Interview with Dr. Drew Endy[1]
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ENDY: Hi, This is Drew.

MICHAEL: Doctor ENDY: This is MICHAEL:, from Duke.

ENDY: Hey MICHAEL:, how are you?

MICHAEL: Good Sir, How are you?

ENDY: Great, thanks for your call. Can you hear me ok?

MICHAEL: Yes,

ENDY: Hey, I'm in a lab here, let me walk outside and try and find a quieter spot.

MICHAEL: Sure.

ENDY: How's the weather in Durham, North Carolina?

MICHAEL: (Laughter) The weather is great, not quite, no snow like we hoped for, but what can you do right?

MICHAEL: How about in California

ENDY: It's raining actually

MICHAEL: It's raining, well, really. Is now a good time?

ENDY: Yeah perfect time, I was just trying to find a good spot to hunker down so we could talk.

MICHAEL: As soon as you are ready then, I have a little disclaimer to read. Is that cool?

ENDY: Sure

MICHAEL: Alright are you ready?

ENDY: Yeah

[1] Dr. Endy approved the transcript without corrections.

MICHAEL: (Disclaimer)

ENDY: I have a question?

MICHAEL: Go ahead.

ENDY: The archive may be made publicly available, do you know what legal scheme is by which it is being made publicly available, is it public domain, is it copyright base protected, is it something else?

MICHAEL: I have no idea? It could it remain unpublic and get back to you.

ENDY: Everything you said sounds great, with possible note that I would like information around the format, legal scheme by which the materials are being made publicly available. Different specifics that matter, not in a way that something would be made publicly available, I want to make sure it is being done in way that is actually correct. I just don't know the details are about this specific repository.

MICHAEL: I can get to my professor as soon as possible, and get those details to you.

ENDY: Yeah, perfect lets just go ahead as that as a note. I'm sure it will work itself out.

MICHAEL: Definitely, thank you. Alright in that case, I would like to start talking about programmable biological systems. I understand the basis of synthetic biology and things like that. What really interests me is when you speak about garage biology and programming in that sense. Or, I have a quote from the bulletin of atomic scientists where you said, "Rather than writing a specific genetic program, I'm trying to make better programming languages, so more people can program in DNA." So I guess I would like to talk about that idea of genetic programming?

ENDY: Sure, the idea of genetic programming is then sort of the consequences of success, one of which you mentioned is as possible consequences of success, by a technology becomes more acceptable. So, there are a couple different ways to cut this, and maybe you know I'm hoping you will keep asking me questions, but I will try by lighting this up from one perspective which is the historical perspective in a different field. Then we can come together and talk about the context of synthetic biology and programming DNA.

So, if you take electronics, and the computer as it exists today and wind the clock back 50 years, you've got a bunch of different worlds for computing. You've got a world that, for example during and immediately after World War II there were significant federal investments in building computers. These were very large devices, and if I have my facts right for example, John von Neumann at the Institute for Advance Studies at Princeton built a computer in the basement there, and the purpose of this computer was officially was to help design hydrogen bombs and compute trajectory and conditions, although

apparently without knowing it was running artificial life simulations on the computer, which is kind of interesting.
Then you go forward only 25 years, and you find the world is different and that people are fed up with limited centralized access to computing and so groups of folks, most notably around San Francisco, via the home brew of computing or other computer organizations, eventually produce the personal computer, Apple. It's really interesting to me that that's only 25 years.

So, and now we are 25 years later, and you look at computing, and the phone I am using is a computer. So that's a pretty interesting transition but the first 25 years aren't as interesting as the next 25 years right?

So, biotechnology in its modern form, starting with Recombinant DNA. PCR, the automated tube sequencing, practically invented in the 1970s, although not really developed for PCR 'til the 1980s, and Sequencing didn't really kick in until the 90s.

As acceptable technology, this gets us biotechnology today that which is 30 years old.

Although there have been huge successes so far, they have been nothing but scratches on the surface I suspect, relative to what the potential of what biotechnologies are. Both in terms of the applications that can be realized but more relevant to your question, the tools and frameworks by which people set out to engineer biology.

That is what I am most interested in, both from a cultural perspective, but also from a technological perspective, i.e., let's go make this happen.

