Maths + Cancer

Episode 3: Medical imaging and radiotherapy with Tom Whyntie

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.

My guest today is Tom Whyntie, a teaching fellow in the Department of Oncology here at the University of Oxford and Director of Studies for the Oncology MSC Radiation Biology programme. He describes himself on Twitter as a reformed particle physicist. He has a PhD in particle physics and has previously carried out research at the Large Hadron Collider at CERN. If that doesn't sound like the obvious background for a cancer researcher, well, that's something we can discuss today. Tom also has lots of experience sharing complex scientific ideas with a wider audience. Tom, welcome to the Oxford Mathematical Institute. Thanks so much for coming over from oncology to talk to me today.

Tom Whyntie:

Thank you Vicki, pleasure to be here, thank you.

Vicky Neale:

So we have this lovely room. We've got wall full of books behind us. I haven't looked to see how many of them relate to maths and cancer so we can check that out later on, but this is a podcast about maths and cancer and I'm guessing that you might describe yourself as a physicist or a medical physicist. I'm not sure. Are you happy if we blur any lines there might be between maths and physics for our conversation today?

Tom Whyntie:

Well, I mean the thing is Vicky I'm not sure I like to be pigeonholed like that, you know I mean, I mean, it's such a broad interdisciplinary topic, no, but yeah. So as you say, I, I'm a particle physicist originally by training and the idea of, you know, look at the very fundamental particles, the very building blocks of matter that make up everything. And so yeah, I spent two years out of the Large Hadron Collider, the LHC, out in Switzerland. Ah, so although I'm, so I am on the author list for the paper for the Higgs boson discovery, which. Was 2012, 10 years ago. Instantly dating the podcast, but yeah well, but I was actually looking for dark matter so this missing 20 odd percent of the universe which. Yeah, we were hoping by smashing the protons together, energy into mass. All that sort of thing would create these. Yeah, dark matter candidates, version of supersymmetry for the experts out there. Yeah, we didn't find it.

Vicky Neale:

I guess that's the nature of scientific research, isn't it?

Tom Whyntie:

That's the thing, but the important thing is we still haven't found it. So you know there's no embarrassing epilogue to write for the thesis or anything like oh yeah, we just weren't looking hard enough, but no, we did have one of the first papers out sort of saying, oh, it's not there but. But yes, 10 years later. Still, still nothing. So in terms of that journey into yeah, medical physics and sort of cancer research, yes, I'm afraid it was quite the stereotypical thing of. I suppose I probably should do something useful now, you know what I mean. So, uh.

Vicky Neale:

And what was it that drew you to oncology?

Tom Whyntie:

Excellent question in that it was quite a, as with most things, it's kind of a serendipitous thing, so initially I, obviously with particle physics you're dealing with billions and billions of collisions a second. It's scanning through the events to look for different things...

Vicky Neale:

So you have epic amounts of data.

Tom Whyntie:

Epic amounts of data. That's the official technical term. Epic amounts. I mean, literally petabytes of stuff coming out sort of every year that you'd have to store and process and all that sort of thing.

Vicky Neale:

OK, OK, I'm glad I got that right.

Tom Whyntie:

Which obviously leads into the realms of big data, which I'm sure you'll be discussing, or have discussed on another episode, but in terms of that concept of. Having masses of data to scan through, pull through, the computing facilities that you need to do that. Uhm, so I had some experience in that. Long story short, a postdoc came up looking at big data applied to medical imaging. And so that was at UCL. And so we had tens of thousands of brain scans, MRI scans.

Vicky Neale:

So this is no longer data about particles colliding. This is now about data coming out of patient's brain scans.

Tom Whyntie:

Exactly and yeah, so MRI scans are magnetic resonance imaging. Uhm, so the particular pathology I was looking at was the atrophy associated with Alzheimer's disease. I where the grey matter areas in the brain sort of shrink and we were looking for automated ways of doing that by sort of applying big data techniques to the MRI scans of the brain. But yeah, that then led to another post doc actually here in Oxford at FMRIB, The Centre for Functional Magnetic Resonance Imaging of the Brain that's over at the John Radcliffe Hospital. So there we were, looking at the UK Biobank data set. Now there they've got sort of systematic imaging programme. For I think people aged between 40 and sort of

60-80 odd, sort of the ageing population basically and it's a prospective study that basically you image everybody now. See what pathologies develop, what sort of illnesses they sort of get and then look back in their datasets to see if there are any clues that would lead you to go, well.

Vicky Neale:

So this is patients who agree to be involved in a research project.

Tom Whyntie:

Volunteers, yeah, not even patients, yeah.

Vicky Neale:

And yeah, they're OK. They're not patients yet 'cause there's nothing wrong.

Tom Whyntie:

Exactly, yeah.

Vicky Neale:

They're just agreeing to take part in this research.

Tom Whyntie:

Yeah, they give permission for their medical records to be kind of analysed, anything flagged up, and again so at the time the sort of ten, twenty thousand odd, uh, imaging datasets, and again, it's all done well, this is the neuroimaging data we were looking at, but I guess since then they, again it's sort of tens of thousands every year, sort of continually being added and analysed in that sense and there I was. Yeah, involved in the analysis of that. And again, looking at sort of big data techniques to look at different sort of, that was focusing on the structure of the brain. Again, sort of. So again, grey matter, white matter measurements, automated ways of doing that, 'cause obviously you don't want to be scanning through ten thousand scans.

Vicky Neale:

It's just not practical for a person to sit through and look at analyse all of these scans.

