EPISODE 14

[INTRODUCTION]

[0:00:00.5] JM: CRISPR is a technique for altering the human genome. It might be the most powerful tool for biological modification that we have ever discovered. In this episode, we explore CRISPR, how it works, why it exists in the natural world, and the implications of being able to modify DNA so easily.

Geoff Ralston is a partner at Y Combinator. He wrote an article entitled *Hacking DNA: The Story of CRISPER, Ken Thompson, and the Gene Drive.* Since Geoff is not a biologist himself, he's actually the perfect person to explain CRISPR to an audience of non-biologists. Geoff comes from an engineering and computer science background.

Since he's an investor, he's also great at explaining the pace at which CRISPR might make it to market and how it might converge with some of the other futuristic trends that we are seeing so regularly today. It's a really exciting conversation I had with Geoff and really enjoyable.

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[INTERVIEW]

[0:03:52.6] JM: Geoff Ralston is a partner at Y Combinator. Geoff, welcome to Software Engineering Daily.

[0:03:56.9] GR: Thanks for having me Jeff.

[0:03:58.0] JM: You wrote a blog post called *Hacking DNA: The Story of CRISPER, Ken Thompson, and the Gene Drive.* Why did you write this article?

[0:04:07.7] GR: I have been fascinated by synthetic biology in general, sort of the merger of biotechnology and software engineering for a while, for several years. I sort of had an epiphany one evening when I couldn't sleep and realized that the programming of the human and, indeed any genome, was maybe not imminent, but coming soon and that the results are that we're going to be staggering and important.

When I learned about CRISPR I realized it was one of the key missing pieces that was going to accelerate that technology and the future that it was going to impose on the human race pretty rapidly. Then, I went about gene drive, and Kevin Esvelt's work on gene drive, and it just reminded me of this incredible hack that Ken Thompson did, and so it just felt like something that needed to be written. I felt like even though there had been a bunch of really good jobs done talking about CRISPR and what it meant, I just didn't think it was really in people's consciousness yet and I think it's so important, so transformative that I want to do everything I could to help be better known that this, I think, impending change for humanity was lurking out there and there just wasn't enough conversation about it, and I just wanted to help make that conversation happen, I guess.

[0:05:57.7] JM: You're not a professional biologist, but you see a lot of cutting edge science at Y Combinator, and I think part of the job of a venture capitalist is to assess things that are somewhere in between research and go-to-market viable products, and there's a continuum between those things and you never want to be too far on the side of research where it's like — Like quantum computing. Probably, quantum computing 5, or 5, or maybe 10 years ago, or maybe even today. I honestly am not up to date with quantum computing, but that's something where 10 years ago we could have talked about quantum computing, but the ways that quantum computing is going to impact the world and the pace at which it's going to do that, less clear, and you probably wouldn't have been — Made good money investing in quantum computing 10 years ago. It takes a venture capitalist mindset to perhaps translate the state of science into the viability of that science having an effect on the broader world.

[0:07:13.2] GR: Yeah. There's a famous investor who responded to the question, "What's the secret to your success?" by saying that he always sold too soon. I think one of the secrets to start up investing is to always invest too soon. I know that's a little contradictory, but it is true that you have to sort of get a little bit ahead. The harsh fact is if you really invest too soon in a technology, if you invest in quantum computing 10 years ago, you're probably going to lose your money, because a company can do great work, but if there's no market, or the technologist isn't ready, they'll run out of money and the company will probably fail.

You want to be sort of too soon, but not really too soon just a little bit before everyone else so that the technology has a chance to flourish at the right moment in time for everything to come together; the market, the viability, et cetera.

By the way, at YC, we did invest in quantum computing, but not 10 years ago, 2 years ago with this incredible company called Rigetti and we're really excited about the work that they're doing.

[0:08:27.1] JM: Yeah, they just raised a big Series A.

[0:08:28.8] GR: They did, yeah.

[0:08:30.0] JM: It's funny because it seems like there's not really — When you think about — One of the technologies today that resemble quantum computing 10 years ago, it's kind of — What are they? Maybe it's like interplanetary transport. You can't invest in an interplanetary transport today because you have no idea what that market is really going to — Maybe you can. I don't know the deal flow well enough at YC to know that, but it's kind of — I don't know. It might be a sign of the pace of technology that it's hard — 10 years ago, you could have said, "Okay. Quantum computing is going to impact something, or genetic editing is going to impact something at some point in the distant future, but we can't really invest in it today." Today, it's like, "Okay. The future, it seems closer," and judging by the fact that you can't really think of an investment that is implausible today.

