possible, but we shouldn?t be carried away by the idea that we can make an accurate representation of what goes on in the body. We only know a very small part.

SHANE HUNTINGTON
When people go to use these models around the world, how will they do that? What sort of information will these models be presenting to them?

PETER HARRIS
Well, that?s been a very much part of the Australian and the University of Melbourne approach is that we have been responsible for building a three dimensional visual interface to a kidney, where we have taken micro CT scans and also synchrotron scans of various parts of the kidney and put that together to make a - it?s a bit like a computer game, if you like. You can see a kidney on the screen. You can zoom in, you can rotate it, you can go and point to structures and then link from that using what is effectively a very high powered hypertext link to the world?s databases on structure, function evidence-based medicine.
In that way, you can then interact with that model using a visual interface, which doesn?t require you know necessarily exactly what name the part has, which is called semantic ambiguity. And the reason we do that is because not all things are called the same in different countries and not all things are called the same things in the same country by different laboratories. We can remove that semantic ambiguity by simply pointing to the object.

SHANE HUNTINGTON

Presumably once you have access to that facility, you would be able to put in an individual patient?s specific parameters to work out what treatment would be appropriate? Is that the goal?

PETER HARRIS
Absolutely. The intention in the virtual physiological human is to produce an integrated computer model in which various systems will work together in their models. It?s what is sometimes called a model of models. You can then use that to look at the generic response, or what is called the personalised, or more recently, the precision medicine approach.
A particular patient might have a particular genetic mutation, which you can then program into the model and see what effect that would have. Would, in fact, a drug or a treatment or a management plan be prescribed differently for a patient with a particular mutation, compared with the next patient, who might respond differently to the same treatment regime?

SHANE HUNTINGTON
You?re listening from Up Close, coming to you from the University of Melbourne, Australia. Our guest today is Peter Harris and we?re speaking about the virtual kidney. Peter, let?s talk more specifically about your team?s work here in Australia on the virtual kidney. Let me ask you, first, why the choice of the kidney with all the possibilities in the body?

PETER HARRIS
That?s a very good question. I think there?s a personal answer to that, which is that the kidney chose me, in that I was sitting outside a professor?s door in Southampton quite some years ago, looking for a PhD scholarship. The door on the left opened and said, ?What are you doing here??
I said, ?I?m being interviewed for a PhD scholarship with the other professor.?
He said, ?Yes, but he?s not there yet. I?ve got a grant for you; come in here.?
He said, ?I?d like you to work on the kidney. I?m not rushing you, but you?ve got 10 minutes; make up your mind.?
I ended up working on the kidney, so I guess I?m one of those people whose interests in the complexity of the problem and coming up with a solution rather than having a burning desire to investigate kidneys, rather than lungs or the heart.

SHANE HUNTINGTON
With regards to the kidney, can you just give us a brief sort of overview of what its function is in the body and how that function gets disrupted?

PETER HARRIS
Well, the kidney is, simply put, one of the regulators of the body. It basically filters the blood and returns approximately 99 per cent of it back into the body and takes out one per cent, which mainly contains the things you don?t need. The clever part about the kidney is that it doesn?t throw away the 99 per cent of the things you do need in the filtering process.
Therefore, very small changes in the function of the kidney can have either short

term or, more likely, long term cumulative effects on the body. For example, if the amount of salt that?s being filtered by the kidney - even if a very, very small fraction of that is then returned to the blood stream in excess of what is required, then over a period of years, the blood pressure may change.
The kidney also secretes hormones and it has regulatory functions. But the kidney is a fascinating organs because it is, in computer terms, a massively parallel organ structure. It has a million sub-units, which on the face of it, all seem to be the same and they all operate in parallel. One of the questions is how do they do that? How can one million sub-units function together and yet give you a stable output?
The programming we use and the computer analysis and the particular breakthrough, I think, we?ve made in Melbourne through the Department of Computer Science and Software Engineering is to use a complex systems approach, which doesn?t say that we have to know all the individual components, as I said before. It says the kidney can be treated as a black box, initially. Things go in, things come out.
Let?s have a change in the way those are treated and let?s not for the moment imagine that it consists of a million sub-units. Let?s suppose that it is only one homogenous unit. Then we say, let?s put in these one million components. How do they work together? In a complex system - and it?s analogous in some ways to the way in which airline traffic scheduling is done or container ship container scheduling - you have systems which demonstrate emergent behaviours. That is, behaviours you don?t expect from the behaviour of a single unit. They show things like stability and they show interaction between each of the individual units.