With that in mind the involvement in helping to start iGEM, the International Genetically Engineered Machines competition, with colleagues at MIT, is probably the best example of the beginnings of a process to really have a radical distribution, not in a crazy way but in a much broader distribution to access to the genetic nuts and bolts that open world use to design and build engineered living organisms.

The iGEM student group is growing by a factor of two. We just had the most recent iGEM Jamboree up in Cambridge, MA. We had about six hundred students from 55 teams from 20-some countries. It was one of the most amazing research meetings I have ever been to. But it was an undergraduate meeting, a teenager genetic engineering competition.

We had students form Melbourne, Australia, showing up. They figured out how to tame some 6000 BP piece of DNA from a marine micro organism that happens to somehow produce proteins that spontaneously self assemble into gas impermeable 15 nm diameter protein shells inside the cytoplasm in bacteria. If you boost these things up by changing the number of these little protein gas capsules inside the cytoplasm of the bacteria, you can change its buoyancy. Bacteria will float or settle or remain neutral suspension. It's sort of embarrassing to me that I didn't know about this biology. I can't figure out how you get a gas impermeable protein shell.

The phage and virus capsids that I am familiar with don't appear to be gas impermeable. So this wider access to biotechnology and the frameworks for bringing people together to celebrate it is immediately teaching me new things.

So the room for improvement is really impressive in terms of how much better we can get at any given biology. Part of what is going to drive that is making the technology accessible to many, many more people.

MICHAEL: I want to talk about building the foundations for the new science.

ENDY: It's not science though, it is engineering. It's not that it is incompatible with science, it is complementary to science. This is a very important distinction. I recognize that this is within a genomics framing but that is not what Synthetic Biology is about. At least the stuff I was just talking about.

MICHAEL: I think I read somewhere that we are not discovering new things, just applying learned things in a new manner.

ENDY: We are also inventing new things that can be redeployed more readily. So if you go to your hardware store down in Durham, if you go to the aisle with nuts and bolts, etc, you will find these different stainless steel objects that are machined in a accordance with a technical manner defined in 1864. Those objects in that hardware store are not natural objects. They are synthetic objects. They are derived from raw materials, ores, that are processed and refined in a mining plant. Then the resulting metals are cast and forged into the appropriate shape and then they are machined. They have sixty degree angle squared off screw heads, which is the Sellers standard, and then they show up in the hardware store.

Those aren't natural objects at all. They are derived from natural material. There really is a fundamental difference in the engineering agenda here, which is really poorly understood. So many people come to biology as a science, not as a substrate for engineering. It's not that Synthetic Biology (SB) is incompatible with science, there are whole branches of SB that are going to take genetics forward in ways that very few people have started thinking about clearly yet, but the stuff I am most involved with now is on the engineering side.

Sorry if that is a little bit pedantic but the landscape is sufficiently new and a lot of people are trying to learn about it. I think it is worth, the whole purpose of your project is consistent with this and a celebration of it, being careful about the meaning of the words sometimes.

MICHAEL: Where do you see programmable biological systems going? Do you think that someday we will be able to sit at a computer and program in G++ and have it compiled through a DNA synthesizer?

ENDY: So there is a good example of a masters thesis in Tom Knight's class at MIT, now maybe four or five years old, called BioJADE. This is a computer Design Environment for engineered synthetic biological systems. You have on your computer desktop a layout pane that lets you stamp genetic devices. Devices are high order genetic objects that perform human defined functions like swim, turn off, communicate, or change colors. Then the devices get compiled down into genetic parts.

At the time BioJADE was written, it was actually synchronized with the RSBP [Registry of Standard Biological Parts] so it would actually pull parts from the Registry including their DNA sequences and then compile those DNA sequences into a composite fragment of DNA. Simultaneous with this, it would send the parameters describing the operation of those BioBrick parts to molecular level simulators so you could simulate the dynamics of your desired system. That is four years old. What is really surprising to me is that that Masters thesis came out and people didn't start using it. So it is going to have to be invented again. "Invention" isn't the right word. It is just going to have to be talked about again.

MICHAEL: That is wild. We have a genetic programming language and it just isn't being widely utilized?

