Maths + Cancer

Episode 6: The shape of data with Heather Harrington

Transcript

Vicky Neale:

My name is Vicky Neale, and I'm a mathematician at the University of Oxford. Since March 2021, I've also been having treatment, on and off, for a rare form of cancer. That's been very educational, I've been learning lots about cancer and the various treatments available. While I wish it was less personally relevant to me, I also find it fascinating. I take comfort and have great pride in knowing that I have colleagues in the mathematical community whose research helps to tackle cancer from prevention through diagnosis to treatment. In this podcast series, Maths + Cancer, I'm going to sit down with some of them to find out more about their research, and about the people behind the research. I'd love you to join me for our conversations to learn more about how mathematics and mathematicians are helping to combat cancer.

I'm excited to be joined today by Heather Harrington. Heather is Professor of Mathematics at the Mathematical Institute, University of Oxford, a Royal Society University Research Fellow, and a Research Fellow at St John's College, Oxford. She leads the Algebraic Systems Biology group in Oxford and is Co-Director of the Centre for Topological Data Analysis, and I'm looking forward to asking her about what algebraic systems biology and topological data analysis are. Her outstanding research has been recognised with a Whitehead Prize from the London Mathematical Society, the Adams Prize from the University of Cambridge, and a Philip Leverhulme Prize. She's also involved in projects to increase diversity in mathematics, such as summer workshops promoting opportunities for graduate study. Heather, thanks so much for joining me today to talk about maths and cancer.

Heather Harrington:

Thanks for having me Vicky. It's really great to see you.

Vicky Neale:

You are, in the best possible way, a hard person to pigeonhole mathematically. How would you describe your current research interests?

Heather Harrington:

My research interests vary a lot in the sense that I'm really motivated to study complex biological systems. And if the methods to analyse those systems already work, that's great, we should use those, right? So I guess the mathematics I'm really interested in are the ones where you know, standard linear algebra might not work. Or a standard statistical test won't give you the answer to your question, often motivated from the biological system. So I kind of think of the problems I work on. They might start initially from this complex biological or biomedical problem, which we then say OK, what available data is there? What is possible to measure? And that's actually changed a lot through my career, because at the beginning of my career we couldn't measure very much. So traditionally we studied mechanistic models, so this is encoding some hypothesis into a model and then analyse the properties of that model, and often we looked at it very locally, so just around a neighbourhood of some parameters of some rates that we think govern some biological process. But

what's changed is we've kind of taken a step back where we can look at things a bit more globally using nonlinear algebra, and as more imaging technology becomes rapidly available and very high resolution over space and time, we need methods that can kind of cope with this. So that's where a lot of the mathematics using geometry and topology have come in, to study complex systems.

Vicky Neale:

I love this idea that you start with a complex biological system and then kind of go What mathematical tools do I need? So I guess maybe some mathematicians say Well, I've got this toolkit. What problems can I solve with this toolkit? And that can be a really productive way of doing all sorts of interesting research. But it sounds as though you're more driven by Here's a problem coming from biology or coming from medicine, what bits of maths do I need? If I need to go and put some more tools in my toolkit or even buy a whole new toolbox, well, I'll just go and find some more tools. I'll invent some new tools. Is that a kind of summary?

Heather Harrington:

More or less. I mean, what I find is that if I think oh actually, this would be this sounds like some type of stochastic process, that's really outside of my mathematical domain. Then I ring someone up and say, oh, I think this might be useful for stochastic. I don't try to relearn all of mathematics, right? I think it's more, oh, this sounds a little bit more like what someone else is working on mathematically. Go ahead and try to connect those dots. Which actually is what I find. With real world biological systems, you can't just take some standard mathematical technique and apply it.

Vicky Neale:

It's not like a textbook problem that's been designed perfectly to work. It's much more complicated and messy than that.