Tom Whyntie:

Exactly, so in a clinical setting obviously you have a radiologist looking at every scan. To be fair, they do that with the biobank scans as well for sort of any sort of incidental findings, but yeah, obviously ideally you have. Again, massive sort of computing nodes. Scanning for all these things, looking for potential signatures of interest. But this thing came up with something called magnetic resonance guided radiotherapy. Radiotherapy is a treatment for cancer where you apply ionising radiation in an attempt to kill the tumour cells while sparing the healthy little tissue around it. Magnetic resonance imaging is obviously where you're looking at inside of the body using a non-invasive, non-ionising technique.

Vicky Neale:

This is one of these quite common scanning techniques that people might have for cancer, but also for all sorts of other kind of things. Doctors need to look inside the body, that's one way of doing it.

Tom Whyntie:

Exactly so, magnetic resonance guided radiotherapy is this concept, which I hadn't heard of before where you combine an MRI scanner with a radiotherapy machine. And use the MRI scanner to look at what you're targeting.

Vicky Neale:

So that you're really trying to make sure that that radiotherapy is damaging the bad cancer cells and sparing the healthy cells.

Tom Whyntie:

Exactly so, so in many areas of the body. Uhm, you don't actually need it because there's not much motion. So if, the prostate, for example, you know you pretty much know where that is, you can do various sort of compression techniques to stop motion. But for the stomach, for example, the gastrointestinal tract if you will, upper GI we call it, there can be a lot of motion. Just through involuntary sort of peristalsis or your bowels move about, what have you.

Vicky Neale:

So during the few minutes that a patient is on the radiotherapy machine, there might be motion going on that would affect the radiotherapy.

Tom Whyntie:

Exactly, and particularly somewhere like the stomach, or pancreatic cancer is the classic one, 'cause of course the pancreas is very close to the jejunum, the small intestine. Yeah, there if you, if something moves and you hit the wrong bit, you're in trouble because you'll have secondary toxicities to the jejunum, could have terrible effects, which is why in general with pancreatic cancer radiotherapy isn't used because the prognosis for pancreatic cancer isn't great, order of sort of months. The last thing you want is. To go through radiotherapy and all the toxicities and side effects associated with that, but with MRI guided radiotherapy. The plan is you can avoid that, and the studies have been done so far indicate yes, that is a promising thing. And it's kind of a. Kind of a no brainer when you think in terms of, if you can image the body live as you're delivering the radiotherapy treatment, and this is the amazing thing, some of these machines actually just turn the beam off, when, so there's live target tracking of the pancreas, for example.

Vicky Neale:

So this isn't the human who's running the radiotherapy machine who's doing it. The machine is taking care of it automatically and could potentially adjust.

Tom Whyntie:

Exactly, yeah, so obviously you have a radiotherapy specialist monitoring that. But yes, yeah, an automated system that will beam off, beam on.

Vicky Neale:

So I think I understand what this magnetic resonance guided radiotherapy is. Where do you come into it?

Tom Whyntie:

Well, so uhm, as a particle physicist, we use very large magnetic fields intentionally in our detectors. So the Compact Muon Solenoid, which is the CMS experiment I worked on, had a 3.8 Tesla

solenoidal magnet at the centre. Which is about 400,000 times the earth's magnetic field. Pretty big, you don't want to stand next it with your car keys in your pocket. Very powerful stuff, so what happens there when protons smash together charged particles come out, as you know, particle, charged particles when they're in a magnetic field experience the Lorentz force and sort of curve round in little tracks, and from those curly tracks. The curvature of the tracks. You can work out the momentum that they have and then with the energy deposit you can then just use Einstein's equation to work out what's the mass of the particles.

Vicky Neale:

You make it sound so easy.

Tom Whyntie:

It was but I mean that's all we were doing though, just sipping coffee and saying run the thing, set up your spreadsheet, and off you go.

Vicky Neale:

But you've got this massive magnet, so you're an expert at kind of understanding ionised particles in the presence of a large magnet.

Tom Whyntie:

Well, this is the thing. So in radiotherapy, obviously it depends on the type of radiotherapy, so radiotherapy machines delivery either the radiation via photons so either kV or MeV photons, basically sort of high energy things. You can get a proton therapy as well, which is a. They're a very different thing because protons are a lot more difficult to produce and accelerate.

Vicky Neale:

And this is this kind of new, specialised therapy, you sometimes hear about in the news, proton beam therapy, but that's not the kind of ordinary type.

Tom Whyntie:

Yeah, so your standard radiotherapy machine will use high energy photons, but of course to produce those photons you smash electrons from a linear accelerator into a tungsten target. And from that radiation, that's what goes into the radiotherapy. But the point is you have charged particles like electrons being used to produce that radiation.

Now, if you've got a magnetic resonance imaging scanner there, they also use very high-power magnets. I hadn't quite appreciated this. So when I was like, oh yeah the CMS experiment, 3.8 Tesla, pop down the John Radcliffe, you know they've got like 3 Tesla scanners. Sort of every other room. I was like, oh okay, we're not so, obviously they're not as big. So the diameter of the CMS experiment was about 1 1/2 inches.

Vicky Neale:

It's a very niche competitive magnet.

Tom Whyntie:

Very yeah, yeah, basically, but your typical bore of the hole that you go into with an MRI scanner is about sort of 50 centimetres, 80 centimetres.

Vicky Neale:

But all of a sudden you're looking at a project and thinking I know loads about high power magnetics. I know loads about charged particles, maybe I could be useful here.

