

**Disruptive: Art Advances Science**

Host Terrence McNally interviews Donald E. Ingber and Charles Reilly

McNally:

Hello, I'm Terrence McNally and you're listening to DISRUPTIVE the podcast from Harvard's Wyss Institute for Biologically Inspired Engineering. Our bodies — and all living systems — accomplish tasks far more sophisticated and dynamic than any entity yet designed by humans. The mission of the Wyss Institute is to: Transform healthcare, industry, and the environment by emulating the way nature builds.

Wyss Founding Director, Don Ingber believes “there’s a huge disconnect between science and the public because too often in school, science is seen as rote memorization. You can memorize scientific facts, he says, but that’s not science. Science is the pursuit of the unknown.”

Ingber’s urge to find new ways to communicate that pursuit were rewarded when he was contacted by Charles Reilly, a molecular biophysicist from New Zealand, who also happened to be a professional animator, and formerly worked at the studio of Peter Jackson, writer/director/producer of the Lord of the Rings and Hobbit trilogies.

Using film industry visual effects tools, Reilly uses animation and simulation to merge data from many disciplines to create more accurate depictions and predictions of the natural world. He’s currently applying his work to rational drug design and understanding the molecular mechanisms of disease. In 2017, was named a Young Pioneer in Physics by the World Frontiers Forum.

Ingber is a leader in the emerging field of biologically inspired engineering. He also leads the biomimetic microsystems platform at the Wyss, in which microfabrication techniques from the computer industry are used to build functional circuits with living cells as components. Founding Director of the Wyss, he has authored more than 425 publications and 150 patents and has received numerous distinctions in his field.

Charles Reilly was looking for an environment where he could make scientific discoveries while making art, and Don had found somebody who might be able to make a longtime fantasy project finally happen.

Ingber:

So out of the blue comes this email from Charles saying, "I'm from New Zealand. I work with Peter Jackson films. I know animation. I also trained in molecular biophysics and know molecular dynamic simulation, "I was told you were the person I have to work with."

I do remember vividly when he came to visit me I said, "Well, tell me your

story." And my memory of this, and he may have a different version, is he said, "Well, I grew up in New Zealand. My parents were dairy farmers. Actually we grew up in the valley that was used for the filming of *The Hobbit*." I always view him as growing up in the shire, but that's a whole other story.

He had been working in Australia on a book version of *Life on Earth* I think it was that Apple Computer sponsored. He showed me this unbelievably gorgeous animation of molecules working in concert, things I had never seen how beautiful it was, so I offered him a job

I wasn't sure what we'd do. He told me about his vision that you could advance science through using this physics-based animation. I said, "I totally agree. I've seen this physics-based animation," and I'm trying to figure out how I could ever get people to work here because everyone I met who does it ends up forming companies and doing ads for pharmaceutical companies. So that's how he became involved.

Ingber:

I think he came really wanting to do science like, "Let's get together on a project and show how this would work."

I told him, "I don't have a question where animating it would address that." I wasn't working on molecules. I wasn't really doing tensegrity-based stuff anymore. But when Charles came, I had this vision like, "Why don't we start with something that's entertaining? To communicate and introduce the Wyss Institute to the world in a different way, in a creative way, in a way to enable public communication's appreciation of science, and let's play!" So we played.

McNally:

Reilly is now a Wyss staff scientist, and together the two of them created a visualization of sperm competing with each other to fertilize an egg that is accurate at the micro, molecular, and atomic levels.

Just under three minutes long, *The Beginning* opens with a crawl, similar to the crawl at the start of *Star Wars*. Yellow text receding into the vastness of space points out that only "the victor will influence generations to come" - a scientifically accurate assessment of the winning sperm's reward.

Oh, and by the way, they actually made a new scientific discovery in the process.

Reilly:

There's many scientists that were inspired and drawn to science through *Star Wars*, and so Don was inspired by *Star Wars*, but also some of the earlier photography of the sperm and the egg We knew we wanted to do a project that kind of paralleled the complexity of biology with the vastness of space.

McNally:

They've seen the Star Wars, they've seen the sci-fi movies. They've thought about that. Now you're telling them, similar adventures are going on at a molecular level inside your body or the bodies of other folks.