Heather Harrington:

Yeah, exactly so you might think Oh, I can take this problem I know about in geometry or topology, so one example is we're looking at the shape of vascular networks or the shape of patterning of cells in a tumour. And you might think OK, we could use some standard approach from topological data analysis, which is this established field in computational mathematics now that can study shape of data. And you might think OK, I can just take this technique and apply it. But what we find is we actually have to develop kind of bespoke mathematics to solve that problem, that the standard theorems don't hold in the real-life situations. And we've seen that as well when we looked at this problem involved in what's called the WNT pathway, which is dysregulation of certain molecules that are involved in like 50% of colorectal cancers. And we thought, OK, we have this model. We have this system of equations. We can use the power that has been developed in kind of computational algebraic geometry and chemical reaction networks and just translate that. But then we find out, oh, our system doesn't satisfy any of the nice properties where people have all these theorems, so then we say, well, what can we do now, right? And so that kind of drives a lot of new math.

Vicky Neale:

Yeah, and it sounds as though this is a really fertile area, that the complexity of the biology is really driving innovative new mathematical ideas.

Heather Harrington:

Absolutely. It's also very frustrating, in a good way, right? So you kind of like, oh, we have all this powerful mathematics that brilliant mathematical minds have created, and you really want to be able to translate it. And then you're like, oh, this is it's similar, but it's not quite that, right. And so to solve a real biological problem, yeah, it's not always just tweaking something. Sometimes it's like it looks so similar and we don't want to abstract the real problem so much so to make it fit into another theoretical framework. So it's a balance, yeah.

Vicky Neale:

I'm really struck that you talked about it changing during your career, because without dwelling on your age, you and I are similar ages and our careers are not decades and decades old, so I'm really struck that even in the time that you've been working in this area, that you've seen a change in the data that's available to you, I guess, driven by developments with imaging software and those kind of things.

Heather Harrington:

Yeah, it's really incredible Vicky. So part of the reason I came to the UK, which I think I've told you, is that I really wanted to work in in biological, biomedical problems. I was pre-med as an undergraduate right? I thought I'd go to medical school and just I majored in mathematics, but in 20 years ago the only possibility to use biomedical data with anything mathematical was do bioinformatics. And I took a bioinformatics course.

Vicky Neale:

What is bioinformatics?

Heather Harrington:

This is the study of kind of looking at genomics and statistics using kind of computational genomics. So looking at you know, DNA sequencing and that explosion that was about 20 years ago, with more traditionally statistical techniques.

Vicky Neale:

So these are the kind of techniques that have meant that looking at genetic data, research has been able to identify particular kind of genes that might lead to a predisposition to cancer or those kind of things.

Heather Harrington:

Yes, yes, exactly. So and that's really looking at more of the genome, the large data sets with the Big Genome project. But that wasn't really what was exciting me. So I took this bioinformatics course when I was an undergraduate and we used kind of the standard, maybe at the time the state-of-the-art, methods to study you know some sequencing. And I did it, but I wasn't excited about it, and I thought, is this the only way to study biological problems with data? And at the same time I had also taken a mathematical modelling course looking at for example, differential equations, studying what was called the loop of Henley in the kidney. And I really liked that, but then when you asked, well, what's the data, there really wasn't any data to use with the modelling at the time. And this was really 20 years ago. And so they had these centres for systems biology in the UK that were just becoming established. And so it was a way to work with mathematicians and data on biological problems. So there were five or six centres in the UK. I applied and then I came to Imperial where I got to. You know, I had mathematics professors for supervisors, but then they were making

connections with various clinicians, experimentalists, so during my PhD I actually worked with a pathologist. So that kind of that exposure led me to realise that the standard mathematics that we're learning in even graduate-level courses don't translate right away. So it kind of requires a bit of creativity to abstract the problem enough to be able to solve the math problem and then come back and give some prediction or insight. Which is happening now, yeah?

Vicky Neale:

I love that you used the word creativity because I think that often people perceive maths as about applying standard procedures, and I don't know, doing long multiplication increasingly accurately with big numbers or those kind of things. And I think what you're describing really highlights that creativity that's needed in mathematical research. That it's not about just taking standard procedures and applying them carefully and accurately, that it involves imagination and finding new approaches and putting together what you've got in different ways. And sometimes what you've already got is not enough and you need to invent something new. So that creativity really comes across the way you're talking about it.