SHANE HUNTINGTON
What sort of information do you begin with? Its outputs or do you test how it deals with particular problems and try and work out where the black box ends?

PETER HARRIS
Very good question and in fact you can start from either end of that question. You can say, first of all, we need to know as much as we can about each individual protein, about each individual chemical reaction. We put those together in a series of thermodynamic equations. That?s how kidneys were always modelled in the past. We can work out from the individual components and put them together and gradually build a more and more complicated system.
On the other hand, we could start with the black box complex systems approach and simply say that there are nodes inside here and those nodes join together in things called edges. We could write equations to describe that and then we can give those a physical reality and we work downwards.

SHANE HUNTINGTON
One of the obvious questions with the black box approach is if you have a kidney that in some ways is malfunctioning or you are testing a particular drug and that occurs within the black box structure, how does the model deal with that scenario?

PETER HARRIS
Well, it would be analogous to a clinical consultation, with somebody who didn?t

actually know how the kidney works. You would say clearly this person is producing no urine, therefore their kidney has failed, more than likely. We don?t know why the kidney failed, but we are already able to say that there is a problem that?s occurred in here.
In fact, it?s impossible to do most of the experiments at an individual sub-unit or nephron level inside the kidney. We can already say, well, what can we infer from what is known from animal experimentation or physical or biological experiments? Really, that is the way that these tests are done.

SHANE HUNTINGTON
What sort of computing power are we talking about to run something like a virtual kidney?

PETER HARRIS
Well, you run it very slowly on a desktop machine. The problem is about speed and complexity, so when you begin, you can run something in, say, a few minutes. We?ve run up to 20 or 30 sub-units together in a pretty powerful desktop machine and it will give you a machine in only really a matter of minutes. Of course, if you put a million of those together and add all the interactions, it would take many years to run one simulation. Then you need a supercomputer to be able to run it and you have to re-write the code in way that each processor within the supercomputer is responsible for a particular part of a job.
That?s one way you can do it; the other way is to use grid computing, where the job itself, and as complex as I?ve described it, it divided into parts. Each part is sent off around the world to a computer, which is not doing anything. It does the job, sends you back the answer and the computer on your desktop puts them together and gives you an output, which is meaningful in terms of the result.

SHANE HUNTINGTON
In terms of the data and the input of data into the model to grow, in a sense, into a more accurate representation of the kidney, is that data coming from all over the world, from all the different experiments that are going on? Is that the idea that everyone would be able to feed into the virtual kidney so that in five or 10 years time, it?s that much more accurate as a result?

PETER HARRIS
That?s exactly the way it?s done. The way we started that is with our French colleagues, with Randall Thomas in the University of Evry in Paris. He really is an instigator of the project and he?s developed a database for parameters. If you build a model, you have to know what is the range of parameters, so, concentrations, lengths, diameters, protein contents. So we developed what we call the quantitative kidney database, which runs from a server in Paris. That?s accessible to anybody around the world who wants to look at what does the literature say about these things?
We also undertook a project to get oral history from people who collected those data because many of those experiments were done under conditions that we really need to know quite a bit about in order to know how reliable and what sort of ranges of

variation was within those data. We?ve gone back to those studies. Anybody can then contribute to that; as they do more experiments can then add to it. Those data are then available to laboratories around the world for people who want to develop another model or to extend a model.
So this doesn?t assume that you know what the model is; it says here are all the data, here are the existing models. This is a library of models collected from the last 30 or 40 years work, puts those together and says, no, this is a toolkit available to anybody around the world who wants to extend it.

SHANE HUNTINGTON
You?re listening to Up Close, coming to you from the University of Melbourne, Australia. I?m your host, Dr Shane Huntington and today I?m speaking with Professor Peter Harris about the virtual kidney.
Peter, the virtual kidney is part of a much broader project, as we suggested in the introduction, of the entire human body. Tell us a bit about this initiative; this seems like an amazingly complex scenario to get right.