Reilly:

Yeah, that's exactly it.

McNally:

What happens next?

Reilly:

I moved to Boston. It's basically you start looking at the data, seeing what's known, what isn't known, understanding what makes up a sperm, seeing if I can model or simulate things, and then just iterating and just working on developing the models and being able to throw them out and start again.

Then once we started to understand that we could produce these models and have them look like sperm, we could move across the different spatial scales so all the way into the dynein molecular machines in the sperm tail, and then zoom back out and see a whole swarm of, not actually sure if swarm is the right term, but flock of sperm and making sure that we could do that.

Then we start doing storyboarding and making sure that we could produce a look that felt like Star Wars and, all the while, my big goal was that this process informed the science.

McNally:

And it turned out, it did. I'm curious what's new for Charles on this project. What's new in the technical side of his simulation work, and what's the new thing they discovered in this process which we did not previously know?

Reilly:

When we're doing simulations, the temperature of the system is linked to time, so the velocity of all the molecules, of all the atoms in the system represent the temperature. By heating it up and running it at a higher temperature you make it run faster...without it falling apart.

Whereas, if we tried to just make it run hotter and faster, the whole system would have blown up, literally the molecule just blows to pieces.

McNally:

So, because you're doing this in the virtual world, you can tweak some of the conditions.

Reilly:

Precisely. Yeah

Reilly:

By using biology and trying to trick the system, we put in a few constraints, a few mechanical constraints so that the molecule wouldn't kind of wander away when we heated it up.

We just wanted to anchor it so it wouldn't drift away, but that provided a mechanical constraint that exists within the actual sperm tail. What happened was - this prevented not just the wandering of the entire molecule but it reduced the degrees of freedom of motion of the whole molecule. It kind of provided a hinge, and so all that extra energy we introduced, all that heat, that hinge was like a funnel for the energy.

The energy was transferred throughout the molecule in a very particular way that wouldn't have happened had that hinge not been in that location. It turns out that the walking motion of the dynein was a result of the transfer of energy throughout the molecule that only happened because of this hinge.

McNally:

So let me see if I'm right here, you introduced an artistic trick based on your knowledge of special effects algorithms and your knowledge of biology. It turns out that that trick confirms something that actually happens in nature that we didn't know happened?

Reilly:

Precisely.

McNally:

Don Ingber goes into much greater detail as he recounts Reilly's process of creative discovery.

First of all, I guess he was starting to do this multi-scale modeling where you can actually see for the sperm tail moving at the level of the whole cell, and then also visualize how that influences what's happening at the molecular level below, or I should say it the opposite way, the actions at the molecular level and atomic level below influence the motion of the tail at the higher level.

McNally:

Let me just jump in for people so they can visualize it. So if you're seeing a sperm, we know that's minute anyway, but what you're saying is that you go inside the sperm's tail to see what the molecular machinery going on inside of that is.

Ingber:

Yeah, amazingly you go down to the atomic scale. Life is a hierarchy of increasing complex structures that self-assemble by components joining together with other components. The atoms make up small chemicals and then these chemicals build larger structures like a protein made of amino acids. Amino acids are made of chemicals.

Those proteins have a three dimensional shape. They then come together with other proteins, let's say, and they make structures like they'll make rods or they'll make a column or they'll make a cube, but in the tail of the sperm, there are these long filaments, they're called microtubules, that are relatively rigid, but somewhat flexible, and they form a hollow shell, if you like.

Between them, connecting them, are other molecules that actually are motors and they're called motors because when they change their shape a particular way, they push on the microtubules and they cause them to slide. Like if you were to row a boat and you pull on the oars, the oars would push the water away. Well, these oars push the microtubules all in the same direction.

It's well known that there's thousands of these molecules lined up on the side of these long tubules and, again, it's three dimensional.

Well these, by pushing left or right, it actually makes the tail, the long column which forms the core of the tail, bend one way or the other. That's actually how you get motion as a sperm.

McNally:

That's what I was thinking, yeah.

Ingber:

At another level, the way you pull on your oars is the atoms in the molecule are changing position relative to one another, due to transfer of forces, compressive and tensile forces. Charles was able to take what molecular biophysicists do, which is they have ... They call it molecular dynamic simulations.

