00:04

Trying to understand life without clearly watching it in action is like an alien species trying to understand the rules of a football game from just a few snapshots. We can learn a lot from these images. For example, there's players on and off the field. There's a band. There's even cheerleaders having a great time watching the game. And of course, despite learning all of this information from watching these pictures, we still cannot piece together the rules of the game. In order to be able to do that, we need to actually watch the game in action.

00:36

Much of what we know about how life works comes from watching these snapshots. Scientists have been able to figure out a lot by looking at similar snapshots, but ultimately, for them to understand how life works, they need to actually watch it in action. And this is essentially where life happens, is trying to understand how the fundamental unit of life works. And to be able to watch this, we need to be able to understand how life is.

01:04

Compared to this ant, a human cell is about a hundred million times smaller in volume. Do you see the cell that's right next to this ant? It's right there. To be able to watch this cell, we need to make the invisible visible, and we do this by building microscopes. Not these microscopes; the ones that we build look something like this. It helps that I'm part of a paparazzi -- well, of sorts. Instead of taking pictures of people, I'm more interested in taking pictures of famous cells.

01:33

Well, my own career path up until this moment in time has been pretty windy, starting with my first childhood obsession and continued passion in computer science, which took a sharp transition to looking at engineering, and more recently, a very sharp transition to trying to understand cell biology.

01:54

Now, it's this combination of disciplines that has led me to where I am today. I'm able to carry out interdisciplinary research with one clear goal. And the idea is to be able to advance innovation and discovery by bringing together experts from these different disciplines to be able to work together and solve problems that each of us can't.

02:15

Now, we're interested in understanding the cell. The cell ... what is it? Well, it's the fundamental unit of life. Simply put, it's just a bag. It's a bag that has trillions of inanimate molecules, whether it's proteins, carbohydrates, lipids or fat. And it turns out, over the past half a century, molecular biologists and biochemists have figured out ways to make these proteins glow. They light up just like fireflies. Now, microscope developers have been able to make better and better instruments to be able to capture this light emitted from these molecules, and computer scientists and mathematicians have been able to understand the signals that are being recorded from the cameras. And by bringing these tools together, we're actually being able to understand the organization of these molecules inside of these cells, understand how that changes over time, and that's essentially what we're interested in, trying to understand life at its essence.

03:11

So we want to go from imaging life, which has traditionally been confined to two dimensions, to being able to image life in three dimensions. So how do you make a two-dimensional image into a three-dimensional image? Well, turns out it's pretty straightforward. We just collect a series of two-dimensional images as we're moving the sample up and down, and then we stack the images on top of each other and create a three-dimensional volume. The problem with this approach is that traditional microscopes, they dump way too much energy into the system. That means that this cell that you see over here, it's experiencing a lot of light toxicity, and that's a problem.

03:46

Let me explain that a little bit better. For example, let's say that on this planet, life evolved under just one sun, yes? Now, let's say I wanted to watch the shoppers on this street to understand their shopping habits: how long they linger in front of stores window shopping, how many stores they go into and how long they spend inside of each of the stores. And if I was sitting down at a coffee shop just people-watching, many wouldn't even notice that I'm watching them. Now, what if all of a sudden I was shining the equivalent of what is, say, the light or the sunlight from about five or, say, 10 different suns? Would they still behave as they normally did? Would they still linger outside for just as long? Can I really believe that their behavior hasn't been altered as a consequence of being exposed to this much sunlight? No. Most microscopes these days, and conventional microscopes, have been able to dump between 10 to 10,000 times the sunlight that we're exposed to on this planet, where life actually evolved.

04:46

And because of this, well, turns out I'm part of the cell paparazzi, so we need to be very careful in terms of how much light we actually put into the cell. Otherwise, we might end up with a deep-fried cell. And, turns out, there's really nothing natural about trying to watch a damaged cell whose behavior has been significantly altered.

05:08

Well, let's take this cell for example. It's sitting on a piece of glass. You see the spots everywhere? Those spots represent molecular machines that are assembling on the surface of the cell in order to be able to shuttle food from outside the cell into the cell. Our lab uses something called the lattice light sheet microscopy, which generates a very, very thin sheet of light, paying attention not to damage the cells or not to put too much light into the system. And when we do this, we're able to watch the dynamics of that process for much longer without really stressing out these cells.

05:44

We've used this microscopy technique and tools to be able to understand how viruses infect cells. In this example, we've exposed the cell to rotavirus. It's an extremely contagious pathogen that kills over 200,000 people every year. And by watching these molecules, these virus particles, how they diffuse on the surface of the cells, we can actually understand the rules that they're playing by. And when we understand these rules, we can start to outsmart them, whether through intelligent drug therapies, to be able to mitigate, manage or even prevent the virus from binding into the cell in the first place.

