DREW ENDY
STANFORD
MAY 2013

INTERVIEWED BY LYNN HERSHMAN

D: Evolution equals tyranny. That is my equation. It was an answer to question posed several years ago by John Brockman. And the question is what's your favorite equation?

Evolution as a natural process creates random mutations that lead to biological diversity. We have little to nothing to say about the evolutionary process. It's just sort of happening. And so evolution is this tyrant like King George III. Why would we want to put up with mutation without representation? We didn't put up with taxation without representation.

D: We are learning how to design and build living systems. And to do that in a way that is complimentary to nature, but also recognizes that living systems operate on three time scales. The third time scale, the longest time scale, is the time scale of evolution. Evolution is not this magical process. I mean, it is magically beautiful, but as a physical process, it's not itself magical. And we should be able to specific the evolutionary performance of living systems and how we want them to evolve. For example, and by the way, very few people have been working on this. it's probably controversial to say that within the research community, but it's also the case that it's physically plausible. Let's say I'm actually going to engineer a living system, and it's going to make oil. It's going to be a photosynthetic algae that's been engineered to make diesel fuel. A reasonable question somebody could ask is what happens if this algae gets into the San Francisco Bay? Will it be powered up by sunlight and there will be a persistent oil spill? Is it going to be way worse than when the tanker runs into the bridge. It's going to be an oil spill we can never get rid of, because the algae will be out of control. I say oh, no, no, no. I'm a good genetic engineer. I'm going to put in these kill switches so that the organism won't survive if it gets out of the pond where the algae is growing.

But then, a reasonable question will be well, what if it mutates? What if it evolves and the kill switch breaks? Now that algae can get out into the Bay and we'll have a persistent oil spill. What if I could make a synthetic genetic code wherein every point mutation was deleterious? That when mutations happened, I can't stop mutation, but if a mutation happened, that organism would be disadvantaged. It wouldn't survive regardless of what the mutation was. When you engineer a rocket and if it's coming off the launch pad and it begins to go sideways and it's heading over to the neighboring town, you don't actually let it land in the neighboring town. You blow it up. That's called a fail fast design. Fail fast system. The natural genetic code is itself an artifact of evolution. That means it's been evolved to evolve. The idea you could have a genetic code where mutations were deleterious, all of them, nature would never provide that for us. We'd have to go in and make it. Evolution equals tyranny is not meant as a claim of decoupling from nature, but a claim of independence and a claim of responsibility for what's happening.

But you don't want to rule out the possibility that if you push biology into a corner disallowing evolution, it could evolve a new way to evolve. That would be pretty cool.

Everybody is familiar with computers made out of electronics. We're making a biological computer. We're taking the elements of a computer and we're implementing them out of the parts of biology such that the computer operates inside living cells. When we implement a biological computer, I'm….I'm not interested in this to replace my laptop or to compete with silicon or any other type of computer. I'm interested in building a computer that will operate in a new space, a new place. Silicon based computers are never going to work inside my liver. I couldn't put a microprocessor based on dope silicon in every cell in my liver. But I could put DNA inside every cell in my body. So if I can figure out how to encode the elements of a computer in genetic material, and I can boot it up and operate it inside living cells, that's going to get me computing in a new space. Not to replace silicon outside of the body, or outside of a…a living system, butcomputing inside.

Computers have data storage for recording information. Computers have ways of transmitting information to different parts of the computer and computers can also implement logic. So we figured out how to take uh sections of a genome, a chromosome, very tiny sections and target them to be flipped and flipped back, and flipped and flipped back. Flip, flip, flip.

And because they can exist in one of two orientations, we get to define an orientation as being a one, and the other orientation as being a zero. One, zero, one, zero, that's one binary digit or bit. So, one bit of data storage just by flipping a targeted section on the chromosome back and forth.

Why are we working on bio computing really? If you read the newspapers, we're working on it because it's going to cure cancer or something like that. That's not why we're working on it. We're working on bio computing because it is the intersection of two fundamental challenges that are faced at the core of engineering biology.