Tom Whyntie:

I couldn’t believe it, it was like surely this is the perfect combination of particle physics and MRI imaging together at last. So yeah, so the actual research that we're involved in was imaging in the context of radiotherapy, so you'd use the imaging to obviously not only monitor the position of the tumours in real time, but also do your radiotherapy plan. So you'd image on the MRI scanner, compare that with the CT scan, the computer tomography, which is a more traditional scan using X-rays. We'll get into that later. That's what you use to create a treatment plan and. So yeah, so because I could go between the MRI and the particle physics of the radiotherapy, it's. like this is, this is amazing. So we were setting up the clinical trial to yeah, look at the effectiveness of this technique for pancreatic cancer. I believe that trial is just started now actually, but yes, I'm not working on that anymore, but I still sort of dabble, it's more teaching these days, but yeah, that's how I got there basically.

Vicky Neale:

Yeah and I guess it's interesting, I was trying to sort of think about oh what might Tom be interested in as a physicist working in this area and I was guessing medical imaging and I was guessing radiotherapy, but actually it sounds as though you're really interested in where those two come together, which is kind of particularly interesting. I guess that sort of brings together those transferable skills from your particle physics background.

Tom Whyntie:

If you mean are we finally doing something useful with particle physics, yes.

Vicky Neale:

That's not what I'm saying at all, I'm a big fan of fundamental particle physics too. But it's lovely that from your point of view that those kind of, intellectual interests came together in a way. And then you're actually seeing the impact on that, potentially for patients. I guess that's a really different experience.

Tom Whyntie:

This is the thing, so I mean you know I used to give a lot of schools talks. You know where you talk about particle physics and the question I get, you know. Well, actually it was more the general public ones. You know. You get people, yeah, but you know why are you spending £5 billion on the Large Hadron Collider sort of thing and you go well, one, 'cause it's quite nice to find out you know the answers to these questions, but you can genuinely say the spinoff technologies from these machines. Say, for example, the superconducting magnets that used to bend the path of the seven TeV protons as they go around the 27-kilometre ring in Geneva. That magnet technology, in terms of the superconducting magnets that you need, yeah, will be applied to the very MRI scanner superconducting magnets that are used to image patients regularly, every day, billions of patients around the world sort of every year.

Vicky Neale:

So that's yeah, I am by background, a pure mathematician. I am interested in mathematical questions for their own sake. I am interested in scientific questions for their own sake, but it's also really interesting seeing these potentially unexpected applications of them where if you have that fundamental understanding of what's going on mathematically, scientifically, you can then use that understanding in all sorts of interesting ways.

So let's talk some more about the maths. I know you said that the maths is not your favourite thing, but let's talk some more about the maths, so I have radiotherapy as part of my treatment. Uhm, I was, I was a patient, I had to lie extremely still, the team looking after me positioned me in just the right place on the table. They positioned the table in just the right place and then this sort of rotating arm would come round with a kind of head on. That stuff came out of that. I couldn't see, of course, because these are particles that I can't see. So you just lie there and trust that something is happening. You can't detect any evidence. As a patient, it doesn't hurt. You can't feel anything, but once I'd done this a couple of times and I kind of learned the drill of what happened. Basically, my job was just to lie extremely still, for a short number of minutes while this happened. And after the first couple that's not so exciting because it's just the same thing every time for however many times you're there having radiotherapy. So, then I start to think about, well what's going on here and there's a sort of circular disc over me that's kind of being angled to direct the beam to the right place. And as you mentioned earlier, as I understand it, this works by the particles damaging, well damaging cells, and you want them to damage the cancer cells and not damage too many of the healthy cells, 'cause that's when you start having side effects and kind of implications and so on for the patient.

So there's sort of complicated things going on in this head. I could see bits moving to kind of direct and shape the beam, and I'm going. Oh well, that's really interesting. How do they do the geometry? I know they've done the scans. They've got this image. If they know exactly which bit of me they want to target, but someone, somewhere must have figured out how they angle that beam to try to maximise hitting the area that they want to hit and to minimise hitting any kind of healthy tissue around it. Is that being done by a human, are they doing some complicated geometry? Is there some amazing software that has it? I'm going what's the maths of this? So is that something that you can talk about a little bit?

Tom Whyntie:

I can talk about it a little bit.

Vicky Neale:

I'm not asking you to do the calculations for me.

Tom Whyntie:

That, I yeah, I won't be producing a radiotherapy plan at the moment, but no, it is yeah, fascinating. You're absolutely right to be thinking you know, how do they do it? Because , yeah, what you're talking about is, you know, the very first rule of Large Hadron Collider club is don't stick your hand into the beam, because you know high energy radiation is very damaging.

Vicky Neale:

And that's the whole point of radiotherapy is that it's damaging you just want to be careful how you do it.

Tom Whyntie:

Exactly, and this is the, so like I say I teach on the MSc on Radiation Biology and the fundamental thing about the course is that it really is this fusion between doing the physics and the biology in terms of just being so interdisciplinary, you need to understand both to understand what's going on. And the thing with radiation, ionising radiation in particular, is that really, the cliche is that it's this double-edged blade in the sense that what ionising radiation fundamentally does in the context of radiotherapy, or indeed cancer in general, is it causes DNA damage. So that's the main sort of thing that you're talking about when you're talking about ionising radiation, both in terms of safety but also treatment of cancer.

Vicky Neale:

So is that the same kind of issue that means that if you are exposed to the sun too much that you can potentially get skin cancer? Is that the same kind of principle of ionising radiation causing DNA damage?