They use computers to model every position of every atom in a protein and you can view it in three dimensions, and the way they get the positions of the atoms are generally two ways. One is they form a crystal. They basically rigidify the protein and they could use x-rays and other imaging to basically get out where every atom is and they get very, very high resolution.

Or they can sort of freeze the molecules when they're flexible so they're in various shapes, and then they could image them with an electron microscope, and this just won the Nobel prize recently, cryo-electron microscopy. And then they can get the various shapes it can be, and not that one frozen one, but lower resolution.

What Charles did, and this really is his inspiration which is, I think, amazing, is that he took the highest resolution image of this motor protein, he depicted that, then he used the physics-based animation software to explore - starting with that shape - what potential shapes could it take on in a smooth, continuous, realistic physical world way.

Then he put it in the context of these microtubules inside that column, like how could it move inside that column so that everything could be consistent and things wouldn't be crossing over, interfering with each other. And out of it came this path of how it moves - the motor generates force - that crosses over with this lower resolution cryo-electron microscopic data that's been published.

So he's able to do things at a higher resolution and explore visually dynamically things that you really can't do easily with conventional scientific software - which is, I think, amazing.

Plus one of the big problems in science is that people do computational modeling at the body level, the organ level, the tissue level, the cell level, molecular level - but they're totally different models. So people in all different fields say there's a challenge of how do you relate one model at this level and integrate it with the other? With the simulation software, this was done just seamlessly.

Yes, an animation and entertainment industry may want to do the sperm fertilizing the egg. It'll look like a sperm, it'll look like an egg, it'll move like movies you've seen on television, but this one does all that and it does it based on molecules changing their shape, sliding these bundles and then driving the tail in a way that scientists have actually confirmed happens in the real world.

The other thing is that scientists usually will give you a model that shows you the average movement, whereas we know from looking at real sperm, for example, everyone is an individual. They move all different ways. With this software, we had thousands of sperm moving in all different ways because you can change the parameters to explore that evolutionary space.

McNally:

Wow. One thing I must say, that image that you described in the animation that I've watched, I have to say it looks like a Busby Berkeley... It looks like the Rockettes.

Ingber:

It's absolutely beautiful. They're all dancing in and that's how it must work in our bodies, but usually you'll see a static diagram of that molecule in three different shapes, which probably aren't all correct. And even if they were correct, it's static and it's one molecule at a time. This shows it all together and it's exciting I think. It's thoroughly amazing.

McNally:

What Charles is able to do, and this I grasped from my conversation with him, is takes the latest, latest cutting edge scientific simulation software and the algorithms they can produce and then he takes the latest cutting-edge animation special effects software and he moves back and forth between the two doing things that neither one would either be able to do or think to

do.

Ingber:

And counterpointing it with real experimental data at different size scales.

McNally:

Right, and so what you had going on was it's a physical depiction. You're taking on that problem that most avoid, which is doing it at different scales. You're doing it with accuracy and, thus, you're sort of pushing the envelope that neither the animators nor the scientific simulators would have taken on.

Ingber:

I think that's fair.

McNally:

What happened when you discovered that the process is revealing things that hadn't been seen or known before? Did that change the way you were working on it.

Ingber:

We wanted to say at the end of the film, and I don't think we did it in the end, but it was something like, "No physics was sacrificed in the making of this film." Right? Just like, "No animals were sacrificed."

McNally:

No physical laws were broken.

I have to say we submitted this paper to a number of journals, many, maybe four different journals that turned it down. Some wouldn't even review it. The big journals wouldn't review it.

But we sent it to other journals and they reviewed it and there'd always been one reviewer who just assumed this is purely animation not linked to reality.

The upside of having reviewers is it did push us to go back and explore and validate what we were doing and was there an advance here? I think it was during that review process where we actually went and took a more scientific perspective, which was ... We knew that we used this high-quality data, so we must be reproducing that visually, but we confirmed that.

But that's when we counterpointed the structures that we were doing compared to published papers on cryo-electron microscopic visualizations of it, and we could show that, yeah, we get that, too, and then we realized but we get better resolution. You know what I mean?