[0:09:19.2] GR: I think that's actually incredibly well-said, that the future is closer. One of the effects of that is have you noticed how mainstream science fiction is now?

[0:09:31.9] JM: Yeah. I used to read science fiction. Now, I don't even read it. I just read the news.

[0:09:38.7] GR: It's really true. It used to be fore geeks like me, who, science fiction was this little corner of the world that was ours. We get that. Science fiction is — Everyone is saying, "I think it's because the future is so close." What can you talk about that we're not quite ready to invest in? Maybe space elevators. Not quite ready. Maybe asteroid mining, although people are starting to invest in asteroid mining, so maybe it's not quite too late or too early for that.

You might have said neural interfaces about three months ago, but apparently that's not too early to invest in. The ability for people to take science fiction and code it into science fact with incredible rapidity is stunning now.

I think it's Alvin Toffler all over again. It's the theme of our world. It's Future Shock. The future is closer. It's here now and it's moving ever more quickly closer to use, right? It's hard to escape.

This is a bit of a tangent, but I personally think that one of the reason it feels like such a disruptive age in sort of every sense, not just in science and technology and investing, but in politics, is a function of that fact. The fact that people feel unsure about their future and unsure about what comes next and that causes incredible nervousness and disruption and change, and we see it all around us now. It seems like it's an unavoidable facet of our time.

[0:11:35.2] JM: Yeah. Not to further us down this tangent, but this morning, I opened up Hacker News and at the top of Hacker News was some API for replicating a voice. It's just like where you can give it a smalls sample of somebody's voice and you can replicate that voice saying whatever you want. I see that and I'm like, "Now, I need to — Do I need to email my family and tell them, "Hey, be on the lookout for scams where it sounds like somebody's voice that you're familiar with, except they're saying weird stuff."

Actually, I'm going to have to send an email to my parents to say, "You have to watch out for this kind of scam." It's just like when I see these kinds of new technologies, sometimes it just raises my anxiety because of the worst case scenario.

[0:12:27.2] GR: It's so funny. If you think of the way of just saying how science fiction turns into science fact. Remember the original Star Trek when they went back in time and saw a future — I think the episode was Kirk and McCoy and one another, maybe Spock, go back in time and they're trying to save the world and there's this guy there who was in our time but has advanced technology, because he's really alien, and he's dictating to a typewriter, which seemed like he's talking to it and it would type. That's so amazing, but not so much.

I just want to relate that to what you just put up. Remember in the original Terminator movie? From 20 plus years ago?

[0:13:16.9] JM: Yeah.

[0:13:17.8] GR: Where he mimics the voice of her mom or whomever. That's just the technology you just talked about. That's all it is. Why wouldn't an android be able to do that? All they need is that little module that you just talked about and they can sound like you.

You think about security in this modern age and it's kind of terrifying. It's kind of terrifying that you set yourself up with two factor authentication and you start to feel good, because you got your phone and you carry it with you everywhere you go and you know that if you want to log in to Gmail, it's got to text you and you're okay. Then, you find out that it's really pretty easy to steal someone's phone number. There's actually two or three different mechanisms you can use to either steal someone's phone number, steal their text, whatever. That's not that safe.

Then, they could steal your phone number and your voice and have all these information about you. They could tell you, "You all know it's me. Here's my social security number. Here's the addresses, the last four addresses I've lived, which is all more or less publicly available." It's stunning and scary. The fact to the matter is you — The best thing to do is not be a target, because if they come at you, you're in trouble.

[0:14:37.6] JM: That's right. It is a social pressure to — Well, I guess not be a target, whatever that means. I did a show with Pindrop Security and it is comforting to know that there are some technologists who are working on this really hard, all of the different vulnerabilities in the voice area.

[0:14:57.1] GR: Yeah, but it just makes me — I think all of us are still living in denial —

[0:15:04.6] JM: Yeah, in a vulnerable state.

[0:15:06.0] GR: I need to get a Ubiki, and I have it, and I need to. I shouldn't even be saying that on a podcast, because there's too many people who listen to this. It's scary, right? This isn't exactly the topic we're going to talk about, but it's scary.

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[INTERVIEW CONTINUED]

[0:17:00.6] JM: Human bodies are big computers and our genetic code is similar to binary. The main difference is that humans invented the compilation of binary. We can encode and decode things in binary. We can compress. We can encrypt. With the human genome, we actually have to reverse engineer the decoding and encoding process, the nucleotide sequences.

How much progress have we made in our understanding of how these coded nucleotide sequences translate to the higher level organic function that we'd like to be able to control and engineer?