ENDY: I mean a programming language is a different thing than a CAD environment. A CAD environment is a tool. In many respects, the BioJADE CAD environment, which you can find the details of by Googling the word "BioJADE," is necessarily limited by the quality of the genetic functions it can call.

If it is hooked up to a registry of standard biological parts, and the parts in that registry are garbage, meaning, there could be some DNA sequences in there, but the functions that the parts provide aren't very well described -- the parts themselves have not been designed to work very well together. What an engineer would say, the parts to perform a reliable function composition. They have not been organized in a way that provides access to higher level function so that you can actually build interesting programs without having to pay attention to all sorts of crazy details. If all those things aren't also true, just having the CAD tool isn't going to cut it.

The obvious but drawn out answer to my own question, how come more people haven't started using it, the real limitation to such CAD tools is that we don't yet have the library of genetic encoding functions that would support their widespread use. That is where most of the effort has gone since such things have been done: to go try and fill out the function libraries.

If you look at any good programming language, like STEAM as an academic example, you will find that there are papers which define the language quite clearly. "Here is a new language, this is how it works, here are all of the functions within a language to do stuff, and off you go." We haven't yet gotten to that point with a set of genetic function defining a first genetic programming language.

MICHAEL: In your review of Synthetic for Nature, you talked a lot about predefined materials and standardization being a big deal.

ENDY: That gets back to what I was saying before. We were talking about nuts and bolts and where they come from. Those are not natural objects they are derived from natural materials that are heavily processed and refined in accordance with standards that allow them to be readily reused. When you go to the hardware store you get a nut and a bolt you put it together and you don't have to do an experiment. They go together so long as you don't mess up the metric. Importantly, after you put the nut and bolt together. When you pull on the nut, it doesn't come flying off of the bolt. It doesn't have some surprising emergent properties. The resulting composite object behaves as you expect. Being able to put things together without doing an experiment, and then having the composite objects behave as you expect those are examples of reliable physical composition and reliable functional composition.

So far in engineering, in other fields of engineering, we get reliable physical compositions and reliable functional composition by investing energy in the process of standardization of the object, so that they go together more easily. That is what, to first approximation, has never been done yet in biology. I'm going to go out on a limb here, are you calling me from a room?

MICHAEL: I am sir, yes.

ENDY: If you look around in the room probably everything in the room is synthetic. From the phone, to the chair. In the sense that the things you see in your room aren't found scattered across the countryside as natural objects. They are derived from an investment of energy into raw materials that then get converted into intermediate objects that are easier to work with that eventually get deployed to make the artifacts that we work with. I don't know if you've got your window open or closed, but if it is closed, then even the air in the room is synthetic. In the sense that it has been conditioned to perhaps change humidity and temperature – but easier for you to use as a respiratory mammal.

Oh by the way, we have never as the engineering community, never invested energy in these sorts of no-brainer foundational responsibilities in biology, biology is just wide open from this perspective. It isn't going to be exactly the same as nuts and bolts or computers or mechanical objects. It is going to be its own thing. We have to learn to be better than we have in past engineering areas, but at least our past experience provides reference for a point of departure.

MICHAEL: So are we finding that the parts in the BioBrick Registry are acting in a standard way.

ENDY: That is a good question. The two types of standards that are interesting are the standards that support physical composition and function composition. Of course there other standards, but let me stick with the first two.

Tom Knight, now five maybe six years ago, put forward a standard called the BioBrick Standard Assembly Standard. What Tom proposed was that BioBrick parts shall be defined as genetically encoded functions. They are sequences of nucleic acid, DNA RNA, that encode some biological function and then the parts themselves are bracketed by forward restriction at the nuclease site, ECOR1 EXPO1 on the left as the prefix and STD1 and PST1 as the suffix. All BioBrick parts follow this definition and have these four sites surrounding the functional sequence. Furthermore, the function sequence has been modified so that if it has any of these four sites within the function sequence they have been erased. As a result of making BioBrick parts in accordance of Tom's standard, what this means practically, is you can take any two BioBrick parts and combine them to make a new composite object, which itself is a BioBrick part. Meaning a composite object has the same four restriction sites bracketing it as the starting parts did. So you can just keep going and going and going.

