© 2018. Published by The Company of Biologists Ltd | Development (2018) 145, dev170472. doi:10.1242/dev.170472

SPOTLIGHT

An interview with James Sharpe

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James Sharpe is a developmental biologist who studies the process of limb development using a multi-disciplinary approach, combining experimental systems, imaging and computer modelling. Formerly based at the Centre for Genomic Regulation in Barcelona, James was recently appointed Head of EMBL Barcelona. We caught up with James at the British Society for Developmental Biology Spring Meeting to ask him about his research, his thoughts on computational modelling, and his vision for the new EMBL Barcelona site.

Let's start at the beginning – what first got you interested in science?

I think there were two main things. I got interested in computing at around the age of ten, when the first computers were coming into homes. My dad got us a Sharp MZ-80 K – a strange black and white computer with no games – and a book on how to program for kids. So I started playing around with programming and really got hooked. There was so much promise in those early days, when computers weren't commonplace: all of a sudden there was the idea that you could program stuff and the only limit was your imagination. In parallel, and I hate to admit it, I was a birdwatcher. It seems a very English thing to do, but I was really into it – I was into nature and the natural world.

During my teenage years, this interest in biology and nature, and my interest in computing, sort of came together. In fact, one thing that really influenced me was Richard Dawkins' BioMorphs program. At that time, Dawkins had written several books and was on various TV programmes, but he also wrote a little computer program called 'BioMorphs', which was a demonstration of evolution in a computer with little shapes and little creatures. I was slightly annoyed about this program because it wasn't a genuine simulated environment – it was only a little tool to help illustrate the ideas – and I thought that there's got to be a better way of doing this. So I started programming things like that, little evolutionary scenarios in computer programs, simple little things. I then started learning about actual biology – DNA and genes. I also remember, when I was about 16, watching a *Horizon* film based on the book *The Double Helix* by Jim Watson, that made me think: 'Wow, molecular biology is amazing!' So I guess it was all of these things that eventually got me really interested in science. In addition to the computer, my dad bought us chemistry sets and electronics kits, so he was also a big influence.

So did you then train or study as a computer programmer?

Actually, my undergraduate degree was in biology – it was called Biology Pure and Applied – so I didn't ever train as a computer programmer. But I have been, in practice, studying programming since I was ten. So I'm basically self-taught.

How did you then get interested in embryology and developmental biology in particular?

For two reasons really. While I was a student at Oxford University, I had lots of developmental biologists as lecturers – Jonathan Slack, Peter Holland, Phil Ingham and Julian Lewis – and it was somehow obvious that, out of the different topics we were studying, development was the most interesting and amazing. Remember, this was in the late 1980s, when there was a huge explosion, and excitement, in finding developmental genes. So it was a lot to do with that. But it was also because molecular biology was essentially a bit like programming – like having electronic circuits making decisions. It seemed to me then, and it still seems to me now, that developmental biology is one of the areas in which the most decision-making processes happen. As a teenager, I had also been dabbling with digital electronics, making digital interfaces and seeing how digital memory worked. Back then, you could still see the connection between the electronics and how the computer actually worked! So I had a natural desire to understand the connection from the individual digital chips up to the computer processor, and I wanted to see the same in biology – from the individual genes up to whole organs and organisms. Development is, I think, one of the most exciting areas in which that's happening.

As part of your postdoc research, you developed the 3D imaging technique known as optical projection tomography. Can you tell us about how and why you set out to develop this approach?

Well, I had finished my PhD in Robb Krumlauf's lab, doing lots of experimental biology and making tons of blue reporter mice, and I had chosen to switch focus and do some computer modelling. I went up to Edinburgh, to the lab of Duncan Davidson, and tried to start