[0:17:42.5] GR: Yeah. The big caveat here is I'm not a biologist and I'm far from expert in these fields. The cool thing is, and I really recommend this, you grab someone like Jennifer Doudna or —

[0:18:02.7] JM: Jennifer Doudna. Okay, I'll add that to my list.

[0:18:04.3] GR: Or Feng Zhang. The people who really invented CRISPR, and they'll do a better job of answering this question. It's actually funny that whenever software people start talking about biology, it kind of pisses biologists off and some of the comments to my post were a little bit angry, because there's so much simplification, like, "You have no idea."

[0:18:30.3] JM: You got the metaphor wrong.

[0:18:32.0] GR: You saw for people think it's a simple matter of programming and the incredible complexity of protein folding and the expression of genes and the interaction with the environment. It's nothing like you think in your little digital minds, in your Silicon substrates. It's not that way in the squishy, wet world of biology.

They're of course right, but I think that they're also kind of missing the larger picture, because, for me — The answer to your question is we've made incredible progress and we're not very far along. The example I use in the essay was, "What happens when we can hack intelligence?" If you, as a parent, could choose to increase the IQ of your child by 10 points, would you do it?

The fact is we have not that much knowledge about IQ and how that relates to the genome or potential environmental factors. It's incredibly complex, and it will take a while. My point is that it's still a — It's merely a problem of difficulty. It's hard, but it's solvable. The more you have technologies like CRISPR, the more tools you have in your tool chest to learn about the problem and figure out what it means. Without experimenting in human beings, by the way, the way we learn so much about humanity without doing unethical experiments is we can experiment with animals and look at mice and see what sort of improvements in intellectual capacity we can make by editing the genome of mice, or other animals. Eventually, we will figure that out.

I guess that's my main message here to all the biologists who are already pissed off at me for not understanding their field, is that it doesn't matter. It's inevitable that we will make progress and that — I find it extremely unlikely that there are sort of unsolvable problems in how genes are expressed. It is a code. It is repeatable. The experiments are repeatable, and we will gain the knowledge. It's merely — In programming, we say it's a simple matter of programming. Here, it is too, but it's a matter of time and programming. You're going to need time.

[0:21:33.8] JM: It's different than the non-determinism of the atomic level, I think. Maybe that's the investment that you couldn't make right now.

[0:21:42.5] GR: Yeah, we're not dealing with quantum mechanics here. By the way, quantum mechanics is pretty damn deterministic in an indeterministic way. The predictions that quantum mechanics makes are incredibly reliable and that's why the macro world is so deterministic, by the way. That reliability gives us the determinism of the macro world.

[0:22:05.9] JM: Right, the macro world, including the lower levels of biology that we're getting into.

[0:22:11.7] GR: Absoluetly.

[0:22:12.2] JM: CRISPR stands — It's an acronym, C-R-I-S-P-R, it stands for Clustered Regularly Interspaced Short Palindromic Repeats. This is the editing technology that, as you say, gives unprecedented power to genetic engineers. CRISPR itself refers to these repeated clusters of the strange nucleotide sequences in DNA.

[0:22:37.1] GR: Yeah. It's kind of a cool name; CRISPR. CRISPR, as I point out in the essay, is not real — It doesn't really refer to the editing technology. It just refers to these nucleotides that are repeated originally in viral DNA which was really just a clue on the path to discovering the editing technology which uses these enzymes called the Cas enzymes.

Really, the technology is CRISPR-Cas together, putting those two concepts together, and I guess no one came up with the better name than CRISPR, so we all call it CRISPR. That weird acronym which I think someday be completely forgotten, because who cares that they're regularly interspaced, or that they're short, of that they're palindromic? It just doesn't matter.

[0:23:39.0] JM: CRISPR, these Clustered Regularly Interspaced Short Palindromic Repeats of DNA, this was originally found in bacterial DNA. Explain why this encoding sequence indicated something that was actually quite useful for the bacteria. What was the useful function?

[0:23:58.9] GR: Yeah. It all goes back to this incredible epic battle being fought on a daily, hourly, by the minute and second, this battle between bacteria and phages, which are viruses that attract bacteria. Bacteria where — They were the only life game in town for two billion years before there was multicellular life. During that time, there was still evolution, and viruses, and viruses would attack bacteria, and bacteria develop defense mechanisms. It turns out that CRISPR was one of those defense mechanisms.