So some of it came from now the scientific attacks if you like, or constructive criticisms if you want, that led us to have to validate that this actually was as good or better than what's out there. And that was after we pretty much had done the film.

McNally:

[something validating their struggle to publish about this new artistic technique being used for scientific discover, and asking what has led them to this point and influenced them to think differently]

Reilly:

First of all, I grew up on a farm. When you're farming, especially in an isolated area, you have to just do everything and figure out everything just on the fly.

I didn't even really know what kind of professions were out there. There was kind of math, English and science and physical education. I was exposed to poetry in my later years in high school, and that's actually when I first started to think more about how I wanted to try and understand the world.

So when I left high school, first of all, I hitchhiked around New Zealand for a couple of months and then moved to London, where I wanted to be a writer, a poet and just trying to understand humanity.

I ended up working for Greenpeace, and at the time genetic engineering was a big topic. I was never comfortable just listening to propaganda, I always wanted to know more about a subject, and so I became more and more curious about biological engineering.

And so I then decided I would go back and get a degree. I felt that I needed credibility in biology and chemistry and kind of the physical subjects in order to explore that with rigor, I guess.

I did my undergrad in biomedical engineering in Wellington, New Zealand. I then went to art school. At this point, I still hadn't found the medium I wanted. I knew the kind of subject matter I wanted to explore, but I didn't know how I was going to do.

Reilly:

In science, I'm very interested in the mechanics of biology and so how changes in the molecular structure influence the way the body works. But then I was also very interested in why do we get along? Why do our emotions cause resentments or why do conflicts emerge? There was nothing really drawing those, nothing that I could find that was exploring those questions.

I got a job in postproduction in Wellington, Peter Jackson's studio, but again because I was a chemistry guy, I always had felt like I wasn't taken seriously creatively.

And again I was just a small cog in a big machine. That's when I decided I wanted to do a PhD

That's when I moved to Melbourne, Australia and I started studying immunology.

During this time, I was exploring animation tools and just art on the side, but still exploring the same subject matter but without any constraints.

I worked on an interactive textbook for a little while at the Walter and Eliza Hall Institute, I'm working with these simulations and animations for an artistic goal, but I'm developing hypotheses and I'm seeing things that are relevant to biological discovery.

McNally:

Charles explains to me how film visual effects artists employ sophisticated computational software and something akin to the scientific method to generate their spectacular images.

Reilly:

You might want an explosion, so then you simulate the explosion. You didn't predict exactly what it would look like, but you tried to define these conditions that would make an explosion effect, and by defining all the rules of physics and this animation scene might be, to produce a cinematic effect that is based on physics and is mathematical, but ...still curated if you like, so there's this kind of allowing the computer to do the work, and then you curate from the other end.

McNally:

Mm-hmm. So you see the result of this particular attempt and you go "I want it bigger", "I want it smaller", "I want it more looking like a certain chemical instead of another", that sort of thing?

Reilly:

Precisely.

McNally:

You know as you're speaking, I remember a moment in my life that sticks in my mind, I think it's 1973. I was actually back in Cambridge at the time. I spoke with a computer artist, if you will, from MIT. He told me that he could feed information into a computer program and create visual products within that program without having started with a physical photo or physical image or anything. In 1973, that notion blew my mind. Basically what we're talking about is where that possibility has evolved over the last what are we talking, almost 50 years.

Reilly:

Precisely one of the movies that really made a big difference in my life actually was The Matrix. In my work, it really does come down to "there is no spoon." There is that idea that, because we're in a computer, we can mix data that doesn't belong together. We can bend the spoon and we can just really expand as much as you can and be playful without breaking.

McNally:

Reilly says he's mixed in scientific simulation and modeling software with physics-based special effects software.

Reilly:

I can borrow from both domains and so I can easily myself just quickly alternate between tools that are normally separated.

McNally:

Mm-hmm (affirmative). Let me ask, in the visual effects world, they are really results driven. There's a timeline on this production, there's a timeline on this sequence, there's a budget on this sequence, and your piece has to be ready when they need it. Has that forced them to move in some ways perhaps further in the modeling in this type of approach you're talking about than a scientist working in a research facility might be forced to?