Heather Harrington:

Yeah, that's absolutely true. I mean and there's all these different aspects with real biological systems. And especially with cancer, which is a heterogeneous disease, and I didn't understand what the word heterogeneity really meant actually. As a mathematician I was like what does heterogeneous mean? And getting even a definition for this is challenging. But I think what it. The way that I've realised is that the disease classification and treatment is not linear. It's not this straightforward disease in any way. It's very complicated where everything is interacting with everything, and even when you have a disease subtype, even within that subtype, for example, they don't all respond the same way to treatments. And this has led us to look at different types of mathematical approaches to try to kind of disentangle in some way what we see in the data and what we yeah, try to make sense of that a little bit more, which is just a great area for mathematics.

Vicky Neale:

One of the things that’s struck me talking to other people in these podcasts is exactly this thing about how varied cancer is. And of course, I understand that there's lung cancer and there's breast cancer, and there's prostate cancer, and there's different types, but within those there are different types, but actually even within an individual patient, their tumour is made up of lots of different types of cell. It's not that they've just got one bad cancer cell. And I think I hadn't really kind of appreciated the complexity that even for an individual patient, there are all of these different types of cells that might respond in different ways or not respond to types of treatment and so on. And that level of complexity is kind of mind boggling.

Heather Harrington:

I think as a mathematician it's mind boggling as well because we want to simplify things as much as possible to solve a really well defined problem, and then as you get into any problem like OK, I'll abstract it enough to simplify it to solve it. This is very much you have to work with a domain expert, right? Whether it's an oncologist or a pathologist. Whoever it is, and then they'll say, Oh well, actually that's not quite right, because that's too simplistic. And you continually get this Oh, but that's not quite right, it's too simplistic. And so we did this project some years ago with Anna Seigal, she's now at Harvard, but she was a Hooke Research Fellow here, and Mariano Beguerisse, who was also a Research Fellow here at the time, and we were looking at a very nice system. So this

pharmaceutical company had hired three people, full time, to take these at 36 breast cancer cell lines, and do the exact same experiment in the exact same measurement in all of them, and that's really special. It was a complete data set and that kind of opened up opportunities for us to develop mathematics to study this data set.

Vicky Neale:

You're recording this data about each of these cell lines, and you've got kind of five different data points, so we kind of think of that as five dimensional.

Heather Harrington:

Rather than five different data points, we really think about it as a 5-dimensional point, if that makes sense. So you have the cell line, you have the ligand, you have the dose, you have the time points, and then you have the actual measurement of these proteins. Maybe the first thing is to think about normally in data analysis we can think of like a table or a matrix. This is a 2-dimensional array. And so you can extend this to more than two dimensions, and that is a tensor. So it's a multi-dimensional data structure. You can think about it, a 3-dimensional or order 3 tensor would be having for example a data point in each, kind of in a Rubik's Cube.

Vicky Neale:

So a tensor is a multi-dimensional array recording the data, and then there are exciting mathematical tools for being able to examine that tensor and kind of find patterns and structures within that data.

Heather Harrington:

That's correct, right, exactly. So we want to keep this multi-indexed data preserved with the tensor, and so I think this was kind of one of the first interpretable ways to study this type of data as a tensor, at least in systems biology that I'm aware of. And what was so nice, is that then we developed a method with kind of the experts that were part of that. You know that helped generate this data. And we're able to cluster. And so we wanted to find some of the cells and some of the ligands that were most similar. And so we developed this method to cluster. And what was really cool, or I think was cool, is that normally in breast cancer there's this subtyping. So they split it up. They split up breast cancer cells into three types based on you know how many proteins are on the outside of the cell, of one type of protein versus another. And what we found is exactly this heterogeneity that I was talking about in what's called triple negative breast cancer. And so we found some of this heterogeneity that certain cells were more similar, and when we went in and looked at well what's the mutations, where's the drug sensitivities, our groupings with this tensor actually recovered some of the biology that was already known about these cell types. But of course we didn't incorporate any of that information, so it just, I think it goes to show that we want to glean as much insight from the biological data that we have, while maintaining the structure.