PETER HARRIS
Yes, it is complex and if you thought about it very, very carefully, you might consider it will take so long to do this and it?s so complex that perhaps this is a daunting proposition for anybody beginning a career in this area. It really began as an international initiative called the physiome, so after we?ve had the genome and the proteome and the metabalome, which is how different reactions works together in the body, the next question is, okay, what are all those things doing if you integrate them together?
This is the business of physiology; it says how does the body function? So the physiome project was born. Three hundred and twenty of us were invited to Brussels to develop a roadmap for this particular project and that took 12 months. There are now around 2000 people involved in the project. The vision is to produce an international resource that anybody can use, which will then contain personalised models for precision medicine and also it can grow as other people see the advantage of it.

SHANE HUNTINGTON
What are some of the other organs that are being simulated? Is it all of the organs in the body or are particular ones being chosen?

PETER HARRIS
Well, most of them are being done at the moment. The heard is probably the best developed. That was really started by the team in Oxford with Dennis Noble, probably about 40 years ago. The New Zealand group with Peter Hunter and there?s a Japanese group now, have been producing really absolutely spectacular images, results and combinations of physiology, anatomy, biology, electro-neurophysiology. The heart is probably the best developed example so far, but the lungs are also being done, skin, the musculo-skeletal system. If a country has a particular expertise or a group who is particularly involved, they put their hands up to work on that.

SHANE HUNTINGTON
Is the brain being looked at as well? I mean, the complexity is obviously quite extraordinary, but also its interaction with all of these organs is incredibly important.

PETER HARRIS
Yes, there are a number of brain projects; the Swiss in Lausanne are working on a major project. IBM, of course, are very interested as a company initiative in building the sorts of computers that could be used for brain problems. Many groups are contributing to it, and it leads you into questions about neural network analysis and brain function and that leads you back into how can you design a computer that will simulate some of the functions of the human brain because that in turn helps you design better computers.

SHANE HUNTINGTON
We talked earlier about the black box modelling and so forth of the virtual kidney. I?m curious as to just how deep some of the modelling in the virtual human as a whole will go. Does it dive down to the cellular function level and will that then link into some of the genetic information that we?re starting to get through our research?

PETER HARRIS
Yes, it does and it many ways, the modelling started at that level; individual proteins being modelled. Each of those connects to the national databases in the genetic information, so as more genes are being sequenced, that information is then available to the modellers and you can get more information. Then you have to do the kinetics of the model and the reactions that each of these molecules can undertake, so there?s another series of databases.
Our aim is to be able to connect to all those databases through web links and through what is now called e-research, which is an integrative approach to the data, which can be shared between different laboratories in the world.

SHANE HUNTINGTON
Peter, just finally, with regards to the overall project, when it?s complete, what sort of impacts will we see occurring? What will we be able to do?

PETER HARRIS
I think we will be able to provide this personalised or precision medicine to many more patients. We will be able to benefit from what is being learned around the world. Much of the information being produced is not available in an integrated fashion and I think we can produce more effective responses to health situations than we do at the moment.
We can probably reduce the number of animals required to produce that. We could look at candidate drugs and the environments in which those drugs are used, meaning the lifestyle and the biology of a particular patient and achieve those things more precisely and effectively than we can at the moment.

SHANE HUNTINGTON
Professor Peter Harris from the Department of Physiology here at the University of

Melbourne, Australia, thank you very much for being our guest today and we wish you the very best of luck with the virtual kidney project.

PETER HARRIS
Thank you very much, Shane, it was a pleasure to be here.

SHANE HUNTINGTON
Relevant links, a full transcript and more info on this episode can be found on our website at upclose.unimelb.edu.au. Up Close is brought to you by marketing and communications of the University of Melbourne, Australia. Our producers for this episode were Kelvin Param and Eric van Bemmel. Audio engineering by Gavin Nebauer. Up Close is created Eric van Bemmel and Kelvin Param. I?m your host today, Dr Shane Huntington. Until next time, goodbye.

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