This is an example of reliable physical composition. You can take any two objects and you can put them together, you don't have to do an experiment. We do have standards for physical composition, and iGEM students, if they are behaving correctly, define BioBrick parts in accordance with Tom's standard.

Now it might be the case that over time we develop and accept and promote new physical composition standards, and they will be defined via an open standard setting process, but the BioBricks foundation is responsible for shepherding it along.

Your question gets back to the next type of standard, which is functional composition. What happens when you put two parts together? Does the composite object behave as you expect? Here as yet, we have no standards put forth in support of reliable functional composition, and so if you were to take any two biological parts and put them together you would then have to put them together and do an experiment to see if they would behave as you would expect. There is a tremendous amount of research that needs to be done to begin to make measurements and characterizations of how parts behave when you put them together so that we can begin to make rules as far as reliable functional composition.

MICHAEL: That leads into another dependency you spoke of: Useful rules. In the review in Nature you talked about decoupling and abstraction as well as software and modeling. How is the current status of software modeling?

ENDY: If you look at biology as a field you would include synthetic, but let me also include systems biology. There is a tremendous amount of interest, whether you are a scientist or an engineer, in having computer or computational models, that are able to explore or analyze the dynamic behavior of living things.

So to make a long story short, our models and our simulations for biology… I would describe them as being merely descriptive. Meaning we are very good at developing models that are consistent with past observations of the behavior of the biological system

that we are studying. The models tend to break down when we apply them to help us predict something new that might happen when we make a change to a natural system, or if you were going to do forward engineering and design synthetic system, how we should design the system.

I thought a lot about that. I don't know that I understand why this is the case. I have some suspicions. For example, in video games people talk about the physics engine, how realistic is the model of the environment in the video game?

It turns out we have the same interesting issue in biology simulations in biology. How good is our physics engine? When you do something on a computer to model a biological system it is a physics engine that you are using. I think that is an interesting question to be asked whether or not the physics engine for modeling biological system is the right one.

There is great amazing work that was done by Dan Gillespie about thirty years ago and then rediscovered by Adam Arkin about ten years ago, and at this point is a state of the art physics engine for modeling biological systems. The heart of the system is to pin down particle collision physics engine. Inside the cells there may be cases where the very useful and useful simplification breaks down. The models are very helpful because they help us learn and think about the systems that we are studying or trying to build. But they are very descriptive in my mind, the most interesting work is to improve the underlying physics engine, If we can nail that one down, the modeling platforms will be much much more useful because they will be more than merely descriptive they will begin to be correct.

MICHAEL: What steps do you think need to be taken to get to that point?

ENDY: By coincidence you catch me while I am visiting Caltech. I am going to visit Dan Gillespie tomorrow. He sent me an email tomorrow right when I got into LA. We are going to talk about it. We need to find the right exceptions to the rules, the places where our current models really break down in dramatic ways, and then use that experience to see how we might revise our underlying framework. And then we have the additional problems of if we improve our underlying framework, how do we make it computationally tractable? So that it isn't too expensive to run on our computers.

MICHAEL:You spoke about decoupling and abstraction, getting things to specified points and reducing complexity, what's being done?

ENDY: We've already talked about it in passing. For example when you were asking about and we were discussing the CAD tool, someone could sit down at the computer and then lay down a genetic program and it would work. What that implies is that the person who is the designer of the synthetic genetic system, who is sitting down at the computer, does not have to be have in the laboratory. They are "decoupled" from the laboratory. From the experimentation. They would lay out their system at the computer, compile it to a piece of DNA, then would then ship that information to a DNA synthesizer that

would construct the genetic material for them. The genetic material would then be given to someone else who will put it in a cell. Maybe that can be automated too.

Decoupling means that we have a really complicated problem like "Design a living cell that makes a biofuel." So then you have to design the cell, then build it, and then debug it. If you do all of those things yourself you have to be an expert at everything. The question becomes how do we take the work of engineering biology and separate it up into many pieces that different people can become expert on, and then those people can be better experts in any one area yet they can all work together to more quickly make many things? Decoupling is a very basic lesson in engineering. Split it up into many simpler problems that can worked on independently.