Vicky Neale:

And I love this phrase "The shape of data" because that I think when people think about data, when I think about data, often I picture maybe a kind of spreadsheet with a kind of table full of lots of numbers. Or maybe a pie chart or a bar chart or something that's kind of summarising it. And I think listening to you talking about this kind of five-dimensional data that you're working with and wanting to keep all of that data so that you understand how the structures work and find those

patterns within the data, I can't visualise 5 dimensions. I mean on a good day I can visualise 3 dimensions because it's the world I live in.

Heather Harrington:

I can't either.

Vicky Neale:

OK, I'm reassured that you can't visualise 5 dimensions either, But I guess the power of mathematics is that we have these techniques to detect structures and patterns in five-dimensional data or 100-dimensional data, which adds that richness to understanding the biological system.

Heather Harrington:

Absolutely, absolutely. And I think that we're going to see these types. Because more and more data, these technologies are just rapidly improving and more and more data is being generated. Trying to really extract as much information from that. Rather than compress it like I said, right? Rather than compress it into something 2-dimensional that we can physically see, as a mathematician we have, there are frameworks to really extract and keep all that structure in high dimensions. So you can think about some of the gene expression data sets, where this is something that's 20 or 30,000 different genes that are measured, and we don't want to flatten it only to two dimensions, right? OK, maybe we want something that we can understand, so 10 or 20 or 30 dimensions. Something like this. But I think we don't necessarily want to require visualisation always. Sometimes it's better to extract something in a mathematical way and say this is how there's similarities. This is how we can kind of track even continuous changes in our data space.

Vicky Neale:

And I think the fact that this is using kind of ideas from geometry, but you're saying let's not make it about visualisation. I think that might kind of come as a surprise because the geometry that we learn at school is profoundly visual. We draw triangles and we draw circles and we understand properties of triangles and circles and even spheres and cubes and so on by drawing them, by visualising them. But actually the fact that we can generalise those kind of ideas to understand geometric properties in higher dimensions, where we stop being able to visualise them, I guess we have lots of colleagues in the Oxford Maths Institute who do exactly this. They do higher dimensional geometry, that is in itself a research topic, and I suppose what you're doing is taking some of those ideas and then applying them in this very complex biological context.

Heather Harrington:

Absolutely. I'm afraid I can't remember now, but there is something like oh biology is, you know, the next physics. And in physics, right, in mathematical physics, there are so many people that are looking at very high dimensional problems, and so I think just with the increase of data and technology in biology, I think that's going to come naturally.

Vicky Neale:

I'm just going to interrupt briefly to let you know that if you're enjoying this episode of Maths + Cancer, then please do head to ox.ac.uk/cancer to find the other episodes in the series, in which my amazing guests tell us about some of the many intriguing ways in which maths and stats are helping us to understand and tackle cancer.

I want to ask you about pure maths and applied maths, because historically we have kind of, people have talked about pure maths and applied maths. And applied maths is maths applied to real world problems, and pure maths is research being done kind of curiosity, no immediate application, just kind of exploring. That's crude characterisation of kind of pure and applied maths. Maybe sometimes people call pure maths 'fundamental maths'. And it seems to me that one of the really intriguing things about your work is that, as far as I can see, you pay no attention at all to these kind of historical divisions, that you just grab bits of maths from wherever you can, that you go and develop new bits of maths in whatever area, and you're finding whatever tools you need for your your particular application I guess. Do you think about pure maths and applied maths? Do you find this a helpful distinction?

