One of the most common ways for heart disease to manifest itself in humans is called arrhythmia—an abnormal heartbeat. For instance, the heart may beat too rapidly (tachycardia), or it may flutter very weakly and irregularly (fibrillation). One of the greatest challenges of computational biology is to understand how a physical disease process—such as the formation of scar tissue in the heart—leads to a disruption in the heart’s normal timing.

In a normal heartbeat, a wave of electrical activity spreads from the heart’s pacemaker node down through the atrium, and then back up from the bottom of the ventricle. The wave front is more or less planar. But in tachycardia, the planar wave folds in on itself, and eventually forms a rotating spiral wave that ignores the heart’s normal pacemaking signal. This self-sustaining spiral wave rotates faster than a normal heartbeat, giving the heart less time to fill with blood and pump effectively. In some cases, the spiral may anchor onto a scar in the heart tissue, making the tachycardia more stable. In other cases, a spiral wave may break over scar tissue like an ocean wave breaking over a rock, and a chaotic pattern of electrical activity results—the sign of fibrillation. But fibrillation can also occur without scar tissue, depending on the conditions. The chaotic electrical signals cause local, unsynchronized, contractions of heart muscle, instead of a synchronized contraction of the entire atrium or ventricle. In the case of ventricular fibrillation, this condition leads to sudden death if not treated immediately.

Mathematical models have been remarkably successful at reproducing these phenomena (which have been observed to some extent in animal experiments). In fact, one of the best signs that we really know what is going on in the heart is that we can take a set of mathematical equations that describe what is going at the cellular level (principally the motion of sodium, potassium, and calcium ions into and out of a cardiac cell), then link all of these cells up into an anatomically accurate heart, set the equations going and produce a qualitatively accurate simulation of a guinea pig,
or dog, or human heartbeat. We can simulate normal heartbeats, spiral waves, and fibrillation.

But for future clinical applications—for the design of anti-arrhythmia drugs, for instance—qualitative plausibility is not enough. Cardiac models need to be quantitatively accurate, and they aren’t there yet. The first heart cell model, by Denis Noble in 1962, was fundamentally flawed because it did not even include the calcium current, which had not been discovered yet. In 1991, Ching-hsing Luo and Yoram Rudy developed a cell model for guinea pig cells that became a standard module for whole-heart models of other animals. For several years, the Luo-Rudy model was the best available cell model because detailed information on human heart cells in vivo was hard to come by.

Finally, in 2004, Kirsten ten Tusscher of the University of Utrecht and her doctoral advisor, Alexander Panfilov, published the first human heart cell model that was designed to be simple enough to incorporate into a whole-heart model. The ten Tusscher model has already been widely cited and has even been used in pharmaceutical research, although as you will read below, the modeler herself feels that this application is premature.

In 2008, ten Tusscher accepted an offer to come to Simula Research Laboratories. Her expertise in the forward modeling problem—computing the heart’s response to different initial conditions—complements Simula’s already existing expertise in the inverse modeling problem. Although her cell models are still too complex to be used for inverse modeling, clearly it is not too unreasonable to hope that the two research programs will interact in the future.

What Simula did not realize, when first contacting ten Tusscher, was that she also had plans to venture out into a field of research where she had not published yet—the study of evolutionary biology. The challenge of updating Darwin’s theory for a post-genomic era, as ten Tusscher describes in the interview below, sounds nearly irresistible, and particularly appropriate for Darwin’s bicentennial year.

While ten Tusscher will continue her research into cardiac modeling, along with postdoctoral assistant Molly Maleckar, Simula agreed that she could also spend part of her time doing research on evolutionary modeling, with PhD student Tim Dorscheidt. This will give Simula new competence in a field that, on the surface of it, seems far from a real-world application. However, who can say what the future will hold?

"Kirsten, could you talk about your background, and where you got your degree?"