MICHAEL: So when I run a PCR I can send it to the sequencing lab who are good at sequencing and I am good at PCR, because I am undergrad…

ENDY: That is an example of decoupling, you are exactly right. Notice that that experience of decoupling has taken thirty years to develop. Fred Sanger publishes the first paper on Sanger Sequencing Method in 1977, I think. We live in a world today that has eventually figured out how to do that decoupling, but thirty years ago that wasn't true. Now when we talk about the engineering side we consider how many opportunities are there for decoupling and can we be aggressive about positioning solutions for them so that people don't have to wait thirty years. Let's figure out what they are a put them in place as soon as possible.

MICHAEL: Do you find that the people working on this are moving towards this goal?

ENDY: They are old ideas in engineering, but they are new ideas in biology. So it's a biased random walk, maybe in the language of Noam Berger. Can I ask you a different question? Why are you sending the DNA off to be sequenced?

MICHAEL: We are looking to identify the sequences of different genes that affect flower genotypes from their phenotypes.

ENDY: So you are taking different individual samples and trying to get them PCR'd and sequences to see how they are different?

MICHAEL: We hope to see where the genes are different that affect Flower Petal Size.

ENDY: What if you could, a complementary approach, you are taking a genetic approach definitely. A synthetic approach would be to take a computer and design some genetic sequence to have some variants, and then push a button to have those turned into synthetic genes and see what happens. You could have decoupling along that path too, where instead of doing a PCR and then turning a PCR product to a lab upstairs, you could design a sequence of DNA and then have that turned into a DNA construction team.

MICHAEL: So is that being done at all?

ENDY: I think the field of genetics will change utterly as DNA construction technology gets better, as it did when DNA sequencing technology got better. I think that very few people appreciate that and are preparing to move along that trajectory today. But if you look at the commercial gene synthesis market, which is by definition in the business of having people push buttons and send them information and then these companies send back DNA, this marketplace is probably 50 million $ per year today. Between 50 and 100 Mil $. Which sounds like a lot but not relatively big yet. The Duke basketball budget is probably bigger than that,

MICHAEL: Coach K's salary is probably bigger than that.

ENDY: Probably, but he seems like a good coach.

MICHAEL: So when you were working on the T7, you were frustrated working from the top-down and you got the idea to work from the bottom-up?

ENDY: This isn't accusatory, I'm just telling you how I feel, but people use those words all the time, and I have no idea what that means. There is something about what you are saying that is absolutely correct, I'm just not quite sure maybe if we get away from those words it will be easier?

MICHAEL: The idea of looking at the genes and then trying to reverse engineer the organism?

ENDY: Yeah, you have this natural biological system that we have the DNA sequence to. Phil Studier and John Dunn got that in 1982. We are trying to figure out how does this thing work, how has evolution shaped this design, if at all? If we could answer that last question it works as a blank: Why does this thing look as it does, if for any reason? It was a very scientific question but wasn't much of an engineering question. I spent a lot of time working on that during my PhD and afterwards, and I built some computer models to help me, and I did some experiments to test my predictions. I had this weird experience where the predictions I was making, the ones that were really interesting, like, "If you make this change to the genome architecture you will get a new T7 a new phage that grows faster than the wild type," then I would go into the lab and make that change and it would grow slower.

So being trained as an engineer, when you have a failure like this, you don't sweep it under the rug, along with the experimenting work. In the same way when a bridge falls down you don't sweep the rubble under the rug. You ask how did that happen and what can I do so that it won't happen again? When I did the failure analysis around the experience, trying to understand and model the T7, and predict and model what happens when you change it, the most important conclusion I came to is that nature, evolution is not selecting for a phage T7 design that is optimized for us to readily understand. If that were true you would see, in whatever your native tongue is, a comment [from] a

programmer, either evolution or god, telling you what the different things are doing and how they are organized. There would be places where you could uncomment and get readouts and debug the program if it wasn't behaving probably. That's all kind of fanciful and naïve and analogous to some of the engineering problems in other areas. But we don't see anything like that, it looks to me like we have the opposite.

These systems are not optimized to be thoroughly understood. Its just not part of nature's objective function. This was an idea that came out of the failure analysis. It actually became more interesting to me to design and build synthetic biological systems. Then we have biological systems that we can understand as opposed to having to reverse engineer these evolved reproducing machines that have been around for billions of years. Not that that is a bad thing to do, there are always good things to do, the question is what is the best thing to do? I think the idea that came out of the failure analysis was a better idea for me.