This guy, Eugene Koonin, kind of — In my understand, is that he had the first insight, these clustered repeats, these CRISPR repeats were discovered in bacterial DNA long ago by these Japanese researchers, but they didn't know what they were for. Koonin kind of said, "I think they are defense mechanism." It turns out that bacteria developed a rudimentary immune system. Even though CRISPR is very sophisticated, it turns out our immune system is incredible. We have armies. They don't quite have that, but what they do have is the ability to recognize certain invaders and to attack them and kill them essentially.

It's a weird — We're talking terms that perhaps suffer from a lack of real accuracy, because I don't know if you can talk about killing a virus. I don't even know — Because it's not really alive. They're rendering it inactive. It turns out that what bacteria can do is chop up a virus, take its DNA and put — By the way, virus and phage, I'll use interchangeably, and put that DNA into its own DNA sequence.

Using these Cas enzymes, it can grab that DNA, put it into this package with RNA, go wandering around its cell, and if it bumps into DNA that matches, these Can enzymes have molecular scissors that chop up that DNA and kill it essentially. What a cool defense mechanism. It just turns out that that defense mechanism, that chop-chop that it does is basically what you need to do to edit DNA, and it was these — Again, these brilliant insight by folks like Jennifer Doudna and Emmanuelle Charpentier at Berkley and Feng Zhang at the Broad Institute at Harvard and MIT that figured this out and created CRISPR. By the way, they're all creating CRISPR companies now, which is really fascinating.

[0:26:56.3] JM: Really?

[0:26:56.9] GR: Yeah, they're all — There's public CRISPR companies already and they're all sort of, in essence, in competition with one another to commercialize this technology. It's going to be an epic battle of its own to see who manages to really commercialize.

[0:27:20.5] JM: Surely not a winner take all battle.

[0:27:23.5] GR: I would think not. I mean, it's a little sad for me, I guess, that it's intellectual property battle. I think intellectual property has unfortunately — Although it's been an incredible thing for innovation, can be a real break in innovation. But CRISPR, this sort of editing technology, kind of feels to me like VI, although people have complained it's nothing like VI. It feels to me like something that anyone should just be able to use it to do whatever you want. Maybe it's sort of that way, but people are — The U.S. Patent Office is issuing patents. They issued one already, and there's a battle between sort of the Berkley folks and the Broad folks, and the Broad folks won the first round.

They were all working in this company, Editas, together, which is a public company, but now Doudna has split off and founded her own company, and Charpentier has split off and found her own company, and so we'll see. We'll see what happens. One of the things that happens when you form companies is that people start to pour money into them and that means that we're going to start to see things happen. There are companies being formed.

[0:28:41.8] JM: I need to do more shows in the legal area, because this is sort of the same question — Well, similar question. I don't want to say the same, because we'll see what the court proceedings bear up. It's like a similar question to the self-driving stuff; to what degree did

Uber steal the Lidar technology. In to what degree is this stuff just common knowledge at this point where — I don't know. These seem like related questions.

[0:29:08.5] GR: Totally. Think about what's happening — Voice is another great example where that happened. There is Nuance who owned everything, and Microsoft who own everything, and there are these epic battles. Even back when I was at Yahoo, there is a battle actually just after I left where folks we had hired to look at Voice from Nuance, and they had intellectual property issues and there are suits. These are some of the core technologies that are going to drive the future. There's going to be amazing battles around each and every one of them, from self-driving, to augmented reality. There were around search back in the day and there will be around CRISPR and there will be around every one of these transformative technologies for sure.

[0:29:57.8] JM: Yeah. A lot of can of worms opening up here and I need to do some other shows around different topics. Just so the listeners get an overview of what CRISPR is. You mentioned this process of a bacteria, this never ending war between bacteria and bacteriophages, and the bacteria in order to have a self-defense mechanism against the bacteriophage, chops up the DNA of virus that it has defeated and it inserts it into its own DNA so that it can use it as a template to recognize viruses in the future.

The technology that we can build around this is essentially — We repurpose this labeling and cutting mechanism, and the labeling, cutting, and insertion mechanism to be able to edit — This is generically applicable. We can apply this to human DNA and basically anything, any sort of animal.

[0:31:01.8] GR: That's sort of the epiphany I had way back when, which was that if you think about it, almost every living thing starts from exactly the same point. You have a cell, which is at least in the animal kingdom, pretty much identical with a slightly different code on the inside. The result of that code is a radically different machine, which by the way sort of self-manufactures itself in every case.

The variety of machines it can create is extraordinary from human beings and the human brain, which is the most complex device we know about in the universe thus far, to tiny flying machines, and large flying machines. It's amazing. That code is editable in essentially, to my understanding, every case by CRISPR.