“Contrary to most people at Simula, I’m a biologist. When I came from high school I was interested in a lot of things, and I figured that biology has it all. It has the chemistry, the physics, the math, and of course it has the biology. I was always very much interested in the complexity of biology and how does all of this diversity come about. But after my first year at the University of Utrecht I realized I didn’t fit in too well, because most biologists are very non-technical. They like the animals and the plants but they don’t like math or physics."
"At Utrecht there is a nice group in theoretical computational biology. I knew this was an obligatory course in the second year. I decided that if I liked it, I would go for that specialization, and if I didn't like it I would switch subjects. I took that course and I very much liked it, and I decided that was the direction for me. I could study biology, but in a much more exact manner than most of my fellow students would do.

"I studied computer science for a year to learn programming and algorithms and more math and physics, then I came back and did a master's specialization. I did one research project there, with Paulien Hogeweg, and one in an informatics department in Amsterdam. I skipped the typical subjects in order to do more bifurcation analysis, nonlinear dynamics, and modeling complex biological systems. I'm predominantly a biologist, but my friends who are biologists think that I am a very strange biologist because I can't determine what any plants are or anything!

"I really like programming and simulating rather than waiting for a long time for an experiment which fails. I had friends who had to grow seeds and wait for the plants to grow, and then there was a fungus on the plants and they had to restart and wait another couple of weeks till the plants had grown. I can just restart the simulation."

"You can grow a plant a lot faster on the computer, can't you?"

"Well, it depends on the application. In the work that I do now, sometimes my simulations are a lot slower than real-life."

"How did you start working on arrhythmias?"

"Going to the cardiac arrhythmias was kind of a coincidence. The group where I come from is now very big, but at that time they were quite small and there was not so much funding. Sasha Panfilov had come to Holland seven to ten years before I became a student. He was from the Puchino Institute, close to Moscow, and I think Zhabotinsky was there as well\(^1\). They did both physical experiments and modeling with excitable media. He had very diverse interests in biology, complexity and evolution and pattern formation. I decided to apply to work with him. I thought probably he wanted a physicist, but he was very happy for me to apply and we started a nice collaboration."

"When did you start working with Panfilov?"

"I think it was in 1999 or the beginning of 2000 that I started my PhD. Then I worked with him for quite a long time, until I came here. Until I moved here I was quite stuck in one place, doing my PhD and postdoc at Utrecht.

"In cardiac arrhythmia there are a lot of things going on, but what I chose as a niche was human-specific modeling. Sasha had done a lot of whole-heart modeling, but they were on an abstract model or a dog heart. A lot of people were combining

\(^{1}\) The Belousov-Zhabotinsky reaction was the first chemical reaction to demonstrate complex pattern formation, including spiral waves that look not too dissimilar to the spiral waves that occur in heart tissue.
these models with cell models that were originally devised for guinea pig cells, so you have strange things going on.

"You want to see whether things that apply for animals also apply to humans, because you're interested in saving humans. The first problem I ran into was that there was not an ionic model for human heart cells. So I just decided to do that, and now this model has been cited over 160 times in four or five years. It's living a life of its own. I wanted to put it in a whole heart.

"Even though the numerics that I used back then are not as sophisticated as what they use here, it's still immensely slow, because you have 13.5 million points in this heart. Each of these points has 16 to 20 variables. To be stable, to not blow up numerically, you need to update each one every 0.02 milliseconds. That's why on a computer we're actually slower than life. Even if I compute five seconds of a heartbeat, with twenty computers at the same time parallelizing it, it takes me two days.

"That's why I wanted to stick to it as a postdoc. In some labs, somebody does the cell modeling, someone else does the graphics, and someone else does the parallelization. I do it all on my own. I had invested so much time in the technical stuff that I still wanted to harvest the fruits of my labor in the postdoc phase. Sasha had written this project of putting a whole heart together using this software. I felt that this was my baby, and I didn't want some other postdoc to work on that! At the end of the PhD things start accelerating, the rate at which you publish articles and get results, because all of the supporting software is in place."

"You've gotten the snowball rolling."

"Yes, now we were at the stage where we can do some really detailed quantitative simulations, and we knew some people in England who had clinical data. Then we could really ask the question: 'How does arrhythmia in these human hearts compare with animal hearts?' Of course it's very useful to investigate general things, like how do things become unstable or how do things change if you have ischemia, no oxygen supply. But if you want to make predictions, if you want to make a drug that will enhance this or suppress that, then of course you have to have something more human-like. By now there are some other human models, but they are not specifically tailored for whole-heart simulations. You need a whole supercomputer to do one cell, so it doesn't make much sense to compute a whole heart."