Tom Whyntie:

Exactly, yes, I think so. I'm less of an expert on the skin cancer example, but certainly yeah, in general, any point where you have something like a high energy photon or indeed alpha radiation, little helium nuclei from, you know, even smoke detectors and radon gas, you know if you live down in Cornwall, you have to have radon sensors to look out for radon gas coming out of hings 'cause that releases alpha radiation. But yeah, any kind of thing that can be thought of in terms of DNA damage. I mean DNA is incredible in the sense of it encodes all of this information a bout how to build a human being, how to build a hamster. All that sort of thing in these, combination of the base pairs: adenine, guanine, cytosine and thymine, this is all held together in an incredibly delicate sort of framework, and Watson and Crick sort of discovered it, obviously, based on Rosalind Franklin's data that she got at Kings College.

Vicky Neale:

They will charge less.

The famous double helix.

Tom Whyntie:

The famous double helix structure. And what's fascinating is all of that information is encoded and tells you how to. Yeah, build a human cell so the human cell I think has about 9 billion of these base pairs. It's amazing when you look at how the body or how even a cell replicates the DNA. Mistakes happen, but then again there are these proteins that correct these mistakes as things go along.

Vicky Neale:

Like a proof-reader fixing the typos.

Tom Whyntie:

Like a proof-reader. But the fascinating thing is that there are these self-repair error checking mechanisms that all exist within the cell that all go in all the time in our body, in every cell which is just amazing when you think about it. Now radiation enters the picture. That's where you've got a problem. When you think about it, the DNA bases are just molecules made-up of atoms and they all have their own little atomic bonds and things together and what have you, and by definition, ionising radiation is stuff that knocks electrons out or knocks different bits out of those things. So you're smashing up this very delicate complex encoded structure, which generally speaking it's not a

problem because like I say these error correcting mechanisms exist that will correct and that is how you know we've got here.

If that system hadn't developed to make sure that we could survive that kind of radiation damage, you know we'd be in trouble. And I think there are even some theories that say that it was that sort of radiation damage that, causing mutations, that lead to evolution and things. And there are various theories, some more crazy than others, some written by people in green ink, you know that sort of thing. But anyway the point is. Radiation in that sense can be bad. Now with cancer as I understand it, the issue is not so much the radiation damaging DNA in the first instance, because there are these self-repair mechanisms. It's where you actually damage the bits that do the repair. And they're all. There are certain sort of things, I think in the cell cycle that's, sort of checkpoints, that the cell will reach a certain checkpoint and go right. Am I going to reproduce now or am I going to stay as I am, or am I going, is this the end for me? Is it time to go? From what I understand some cancers, not all, I mean cancer is phenomenally complex stuff because, I'm sure you're aware, but sometimes for example, radiation would damage one of these bits that says, right we shouldn't reproduce anymore.

Vicky Neale:

And that's where you could end up with uncontrolled growth and a tumour growing.

Tom Whyntie:

Exactly, yeah, yeah. So in that sense from the how does cancer start side, that's where radiation can be bad. In terms of radiotherapy and treatment what you're hoping is, because the cancer cell, the DNA has been affected in these uncontrolled ways and a lot of the mechanisms are broken, what you're trying to do is induce so much damage with additional radiation that then the cell just goes, yeah, now I'm out and the tumour stops reproducing and all the tumour cells stop reproducing. And then yes, hopefully the tumour goes away, and cell death occurs as, not as normal, but the cells just die.

Vicky Neale:

And the amount of the amount of radiation in radiotherapy is much more than we would ever stumble across in our daily lives to achieve that effect.

Tom Whyntie:

Absolutely yes. Phenomenally more, yeah, many orders of magnitude, so yes. So while you're sitting there and thinking nothing is happening or you can't see anything. Yeah there will be something, but of course the way that they calibrate these machines and make sure, there are various things called quality assurance plans that that make sure, and they'll rerun the treatment essentially that you've had, with detectors in place to make sure, right what we did there that was exactly what we saw here, so we're very confident that that was the dose received.

But the idea, so you mentioned that you went back to several sessions of radiotherapy. It's not just one thing where you go back and the idea there is, again it goes back to mathematics in a way in terms of cell survival and regeneration. The idea is that normal, healthy tissue, because most of the, well hopefully all the cell repair mechanisms, DNA repair mechanisms in normal tissue will be working just as expected, so you break up that prescribed dose into multiple fractions. And the idea is that the normal tissue recovers and does that repair before the next lot and then, but the tumour cells just can't.

Vicky Neale:

And in terms of that frequency, I think it's common, certainly I was having mine daily Monday to Friday over a period of weeks, so there's sort of 23 hours and 45 minutes or something for the cells to kind of recover. For the healthy cells to do their best to recover in between times.

Tom Whyntie:

Exactly but it also, not bizarrely, 'cause when you stop and think about it, it's kind of, all the cells in that cell cycle will be at different stages at the very instant that you get that radiotherapy. So if you hit the cell at a certain point in the cell cycle, you'll have more effect than you will at another time.

Vicky Neale:

That's really interesting. I tend to think of cells as a static thing, but they're not. There's this kind of cycle of processes.

Tom Whyntie:

Again, this is why I have infinite respect for biologists, because when you start to think about the complexity of what's actually going on inside your body, I mean. Think of particle physics fundamentally, you've got two things colliding together, you know, two body problem, easy, math is fine. Conservation momentum, easy peasy. Biology, you have all these systems, molecules, atoms interacting. And yeah, as you say, the stuff is going on, but if you stop and think about too much, I mean.