We have been given this incredible tool to allow us to essentially make that code whatever we want. Now, we don't necessarily have the knowledge yet to be able to make it things that are useful, and useful can be thought very broadly. Useful could be something dangerous and horrible, or useful can be something wonderful. Just to do something that matters is a little bit beyond our capability in every case, but we do know a lot of things that we can do with editing technology.

For example, we know a whole bunch of diseases that are determined by single gene errors. That's sort of a piece of cake for CRISPR. When you find things — You can determine which genes confirm munity to diseases. For example, HIV, you could edit that and create that. For example, if you know what genes are the ones that make solid cancers immune to our immune system, allow them to fight off our immune system, and you can change those. You can then allow our immune system to defeat the cancer. These are all real applications of CRISPR that we're going to see in the short term, that the ability of CRISPR to be broadly applicable, I think, is its most extraordinary feature and broadly applicable in multiple dimensions, in the set of different organisms in which it works; from mosquitoes to human beings, and these set of applications within each of those organisms that it can apply to.

[0:34:06.0] JM: CRISPR itself only allows for modifications of one gene at a time, one organism at a time. If we wanted to do what you call a species level change, we need additional technology. Explain why that is.

[0:34:24.4] GR: I believe what you said is not quite correct, that you could actually use CRISPR to modify multiple genes at a time. The limitation, if you want to call it a limitation, is that just changing those genes in you, for example, let's say you suffer from macular degeneration, and that's a genetically predicated disease and that we can fix that by going into your eye by placing CRISPR into your eye and changing all of the DNA in your retina to no longer have that gene and therefor no longer express whatever gets expressed to cause macular degeneration.

Unfortunately, if your children — If you subsequently have children, they'll still have that gene because the DNA in your eyeball does not get passed along to future generations. However, if you use CRISPR to change either sperm or eggs, then you actually can affect future generations. That is something that CRISPR can do.

The reason I brought up gene drive is because it just makes the impact — It's a multiplier on the impact, because if you change your reproduction DNA, the DNA in your sperm, to do something different, it only has a 50% chance in each subsequent generation of being present in your offspring. Gene drive changes those odds essentially, and the gene drive that Kevin Esvelt created essentially can get that close to 100%.

There's a lot of complexity there as to how effective it can be and as, again, biologist would point out, biology is complicated and there's ways that CRISPR create a gene drive can run into barriers. Those, I think are again amenable to rigorous hard work to overcome. What that means is that you can get characteristics, genetically derived characteristics to spread throughout a population with startling rapidity.

Probably won't be used so much in human beings as it will be in other species that reproduce more rapidly, like mosquitoes for examples where Esvelt was first experimenting, so that you could, for example, create a mosquito population that could no longer carry malaria.

[0:37:18.7] GR: Right. I understand what you're saying and, again, I'll forgive you don't know the answer to this question. I clearly need to have some people who are total experts in this field on the show. Actually, I think it's — As a side note. I really think it's a good — When I start to do a series of shows, I actually — I think it's sometimes good to start with a non-expert, like somebody that's just sort of external observer, because they are a little better bridging the gap between the layman and the advanced shows.

I think this actually makes a lot of sense, but tell me —

[0:37:51.7] GR: By the way, it's especially hard in biology and biotechnology because you talk to folks. It's very easy to get lost, not just the terminology, because everyone has jargons, there's lots and lots and lots of jargon and lots and lots and lots acronyms, but it is actually incredibly complex how this stuff works. I think — Very useful to pullback, but there are these underlying levels of complexity that, you're right, it sometimes helpful to even to know about.

[0:38:19.2] JM: I fully understand how if you change at the sperm or the egg level, you change the DNA and then mitosis takes care of replicating the change to DNA as time goes on in the organism and then it's also changed in the offspring of that organism. If I'm a fully grown human and my phenotype includes some kind of macular degeneration, I think that's the term, how do you change all of the cells in my eye with CRISPR? Do you spray my eye with the CRISPR juice, or do you have to insert something, or is it a surgical procedure? Is there a way to do that in a fully developed human?

[0:39:03.2] GR: Yeah, and people are developing them right now. I think the question you're asking is; what's the delivery mechanism? People are developing those as we speak. We're actually funding companies that are creating delivery mechanisms at YC, so it's a good question; how do you get the CRISPR inside the gene?

I think I'm not an expert at that, but I'll be willing to say that you might as well think about it as spring the eye with CRISPR and it gets inside the cells and does its stuff. There are definitely ways to do that. There are ways to get chemicals, enzymes, packages across cell barriers. Once you do that, there are ways that it can do its stuff. Yeah, there are ways to get CRISPR inside. That wasn't a made up case. People are trying to create CRISPR systems that will correct things like macular degeneration.