I'm an engineer. I like to make things. It has become apparent that biology is the ultimate platform for manufacturing. It makes these incredible things from everything we see in the natural environment to ourselves. We're very, very bad at engineering biology today. Our capacities to engineer biology are incredibly limited. What I'm most interested in is advancing our capacity to engineer biology . You can take biology apart but how do you get it back together and working? And then the second issue that's a fundamental engineering challenge how do you get biology to behave, so to speak? Living systems are noisy. They're spontaneously diverse, whether there's mutation or just the random fluctuations from the thermal noise.

If I'm running a bio computer that's counting how many times a cell divides. What if the cell mutates at a hundred generations? I don't want to lose track of how many times it's divided. So the computing applications force us to get better at thinking about evolutionary reliability and just precision performance in general. So, the computer work we're doing is almost an artifact of our motivation to get generically better at engineering biology.

If you ask me today what the implications of a bio computer are, what bio data storage is, what genetic logic you know, I'm going to give you my lame answers for the moment. We just heard from Thailand where they make spiralina. If you see the Odwalla green smoothies with the super food in them, that's an organism typically called spirulina, which is grown in open ponds. It needs sunlight. Wouldn't it be nice to know if the water supply coming out of those ponds is clean or if it has a pollutant showing up? I would never have thought of this, but to my surprise, they were interested in not engineering the food organism but engineering another microbe that could be a sentinel that would listen to the environment and detect whether or not mercury ,or other heavy metals or other pollutants had shown up into the water supply and flip a bit inside the cell that would change colors and could be diagnosed later to just do quality control on food manufacturing.

Most of our medicines are based on chemicals. Right? The chemical is a way of transducing human intentions into a medical outcome. It looks like we'll be able to increasingly develop living cells as therapeutics. It's called cellular therapeutics. The way I think about this is to go back to the movie Fantastic Voyage.,

TRT: 3:35

If you have an inoperable disease, the best thing to do would be to take a submarine, fill it with doctors, give them lasers and shrink them down and put them in your body, and they're going to make you better. That would be really great. Except that the physicist have never delivered shrinking rays, right. So how do we actually make Fantastic Voyage a reality?

We have to take the intentions and prescriptions of the doctors and shrink them down. They're going to be living cells. And you see today, for example, engineered T cells being used to treat leukemia. There's projects coming out of UCSF where people are actually taking bacteria, which you would think of as being incredibly dangerous to inject into the circulatory system, but declawing the bacteria so they're safe to put in a human circulatory system, and then give them a little bit of sensing capacity so they can detect a tumor, a little bit of logic so they can compute what they should do, and then actuators that allow them to try and invade the tumors, make the tumor a destroying drug right at the tumor . I guess what I think about realistically optimistic is that living programmable cells will be a new platform for therapy. Just to be very clear though, there's almost no chance we're going to do that work.

Our jobs as engineers is to do the fundamental engineering research that makes the whole process of engineering biology more capable.

It's certainly the case that we can reprogram DNA. We're using enzymes, which are taken from bacterial viruses, bacterial phage. Bacteria phage are the most abundant living system on the planet. In the surface water of the oceans, there's about a

They have within them, enzymes that infect the ocean growing bacteria., they have to make it a decision often times. A choice or they just do something spontaneously. Option one is, they infect and they insert their genome into the chromosome and they go dormant like HIV for example, might in a human. Or they go into the cell; they blow it up and release more virus particles. There's an enzyme though that does that insertion reaction, it's called the intergrace.

And what it literally does is it takes the virus genome and grabs onto it and finds a specific site on the bacterial chromosome and inserts the genome right into that spot. That's the integration reaction. And those are the enzymes we're using to flip DNA when we reprogram how they work . So, note that we have enzymes that allow us to reprogram DNA in real time. So what we could do is set up genetic programs and they'd be running in one configuration and then we could come in and they'd be out in the environment or they'd be in a patient and we'd come in with a bunch of signal sthat would cause the DNA to be reprogrammed in a determined way. We can push it to be deterministic.