"Can you say what you've found out from your comparisons with clinical data?"

"Sasha investigated how the number of spiral waves depends on the size of the heart. The funny thing is that people thought if you have a larger heart, you have more complex and chaotic behavior. Basically the end result of my model is that the human heart is simpler! Look at this picture of a pig model. You see lots of spirals. Now, here is a polar map of the whole human heart during fibrillation. This is clinical data!

"Believe it or not, people in England were willing to let doctors pull a sock over their heart during open-heart surgery and do measurements, and stay open-chested
in cardiac surgery a little longer. During the surgery, ventricular fibrillation was induced. I was shocked to hear this, but it seems to be quite normal. If you’re installing a defibrillator, you want to make sure that it works. I have been assured this was normal procedure, and the only extra risk was that the patients remained open-chested a little bit longer.

“One of the things you notice in the data is that there are many fewer of these spots\(^2\). One of the other things is that if we look at the frequency of ventricular fibrillation in humans, it’s like 4–5 hertz, but in pigs and dogs it’s 10–13 hertz\(^3\).”

“What got you interested in coming to Simula?”

“It worked the other way around. They came to me. They had seen both my model of single-cell stuff and my whole-heart stuff. Per Grottum, who has a part time position here, apparently discussed with Aslak Tveito that I would be interesting for them and it would be nice for me to give a presentation. They asked for two, one on single cells and one on my whole heart work. And I gave them, and at the end of the day they just offered me a job!”

“Did you accept it right away?”

“No, by that time I was doing other research on evolution, more with Paulien Hogeweg than with Sasha Panfilov. Aslak said to me that if I was interested in working with them, I should send them an email. I said it was definitely an interesting option because my postdoc contract was ending in six months. In Holland, as in most places, to keep going in research you’re supposed to go abroad for awhile. So I thought for a while and decided to go for it.”

“What were your reasons?”

“If you go abroad, most opportunities are in the States. I didn’t want to go that far, because you’re so far from family and friends that you’re kind of disconnected from

\(^2\) i.e., centres of the spiral waves.

\(^3\) At this point the explanation becomes fairly technical. First, ten Tusscher verified the clinical count of spiral waves with her model. In fact, she demonstrated that the surgeons were undercounting slightly, because some of the waves can only be seen from the inside of the heart looking out. Even so, the undercount was not nearly enough to explain the difference between human and pig hearts. Next, ten Tusscher modified various aspects of the cells’ behavior to make them less human-like, and see which changes would most affect the number of spiral waves. She found that the most effective change was in the “action potential duration,” which is the minimum length of time that a heart cell can remain excited. In effect, it takes longer to de-excite a human heart cell than a pig cell. Therefore the spiral waves turn slower, the spirals have to be larger, and not as many spirals can fit into one heart. This is good news—it means that the human heart does not fibrillate as readily as it might otherwise. Interestingly, the action potential duration had been hypothesized as an important ingredient in determining whether fibrillation does or does not occur—but the mechanism was believed to be slightly different.
them. It would be nice to see them more than once a year. Also I have a boyfriend who was still getting his PhD, and he was still stuck in Holland.

“So it was convenient to go to a country that was not so far away. Scandinavian countries also have a very nice reputation… The way that people think is quite similar to Holland, it’s egalitarian and quite liberal. And Norwegians have a reputation for being very sporting, and I’m a passionate runner. I thought probably that Norway will fit quite nicely who I am and the kinds of things that I am interested in. Indeed, most of the friends I have made in the last six to seven months are from my running club.

“Also, I am getting a lot of freedom. One part of my accepting the job was that I asked if it would be okay to work both on the cardiac research and the evolutionary stuff. And they agreed on that. In science, if you don’t have a track record in an area and don’t have any publications you can show, the chances of getting money are almost zero. Here, now, I can do both and there’s no problem. I can gradually start building publications in that area as well.

“Simula also has great computer resources, of course. I can just put on 30 or 40 simulations without thinking about it, and it’s no problem.”

“How do they compare to university computers?”