Of course, it would be better if you it was indeed a genetic disease that you just got rid of it first before it's in your DNA, and that's why changing the DNA that's undergone meiosis in the sperm or the egg can make sense. It's ethically incredibly challenging, right? Where exactly is the consent to modify the DNA of a person that isn't born yet?

A couple of Chinese researchers did some experiments on human embryos using CRISPR, and indeed change the DNA in a way that it would have been — It had those embryos. They were nonviable embryos, so there's never any possibility of this, but had the embryos been viable and had they grown into human beings, their DNA would have been generational DNA and those changes would have been generational. It was very controversial. Even though they are nonviable just because there's all sorts of questions, consent is one of them, about whether it's ethical to change the genome of a human before they're a human being. I think those are complex questions.

I actually, in one sense though, think from the perspective and uniquely from the perspective of whether the technology goes forward and whether people try that or not, it doesn't matter. People will try it. I think — That doesn't mean that the ethical considerations don't matter. I think they're incredibly important. The Pandora's box has been opened and it's very hard to contain a technology once it's out there, and so I think it would be very naïve for us to think that whatever ethical restraints we put on ourselves will be enforced elsewhere.

[0:42:06.8] JM: Many of those questions are going to be sidestepped, because there's plenty of things that you can do with people who have some horrible genetic malady that they're willing to do any sort of experimentation. That's in the post-developed human being area of things. Even if you're talking about the developmental side of things, or the gene drive experiments that you would want to be doing on an embryo. It doesn't even have to be a human. You can do this kind of stuff on a monkey embryo or on a mouse embryo and it's not like that totally sidesteps the ethical questions, but at least reduces the passion around them to a level that's not at the abortion level controversy.

[0:42:58.8] GR: Case in point, I believe those Chinese researchers had something like a 28% hit rate. In other words, their CRISPRzation of these embryos failed 72% at the time, which sounds pretty bad. Although getting 20% to work is something. If you're doing IVF, that rate sounds about right.

Further advances in their techniques were tried in mouse embryos, and my understanding is they were 100% accurate, 100% successful. The science is advancing all the time and incredibly rapidly. I think the hardest thing to keep track of will be the set of things that CRISPR is being used for. There's going to be thousands of applications.

CRISPR can be used, as I was saying before, on disease vectors. CRISPR can be used potentially as a kind of super antibiotic. CRISPR can be used to fight cancer. CRISPR could be used to create biofuels and to create more efficient crops or crops that have defense mechanisms against their own disease vectors.

Once you have an editing — It's sort of like software, trying to keep track of all the things you can do with software, because once you can edit the software, it goes from the set of things that you can research as a biotechnologist for your Ph.D. has just expanded many, many fold. Likewise, the set of companies you can create in the set of things you can — That are approachable now that were never approachable before, solvable, is extraordinary. That's why it's such an important technology, and it's been recognized as so transformative.

I think it's sort of separate, orthogonal to all that, will be that someone is going to try to change human beings with this in fundamental ways. I just think there's this theme, Yuval Harari has written about this, I think, eloquently in Sapiens, but especially in Homo Deus, about the fact that we might — I don't know if you have kids, I do, but it might sort of be the last generation of homo sapiens, the way we think of homo sapiens. There's these three forces that are going to, I think, change humanity forever. One is CRISPR and one is AI and the other is human augmentation, which is kind of connected.

This is a train that has left the station. This is going to happen. I told my kids, "You are living in probably the most interesting time, incredible time ever. You may be able to achieve immortality. You may be able to change your bodies and your children in ways that had never been thought of before."

[0:46:23.5] JM: It's probable at this point.

[0:46:25.2] GR: I think the only argument might be whether it's this generation or the next generation — Are we talking 10 years, 20 years, or 50 years? I don't know. The timeframes are not long.

[0:46:42.0] JM: Yeah. Frankly, I'm just not really even thinking — When I talk to people about having kids or not, I'm just sort of like — It's kind of a moot point. Sure, it'd be fun to have kids and it would also be fun to just have complete independence as we begin to explore this crazy frontier. In any case, it doesn't really matter, because even the idea of individual human beings is going to be a moot point in like 30 to 50 years.

[0:47:10.6] GR: I don't know. I'm not sure I know what that means, and I think — One of the points that Harari makes is that it sort of like pre-humans; chimpanzees, or gorillas, trying to imagine how we approach problems and what sort of things we're solving for us to try to imagine what the next set of thinking beings are going to be preoccupied with.