If you look at all the DNA that's been sequenced by by scientists around the world today, iyou notice that the human genomes tend to the tenth base pairs. A billion to ten billion base pairs and we just sequence that for the first time back in what…2001. So a decade plus later, how many more base pairs have we sequenced?Approaching ten to the fifteenth base pairs, right? So we've got an enormous factor more to go. Like ten to the twentieth fold more DNA to be sequenced. So, it's absolutely true that we couldn't do any of our work without DNA sequencing information and we think of DNA sequence information as being so advanced but we're really have one in ten to the twentieth of the information for sequencing. The extraordinarily greatest, vast majority of biology is totally unknown to us. Right, so it is wonderful to have a little bit of sequence information. We only have ten to the fifteenth base pairs.

Stanford, we have a new program in bio-engineering. We have a new undergraduate major in bio-engineering. We are shipping would be engineers of biology and it would be great and more than great , critically important to have a capacity to hire anthropologists, lawyers, social scientists, ethicists, artists directly into the faculty so that our students and ourselves are multi dimensional. When we think about the ramifications of getting better at engineering biology and also when we explore what bio-engineering is. You know, whose voices are represented and the problems that are defined and pursued, how we view the world. And…and right now,Stanford included but every bio-engineering department I know is in the grand scheme of things, one dimensional. A very technically focused and often times very medically focused and by medical, I mean first world medical. Rich nation medically focused. So it's dissatisfying and tremendously limits what bio-engineering is. So the things that practically limit what we do in the laboratory, have nothing to do with our thinking about science or technology or what our ideas are for research. The things that actually limit what we do are our capacity to explain what we're doing. Figure out how to represent and shape it so that it's more like let it be good. And… and to navigate a process where if I simply go around and report results which say, oh by the way, we just got a little bit better at engineering biology. The default response for majority of people is to freak out, right. Politically or otherwise, very few people default to cool.

I can't possibly know because everybody has their own opinion. But biology can be very scary, right. You know, the miracle of life, implies it's a miracle and we don't understand it and so to try and plug into it and take so responsibility for what's happening in a context world. We know we don't know what's going on, can be frightening. In addition to that, natures doing all sorts of things which sometimes cause a lot of hurt. The next emerging infectious disease that hurts people is quite troubling in part because you can't see it when it happens. It's an invisible thing that hits you and then you're sick and maybe you survive or maybe you don't. And we don't know when it's going to come next.

Engineering biology is limited not by the science or engineering of engineering biology, it's limited by the public conversation and the policy and the ethics. And that's where most of the work is to be done…to figure out what the good is.

And most people don't want to have that conversation. The default path for a human being is to be born and die and in between, experience life. But not to reengage and apply your opposable thumbs to figure out what life might become besides what it is already. Although some folks are beginning to insert themselves into the process of life, most people don't want to do that.

D: This is why I need others to help with the thinking. How do you make decision?How would people feel about unenlightened leadership that applied advancing biotechnologies to create a speciation event. Right, just to do something fantastically innate and wrong.

From a thermodynamic sense, all of biology is really improbable. It shouldn't be there but here it is sustaining itself and that's what life's about .

A bio-brick --In Tom's initial invention, it's defining a stretch of DNA such that the tabs or the sequence at the ends of the DNA, can be cut and paste identically, no matter what's inside the brick. That's now over ten years old. Over a decade later, the bio-brick part brand, involves not just physical assembly but things like how you measure the activity of a biological part. How you define its functional performance. How you transmit information about the part over the computer networks and other technical standards. And collectively, this defines a free to use technology platform for programming life. Our long term goal is to literally create…a dictionary. Right, so…so this is a dictionary for the English language. We'd like to have a dictionary for the biological language where you could open up a catalogue if you will and find different functions that have different meanings and you could pull them off the shelf, along with the dictionary you'd have your grammar. And the…the rules of composition and…and when you want to make biological poetry or biological novel, you could put it together and it would work. So, that's what we're building and that's what the bio-brick programs about. Long term program.