Vicky Neale:

And elsewhere in the podcast we're talking about the role of mathematical modelling and biology and how you can take those immensely complex systems and try to abstract out the kind of key essence of them to try to make sense of them. Because they are so mind-blowingly complicated with all of those details.

Tom Whyntie:

Yeah, and of course the, you know the stereotypical cliched thing you do as a physicist is like, well, a cell is just like a sphere, basically a sphere of water maybe, but then yeah, biologists will get very cross with you, and rightly so you know, it's very complicated.

Vicky Neale:

So I think we've got to the kind of idea of radiotherapy, and this idea of using very high energy radiation that will damage the cancer cells beyond repair, but you structure the treatment in such a way that you give the healthy cells the best chance of recovering. But you also try to direct the beam carefully, and I'm going to pick up on this again, 'cause I'm really, genuinely interested, having sat in this machine, lay on this machine for a long time, thinking how do they get the geometry to try to work out to hit exactly the stuff they want to hit and not too much of the rest? Is this feeding in some parameters to a piece of software that does some interesting calculations based on previous work, or are the radiotherapy teams sitting there doing that on a kind of bespoke basis for each individual patient? Or how does it work?

Tom Whyntie:

Excellent question. Thank you for bringing us back to the point. I kind of went off on the physics there but yes so. I imagine the first thing you will have done as part of your treatment is have a CT scan. A computed tomography scan based on X-rays which will produce a three-dimensional image of inside your body. Now CT scans in contrast to MRI scans, do feature ionising radiation. The X-rays that are used in that are ionising. They are lower energy obviously.

Vicky Neale:

Yeah, so the amount of radiation you get from a CT scan is tiny. Nontrivial but tiny.

Tom Whyntie:

Yes, but it is absolutely something that is considered in terms of patient safety and the yeah, the guiding principle is ALARP I think, as low as reasonably possible, in terms of the amount of radiation that you receive.

Vicky Neale:

The benefit to the patient of having the scan outweighs the kind of potential risks of having it.

Tom Whyntie:

Exactly yes, whereas MRI is completely non-ionising and so you know there's no risk to the patient like that unless you've got like a metallic implant or are claustrophobic and they do take longer, but with, yeah so you start off with the CT scan which provides the map of the body, and from that and possibly in combination with other imaging, they will know where the tumour is, where the target site. It can be called either the, well the gross tumour volume, the GTV, is the sort of big bit that they're aiming for. The PTV, the planning target volume is the bit where they will aim to deliver the radiation uniformly, as much dose as possible to the tumour.

Now within that you have the constraints of the organs at risk, the OAR's as we call them, and yeah, they are the bits that you don't want to hit, so there are particular parts which are more sensitive than others, for example the colon or anywhere where you have lots of cells reproducing, basically anywhere yeah, sort of bowel like or intestinal you want to avoid, obviously lungs, hearts, all the key vital organs basically yeah, don't hit those. So what you'll do typically is a, the radiotherapist will, or radiographer depending on who it is, basically trace out the bits that you want to either hit or not hit. It's called contouring.

Vicky Neale:

You're describing just drawing with your finger. You're sort of drawing a squiggly outline that captures precisely that region.

Tom Whyntie:

Basically yeah, so there will be a screen. And yeah, either using the mouse or scribers. And because it's not always clear from a CT scan or MRI scan exactly where the boundaries are.

Vicky Neale:

Yeah, and sometimes I guess the radiotherapy is trying to hit an actual tumour and sometimes it's more of a precaution where the tumour has been removed and you're just trying to make sure that there aren't cancer cells remaining.

Tom Whyntie:

Exactly, and there is an entire subject discipline focused around auto-contouring as they call it, so using big data, deep learning image processing techniques to automatically identify organs, tumours, and what have you, and they'll do that for each slice of the CT scan, ‘cause although it's a 3D image, it's essentially made-up of each kind of slice of 2D images basically. And that will create these regions that you want to hit, and want to avoid, and then yes. In a nutshell, there is a very nice bit of software that will perform the optimization problem and actually the mathematics of that is fascinating. Well beyond my expertise I'm afraid.

Vicky Neale:

But it sounds like that just the kind of thing that maths is really good for, optimization problems. I want to hit as much of this while hitting as little of that as possible. Those kind of problems are areas where mathematicians have lots of expertise, so it sounds like the kind of place where I can see maths is relevant.

Tom Whyntie:

There are terms like, it's a convex problem, is that it? Or a concave problem? In terms of optimization, it's like which way does the curve go, but there are obviously you know practical constraints like we can only run this many beams,, for this amount of time at this sort of angle.

Vicky Neale:

Right yeah, what can the machine actually do? Not just what is mathematically, theoretically, an ideal solution.

Tom Whyntie:

Exactly, so you can imagine you know the mathematics just going, oh yeah, yeah so. If you had 10 million beams all here at the same time...you know. Obviously it's not. You're within the constraints of what the machine can do, but again, there's a whole industry and that’s actually, I think it's fair to say done more in the commercial sector in terms of yeah, not only producing the best results, but also in an optimum time 'cause you've got to run these optimization problems, you know, in a computer somewhere in a hospital.

Vicky Neale:

Yeah, it's no good if your mathematical process is going to take three years. Because actually the patient needs the treatment and again, mathematicians with optimization numerical analysis techniques are really good at those kind of questions.