I don't know that there's any — Some things I find are inevitable. I find it inevitable that these changes we've been talking about will happen. I don't know that it's inevitable that we'll lose the concept of individuality. The reason is, is that still one of the deepest mysteries is the one of consciousness. I suspect that — We're talking about how the complexity of biology, and I find it hard to imagine that there's complexities of biology that are not amenable to human intellectual approaches and understanding, so that we can open them up. I don't think that's so likely. It's possible, but I don't think it's so likely.

Consciousness, there might be knowables there. I don't know that, because there's this subjective quality to it that might be difficult to get at. It just might be true that we'll be able to know everything there is to know about consciousness and that maybe AI will help us figure that out if we can create consciousness on a different substrate on a brain than we'll probably understand it fairly well.

That being said, we don't even understand why deep learning does what it does, so it's not so obvious to me that human beings in our current intellectual capacity will be able to do that. We might just run into limits that we don't understand yet, but consciousness and individuality are obviously tightly intertwined. Whether it's inevitable that we have to let go of that individuality, even just because we're connected in a much more tightly understood fashion to other consciousness isn't so clear to me.

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[INTERVIEW CONTINUED]

[0:51:24.9] JM: I wonder sometimes how much of this kind of stuff can I talk about, because it's almost like one of these things — It's like that Paul Graham piece; what you can't say. It's like; can you even talk about this stuff at the dinner table these days? At the Thanksgiving dinner table without making people really upset and uncomfortable that you're questioning the nature of humanity in this lifetime.

[0:51:51.2] GR: I think that goes back to the point I was making earlier, that people are getting nervous. I just think that — It's maybe a step too far, but I think if you look it from Brexit, to Trump, to the recent French election, the way populations are just —

[0:52:12.4] JM: People are freaking out.

[0:52:14.1] GR: people are freaking out, and I really do think so. I think that — I sort of feel in 2008 during the financial crisis that sort of one of the fundamental underpinnings or the world that I had made some assumptions about, that they kind of knew what they were doing, like the —

[0:52:31.7] JM: Efficient markets.

[0:52:33.1] GR: I realized that that's not so much, and there was this unsettling that happened. It's like, "That could happen again." What's stopping it? We haven't gotten really any smarter. We're just going to do some regulations and then a bunch of people will say, "Oh, those regulations suck. We need to get rid of them," and we get rid of the regulations, and we'll be there again. It's the same thing, right? People are nervous and freaking out.

I think you can have these conversations and people don't quite know what to make of it. When you tell people, "Oh, yeah. This could be the last generation of human beings, which sounds like — That's like the guy walking around with the placard saying the end is near. That's crazy talk. It might be maybe not crazy talk, but not — It could be wrong, but it's not wrong for long. I think people — Normally, when people act crazy and say crazy things, it makes people nervous, and there's enough people saying it now that they're really nervous, because who knows? The sky might just be falling.

[0:53:44.9] JM: Yeah. It almost doesn't matter how you personally are updating your societal norms. It's more just like how do you — It's almost like this explains the prepper phenomenal, or people talking about prepping. It's just like there are some crazy stuff going on and it's —

[0:54:05.6] GR: Look. Here's the thing. Here's the thing. I was thinking about this as I was reading Homo Deus. Early on, he has this discussion about what happens when as you get to this new level of humanity and you can start to think about populating the galaxy. You can. The math is such that it doesn't even take that long, that once you start being able — If you can imagine a Silicon substrate, or you can imagine humanity being able to take a whole bunch of different steps. Interstellar travel is not beyond us if you talk about time frames. It sound crazy now, but if you talk about it hundreds of thousands of years, or millions or years.

This begs the incredibly important question that Enrico Fermi asked, right? Which is; where are they all? Where is everybody? Why haven't we seen anyone, because we're not that young in the universe? The universe had been around for 14 billion years. If this is sort of a natural evolution and life is common, how come other folks haven't sort of spread out throughout the galaxy? If they have, how come we've never met them, or how come they're hiding from us, or maybe there isn't anyone?

There's a few assumptions you have to make there, but maybe the most popular is that there's a great filter, right? Which is that you make it to this stage and then something bad happens. The preppers are — Maybe they wouldn't put it quite this way, but they're thinking there really is a filter when something bad is going to happen.

[0:56:01.0] JM: For sure. I don't say prepper in any sort of derogatory term. I do think when you get to the Fermi question, you're on grounds where it's equally plausible that the others are invisible or they completely transcend the world that we can sense, or we're in a simulation, or any one of these different things. I think those are all equally plausible.