So, right now when we put DNA programs into cells, every type of cell we're putting our DNA program into, is a preexisting type of cell. It's a human cell or a plant cell or a fungus or a bacteria, right. Nobody's actually made a cell, right. There's not the ACME incorporated cell, right, that's been made from scratch really. So, that by itself is pretty interesting. There's a hard limit right now, that all our DNA programs that we engineer, no matter how fancy we think we

are, we're actually plugging them into a natural context. That's very wild still, not heavily engineered. The interfaces are very raw.

A different way to think about that, just coming at it from a different perspective, we've got this fancy new bioengineering department at Stanford. Bioengineering is such a young field of engineering, that it's relatively trivial to jump into the top ten because it just doesn't exist yet in its…in its…in its future form. And most of its still to be done and…and I mean it as an observation, not so much as a criticism. I got a question from a student in class this week, could you take a plant cell and convert it into a…a neuron, a human brain cell. What a great question. We know that you know, both types of cells are made of atoms and biomolecules, so from a physics and chemistry perspective, why not. You just have to convert a plant cell into a brain, right. And there's probably some movie about this, right. But…but to do it, really you'd need to have the genetic information that you'd load into the plant cell and boot up and it would run the conversion process to turn it into a meme lion neuron. That's crazy, right. I can imagine doing it but it's… well beyond current capacity.

It's well known that there's two cases before the U.S. Supreme Court right now, involving genetic material. The Bowman versus Monsanto Case having to do with reproducing plants and whether or not the concept of patent exhaustion applies. And then the Case, having to do with patent claims over natural genetic sequences or what's a natural genetic sequence in the first place as it relates to in this example, breast cancer diagnostics.

We'll see what the court decides. I didn't find those arguments to be fairly sophisticated if you go read those arguments. Not because they we're bad arguments but…but…but they represent a sort of backwards look on reality and don't recognize that we are getting better at engineering biology and we're developing tools for engineering in biology that are scaling impressively, right. Our capacity to print DNA from scratch is increasing faster than computers are getting better.

Theability to abstract genetic programs from raw DNA sequence. If I'm trying to engineer a cell I would start talking in the letters of DNA.t I can't memorize that many sequences really. So, I have to create this hierarchy of function that abstracts the bio-complexity away, yet can be when I need to, compile it back down to the sequence. That's actually coming true, so what for example I mean by that is, let's say I wanted to engineer a tumor destroying bacteria. I need a sensor for the tumor. I need a logic app. I need an actuator that takes out the tumor. What if I could take those three elements off the shelf and I don't need to know that DNAs made up of four bases. That type of abstraction is becoming very controversial for the last decade because it's so hard to do . As it becomes true, the future engineers of biology don't need to know that DNAs made up of four bases. So you're actually doing your bioengineering work at a very high level programming language, that looks like code.

So why are we talking about patents as a property right to begin with. Why aren't we talking about copyright, right. Or just a total different property righta. Beginner conversations are going to be outstripped as the technology changes. That's my prediction.

The latest bio-computing element we made, these transcriptors leading to amplifying logicates so called Bill Gates, we're able to put that in the public domain. So Stanford engineers contribute to Bill Gates to public domain. It's done. Other things where companies have or other inventors have begun to mark off the property right space using patents and when we look at that, we go wow, they're really screwing that up. We have the option of…of putting in our own patent to try and clean it up and preserve for him to operate…
END, DREW 5

I think all of this is a legacy of a first generation biotechnology and the second generation biotechnology is going to be on a tool platform that…that fundamentally challenges the property right, the system to begin with. Not the property right system but just what is the property right that applies to living material,. Maybe it moves to copyright Maybe biology and biotechnology are so important, we need our new…a new property right.