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Development (2018) 145, dev170472. doi:10.1242/dev.170472

building computational models of limb development. However, I realised that the major problem was that we just didn't have enough data, so building the model was proving to be difficult. I wanted to know the shape of a limb-bud in 3D and how it changed over time. I had been slicing limb buds into pieces, creating confocal images and then digitally reconstructing them. But it was not good enough. I had heard about this idea of trying to do tomographic reconstructions with light. In fact, someone had mentioned it during a coffee break, and I thought, 'Oh, that would be cool, someone ought to do it'. But it became clear that no one was going to try; it wasn't part of their plans to be building technologies. However, I was a free postdoc (and being a postdoc is one of the best times of your life!) so a couple of years later I just decided to have a go. So my dabbling in computing and electronics came in handy in a way that I wasn't expecting at all. I went out to Maplin, an electronics store where I had been buying bits and bobs for years, and did it. The most exciting part was that I didn't tell anyone – I didn't even tell my boss! I just announced it one day. It was really fun and exciting. I nearly made it out of Lego, but didn't in the end. I've still got the old original ones in my office, like a little museum, because they started very simple and gradually got more professional. It was pure need. I didn't have any intention of developing an original technology – I had to do it because the data we were getting weren't good enough.

In 2006, you moved from Edinburgh to Barcelona. How did you find this move, in terms of academic and social culture?

It was absolutely amazing and wonderful. I've always been a bit of a Latinophile. I travelled a lot around South America – I actually did a short postdoc in Chile in Santiago with Roberto Mayor. I also did a 4 month project in Madrid with Miguel Torres. I always thought it would be nice to live in Spain, but didn't think it was going to be possible. However, a few years later I heard that there was going to be a new institute in Barcelona, the Centre for Genomic Regulation, and it looked as if it was going to be really good scientifically and very international. I already knew that I loved the culture in Spain, and that I would like living and working there, so I decided to move. And it's been wonderful: the people are fantastic, the place is fantastic and it's got fantastic scientists.

For years now, you've been studying the vertebrate limb – using it as a model for understanding tissue growth, gene regulatory networks, patterning and morphogenesis. What makes the limb such an attractive model?

So the funny thing is that I got to know about the limb by accident, when I was making transgenics for studying Hox genes and hindbrain development. I remember that one of my colleagues at the time, Alex Gould, said: 'If someone makes enough transgenic reporter lines, surely by chance one of them might land somewhere interesting by accident.' And that's exactly what happened to me. I had a reporter construct for studying hindbrain development, and the animal technicians phoned up one day and told me that all of my reporter mice were polydactyls – they all had seven fingers. It turned out that that reporter gene had fallen next to the limb enhancer of the sonic hedgehog gene (*Shh*), which is something that had been sought for quite a while. The enhancer was one megabase away, which is why no one would ever find it unless they found it by accident. And luckily I did. I didn't really then follow the direction of studying *Shh*, but this chance finding did introduce me to the limb as a model. The real advantages of the limb, which of course has its cons as well as its pros, have been clear to me from the beginning. It's not an essential organ, so you're able to do all kinds of manipulations without upsetting the life support system of the embryo. You can't do that for the heart. In fact, lots of classical embryology studies, especially in the 1940s, 1950s and 1960s (e.g. John Saunders' work in chick embryos), used the limb as a model. The limb is also a little isolated from the rest of the body, so you can think about it as a mini-system in its own right. I also knew, because of my interest in theoretical biology, that the limb was often used as system for modelling patterning and gradients. So, it's because of all of these advantages really that I realised the limb was a good model system to work with.

You are also coordinator of the SWARM-ORGAN project – an initiative that aims to use robotic swarms to better understand, for example, collective emergent behaviours and self-organisation. Can you tell us more about how you got involved in this?

Ever since my childhood with computers and electronics I've always thought of robots, and what's being done with robots, as quite interesting. I came across a paper about swarm robotics, in which they had used gene regulatory networks to control the robots in the swarm, and I realised that it might be an opportunity to do something fun! I don't really see biological systems as being necessarily unique – you've got cells and they have to make decisions, incorporate information from their surroundings, and work together, but there may be other systems, human-made systems, that could work in the same way. So, I decided to put together a little consortium to investigate this. I'd heard of a European funding scheme called the 'Future and Emerging Technologies' programme that liked to fund crazy, high-risk, high-gain projects. I didn't have any credentials in robotics at all, so I approached Yaochu Jin, a roboticist at Surrey University in Guildford, about joining the project. After that, I approached two people from the modelling biology field: Veronica Grieneisen from the John Innes Centre in Norwich and Yaap Kaandorp from the University of Amsterdam. I really did not think we were going to get funded, but we did, and the project has turned out to be very interesting and successful. By collaborating also with Sabine Hauert at Bristol, we managed to get a little swarm of about 350 robots dynamically arranging into self-organised shapes. It doesn't do anything as a robot, but it is proof of concept that we can get developmental principles into purely physical or technological systems. The project is finished now, but we're still trying to get the papers published.

