Professor Denis Noble

Interviewed by

Jane Bird

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Via Zoom

Welcome to the Archives of Information Technology where we capture the past in order to inspire the future. It's Tuesday the 21st of September 2021 and we're talking on Zoom, as has become customary during the Coronavirus pandemic. I'm Jane Bird and I've been writing, er, reporting on the IT industry, for newspapers such as the Sunday Times, and the Financial Times since the early 1980s.

Our contributor today is Denis Noble, Professor emeritus and co-director of Computational Physiology at the University of Oxford. As a pioneering researcher in systems biology, in 1960, Denis developed the first computer model of the working human heart. The use of software to simulate biological organs has expanded hugely since then and Denis's books on systems biology have introduced the subject to a wider audience and extended its scope to evolutionary biology.

Denis, welcome, I'm very much looking forward to hearing more about how you came to be working in the modelling of biological organs, your original aims, how your computer technology helped you achieve them, and how your work has changed lives.

[00:01:15]
Okay, very good to talk to you, Jane, where would you like me to begin? [laughs]

[00:01:19]
Well, if we could start perhaps, erm, about, what, where, what you got into biology in the first place, was it love at first sight at school, did you have an inspirational teacher? Perhaps a mentor when you were at University College London because I think Otto Hutter was your doctoral supervisor then. Um, so, perhaps you could, could give us a bit of, erm, thoughts about that.

[00:01:40]
All of those. Stanley Inwood, who was my school teacher, um, of biology teaching me through the textbook, very popular at that time, called Animal Biology by Grove and Newell, absolutely fascinated me. He was a lovely man, with a lovely Bristol accent, very proud of the fact he'd been at Bristol University with all its Nobel Prize Winners in Physics and so on. He, he got me interested and intrigued. He also taught

me about evolution, but I have to say that most of what I learned from the book, Grove and Newell's Animal Biology is actually incorrect, but there we are. That's one of those things you discover much later in life. At University College London, erm, as an undergraduate, the great inspiration was J Z Young, the great Anatomist and evolutionary thinker, a brilliant man.

Then I was allocated as a research student after graduating to another extraordinary man, Otto Hutter. He had come across in the 1930s, the late 1930s from Vienna to escape the holocaust problem and was one of the last to come across on a Kindertransport, erm, he…he was an inspiration too. So, I've been extremely lucky with one teacher and tutor after another who have been a…absolutely superb in leading me through my career.

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Yes, er, so, how did you get involved in computer simulations for, for studying living organs?

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Well, strictly speaking, I shouldn't have. I had no qualifications to do it. I had to give up mathematics at the… roughly the age of, let me see, 16 at… Schools in those days, in London, that did not include learning calculus, so, I knew nothing about how you solve differential equations and so on. But, up to that point, I was actually one of the top people in the mathematics class, so, I obviously had some kind of natural talent for it. So, when I was faced in my work with Otto Hutter, with the discovery of several ion channels, those are proteins in cell membranes that control the flow of electric current in the cell, we made some important experimental discoveries.

I was strongly motivated to try to see whether I could do exactly what Hodgkin and Huxley had done, just 8 years previously on nerve excitation. They developed the first mathematical model of a physiological process. But I, I went to, first of all, see whether there was a way of doing it by hand, there was in the laboratory, there was a Brunsviga hand calculator. Most people will not know what that is, but it's a great big machine you turn around with your hand like this, and you can do multiplications and divisions and so. It crunches away, oh, my goodness, I calculated it would take

me 6 months to do a single calculation and that sort of went down the drain as it were because clearly, there wasn't that amount of time.

So, I learned that the University College London had access to the only big mainframe computer in the whole of London, it was situated in London University. It was called a Ferranti Mercury, it was made of light bulbs, well, I use the phrase "light bulbs" because nobody nowadays seems to know what a valve was. A valve was a bit like a light bulb, but it actually was a switching device rather than an actual light. It did light up because there was a glow from it. This machine was extremely valuable, extremely expensive but very slow. Nevertheless, it was capable of doing, in 2 hours, what I calculated would take me 6 months to do by hand.

So, I asked the IT people, the computer engineers could I use the machine? They tested me out, you… Er, Mr Noble, do you know how to programme? I had no idea. I came with a set of little equations you see for each of the ion channels, I thought, if I give these equations to the computer people, surely they know how to make the computer give me an answer. So, the next step was for 5 shillings to buy the computer programming method for the Ferranti Mercury computer, mostly, of course, machine code with a little bit of organisation. So, I don't know, I was more or less self-taught. They didn't think initially that I could possibly do it, and they gave me the worst time slot possible between 2 and 4 am.