In the last eleven months, we've had a really good run. So, in May of 2012, we we're fortunate to be able to report that we could make this rewritable data storage element, the so called _____ data module or RAD system. And that was the first time people had shown that you could flip a section of DNA and then flip it back. And when you flip it back, you perfectly recreate the original sequence which means you get to do the whole cycle again and again as many times as you want. And it probably is still the best genetically encoded data storage system. It solved that problem really nicely.

In the fall, in September, we published a paper that Monica Ortiz did, where she engineered cells to autonomously package DNA that she could target, into virus particles so the cells would package up not the virus DNA but her engineered DNA. Any DNA she wants and the cells secrete the virus particles into the environment…these virus particles are now packets containing the DNA information that she chooses.

But the virus particles behave like viruses, so they go infect other cells and insert her DNA programs. So this is a cell/ cell communication platform and…and her invention represents the first time you can take a cell/ cell communication system and on the fly, reprogram the message. Right, so in a formal sense, it's decoupling of the channel for communication and the message carried by that channel.

Cell phones are a great example where this works, right. You can say anything you want through your cell phone. Hey mom, you know happy mother's day. You know, whereas previously, all the cell/ cell communication systems we're…we're the message you we're sending was a specific molecule. Like I'm sending you this much sugar. I'm sending you a lot more sugar! Very boring talking with one word. And then most recently, Jerome, _____ and Monica all came together and we used the bits and pieces they've been playing with to make these amplifying logic gates.

What's distinctive about their work is the first word in…in describing it, amplifying logic gates. An amplifier, if you play guitar, right, if it's an acoustic guitar, there will be a certain amount of sound volume. But if you play an electric guitar, you're going to plug that thing into an amplifier,

you're going to make a lot more sound. More people can listen to. So amplification is this process where you take a signal and you increase the volume or the dynamic range of a signal. In computing, amplification is hugely important. People had over the last decade, developed genetically encoded logic but they've not developed amplifying logic. And so if you don't have amplification, what happens is you know, here's my logic gate. I've got some signal controlling the gate and it's swinging across a load of high range and the output signal that's generated by the gate is across a smaller range.

. What we figured out how to do was to take a small signal, run it through the gate and have the gate produce a bigger signal. And that makes it trivial to connect gates up as long as you want. So that's a big deal. And then what was also cool is you can take everything they've done previously, like the cell/ cell communication and they can package up the gates and send the gates around and reprogram populations of cells to implement distributed logic. So it's not just one computer running in one cell, it's a whole population of cells. Each running a collective computer.

It's been a good year.

We stumbled into it by trying to figure out what we had just done with the data storage and…and basically what it comes down to is story telling. We're trying to be honest with respect to what we've observed and what we've done.

With the data storage system, we had been borrowing the metaphors for electronics and…and we had been saying, we're making what's called a latch. A latch is a system that can lock into one of two states. And when it's in you know, zero, one, zero but…but a latch really implies that in any given state, it's held tight. It's not going to spontaneously switch states. It's locked in. And…and so for three years, we're talking about making our genetic latch because that's what electrical engineers do. They make latches…electrical latches. But when we we're going to write up that and…and when I actually got invited to go give a talk in electrical engineering course, I realized that we hadn't made a latch. I couldn't hide that reality and telling the story.

And we freaked out because we had misrepresented it to ourselves. . And we had to reinvent the story of what we had done. As soon as we reinvented the story, we came up with a new story and…and the new story is, we didn't make a latch. We made analog to digital converters. I take an analog signal from low to high and at some threshold, I either flip the DNA or I don't flip the DNA. And that's a digital output because the DNAs in flipped or not flipped….flipped or not flipped. As soon as we knew we had conceptualized A to D converters. Then it became very easy to make switches that led to amplification and logic. So this has been an accidental year that has been driven by storytelling.

Storytelling that is not fiction but to be honest about it is our struggle to represent what we've done. When…even as the doers of it, we don't perfectly understand it as we're doing it. And I

don’t mean that in some risky way, it’s just how you think about what your doing is…is different during the process than after the process and you reinvent the narrative.