Reilly:

Absolutely. I think that that is part of my motivations for really trying to get this kind of work done in a place like the Wyss Institute is because they are making these huge leaps because of those essentially market constraints.

It's not that you're abandoning this concept of curiosity-driven but it just pulls it in a different direction. I think that that's what the entertainment industry has done on a lot of these tools. If the Wyss Institute is one of the more collaborative institutes in the world, I would say for science, the film industry is one of the most collaborative art forms in the world.

McNally:

I ask what led to his contacting Don Ingber.

Reilly:

I was always sharing what I wanted to do. There's a lot of people just rolling their eyes or saying, "sounds like you want to make up your own field". I was kind of "well yeah, I kind of do." I was just sharing that idea with somebody who was an illustrator.

I shared with them how I wanted to do art not just illustration, and have that art drive the science. They said "you should talk to Don Ingber."

Ingber:

Well, I view the world as not having any boundaries between disciplines or focus areas, even application areas, and I've sort of always been that way, even since the time I was a Yale undergrad. When I was an undergrad at Yale, I actually was a science major, but I just had a passion for wanting to learn about art, and I had an experience in an art class, a sculpture class, that actually transformed my view of the world and launched my trajectory in science.

I always view, in the back of my head, as art as a potential medium to play in that could be valuable in science, but that was pure serendipity, so I never had the experience in a proactive way, trying to explore whether one could use art to advance science. [DI-03:52]

McNally:

Can you tell us about that experience in sculpture class?

Ingber:

It was almost impossible to get in art classes at Yale, but I was walking around campus and - at this time I was taking classes which were teaching us about molecular design, which is like the shape of molecules governs their function.

We were learning about viral structures being like geodesic structures, and all of a sudden I see these kids walking around campus with these polyhedral structures that were shaped like a virus - They looked like viruses. And I asked them, "What is that? What are you doing?" And they said, "Oh, it's my sculpture class." And I said, "What's the class called?" And they said, "Three-dimensional design," and I was like, "Wow, that's exactly what I do. That's the way nature works."

I tried to get in the class and it was this big hulking Austrian professor, Erwin Hauer. I had a girlfriend at the time who was a sculptress taking a human body course with this same Erwin Hauer. She said, "Let me introduce you to him," so I met him. He was really tall and he looked down at me, really imposing, "Why do you want to take my course?"

And I basically said, "Well, in biology, everything is three-dimensional design." He said, "What do you mean?" And I basically said, "Well, when I contract my muscle, there are these helical fibers that would twist and shorten, and actomyosin they're called, and that would create tension." And he said, "You're in my course."

I kind of didn't get it, and I just kept giving him examples and a smaller size scale and viral structures and DNA... "It's the shape of the DNA, the double helix," and he said, "You're in my course. Just come Monday." So I showed up Monday.

One day he said, "Go out and buy 3-foot long dowels and high-tension fishing cord," and we did that. And then he brought us to a machine shop and he cut the 3-foot dowels into 1-foot dowels and we were all sitting in this classroom, like work tables, and he said, "You have three hours. I want to see you build structures that hold themselves up off the ground in three-dimensional shapes, but the sticks can't touch. You can only connect them by strings." And he left. And we all looked at each other and we're trying to pile sticks on top of each other.

Finally, one student who probably had seen the sculptures of the artist,

Kenneth Snelson, built one of these, which are structures where - it's like our bodies - they're held together by continuous tension rather than compression, so it's like the muscles pulling up our bones against the force of gravity through continuous connection of tensile muscles, tendons, and ligaments.

This has sticks that are oriented in such a way that you could put strings, connect their ends, and they pull themselves up and open. That was amazing. Once one person did it, we all started building every possible shape, which was a really wonderful experience in the creative process.

At the end, Erwin Hauer came in and he had his own round sculpture that was bigger and it had bungee cords for the cables, and it was spherical. As he talked about this thing and introduced us to what tensegrity was and Buckminster Fuller who had first coined the word, he would squish down on this round sculpture and it would flatten. Then he would let go and it would bounce off the table.