Tom Whyntie:

Exactly and yeah, and those constraints will be set by, you know. Medically agreed limits on what the organs at risk can take as a dose, and they'll be your main constraints, but also at the same time you want to maximise that dose that you are delivering to the tumour, and going back to the MRI guided thing. You also have to account for uncertainties. So for things like motion, so respiratory motion is the big one, because obviously you have to breathe.

Vicky Neale:

So you’re trying to avoid the lungs, but actually the lungs are moving a bit while the patient is lying there.

Tom Whyntie:

So there are things you can do, like place sensors on the chest to kind of trace respiratory motion and only deliver the beam at certain points, when you're at that right point of the respiratory cycle. So you know the beam is going in the right place, but you can also just make those margins, those sort of boundaries, a bit bigger and the doses a bit lower just to be on the safe side.

Vicky Neale:

I think this is such a fascinating area of bringing together the biologists, and the clinicians, and the physics, and the maths, and this doesn't work unless you have all of those ingredients coming together, I guess.

Tom Whyntie:

Exactly, yeah it. It's again one of those examples of bringing in, you know, seemingly abstract optimization problem into a clinically relevant field.

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.

Tom Whyntie:

When you're developing these radiotherapy plans, what you need to know as well as you know where are you pointing the beam is, how far is the beam going to penetrate the body in order to reach the target? So that's the other nice thing about CT scans because it's the same type of radiation that's lower energy, but still, fundamentally, photons. You've already got that information. About the, what's called the electron density, of the all the tissue.

Vicky Neale:

So you can see how much it's being absorbed and how much it keeps passing through.

Tom Whyntie:

Exactly, so you can feed that into your optimization problem to work out how far the beams need to go, or how far they will go. Depending on where you're angling them. Things like that. Of course, with MRI scans you don't have that information. So in terms of doing the radiotherapy planning at the moment you still have to have a CT scan, so there's a very cool thing in deep learning called transform learning, so just to give a sort of concrete example, suppose you've got the human body imaged with a CT scan and you train up a deep learning model to do sort of analysis based on the data from the CT scans.

In transform learning, what you do is you take what that model has learned about how CT scans are done and literally transform those lessons about it to scans that you might have taken another way, for example with MRI scans. So the idea is that all the stuff you worked out with the CT can be applied to the MRI scans. So for example, you could then produce a sort of, what's called a pseudo-MRI scan from that CT data of the object and vice versa. And actually, that's the way around you do it because you want to create the pseudo-CT scan, i.e., one that involves ionising radiation from the non-ionising one, i.e., the MRI scan.

But that of course started out in a completely different field in deep learning, you know the very first sort of image analysis and identification stuff going back to AlexNet you know back in 2012. Where all these things, it was basically mainly about identifying things on the Internet and you know doing sort of object searches like that. But again, it's finding all these applications.

Vicky Neale:

And there's loads and loads and loads of maths in all of this deep learning, machine learning, all of these kind of things.

Tom Whyntie:

Exactly, although the thing I didn't realise about that, was these kind of algorithms and techniques have been around for quite a while, in terms of neural nets, but it was only in sort of 2010-2012ish, so again, about the time that the Higgs boson was discovered, that it really kicked off. It was GPU's, graphical processing units, really became available and cheap enough to sort of run these massively parallel calculations that you need to make neural nets work. Uhm, so you can thank the gaming industry for the deep learning stuff, which is then likewise fed into the medical and all this sort of thing. It's just how it all sort of relates together. It's, yeah I think that's the main thing about medical physics for me is it does bring in all of these kind of topics together into, ultimately, yeah, hopefully treating patients and making people better.

Vicky Neale:

So how much of your work now is kind of directly with clinicians and directly having an impact on patients 'cause that feels like a really different experience from being a particle physicist working at CERN or something, and how is that?

Tom Whyntie:

So I'm very much involved on the research side. I don't have much contact with patients. The timeline between you know, doing the research, the fundamental stuff in the lab, and, you know, actually bringing that treatment to patients can be quite long, and obviously a massively important part of that is the clinical trials part in terms of bringing an experimental technique or treatment or intervention to patients.

Vicky Neale:

And checking that it's safe and checking that it does what you think it's going to do and all of that kind of stuff.

Tom Whyntie:

Exactly, so yeah, I have again a phenomenal amount of respect for not just the clinicians and clinical trials teams who run these things, 'cause rightly so, there is a huge amount of paperwork because you've got to make sure everyone is safe, all the procedures are being followed correctly, so that's a you know, a hugely important part of that process, and Oxford has our clinical trials unit which does all that

But also the patients themselves who agreed to take part in these trials, 'cause you know it can be quite an intimidating thing to, or at the same time it could be a very exciting thing, but you know, without them we wouldn't be able to make this process and ultimately bring these things into the clinic. But it's interesting, you know, teaching on the master's courses when different students will have different, you know ambitions and thoughts about what they want to do. But it's fascinating

some of them really just hone in on the research, and just want to do the maths. But some people really want that sort of interaction with patients and seeing the impact that the treatment is having. So you know, just to plug the course, we offer the whole thing.

Vicky Neale:

And I wanted to ask you about your teaching because you and I have this shared interest in teaching, my students are maths undergraduates or sometimes they're school and college students who are particularly interested in maths. Who are your students? Who are you teaching, what is their background when they come to your MSc course?

Tom Whyntie:

Well, again, that's one of the great things about the course and why I find it so fascinating. The range is incredible, so from the very sort of, so this year, we've got someone doing astrophysics, and so we want to, you know, apply it to that sort of treating cancer, that kind of radiation therapy sort of thing, to biomedical engineers. I've got some people who're already in the clinic who are sort of doing this as a sort of more theoretical thing to possibly lead into a PhD or further sort of research study.