“I guess for some people it might be better here, but for me I was quite spoiled in Utrecht. We had this self-taught system administrator who had built his own Beowulf cluster, and no one was computing on it, so it was just mine. I was sharing the same room with him, so I knew when he was going to shut it down, and I could say, ‘Don’t do it today.’ I was quite spoiled.

“In general it’s quite nice here to have your own in-house computer. I’ve also been at the supercomputer centre in Amsterdam, and that would just be horrible. It’s very nice if your simulation speeds up from three weeks to five hours, but then if you have to be in a queue for three weeks it doesn’t help much. Or if somebody changes your root path and all of a sudden your simulation can’t find a startup file, you’ve waited three weeks and it crashes immediately! In that sense it’s always very nice to have people who run things just across the hall. And it’s not very full yet, the cluster here, so it’s great.”

“As far as your research, what goals do you have?”

“Looking at different mechanisms of arhythmia. Thus far I have looked just at one mechanism. Related to that, I would like to incorporate still more realism in the models. Right now I have a human cell model, but the heart is completely homogeneous. You don’t have any cells other than heart cells, whereas we know that there is connective tissue that is needed to give the heart its shape. The amount of connective tissue increases when you have diseases or get older. Usually people only look at the electrical signal to see whether things go wrong, but now we know that intracellular calcium, which leads to contraction of muscle cells, is also important. A lot of people are doing these things, but often in such a way that you cannot use these models in a whole heart. I want to develop models always in such a way that I can do them
on the whole heart level. On the one hand I want to have more biological detail, but always to keep in mind that it should be computable. And I want to do it specifically for humans.

“In these models there are so many things to consider. You can look at blood flow. You can look at metabolism, or the influence of the nervous system, or you can look at contraction and the feedback you get from contraction. A fundamental problem is: Do you want to put everything into one model? I have been raised as a theoretical biologist to believe that models should be simplifications, and that you should see if something matters, instead of piling everything into one model. On one hand you can analyze them better if they are simple. On the other hand, if they fail and they fail miserably, you know that you’re missing something.

“Some people are now focusing on coupling electrical stuff to mechanical stuff, but as for me, I’m going for the connective tissue and the calcium. If you try to do it all, you get these huge monster models and it’s hard to say what’s causing what.”

“Explain how the connective tissue affects the way the model behaves.”

“Put very simply, the cardiac cells are electrically active, so if they generate an electrical signal the next cell senses it, it also produces an electrical signal and so you get this wave going. Connective tissue cells are just different cells, and they make proteins that they deposit outside cells. These proteins are just barriers. They don’t generate any electricity, and they don’t let through any electricity, so they form blocks for the wave fronts.

“Normally, the connective tissue forms a scaffolding or a matrix for the body. But if you have diseases or get older, heart cells get damaged or die. The problem with differentiated cells like nerve, brain, and heart cells is that they don’t divide that readily any more if you’re an adult. If a cell dies, its space usually fills up by other cell types proliferating and connective tissue being deposited there. If you look at a very microscopic level, you see small disturbances in your electrical wave. On global level you wouldn’t notice that. If you have a disease or you’re aging, it increases very much. On top of that you have other problems. Certain ionic currents get more or less, the cardiac cells are not so coupled any more, and you can get local blocks or delays in this electrical wave. It’s the electrical wave that tells cells when to contract. So instead of one nice wave front that tells everything when to contract, you get local delays and the whole synchrony gets lost.”

“Is there a clinical relevance to that?”

“It’s clinically very relevant... It is well known that all kinds of diseases that are associated with increased connective tissue are also associated with increased levels of arrhythmogenesis. There is a lot of clinical research on trying to prohibit cardiac tissue from forming so much connective tissue. It’s an inflammatory response to cardiac cells dying, so there’s a lot of practical research going on there.”
“Do you have particular applications in mind for this research?”

“I’m a basic researcher. That’s the short answer. Of course I hope to contribute to insights in arrhythmias that can help make better drugs or treatments. But in the sense that I want to commercialize things, it’s not my primary interest. I know that my cell models are used by other researchers to predict about drugs. I’m always very reluctant to see that, because models are never complete. They are always simplifications. I don’t think they can yet be used for drug testing.”