By pure serendipity, the week before I had started culturing cancer cells in the medical school across campus. And it was the mid '70s and I had been reading papers where they had just discovered a thing called the cytoskeleton, the cell skeleton - that there are these molecular filaments inside cells, including actomyosin filaments like the ones that generate tension in muscle.

When you cultures cells, they grow on a dish, you use enzyme to clip their anchors and move them from one dish to the other, and when they come off the dish, they're round, but when you put them on the next dish, they attach, pull against it, and spread flat. Then when you clip the anchors, they round.

The rounding looked exactly like when I was trypsinizing cells using an enzyme, trypsin, to clip their anchors and they were coming off the dish. Because I'd heard about a cytoskeleton, I assumed that that's the way cells were built.

So when I went back to the biology lab one day, we were using a drug that actually caused the shape of the cell to change. And I remember saying, "Oh, the tensegrity changed." And the post-doc, the research person who was older than I was, said, "What did you just say?"

And I said, "The tensegrity changed."

He said, "What's that?"

I said, "Well, I'm taking this sculpture course and it's like Buckminster Fuller and this artist," and he said, "Never say that again in this lab."

So I shut up and went to the library, and that was sort of the beginning of the rest of my life.

McNally:

So you mentioned Buckminster Fuller there, who as you said, was the first one to either discover or coin the term tensegrity. I'm going to ask you first, one more time, what does tensegrity mean?

Ingber:

Tensegrity stands for "tensional integrity" and it describes structures that gain their shape stability, their mechanical properties like their stiffness or flexibility, based on having a continuous transmission of tensile, pulling forces, rather than brick-upon-brick compressive forces like the weight of one stone on top of another - like Stonehenge where if you hit it from the side, it falls like dominoes.

Structures like our bodies, which use tension in our muscles to give us ... Whether your arm is stiff or flexible ... We're independent of gravity and direction in terms of shape stability. It's really a building system.

MCN

I recall that Fuller, whom I'd made a documentary about in the '70s, was the first I'd heard point out that there are no departments in nature.

McNally:

In talking about art and science, art versus science, art mixing with science, am I in some way making a false dichotomy?

Ingber:

Everybody is kind of interpreting the world around them based on the tools and the principles that they learn, and the medium they can work through. Artists try to describe their worldview and they do it through the visual arts or music or other types of art, so we're all trying to describe the world and hopefully advance understanding of others by it. The difference about science is that we have to be able in the end to lead to an outcome that's just not your opinion, but that can predict. That others can repeat.

In art, there's just these big people like Cezanne, Picasso, make these jumps of how you view the world and present it to others, and the others who become incredible, great technicians at the process and do things in wonderful ways.

I think the quantum leap scientists who try to get the big picture are not so different than the big artists who try to convey the big picture.

Therefore, they're looking at the gestalt, the whole system, not every little element, but how things relate to one another, and that often comes out in patterns, which scientists are looking for patterns, like detectives in a way.

But, artists are looking for patterns that they can convey, that convey to others some insight about how things work. So it's pretty similar, but we're

all searching for patterns to give us insight into how things work.

McNally:

Because of his work on tensegrity, Don tells me he's participated in many meetings crossing art and science and was aware of the advanced and rigorous work of cutting edge special effects animators.

A student who was in scientific communications grad school in Toronto out of the blue sent me a DVD that was hours long called "The Architecture of Life" about tensegrity in cells. My *Scientific American* was called "The Architecture of Life." And he basically sent this to me saying, "This is my master's thesis and I hope you enjoy it."

And then he asked me whether I'd be an advisor on his thesis committee, and I went up to Toronto and we talked about this and then rather than going further towards a PhD, he decided to form an animation company, which now is very successful in advertising communications.

That's where I first learned that people in the animation industry and entertainment have been putting real physics into the animations. When I was a kid and they had a Mickey Mouse cartoon animation, to get the arm to move, it would be the equivalent of a puppet

That was the first time I became aware that these entertainment people are being able to visualize what's going on physically better than my scientific engineering collaborators who model tensegrity, but give me a graph. And I can't communicate that to anybody, right? I definitely had that spark in my head.

McNally:

I'm curious for someone like Charles who rejects silos, who focuses on a question or a problem with little regard for specialization, what it feels like to work at the Wyss.