Because that's the other great thing, particularly in Oxford as well, I've come across some amazing clinicians. Who, you know not only are just saving people's lives, applying this sort of treatment, but then they're like, oh, I fancy doing a DPhil now, I'll just do a PhD in my spare time. And they will, and they'll sort of do all this stuff, but because they've got that clinical background, it's much more, not easier, but just, there were already sort of the links there to work with patients, to obtain data to feed into the research, so that's a very sort of common pathway as well. All the way through to the b iologists, who again maybe have more an interest at the molecular biology on the DNA side but want to get that greater grounding of, well, how does the physics work? How does this DNA damage occur? What can we do to stop it or optimise it?

Vicky Neale:

It sounds like a fascinatingly diverse cohort with biologists and people whose background means that they know lots about the biology, but maybe they have to learn a bit more of the physics, right through to the other end of whatever this spectrum might be with people who know loads about the physics, but maybe have to learn some biology pretty quickly, is that a kind of fair summary?

Tom Whyntie:

Exactly, yes. And yeah, one of the things we really try to emphasise is working together 'cause I mean, you know science is ultimately a team sport and this is almost the problem with, you know undergrad. You're always doing something very much on your own. Something we really try to emphasise is you've got to work well with other people, other people in your lab, other people from know you know, different areas that you might not be so familiar with. But, yeah, they do a kind of research dissertation project as well as part of the studies, and I mean, they're all great, but the ones I enjoy the most is where you've got like a physicist who has come and gone, right, now I'm gonna get to grips with the biology and they'll be there you know, with petri dishes and pipettes and things, but then sticking it in the radiator and seeing what the cells do when they're zapped and what have you. And it's, it's like, yeah, that's kind of for me that's one of the most satisfying things of the course. It's just bringing the physics and the biology together to ultimately yeah, hopefully improve patient outcomes and make people better.

Vicky Neale:

And thinking about your own personal story. You studied physics as an undergraduate. Did you do any kind of applications of physics to biology and that, did you have the option to do that, but you chose a different path? Or were you not aware that physics had these kind of potential applications to medicine?

Tom Whyntie:

Ah, that's a good question. Particle physics was all about how does nature work at the sort of fundamental level? How do we, you know...

Vicky Neale:

They're massive questions.

Tom Whyntie:

The massive questions, with the Higgs boson, literally the massive question. But yeah, I heard about the Higgs boson, this last piece of the standard model of particle physics that explains how we think everything works. And I was like, yeah I'd quite like to work on that.

Vicky Neale:

What do I need to do to get to the Higgs boson.

Tom Whyntie:

Exactly and the very kind of, I'd say pinnacle, peak physics for me if you will, was 4th year undergrad going through the mathematics of the Higgs boson. And actually, the quantum field theory of like oh, this is how this 125 GV, we didn't know the mass at the time, but. This is how this massive particle pops out with the maths. You know reaching that point I was like. Yep, okay, fine, I'm done now. Let's go find it and then and then we'll go from there. That said having done all that, the mathematics and the physics behind magnetic resonance imaging, I still think it is indistinguishable from magic, basically. Have you had an MRI scan?

Vicky Neale:

I have had numerous MRI scans.

Tom Whyntie:

And I'm sure many listeners will have as well. So basically, in a nutshell, you go into the scanner which has this very high uniform magnetic field.

Vicky Neale:

So, the scanner for people who haven't seen it, is this sort of donut arranged vertically and you slide through the hole in the middle.

Tom Whyntie:

And the doughnut is this massive coil of wire that is super cooled down to superconducting temperatures so you can get that high magnetic field and, long story short, that lines up all the magnetic momenta, in every hydrogen atom in your body, to point along that direction, and then you essentially tap it. We'll tap all of those with a pulse of radiofrequency radiation, so it's the same

frequency literally, as FM radio. There are two magnetic field strengths clinically used, 1.5 Tesla and 3 Tesla and the way I remember it is the Radio 4 frequency, sort of 92 megahertz, it is halfway between the two. So that's the thing that's stuck in my head, but anyway you apply this pulse of RF radiation and that knocks all of these spins off that equilibrium position.

Vicky Neale:

So they were all lined up in this particular direction for the magnet, and then you kick them a bit.

Tom Whyntie:

And that changes the frequency of each of these little spinning things in your body.

Vicky Neale:

So each of these things are going round and round, but then they're not going round and round at the same speed.

Tom Whyntie:

Exactly, and then what you do.

Vicky Neale:

I love how excited you are.

Tom Whyntie:

Well this is the thing, the signal that you then listen to, sort of the radio frequency broadcast that you get out. You apply Fourier transform to that and you get your image out.

Vicky Neale:

Just like that.

Tom Whyntie:

Literally, just like that. And the thing is, so Sir Peter Mansfield was one of the Nobel Prize winners for MRI scanning. He's one of the people to make those conceptual leaps to not only go through the physics of nuclear magnetic resonance to then applying that to a sample with the RF pulses, but then to go, we can make an image, just the conceptual leaps that you had to make. I think. I mean, it's why the Nobel Prize is fully justified for that, because if you think about the impact that MRI has had on clinical treatment diagnosis...

Vicky Neale:

The ability for clinicians to look inside a person's body in that way.

Tom Whyntie:

Exactly without having to cut them open without having to, yeah use ionising radiation. Yeah, is phenomenal. And like I say, to paraphrase Arthur C. Clarke, you know, any sufficiently advanced technology is indistinguishable from magic.