Heather Harrington:

I really don't actually. Maybe there's something that's very unhealthy about wanting to, you know, pigeonhole someone. It makes it easier. And it's the same thing for a subject. It makes it easier, but I think fundamentally mathematicians want to do maths, and whether it's because someone that's kind of very senior in the field stated that this is a very important problem to solve, or whether it's we really need to understand, for example, the complexity in this new technology and how we can get a hold of it because current approaches won't give it that. If it's a math problem, it's a math problem, right?

Vicky Neale:

I'm with you, I'm not arguing, Heather, I'm not arguing.

Heather Harrington:

Yeah, but I think it's a fine line, right? I think we don't want to only solve problems for other people. Sometimes we want to solve problems for ourselves, right? And so, so I think in science there's this very nice and in mathematics there's a very nice way of kind of thinking about this as a loop, right? So, and at least that's how I feedback loop. That's how I think about a lot of these problems is that the reason that we're studying some mathematical problem is because it's difficult? If it was easy, then we would already have a solution and it would be straightforward. And that's in any area of mathematics. And some of the mathematics we're using, for example, in topological data analysis, I mean algebraic topology historically has not been something that's computing, right? And it is a very theoretical area of mathematics. I mean, Christopher Zeeman actually wrote a couple of papers in the 50s and 60s saying that the field of algebraic topology would be useful for the brain. And this was way before we could compute anything, and I think he saw that studying complex shapes that we could actually characterise and quantify with these topological invariants could be useful. But I guess I'm getting a bit off topic because really things come round in some way, right? So the reason that we're using topological data analysis now is because there's been so much progress in the algorithms and the implementations. So rather than run something on a supercomputer which we were doing 5, 6, 7 years ago, you can run the same computation on a laptop, so it's just more accessible, and can be used by scientists much, much easier through a lot of work by a very large group of mathematicians and computer scientists and engineers and statisticians developing statistical approaches to be able to make statements about these topological invariants. So yeah, no, I think saying that, oh, let's say this is pure or applied or fundamental, or I mean even in different communities around the world, right? We call applied mathematics and pure mathematics different. Some departments, some places have separate departments. So I think in the UK that's something that's very special is many places, it's the mathematics department and all types of mathematics

occur in the mathematics department. And so I think in that way in the UK, where this you can have these interactions, I can go anywhere in the in the building and have a chat about something and say, ah, if this is. You know, actually I was speaking recently about whether we could think about some of these path signatures, that you know the group that Terry Lyons, and if any of that would be relevant to some of the problems we were actually looking at. I was like, oh, is that what you would call a rough path or a data stream? And so I think it's just mathematics is nice because we we might sometimes speak different languages even within mathematics, but, yeah, trying to boil something down to kind of what's the essence of the question and the problem and formulating it and then to answer that question, we'll use different fields, even if the same kind of underlying structure is the same.

Vicky Neale:

Yeah I worry sometimes that people are reluctant to support quotes pure mathematics because what is the value? And it seems to me that our conversation today is really highlighting the paramount importance of all of mathematics, not only the bits where you can immediately see the application, because you get these surprising moments where people like you come along and make a connection and go well, actually this idea that's been around for a long time, we can use in this really interesting, creative way and have a really profound impact on the real world. I just feel like that's such a strong case for the need for all of mathematics, and also for promoting communication between mathematicians. You just mentioned that sometimes we talk different languages. Sometimes, even within the Oxford Maths Institute, it's hard for us to understand what our colleagues are doing because it's quite specialised and we have this whole kind of language and way of thinking and so on. And it seems to me that you're really interested in communicating with lots of different people and collaborating with lots of different mathematicians. How do you navigate those kind of language barriers? Do you you just kind of sit down and ask lots of questions of people? Do you go and read lots of books? How do you manage to communicate with such a wide range of mathematicians?