Reilly:

It's the *je ne sais quoi*, if you like, because if you put it on paper - why would I live in Boston with these winters to sit on a bus every morning to go work on my own at a computer in Longwood? It doesn't make any sense, but it's amazing. I can swivel on my chair and talk to my colleague and he answers a question because he comes from a mechanical engineering background.

When I showed him the simulations and I said, "This is cool, this hinge like thing is enabling the system to work." and he's like, "Of course, that's mechanics."

Then I rotate to the other direction in my chair, and I'll be speaking to someone from the communications team. They just had an interview with somebody at the Cambridge campus and they were working on some sort of robotics—a critical component in the next collaboration. Then you walk down

the hallway and you run into the director and you start the next project. That's really how it works.

Don talks a lot about self-assembly. It happens on a daily basis and it really is by not forcing but removing the obstacles between collaborations or self-assembly.

McNally:

What's next for you, what are your next projects?

Reilly:

The immediate project is actually using a lot of the tools and simulation strategies that came out of The Beginning movie for therapeutic design so designing of drugs for specific diseases, and also discovery of targets for drugs.

McNally:

How does using a simulation approach help in drug discovery?

Reilly:

Drugs always have a target and those targets are often large biomolecules such as a protein, and if we were able to simulate a more accurate representation of what a protein looks like, we take a more rational approach to designing a very specific targeted drug that will interact with that protein in a very specific way. And so by having a more robust or just a larger suite of simulation strategies, we can depict and predict how our targets might look and how they would interact with any drug we designed.

McNally:

Interesting. This isn't just theory, you're beginning this work and you're finding that it feels like it's going to be positive.

Reilly:

Yeah or they got very good results that yeah, it's very exciting.

McNally:

In addition to his own work, I wonder how Charles sees his relationship to his field. Does he have a message for his fellow scientists?

Reilly:

Yes I think that I do want to encourage more people to take risks with their approach, risk in the sense that to become more comfortable with doing things differently, and to expand the paradigm of what it means to be a scientist.

McNally:

And in his artistic work, Reilly wants to continue to grapple with some of the larger questions that have been driving him since his teen years on a farm in New Zealand.

I want to tackle some of those questions of - how do we connect our social behaviors or the social biology with the molecular and cellular biology or understand how we're connected on this kind of biological continuum, right from the molecular cellular level right up through the humanistic scale, right the way through to the ecosystem, and through exploring this in sort of an artistic and scientific way together I think we can start to learn things from one scale that can be applied to another scale - so through this kind of a metaphorical inquiry.

McNally:

Right, in addition to what you plan to do in the science side, your artistic side may be where you're able to really take on some of that.

Reilly:

Exactly.

McNally:

Okay, thanks a lot Charles Reilly.

Reilly:

Thank you.

McNally:

Don Ingber is excited by the potential of combining Reilly's simulation work with the Wyss's organs-on-chips...for example, in drug design.

Ingber:

There's already what they call rational drug design, computer-assisted drug design, where they'll use simulation to depict a molecule and then sort of figure out where a drug binds to that molecule, where the key goes into the lock if you like. And then they will on the computer try to put arbitrary shapes that are known chemical structures to fit that space and try to build some new molecule that will bind that site and thereby competitively inhibit with the key. That's a simple example.

We're basically doing similar things like that, but with what we think is a higher resolution capability.

We combine this sort of computer design with our human organs on chip systems where we can actually go very ... Rather than just simulate it on the computer, we will come up with a molecule. We'll synthesize that molecule, and then we can test it in a human organ on a chip, and a human organ on a chip recapitulates the organ level structures and functions of part of our lung, part of our liver, part of our kidney. So we can then test our model or the molecule that we modeled, designed, and we can make various versions of it.

Then we can get results saying that actually when you test it in the human

lung, this is better than that, it's better than this.

Then we can iterate in by having Charles go back on the computer and figure out where all those molecules actually bind, because they're all subtly different, and we can kind of triangulate in on like what's the best site to target, and then go deeper with designing the molecules and have this iterative loop of design testing in a very high-value, high-content system.

McNally:

Are there other things which now, as you imagine the next few years, challenges or inspirations that this is evoking in you.