06:17

Now, we've made the invisible visible, but the question remains: When can we believe what we actually see? Everything I've shown you up until this point has been a cell that's been held prisoner on a piece of glass or in a petri dish. Well, it turns out that cells didn't really evolve on a piece of glass. Right? They didn't evolve in isolation, and they didn't evolve outside their physiological context. To truly understand cells' natural behavior, we need to able to watch them in action where actually is their home turf.

06:47

So, let's take a look at this complex system. This is a developing zebra fish embryo, where you're looking at cells that are organizing themselves in order to form tissues, in order to form organ systems. And when we watch the movie again, you'll see that at about 20 hours, you start to form the eye and the tail of the zebra fish. Now, we can watch this, not in this low resolution, we can watch this in exquisite detail, and we want to be able to watch this in three dimensions over the course of minutes, seconds, hours or even days.

07:17

So the problem with these complex systems is that we scramble the light, or they scramble the light that we actually shine onto them, which causes us to record very blurry images. And it turns out that astronomers have had a similar problem, but for them, the problem comes when they're trying to record the light from distant stars on telescopes that are ground-based. The problem is, when the light travels thousands of light years and it hits our turbulent atmosphere all of a sudden, the light gets scrambled. They've also, luckily, figured out a solution to this for over half a century. What they do is they generate an artificial star at about 90 kilometers above the Earth's surface, and they use that light, which passes through the same turbulent atmosphere as the distant star's light, and they're able to understand how the light is getting scrambled, and they take a mirror that can change its shape in order to compensate or undo that scrambling.

08:11

So what we've done is we've taken those ideas and we've implemented that with our microscope system. And when you do that, you can more or less unscramble the complexity of the scrambling and the fuzziness that's happening as a consequence of complex systems.

08:25

And we do this in zebra fish. We like zebra fish because, like us, they're vertebrates. Unlike us, they're mostly transparent. That means that when we shine light on them, we can watch the cellular and the subcellular dynamics with exquisite detail.

08:40

Let me show you an example. In this video, you're watching the spine and the muscle of a zebra fish. We can look at the organization of the cells -- hundreds of cells in this particular volume -- in the presence and absence of adaptive optics. Now, with these tools, we can watch more clearly than we've ever been able to before. And in a very specific example, looking at how the eye develops in the zebra fish, you can really see the commotion inside of this developing zebra fish embryo. So you can see the cells that are dancing around. In one example, you see how the cell is dividing. In another example, you see cells trying to get places and squeezing past another cell. And in the last example, you see a cell being completely rowdy to its neighbors by just punching its neighbors. Right?

09:30

This technology really enables us to watch deeper and more clearly, almost as if we're watching single cells on a piece of glass where they've been held prisoner. And to demonstrate the promise

that this technology holds, we've partnered with some of the best scientists from around the world. And we've started to ask a range of fundamental questions that we're starting to work on right now together. For example, how does cancer spread through the body? In this example, you're looking at human breast cancer cells that are basically kind of migrating, where they're using the blood vessels that are shown in magenta. They're basically using these blood vessels as highways to move about the cabin. You can basically see them squeezing through the blood vessels. You can see them rolling where there's enough space. And in one example, well, you see what looks like Ridley Scott's trailer for the next "Alien" movie. This cancer cell is literally trying to claw its way out of the blood vessel in order to invade another part of the body.

10:25

In the last example I'm going to show you, we're trying to understand how the ear develops. In this case, we were completely upstaged by crawling neutrophils. These immune cells are basically on patrol all the time. Basically, they don't get any time off. They're working constantly to understand whether there's stranger danger, trying to understand whether there's an infection. They're sensing the environment, constantly moving around. Now, we can watch these images and these movies in greater detail than has ever been possible before in our time up until now.

10:57

Now, as with all new technologies, new capabilities come with new challenges, and for us, the big one is how we handle the data. These microscopes generate a ton of data. We generate anywhere from one to three terabytes of data per hour. To put that into context: we're filling up two million floppy disks every hour, for our more experienced audience members.

11:20

(Laughter)

11:23

Roughly equal, then, to about 500 DVDs, or to put things into better context for the Gen Z, that's about a dozen iPhone 11s that I'm filling up every hour.

11:34

We have a ton of data. We need to find new ways to be able to visualize this. We need to be able to find new ways to be able to extract biologically meaningful information from these data sets. And more importantly, we want to make sure that we can put these advanced microscopes into

the hands of scientists from all around the world. And we're giving the designs of these microscopes for free. But the key important part is, we need to collaborate even more to make an impact. We're bringing together scientists who can develop new biological and chemical tools. We're working together with data scientists and instrumentation scientists to be able to build and manage the data. And because we're giving these instruments out for free for all academic and nonprofits, we're also building advanced imaging centers to house them, to be able to bring together the group of people that are microscopists, that are the biologists and the computational people, and to build a team that's able to solve the types of problems that each of us individually cannot.

12:31

And thanks to these microscopes, the frontier of science is open again. So let's take a look together.

12:37

Thank you.

12:38

(Applause)