[00:07:12]
Oh, goodness.

[00:07:14]
Now, actually, that was, I think because they had no confidence that I would do anything worthwhile, they were allocating the best time to the X-ray crystallographers, to the particle physicists, and all of these people who knew their mathematics backwards and knew how to programme computers. So, I was given what they regarded as the worst slot, but actually, it was the best slot because I was doing experiments during the day, so, I do the computing at night. When did I sleep? Well, for about 3 days, I probably didn't.

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[laughs]

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Anyway, despite all of those blocks on the way, somehow I forced myself to learn the Mercury Autocode, which is what the programme language was and started to get some rubbish. Well, that's what happens when you first programme a computer, of course, you make all kinds of silly errors, there are bugs in the programme. So, I got introduced to the next stage, you have to debug your programme [laughs] so, I spent the first few weeks just debugging the programmes and eventually getting some slightly nonsense figure out, some real numbers at last. But they showed something fascinating, after each electrical pulse of this model heart which I was building, there was the hint that it would take off again. It was trying to do another pulse and I thought, well, this means that if I fine-tune the equations within the limits of the experimental technique that gave us the results, maybe it would take off again and I would have a model of cardiac rhythm, and that is exactly what happened. So, 6 months from getting access to the computer, I had a paper in Nature showing that it worked. So, that is how I did it.

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Wow, how exciting that must have been.

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Well, well, I'll tell you for a young research student looking for a thesis, it was… it was unbelievable, you know. I don't know what bigger problem you could have had in those days than reproducing heart rhythm, to produce a model of heart rhythm. Er, nobody knew how the rhythm of the heart was generated, erm, there were some early mathematical attempts to represent oscillators of one kind or another, but in effect, they would incorporate an oscillator in the equations themselves and then modifying that a bit to look like the heart. I see that as a fudge rather than a real reconstruction from the molecular processes themselves. So, I was indeed excited.[00:10:00]

I went back to my supervisor, er, the day I got the first pacemaker rhythms out and said, "Well, Otto, it works, I've got it." He said, "Come on, you can't have done,

erm, are you really sure?" [laughs] He said, "You better be sure because if you're right, you've got your thesis, you better write it up, but you will be examined by Alan Hodgkin" Now, Alan Hodgkin was like a god in the field of electric excitation of nerve, he was one of the kings, there is no question about it. So, I was faced with this dilemma. Yes, Otto told me, "You're going to get your thesis, but you're still going to be examined by the toughest person to examine you." [laughs] I think—O…Otto was… was a terrific er, inspiration for me but he was also somebody who liked giving students a challenge, you see.

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Yes.

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However, when I appeared in the examination room, er, Otto was present, as he had the right to be, in those days, a supervisor could be present at the examination. Erm, Alan Hodgkin was very kind, but he said to me at the very beginning, "Denis, you've got one major error in the first sentence of your thesis." I thought, oh, my God, what has he done now, you see, what have I done? He said, "You've got an unreferred "it". Now, I was from an uneducated household, a working-class household, I had no idea what an unreferred it conceivably was. Well, yes, but there it was, I had said, "It would be interesting to know whether Descartes was he wrote this bom, bom, bom, bom, bom" and of course, it was unreferred, because what did the "it" refer to? Anyway, I know what an unreferred it was but then I knew, well, if that's the only major error he's found [laughs] he must be prepared to pass me; and he did. I don't know, it's like a dream. When I think back on it, nowadays, 60-odd years later, I still find it astonishing that I managed to do what I did.

Now, as you said in your introduction, er, Jane, erm, the field has now utterly exploded, I mean, the… the, what is called the Physiome Project, which is the project to model all the cells and organs of the body, erm, that is now a major international project. So, I feel I can say that something developed out of what I did in those early days, but there are other things that came out of it. Er, that early model was very simple, the later models are much more complex. That introduced me to why does nature bother to be so complex? After all, I could do it with just 4 channel

mechanisms in 1960, but if I had knocked out any one of those, the heart would stop beating. Your and my heart does not stop when we block major channels that take part in the rhythm. That is a major discovery incidentally that has led to a drug, Ivabradine, which was developed by the French company, Servier, was based on producing a gentle, slower of cardiac rhythm for people who suffer from too high a rhythm particularly during exercise, and it is now used worldwide. But what that taught me is what led me into evolutionary biology, which is this, nature is beautifully robust. A major function like the rhythm of the heart doesn't rely on just one or two, or three or four genes or their proteins, it relies on hundreds.