Ingber:

One thing for me personally is that people had a hard time with this idea of tensegrity, that there are sort of sticks and strings inside cells and tissues and so forth, but I convinced a lot of them experimentally that this is true. That the microtubules that I mentioned before are kind of like relatively stiff tent poles and the actomyosin filaments are contractile, and I think people were convinced.

What they could never get was when I suggested that this is a design principle that guides how nature builds at all size scales in life. In my *Scientific American*, I started from the atomic level to the molecule to the multi-molecular structure to the cell to the tissue to the organ to the body.

Artists had described the human body this way. People accept that. I describe the cell, people could not get it, but I think they kind of accept it now.

But with this video, with the sperm fertilizing the egg, tensegrity just fell out of it. We saw it at multiple size scales in our models and the models wouldn't work without it. For me, it may be a way to get back to actually visualize how tensegrity applies at all size scales. So that's something that's in the back of my head as well.

McNally:

Finally, you care that scientific discoveries get translated into impact in the world. You also want better communication of science to the world. Can you talk a little bit about that?

Ingber:

Yeah, I had intersection years ago with the entertainment industry through comedy writing. I never really did it professionally, but I was damn close. The one thing I guess I learned out of the process is that I really believe you don't truly connect with people and get their full attention unless you ignite their emotions. It could be laughing, it could be crying, but if you are telling a story that is passionate and personal or gets them laughing or crying, they're there. You are linked.

But if you are trying to be didactic and just tell people how excited they should be because of how something works which you're excited about, which is often how a lot of scientific communications is, is just telling it in a relatively dry way. Some people will like it, but you're not going to get the broad population that a really funny, humorous film would get.

McNally:

And how does he see this short film, *The Beginning* in terms of that challenge...

Ingber:

I think it's a process where you're trying to put little breadcrumbs out to get people to move in the direction and that you're not going to teach people about molecular biophysics by showing them a sperm film. But, at least one out of a hundred kids might see how beautiful those molecules dancing in unison as you described, Busby Berkeley motion, and be intrigued by that, and go on and want to learn more about science.

I remember as a kid going to the World's Fair in New York and seeing these exhibits and conveyed the hope that technology will solve the world's problems. That dragged me in that direction. Life's a nonlinear path.

I once described my life as sort of a Brownian walk. A Brownian walk in physics is the atoms sort of move randomly, and cells move in a Brownian walk. They lean this way, they move that way, they move this way, they move that way. But with cells, if you have a stimulus, like if you have a wound, chemicals are given out as a gradient and so they move in what's called a biased random walk. That means they go this, they go that, but they tend to go that a little bit more than they go this.

McNally:

Right, right.

Ingber:

And they end up moving towards where they want to be. I said if you do that towards your passion, then you'll end up where you need to be in life.

I think if we can get kids seeing things that are exciting and attractive and look so cool, we might pull more of them in that direction. I'm not going to necessarily convince people that are a lot older, but I think for kids, it might just do it.

Ingber:

The key is getting people emotionally involved, whether it's because you're telling a story and they're just following every word, that's very personal, or laughing or crying.

Communication should be pulling people into this story, into this narrative, that it's like reading a book, like they may not want to put it down. I think in

the current culture, we need to get kids coming into science, especially in America where there seems to be less and less children that are American going into science. People from all over the world are coming into science, but they tend to go into different areas.

McNally:

That's funny, I often hear people say, "Well, everything is biology." And then I often hear people say, "Everything is narrative." And it seems to me what we're talking about is that everything is both.

Ingber:

Yeah.

McNally:

Thanks a lot, Don.

Ingber:

Good talking, as always. Bye bye.

McNally:

Yep, bye bye.

McNally:

You've been listening to DISRUPTIVE: Art Advances Science. I'm Terrence McNally and my guests have been Don Ingber and Charles Reilly.

You can learn more about their work as well a broad and exciting range of other projects at the Wyss website - [wyss.harvard.edu](http://wyss.harvard.edu) - that's W-Y-S-S dot Harvard dot edu - where you'll find articles, videos, animations, and additional podcasts. In fact, Don Ingber has been featured in another episode of DISRUPTIVE.

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