[0:56:29.0] GR: I think, probabilistically, if there's lots and lots of life out there — If life actually is fairly common in the universe and it's not that usual for technology to be developed, then I think it's quite surprising that we haven't seen any indication of it at all, at all, ever, nothing essentially. That's surprising to me.

It feels like there's something wrong in that equation. It just doesn't — I don't know about plausibility, but it just — If that were true, then there would have been very, very ancient species that would have gotten as far as us and probably would have tried to go out to expand throughout the galaxy and they probably would have found us.

[0:57:20.2] JM: If you're taking a probabilistic mindset, one conclusion I got to do sometimes is like if you're playing in the simulation realm of possibilities, if you just look at humanity and it's like, "Wow —" Just like as you're talking to your kids and you're saying, "Today is literally the most exciting time you could live in."

If somebody were going to build a simul — If a future world of humans was going to build a simulation to simulate people like us, the most fun simulation would be the reality today as far as we understand it, which could — I don't know. This gets into pretty far over-stepped. I don't know.

[0:58:03.0] GR: For what it's worth, that kind of my interpretation of quantum mechanics, is that quantum mechanics for me increases the likelihood that this is a simulation and what all those probabilities means is just — It's a shortcut. It's delayed calculation of things that a software programmer did so that they didn't have to, you know, decide where all the locations were all the time. You don't care until you have to care. That's why we're in a simulation, but — Oh, well.

[0:58:41.5] JM: Right. Yeah. Let's get back to reality as we close off this interview. You are doing some investment in CRISPR. What are the company — Can you talk about some of the companies that you've invested in?

[0:58:56.2] GR: A few. It turns out that — I'll mention a couple. A lot of them are so new in our current batch that I can't really talk about. One of the interesting ones is a company called Benchling. Benchling is — Sajith will kill me for saying this, but they're sort of not — They're maybe a little on the boring side of CRISPR. They enable CRISPR companies. They're not creating CRISPR technology, but they help people manage all of their DNA, and so they're being used by every CRISPR company. That's essentially a CRISPR company. That's core CRISPR infrastructure, if you will. In fact, infrastructure is not at all boring, so I'm sorry, Saji.

PROLARA is another example, and they're doing something really fascinating. They take organisms that are in important ways have similarities to human function and use CRISPR to modify those organisms so that they have rare diseases that appear in human beings and then they use those organisms to test drug compounds to see what will work those rare diseases. So that these diseases that are incredibly difficult to deal with that people are loathed to spend lots of money on because it's so expensive to find drugs for rare diseases can be much more, if you will, economically approached and dealt with. That's a really cool company. It's just another way that CRISPR can be used to sort of a tangential way, if you will, that CRISPR can be used to help approach diseases that were tickets to either a foreshortened life, very difficult life, or really no life at all.

[1:01:15.1] JM: In pure software realm, AWS has removed a lot of the execution risk that you might have had in investments in the past, like pre-AWS era. Is there still a lot of execution risk around the stuff that CRISPR companies are building on top of?

[1:01:36.7] GR: I think it's almost certainly true that the — The execution risk that has been — It's important to start with what the execution that's been removed, that CRISPR has removed, which is that it used to be incredibly time consuming and way too expensive to do the kind of edits that could have substantive impact.

You had scientists wasting years of their life trying to do this, and sometimes coming up empty and sometimes not getting nearly as far along as they wanted to in just huge, long periods of time. CRISPR makes it fast, cheap, accurate, easy. That problem is mostly been solved.

What hasn't been solved in the real execution risk that still exists is that we're talking about, for the most part, for a lot of these things, technologies, they want to change human beings, cure human beings, impact human beings. We have to go through FDA approval, and that's still hard and risky. You have to do trials. You have to do careful trials, because these technologies have the potential to do harm as well as incredible goods. We want to be — Companies will have to be careful. We want a society to be careful.

That's why, by the way, why PROLARA is so genius, because it's found a way to nuance that so that you can do the drug discovery of drugs that already exist in organisms so you don't need to get FDA approval to CRISPRize those organisms and you can solve disease that way, which is really cool so you can move very quickly to market. That risk, that infrastructural risk, probably shouldn't go away and it hasn't.

[1:03:38.2] JM: All right, Geoff. Thanks for coming on Software Engineering Daily. This is a really great wide range of conversation. I really enjoyed having you on.

[1:03:44.5] GR: Hey, I enjoyed it a lot, Jeff. Thanks a lot.

[END OF INTERVIEW]

[1:03:51.5] JM: Artificial intelligence is dramatically evolving the way that our world works, and to make AI easier and faster, we need new kinds of hardware and software, which is why Intel acquired Nervana Systems and its platform for deep learning.

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