Heather Harrington:

I ask lots of very dumb questions, I think is the answer. And I listen a lot, actually, I just sit and listen and think, oh, so this actually sounds very related to some problem I heard about a long time ago. I mean, actually I spent a few months in a fruit fly lab. They were looking at mutations, certain cancer mutations. And so I spent a few months in a fruit fly lab. I am rubbish at experiments. I let all the flies go and they'd catch them with. Anyways, it doesn't matter, I'm not going to go into it, that was awful. But while I was there, I was asking lots of stupid questions and the head of the group had said to me, you know, you're a very different type of mathematician than most mathematicians here. And I think that at that institution it was primarily very theory based, and so that was, and I think the comment came because I was asking so many maybe fundamental biological questions. Really trying to understand how the system worked and what were the assumptions, and what was important to the developmental biology lab they had, and what was important was specific to some of these mutations that we were looking at. And so my questions were very frequent and I think that is not necessarily typical, but it's an interest, right? You have to be curious to be able to, to actually say, OK, let me really understand. What's obvious to somebody else in a field is really not obvious, yeah, when you when you translate between mathematics. And we use the same words that mean different things. So we wrote this recent paper like homology of homologous proteins. And homology, which is a tool in topology, is also something that's used all the time for studying proteins that are similar, or homology in the brain. Again, like the same word. And so being able to figure out exactly what someone means requires this communication, as you said, which, I don't think I'm

necessarily doing it very well, but I'm trying to understand enough of what other people you know what an expert is working on to be able to extract what are the kind of assumptions that we can encode into some mathematical problem? But we want to gain insight about the data and this is where we use the mechanistic models. So for example, even in this breast cancer you know project, we then used these differential equation models to understand each of these different separate clusters we found in the data. Or with the problem that we've looked at whether it's the spatial vascular networks, these tumour blood vessel networks, we're analysing that type of data. We're doing this now and then trying to compare that type of data with different models. And so the idea is that certain parameters or certain you know the rate of a reaction or interaction between species, that will change in different data sets, and that's actually what we found when we looked at some of this fruit fly data related to cancer. That the mutation we compared, the mutation versus the wild types of this cancer mutation versus wild type and we actually showed in a number of studies that this rate is very different. So they saw this in the experiments, but then we also were able to kind of pull more information out in the in the models. So it is really important to get that mechanistic understanding that only mathematics can provide. It's not a statistical problem.

Vicky Neale:

You talked about sort of historically, there being more focus on the mechanistic models, and now you've got these sophisticated data analysis techniques, but I guess the point is that that's not getting rid of the mechanistic models. Those are still really important, and in fact it's kind of in some ways the interplay between these techniques and these approaches that adds to the scientific understanding.

Heather Harrington:

Exactly, exactly, and I mean with some of these mechanistic models, they're too complicated in certain aspects, and so we've been developing mathematical approaches that are using pretty deep mathematics. So, for example, differential algebra, which is an area of mathematics that is really difficult to penetrate in certain respects, but we're using these approaches, computational approaches, to try to say OK well, actually the model that we have, it might be the best model that represents our assumptions, but it's not possible to compare the model with the data that we have. So we need to actually reparametrize. We need to change the model, we need to simplify it or reduce it, to make it so that we can compare the available data, which is very high resolution etc, but just sometimes we can't actually make predictions and get insights from the very large model we have to reduce it in a certain way, and that's something that we've been, yeah, really, using the available observations to motivate, yeah, these methods.

Vicky Neale:

I have lots of words beginning with c in my mind, just listening to you talking about your experience of research. We talked about creativity, curiosity, collaboration, communication, making lots of connections. It seems to me that you really enjoy making connections between between intellectual areas, but maybe also between people. It sounds as though you enjoy that aspect of what you do.

Heather Harrington:

Absolutely. So we have this group meeting and occasionally we have somebody within Oxford come. And I mean Oxford's very small, right. So I meet them somewhere within Oxford. They tell me about a problem. I say, oh, why don't you come and tell us for 10 minutes about this problem, and it could be another PhD student and they want to do something quantitative with their problem. And I say,

well, just come in and give it a 10 minute chat about what your problem is. And then you know there's a group of mathematicians, and I kind of think of as a mini study group, you know? Or one of these very small. It's just a 10 minute chat and say Oh well, actually I think if you're only looking, you want to answer this specific problem, you don't necessarily need math for it, maybe just a machine learning task. Or if you want to do this then you might not want topological data analysis. This system might be better for, you know, putting into a linear algebra framework where you can solve some linear algebra problem, or you know. So what we're doing is not saying, OK, let's have someone come and talk, and we use one or two different tools. We say maybe this is the best thing and that's really fun, connecting people with other areas as well.