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Mmm.

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That is an important insight, that is what got me, many years later [coughs] into evolutionary biology, which might seem like an extraordinary jump to make but there is a logic to it. It is the discovery that important functions in our bodies are beautifully backed up. It's like having both belts and braces to make sure your trousers don't fall down; one fails, the other works.

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Yes. There is lots of redundancy, isn't there in the human body?

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There is lots of redundancy of biology and the mathematics have shown just how strong that redundancy is. Without the mathematics, I don't think we would have understood that as clearly as we do. That, that, that protein that the Servier company targeted to develop Ivabradine, is a very good example. I think it normally contributes about 80% of what we call the depolarizing current, the current that generates the rhythm, but when you knock it out, the change in frequency is only 10% or 15%, it is very gentle.

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Yes.

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So, that shows exactly how robust the system can be.

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So, all these discoveries and developments from your starting place must have been hugely enabled by the dev…development of computers, bearing in mind we are talking about er, about the technology here to… to some extent. Er, but now there is more power in the PC or in your mobile than probably there was in that original Ferranti machine. Has that made a big difference?

[00:16:24]
Oh, enormous difference, Jane because you see, in 1960, it took 2 hours to reproduce 2 seconds of heart rhythm, that meant just 2 beats. Erm, now, you can put the same equations on my PC, and it will do the calculation before you blinked your eye, it is milliseconds, it may even be microseconds, I don't even remember now. Things have become so fast, but I've lost count of the number of Moore's laws I've been through.

[00:17:02]
Yes.

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Moore's laws, of course, are the doubling of computation speed every, what is it? 1 and a half years, so, I must have been through at least 40 Moore's laws. Well, 2 to the 40 has an enormous number [laughs]. Now, what has that enabled us to do? It has enabled us to tackle very much greater complexity in nature. As I said earlier on, that is necessary to understand why organisms are so robust, erm, only rarely go wrong because of genetic problems. There are rare genetic diseases, of course, so, they do sometimes go wrong, cystic fibrosis is a good example. But by and large, we don't depend terribly much on our genes. I know that is a funny thing to say, we need them to make the proteins we use, certainly, but we can do that with almost any set of genes we wish [laughs].

[00:18:02]
Goodness, okay.

[00:18:04]
Goodness, yes, very important, but you know, I'm not alone in saying this, Jane. The most recent hypothesis from the Genome-Wide Association studies is called the omnigenic hypothesis, which means all genes are involved in every function. I'm not the only one saying this by any means.

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So, are… Okay, so, l…let's look at practical applications a bit, erm, and… and what difference the tech… these discoveries have made. I mean, you've touched on… on new drugs and pharmaceutical uh, companies, you know, developing heart drugs and so on.

[00:18:41]
Yes.

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Um, so, and…and I think alternative therapies as well because you can do this complexity, you can look at things like the effects of nutrition and… and herbal remedies and that kind of thing as well, so, that is quite an important area by the sound of it.

[00:18:57]
Absolutely so. In fact, the latest modelling work I've done has been in skeletal muscle rather than heart muscle and it was to work out the mechanism of a multi-component medication for the relief of cramp.

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Yes.

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Now, you might be puzzled by that because there is no such medication in the West. So, where did it come from? No pharmaceutical company has made a chemical that will relieve skeletal muscle cramps; sportspeople would love something like that.

Where did it come from? It was Shakuyaku-kanzo-to, which is Japanese for a… an ancient Chinese remedy which has shown in the Shanghan Lun of about AD 200 to relieve muscle cramp, and it does.

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So, this is a revolutionary discovery for Western medicine, isn't it? that they're… that they're… because Chinese medicine is…

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Look, again, there is an evolutionary perspective on this, Jane. The fact is that plants have had hundreds of millions of years to get used to us because they rely on us. They don't walk, they rely on us and other animals to disperse their seeds, to eat them, deliberately eat them, and plants love us eating them. We then distribute the products around in the various secretions and excretions of our body. The fact is plants like us and like insects in particular, of course. Now, how do they manage to do that? They have very many ways of attracting animals. They've worked out the chemicals that are worthwhile putting together.