I actually think that biology has as much to learn from the discipline of engineering as it does from the discipline of physics. Physics has very successfully come into the field of biology. However, physics is usually about simplifying things to understand the basic underlying principles, whereas biology is a discipline that considers the construction of things, in the sense of understanding the complexity of what happens when there are many interacting components. For this reason, I think engineering is a natural ally of biology.

As someone who's always had a strong interest in computational modelling, do you think that we should be pushing more students to be studying programming or 'computational thinking'?

I do, although sometimes I worry that I'm in a minority. I think that the skill of understanding how to construct computer code should be as basic as writing. Even if only for our own 'empowerment', people should be taught to understand what it means to program, what programs can do, what they can't do… and that they're not magic! I think this encourages rigour and logic, because you can't make mistakes with a program; if you make a mistake, it doesn't work. You can't argue with it because it's just a computer. So you get this silent but unrelenting mentor forcing you not to make mistakes.

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It's also clear that computing is already dominating all of our lives – and this will only increase. We interact with the world in more and more complicated ways, and a lot of this is done using computers and logic-based computational frameworks. So we can engage with these passively – submissively – or we can engage and think: 'Hey, maybe I can program my computer to do more of what I want.' It's not complicated. I think learning how to write, learning how to spell in English for example, is ten times harder than learning how to program.

But we need to start teaching people at a younger age. In fact, there are some very successful projects (such as Scratch, a cool programming language developed for kids) that allow children to learn coding concepts. I genuinely believe it would be a sensible thing for everyone to learn how to program. Even if you're not going to use it that much, even if it's only to understand what's going on when you press a button on your computer. Because at the moment it looks like magic. But it's not. So, yes, I think there are many advantages to being more computer literate.

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In recent years, we've seen huge technological advances with regard to both imaging approaches and systems/computational biology approaches. Do you think this is now making it much easier to study developmental biology?

It's not necessarily making it easier, but it's definitely making it more exciting. I believe that we can understand developmental biology better by integrating lots of approaches. I don't think we're necessarily there yet, though. What's been happening recently is a huge explosion in technology development. The next thing that really has to develop, however, is using computer modelling to take advantage of all these technologies that have been developed. All of these new techniques are providing us with more data, and the data is wonderful, but we have to make the best use of it. It's not about just putting it in databases, it's about using it to inform predictive dynamic models that actually explain how things might be working. And again, computing should be a tool. I think every lab should have some computer modelling – like you'd have a microscope – and everyone should be equally familiar with both. We're not there yet, obviously, but I imagine in the next 10 to 20 years we could be there, and that you wouldn't ever try to understand a complex biological phenomenon without using computer modelling. This is why I'm very keen on interdisciplinary groups, which contain both the theoretical and the experimental sides within the one group. Some of the best results I've seen occur when these two sides are in intimate contact with each other, not only having a check-up meeting once every 2 months, but sitting together and working together every day; the project evolves much better like that.

One thing that's been debated at this meeting is the extent to which there are 'open questions' in the field; are there fundamental questions in developmental biology that are still unanswered, or are we now filling in the details? What are your thoughts on this – what are the key questions that you're trying to address?