Vicky Neale:

You mentioned that you had initially thought you might study medicine, so you studied applied maths as an undergraduate in the US and then came to Imperial as you mentioned for Masters and PhD. At what point did the medicine dream disappear? At what point did you decide mathematical biology was kind of what you were going to do? Has the medicine dream disappeared? Are you still secretly planning to go and retrain as a doctor?

Heather Harrington:

No, I'm not planning to retrain as a doctor. I realise that I, I don't think I'd do very well, yeah, with that type of pressure with patients. Actually I think it's, I'm much more comfortable to work on a problem a little bit slower. Not necessarily we're working slowly, but just take a bit more time to really get into some of the details which I think in medicine, if you're trying to treat patients and kind of juggle all of this, yeah, it's not necessarily right for my personality. But I think that my interest in biomedicine hasn't stopped in a lot of respects. So I talked about this loop of Henley modelling course in undergraduate where that was one of the examples which has remained in in my mind, and and that actually, looking at the kidney, I then spent a couple of summers working in nephrology division, interning, and I had many interesting discussions with people there, and they were used. They had statisticians that would come. And I just thought, oh I really want to use mathematics to look at some of these problems, and I've never studied anything in the kidney until recently, where now we have a collaboration with experimental and clinicians here in Oxford, and this is a current collaboration which is very exciting, where we're trying to make sense of when you have different levels or organisations of data. So sometimes you have data that's gene expression and sometimes you have the gene expression at different locations, so it's what's called spatial transcriptomics. And I mean the technology is just so incredible and they're looking at this in a mouse kidney model. So looking at, yeah, studying the kidney and the response of the immune system and the kidney. And so we're trying. Well, it's very cool. We came up with some mathematical method and it gave a prediction about about the immune cell function or immune cell, kind of location of immune cells in disease versus not, and they've gone through and done some further tests and we found we validated it. And so that that feels really nice. So I mean, that's not going to be translated immediately to the clinic, but at the same time, there's other problems where it definitely has more clinical relevance. For example in collaborations with the Ludwig Institute, which is a cancer research institute in Oxford where we're looking at clinical trial data. Or with the COVID-19, There's a COMBAT consortium where we were looking at many different types of measurements of data with COVID response patients early on from COVID. So I think that there are definitely connections to kind of personalised medicine and patient subtyping and all of this using some of these sophisticated mathematics.

Vicky Neale:

Can you say a little bit more about any of the collaborative work you're doing with the Ludwig Institute? Is there an example there that you can talk about a little bit about this kind of connection with clinical trials?

Heather Harrington:

Right, I mean, well, one of the problems they're looking at is of organoids, so that's not the clinical trial project, which we have a number of things going on there, but something that I think is maybe a little bit easier to kind of explain is that they look at mini organs. So you can grow organs, mini organs. This is just a collection of cells in a dish, and they can do that many times. And you could have some organs, mini organs, that have some mutational status, for example with cancer and some that don't. And so the question is something about kind of shape of these mini organs over time, and so we've been developing topological approaches, and that seems very promising for being able to study that and characterise it and understand,yYeah, the shape of these organoids over time, and that's ,yeah, that's really exciting.

Vicky Neale:

You've talked about how quickly things have developed already in your career. Are there things that you are kind of looking forward to now? What are the next developments that you're excited about? The things that might be just around the corner?