“Can you tell us about your new research on evolution?”

“Evolution was my first love in biology! I read The Origin of Species when I was 16. Darwin was saying that you need heredity, mutation, and competition, and then you get natural selection and gradually fitness goes up in the population.

“There is a relatively new idea in evolution that was not applied in classical population genetics, which is that the mapping from DNA to genome to proteins to cells to organisms is very complex and nonlinear. You can have genomes that are very different and give similar organisms, or very similar and give different organisms. So the genome is not just a ‘bag of genes,’ as it was seen until recently.

“A question that I’m interested in is speciation. How do you get a species to split up? The first thing I showed is how you can get two populations that are not really different species, just different morphs or different shapes of the same species. For example, you can have two different colors of cichlids in the same lake. This doesn’t make sense if you assume you’re just a bag of genes. In a classical population genetics model, if you have a blue parent and a red parent, the child will always be purple. Unless the formation of morphs and species is simultaneous, you can’t actually get to a population of red and a population of blue, because you will keep collapsing back to purple.

“The essential part of my model is that even without separating into two species, you can still have this differentiation into different morphs. Because of the need to blend into the background, it may be advantageous for a fish to be red or blue, while a purple fish may have very low fitness. By using the genome and the gene regulatory network in a clever manner, you can largely resolve that problem. The child of the red and blue parent can become very reddish or very bluish. They can be quite good at what the parent is doing, although never 100 per cent. This is a simple way of having different forms in one population.

“In the current model setting, if I give the animals the ability to develop a preference to mate with others of the same type, they will; it will always be more advantageous to become real biological species rather than two morphs within the same species. But in my model the two things do not have to occur at the same time. In the classical model, it has to be simultaneous.”
"What does a gene regulatory network look like? How does it differ from the 'bag of genes' model?"

“You can think of a graph with a lot of nodes, representing the genes, and links that represent the interaction of genes. This gene is repressing that one, but that one is activating the first one, and so on. It’s like a jungle of genes and interactions.

“For each node you can have an activity level for that node, so you can model that with a variable. Then you get a very complex set of coupled ordinary differential equations with many nonlinear terms, because it is this protein binding to a site on the DNA that affects that protein, so you get a lot of Michaelis-Menten saturation constants.

“In classical population genetics they used differential equations, too, but the equations are often linear. This means that if you want to have very different looks for an organism, you will also need a different genome. We know now that is not true. In the gene networks, with all these interactions, first of all you have lots of differential equations, so you cannot solve them analytically—you have to do it numerically. Also, because they are not linear, a small variation on the genome can be amplified, through nonlinearity, to have a very unexpected effect. All of a sudden your animal has a horn, or teeth where it didn’t before.”

“Are there other people doing these kinds of models?”

“Gene network modeling has not previously been done for speciation research, as far as I know. Gene network models have been used quite a lot to model differentiation and pattern formation in multicellular organisms. (Different cells form different colors, even though their DNA is the same, because the regulatory networks switch on different genes in the same animal). In the literature on pattern formation, people have mostly looked at only two types of cells (for example, black and white hair cells forming a pattern of stripes) and hence two different combinations of genes turned on and off. I have been looking at the evolution of a range of different cell types in a row from head to toe, forming the body plan of an organism.”

“Darwin would be very happy, I think, to see that he didn’t actually finish evolution!”

“People say that there is a new synthesis needed. After Darwin, when they rediscovered Mendel, there was the synthesis of Darwin’s theory with population genetics. Now you see that simple population genetics is not enough, because you have to consider this whole mapping between the gene network and the phenotype, which involves cell differentiation and development, and also the impact of the environment on the characteristics of the organism. That is why people are calling for a new evolutionary synthesis, so that evolutionary theory not only involves Darwin’s original theory and population genetics but also gene regulation, developmental biology and ecology. Evolutionary biology is far from finished, and lots of interesting changes are currently occurring!”
Simula Research Laboratory
by Thinking Constantly about it
Tveito, A.; Bruaset, A.M.; Lysne, O. (Eds.)
2010, X, 656 p., Hardcover
ISBN: 978-3-642-01155-9