For me there is definitely a big question, although it may not be a question for everyone. We're getting better at understanding basic principles and modules of systems – we've made huge progress with this and that's been fantastic – but, to me, the big remaining question is what happens when you put modules together to make more complicated things? So, for example, a limb bud has got a proximal-distal (PD) patterning mechanism, a timing mechanism and an anterior-posterior patterning mechanism, that may all be working together to control cellular activities. We can study, and do tend to study, each of these independently. However, there are two interesting things to think about when you put all of these modules together. First, a lot of the molecules that control these different modules are the same, so how does the system actually work when you put it all together? For example, Wnts, FGFs and BMPs in the limb seem to do everything, and it is clear how they might work when we think about just one patterning system (e.g. PD patterning) but how do they work when we put the whole thing together? That's not clear, but is where the modelling comes in. The second issue, which is directly related, is that many of the same molecules seem to be involved in building almost every part of the embryo, so how does this work? A simple possible answer is that we have lots of cell type-specific scenarios whereby the responses to a given factor can be different due to significant rewiring. But is there really dramatic rewiring during development? Or is the difference between a kidney and a limb much more subtle? And how about the differences between the limb and your facial structures, which have all the same cell types (bone, connective tissue, cartilage, etc.) and use a lot of the same developmental pathways? So, for me, the big question is how do these gene circuits use the same players but build totally different structures? We can show, using modelling, that two quite different patterns can be created from the same circuits without making any dramatic changes to the circuit, but just by tweaking parameter values. So what if that's the norm? What if a lot of differences actually involve only minor changes to the same circuit? Alternatively, it may be that there are binary on-off decisions that dictate outcome. We don't have a clue about these types of issues yet, because they involve integration at a higher level of complexity. We've done well with little models and modules, but integrating it back together? That's going to need computer modelling.

What would be your advice to young researchers starting out in developmental biology today?

The only advice I can give to any biologists, developmental biologists or scientists, is to do what you really love. Follow your passion. Research careers have such an uncertain trajectory that if you're trying to be strategic you might end up going down the wrong route. I made many decisions that were strategically ridiculous, but I never chose something I wasn't passionate about or obsessed with at that moment – and it appears to have worked out. Although, whenever I'm asked this question my main worry is that I made these decisions 20 years ago and the world has changed so much that my advice might not be relevant any more. But I do think the core thing is true: you've got to follow your passion rather than going with something that is more fundable, fashionable or sexy. You've got to follow what is genuinely your interest, even if it seems a bit weird to other people. Being obsessive also helps!

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You've recently been appointed as Head of EMBL Barcelona. What is your vision for this new EMBL site?

The vision is to think about multicellular tissue-level questions in a broader sense than just embryo development. I think we're

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increasingly at the point where a lot of the tools and concepts that have been worked on in developmental biology can be extended out to many other scenarios: homeostasis of adult tissues, regeneration, organisation of vascular systems, tumours. Organoids and organoid-based modelling of certain diseases are also topics that we're very interested in. Tissue engineering in its broadest sense is also fascinating – I think a logical continuation of understanding how tissues and organs build themselves is trying to build tissues ourselves, or maybe invent new tissues. And following what I was saying earlier, we're trying to look for groups that will have both an experimental side and a theoretical side; I believe that's a strong way to go. So, technically, we'll be focussing on three things: mesoscopic imaging, experimentally manipulable systems (especially *in vitro* 3D tissue culture in its various guises) and computational modelling. So far, we've recruited two excellent young group leaders who embody these ideas perfectly: Miki Ebisuya from Kobe, and Vikas Trivedi from Cambridge.

I note that you have recently joined the 'Twittersphere' – how's that been for you?

Yes, I joined Twitter for two reasons. The first is that I think you can get genuinely useful information from Twitter, such as updates and information from people you know. Beyond that, it's sort of an experiment to see whether I like it. I am a bit (or should I say very?) old-fashioned. I never joined Facebook – I'm naturally wary of this sort of thing – and that's why it's taken me so many years to get round to trying Twitter. I basically told myself I'd do it for a year, and at the end of the year I'll consider whether to continue. So far, though, I think it could be a very useful tool.

What would people be surprised to find out about you?

Given that I'm basically such a nerd, I guess people might be surprised that I have actually represented my country as a junior in a sporting event! I was selected to row in an official Anglo-French regatta when I was 17. I continued rowing at university, but haven't rowed since then. The fact that I chose to do a postdoc in Chile also surprises some people.