Heather Harrington:

Oh goodness, I don't know where to start, I mean. Maybe things that are not just around the corner, but I believe that, so I started out using computational algebraic geometry to look at kind of the global behaviour. So this is nonlinear algebra to look at the global behaviour of what can happen in a mathematical model or hypothesis. So rather than look at something locally with just what's around a very small region of the possible kind of space of solutions or possibilities or cell decisions, etc, looking at kind of the global behaviour. And what's very cool is that there's a lot of connections between algebra and topology. And these connections are. There's a lot of theory, but then, actually being able to put together the different computational and mathematical approaches to solve some of the bigger problems. I think that's kind of the next big kind of mathematical problem. So I'm very excited about computational algebraic geometry, as well as the of course our centre for TDA and the computational algebraic topology. And here in Oxford, I mean I'm not doing this now, I'd be very excited to, but here in Oxford, right, we have a quantum computer. And in 10 years or 15 years or whatever, within some short period of time, we'll be able to compute things that we can't currently do, and that is the reason we don't use some of these very sophisticated mathematical techniques.

Vicky Neale:

They would take too long to run on a computer.

Heather Harrington:

They would take too long, or there's not enough memory to run them. I mean, there's just all of these reasons that they're very powerful. Theoretically, we can compute these things right, but then practically we can't. But a quantum computer we could. And so I mean I don't have any, if you ask me for references and all of this, I won’t be able to give them to you, but I think that's something that's the future is really thinking about. Big data and making sense of it will be possible. We won't have to compress you know these super large files. OK, we might still need to compress the large data files in some way, but actually extracting the information, we won't have to compress it when

we do that analysis, we'll be able to exploit all of that very high resolution yeah data. So I think, I don't know, I think that there's a lot of cool mathematics, and yeah, mathematics integrated with statistics and computation, and I really feel like this will be kind of the symbiotic relationship between maths and biology will continue and just become more and more important.

Vicky Neale:

Fantastic, and what advice would you give to somebody early in their studies now who's interested in using maths and stats to understand cancer?

Heather Harrington:

I don't know where to start. I think people should follow what they're most excited and most interested in, right? And this is a journey. I really thought I would go into medicine, but I loved math, right? I went to a geometric combinatorics thing when I was an undergraduate, spent a summer and I just loved it. I loved the beauty and the elegance and the how perfect and crisp some of the mathematical problems were. And biology is very messy and can be frustrating to try to make sense of this. I think having a strong foundation in mathematics is really, really important because math gives you a way to think logically about problems and to formulate you know these problem statements. And this is as a mathematician speaking, but I think that it is really important to have some strong foundations to be able to apply some of the more sophisticated mathematics.

Vicky Neale:

Would undergraduate Heather be surprised at what current Heather is doing now?

Heather Harrington:

Absolutely, absolutely. I mean, I did an internship in nephrology so that I could go to grand rounds and I got to, I don't know if I was allowed to, but they let me go watch lots of operations and surgeries. I thought I wanted to be like a vascular surgeon. I'd watch tons of vascular surgeries because many of the surgeons would say, oh, we have a student that's observing and patients always said yes and it was amazing, and I just realised I couldn't stand for 16 hours for some of these complicated procedures and not move. And absolutely I mean now to think that I'm in England, which I never thought I would have come over here. But it's a really special place to be able to carry out this type of research.

Vicky Neale:

And your love of the mathematics and your curiosity and desire to understand these complex biological systems just comes across really clearly. And I love the fact that your, I guess your desire to help patients through medicine, well you're helping patients now through mathematics, so it's another way to achieve that goal, I guess. Heather, thank you so much for your time today. I just found our conversation fascinating. Hearing about your work was great, and thank you also for all of your energetic work driving forward these areas of research and finding new ways to use maths and stats to treat cancer. Thank you.

Heather Harrington:

Thank you Vicky.

Vicky Neale:

Thanks for listening to this episode of Maths + Cancer. I hope that you found the conversation as interesting as I did. There are more episodes of Maths + Cancer, as well as features about Oxford's research into cancer, at ox.ac.uk/cancer . If you're enjoying exploring how maths and stats help us to understand and tackle cancer, I'd love it if you'd tell your friends about the podcast. And please do join in on social media using the hashtag #MathsPlusCancer. That's plus the word, not the mathematical symbol...