Vicky Neale:

And I think the Fourier transform, the Fourier analysis is one of those things where it wasn't created for this reason, this was a piece of mathematics that arose for completely different reasons. It has

very pure, very fundamental questions to be asked about it, but it also has these extraordinary applications that literally change lives, like for example in MRI scanning. And yeah, the next time I have an MRI scan, I don't know when that is, but I bet there will be one, I'm gonna lie there in the scanner and sort of picture all these little things whizzing round at the frequency of Radio 4 or whatever before they are kicked to their different frequencies.

Tom Whyntie:

That's the other thing as well, so if, well, you'll notice if you've been in an MRI scanner, and I have been in for research purposes, is the noise. And the reason for that is when you're creating these changes in the magnetic gradients, that involves applying voltages to these coils, and it's actually very noisy, and depending on the magnetic field strength of the particular scanner that you're using, you have to apply these pulses in different sort of frequencies, which you can actually programme into audible musical notes. If you've got the right sort of frequencies.

But there's a clip on YouTube of someone who has programmed that MRI scanner to play the Bach Cello Suites. But there's a serious point to that, in that there's a certain type of scan where it doesn't actually matter what order you apply the gradients in. It's called MRI fingerprinting basically, and it's a particular type of scan but great potential to do some very clever things in terms of identifying different tissues. And that sort of thing.

But one thing they realised was that you can essentially play out these gradient sequences in any order, including as music. So you know some people find MRI scans very, you know, claustrophobic or intimidating. You have to be there for quite a while, so there was genuinely a thought of oh well, if we can make this scan sound actually play out some music or something that's at least more comforting, that would like be better for patients. That's the thing that always gets me about MRI scans, is just the sounds that they make and when you hear that sort of yeah, personally anyway, that sort of sounds like you know it's working. You know you're getting a sound, but then ultimately that's going to be converted into an image. The power of maths and physics, and more impressive than the Higgs mechanism for me, I think.

Vicky Neale:

I'm finding this fascinating, and having spent all this time in medical scanners and having radiotherapy and so on, to be able to explore some of the maths and physics of that is great, we're going to have to wrap up in a moment, I think, but I just want to ask, what advice would you give to somebody starting their studies now who might be interested in using maths or physics to diagnose and treat cancer?

Tom Whyntie:

So in terms of advice for someone, yeah, looking to apply mathematics and physics to any area of sort of medical practice, or in the clinic, or helping patients, or what have you. Yeah, the first thing to establish is, what's your motivation? I mean I think it's fair to say maths can be quite, not hard, but it requires, you gotta work at it, and there's nothing you know that's not worth doing that doesn't require a lot of work, and sometimes that work can be quite dry and repetitive, and sometimes it can be great. You know when you do finally make that equation work, it's like yes, but there's those moments of frustration, where it's like ugh, but behind all that you've got to have well, yeah, why am I doing this? What's the ultimate goal?

So as we said, you know, for me at the start it was like Higgs mechanism, particle physics, all that sort of thing, but lots of the students I talked to and worked it out, either know someone who has

been affected by cancer or some other sort of medical thing, and that could be a very strong sort of motivation as well, and rightly so. If you're thinking, why isn't this equation working? Is like, yeah, one day someone's life might depend on this, so you know keep going in that sort of sense, but again, an important thing to consider is you know, where on that spectrum of impact, am I going to be best sort of placed? You know where am I going to, not even have the most impact, 'cause I think you need every bit of the process from the very, you've got the maths at the very start to the sort of physics and the lab-based things where you're doing things on you know, literally on cells on a Petri dish. Where you can do lots of experiments and again, they can be quite frustrating 'cause something will get contaminated, or you have to read all of that, and you know there's frustration and difficulty at every sort of stage but this is the thing. When you do get that moment of the kind of the breakthrough of, no one has seen this before, that's the bit of research. It's like for just that brief moment. You're the only person in the world who's seen that result, and then you get to tell other people about it. And again, in medical physics you can say, well, this might have this impact on that sort of thing. That's the thing to sort of keep bearing in mind I think.

Vicky Neale:

So, have that motivation. Remind yourself why it is that you're working at this.

Tom Whyntie:

Exactly, and if you can try it, try it before you buy, so badger doctors and clinical people for like shadowing experiences. Oxford run the UNIQ programme I think, which gives students in secondary schools and higher education the chance to you know, come to Oxford and actually experience you know, working in the lab or what research is like.

Vicky Neale:

Yeah, and then there's also UNIQ+ for undergraduates.

Tom Whyntie:

Yeah, but get experience and actually try it and you may well find, actually I don't like working with patients, I just don't have the patience or the people skills. Or actually. This is what is getting me out of bed every morning like actually seeing, you know, interacting with people and seeing the impact.

Vicky Neale:

One of the things that I love about this podcast series is that it's a privilege for me to be able to talk to the people who are using their maths and stats and physics expertise in so many different ways, and I guess that's really that kind of playing to people's individual strengths and their interests and what gets them out of bed in the morning.

And it's been fantastic to hear you talking so clearly about what gets you out of bed in the morning, that just kind of comes across in everything you say. Thank you so much Tom, for our fascinating discussion today, but also for your research and your teaching which are helping to improve diagnosis and treatment for cancer patients now and on into the future. So, thank you.

Tom Whyntie:

Thank you for having me, my pleasure.

Vicky Neale:

Thanks for listening to this episode of Maths Plus Cancer. I hope that you found the conversation as interesting as I did. There are more episodes of Maths Plus 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...