So, herbal remedies have done, through hundreds of millions of years, the trial-and-error type experiments to work out what will give this animal joy, excitement, relieve its…its diseases, and so on. It is easy to understand. What we should be doing therefore is more of the kind of work that I've just succeeded in doing. We should be working out how do those herbal remedies actually do what they do when they do? Of course, there is some doubt about whether all this will really work in the way that people say, but that is also a question, and you can only answer that by respecting the complexity of multicomponent treatment, which is what a herbal remedy is.

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That… those... so, those sorts of things can now be explored, what? using a desktop computer or would you still need a super-computer?

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No, that… those experiments modelling experiments were done on a desktop, a…a standard, erm but reasonably powerful processor Mac computer can do it. And we were able to reproduce about an hour or so of muscle activity, skeletal muscle activity in probably, about, erm, 20 minutes of computation on a desktop. Obviously, that would go even faster if you went to one of the big mainframes, but why bother with mainframes anymore?

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Right, yes.

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You can bang together a number of desktops, you could go to the cloud, you could do cloud computing.

[00:22:27]
Yes, er, absolutely, yes. So, so, looking into your crystal ball, how do you see the next sort of erm, decade or two, are we going to have an entirely virtual human created in this way?

[00:22:41]
Ahh, oh, that's a lovely question, Jane, erm, I'm going to be very blunt, no. Now, that may puzzle people because surely it must be the case that if computing power continues to increase in the way that it is and resources increase then not only will AI beat us at chess, and various other contexts, processes of algorithms of one kind or another. They will surely end up even replacing us, there will be the virtual human, not just as a computational model, but it would actually be acting like us.

Well, I wrote a story about this, which I'm going to publish in a book that I'm working with a co-author, and I call it a love story because I imagine, that somebody has actually done that. They have created an AI brain that can be put into a human-like body and this woman that has been created, I call her, Julie because she calls herself Julie and she has got this extraordinarily micro-level brain, which is connected

to her body and… and so, erm, she goes out into the world and finds a… a nice boyfriend to have a love affair with.

Now, how could she possibly do that? What the AI inventor has done is to put a random number generator into the brain so, she always behaves in a different way. She has got, if you like, a kind of creativity but there is something missing and after 6 months her boyfriend notices it. He says, "But Jane, where are you really going, what do you want to do in life?" She has no idea what he means. Now, why is that? I think there is a very simple answer, that big computer I used in 1960 and your desktop today, or even the most powerful computer in the world is made of fixed components. The microchip material, whether it is semi-conductor or metal, is a fixed solid structure. Cells in the body are not like that, there is stochasticity occurring the whole time and we use that stochasticity, we use it to be creative.

That is again, work that has come out from what I have been doing recently. That was published, incidentally, in the Royal United Services Institute Journal because the military and the surveillance people are fascinated by the question where is AI going, will we eventually have, well, what shall we call them, virtual soldiers? You don't even need to send human bodies to be killed in war, you send an AI agent out there and let them do it. Well, what I'm saying is that you might indeed succeed in producing things that can kill and do a lot of what a soldier can do. But what it won't have is that ability to access creatively the way in which water-based systems make that possible through the fact that we can harness stochasticity.

Incidentally, we are doing that during the pandemic. If you ask the question, how do we react to the Coronavirus, when we do react and produce antibodies, whether just naturally or through having a jab that gives us a vaccination? It is because we are using chance events down at the bottom level, there is a way in which the organism uses all of that to generate new sections of DNA. That is hearsay, because in principle, according to the central dogma of molecular biology, you should not be able to do it; organisms are doing it all the time.

There is another aspect of evolutionary biology incidentally, that I… modern evolutionary biology that I tend to disagree with, organisms can use their genomes

and they can even make new ones, they do that all the time with the immune system. Bacteria do it to avoid antibiotics killing them, it is a feature of life. Now, I don't know what to say here because nature took a billion years to work all of that out.

[00:27:45]
Mmm.

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Are our AI people going to work out how to do that with metallic and semiconductor materials? I don't see how it can be done. I can't say it never can be done, who knows. But nobody is going to walk in with er, a.. a Denis Noble who can give this talk to you in the next 10 years, 100 years, maybe even, 200 years [laughs].

[00:28:14]
Yes, well, I must say, on that mind-boggling thought, I think perhaps we… we need to leave it now as we've been speaking for more than half an hour, but it has been absolutely fascinating, Denis.

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Well, that's my story, for what it's worth, Jane, and we've gone all the way from 1960 to now, 2021 because that is when the latest work was published.

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Well, thank you very much indeed, it has been absolutely fascinating.

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My pleasure, Jane, thank you very much too, bye-bye then.