MICHAEL: I like your quote from the bulletin of atomic scientists. You said, "We can liberate ourselves from the tyranny of evolution." And that "intelligent design would have documentation and we don't see that." That leaves me to wonder then that the idea that we can impose an anthropomorphic logic on this genetic sequence. What happens if it turns out since biology is not a human product, what if it does not respond in a logical human manner?

ENDY: I think there will be some surprises. I mean I think biology will be different from other experiences in engineering with natural materials. I'd certainly hope so given the costs that accrue from our current engineering practices. They don't appear to be sustainable and all sorts of other things.

We certainly need to become better engineers, and biology gives us an opportunity to improve all of engineering by learning new things. The short answer to some of the questions that are wrapped up in what you are asking me is, that we are only going to find out by trying. So long as we can frame our explorations and cast them in ways that are responsible, then we should go do that.

MICHAEL: You talked about the optimization of systems, if we could optimize biological systems could we make super organisms that can run faster and jump faster, while operating on 20 calories a day?

ENDY: I don't know, things are going to be physical systems, subject to the constraints of physics. But I think, this will sound esoteric and maybe it is, if you drill down at the quote "liberate ourselves from the tyranny of evolution." What does that actually mean? That means that natural biological systems are by definition reproducing machines. They have to be able to copy themselves to go from one generation to the next. Being able to copy yourself is a really impressive thing, if you look at the design of a system there are a lot of things you have to do in order to design a machine that can copy itself. Moreover to design a machine that can copy itself and do so with high fidelity so that it can persist so over many many generations, moreover so that it can copy itself with high fidelity

over many generations and also be evolvable, that as the environment changes, the design of the system itself can change.

If you were an engineer and you were sitting down at the drawing board and you needed to design a machine that was going to be able to have a phone conversation, and go get dinner, and watch TV, but it also needed to be able to copy itself and persist for many generations accurately producing its offspring over many generations yet still be evolvable. All of those extra things that I am saying would be extra things that you would need to figure out at the drawing board. So that the design of your system would be more and more challenging, presumably more involved and so on.

What is very interesting to me about synthetic biology is that we have the possibility that we could decouple the design of biological systems that we care about from this constraint of being a directly reproducing machine.

Direct descent, replication with error, those are really powerful restraints on the designs of these object. So if you could synthesize genomes from scratch every generation when you needed new organisms, the organisms themselves would not need to support reproduction or evolvability. The designs could focus or optimize on different things being the short timescale performance. I have no idea how this plays out in any specific example yet, but at the abstract level it seems like a very powerful idea to me and then because machinery production, reproduction with error, evolvability, sound like hard things like me to design, if we can use DNA sequencing and synthesis in combination to decouple designs of organisms from this constraint these constraints of direct descent, replication with error, the designs we're left with are going to be much simpler.

Obviously there is going to be a tremendous risk associated with doing this, the risk is, if DNA sequencing and DNA synthesis technologies collapse or cease to exist, disposable biological organisms won't be able to propagate themselves. They will go extinct within one generation. There's presumably a pretty serious tradeoff there.

MICHAEL: That is interesting the idea that reproduction is a biological constraint and the possibilities if you didn't have to worry about that.

ENDY: How much more complicated would your computer or car be if it had to replicate itself?

MICHAEL: A third dependency you spoke of in the review were skilled individuals? I would like to talk about the history and values of iGEM as well as other things that are a part of the educational foundation?

ENDY: I mean a point of context, you can see that people are excited about learning how to program computers. As they exist today, inert pieces of silicon that you can get to do what you want.

Learning how to engineer biology is more exciting, because in biology you do not have inert pieces of silicon, but living reproducing machines that accept programs as genetic material. If we come back some of the earlier stuff we were talking about, how some people were fed up with computing resources thus we got personal computers. I think the pressure to having access to biotechnology is going to be greater than it was for computing. I think the drive to democratize widespread access to biotechnology is going to be much more powerful. I say that because on the surface it looks like I am pushing this, and superficially that is true, but my own thinking on the matter is that I am responding to pressure because people want to be doing this.

We have as educators our own responsibilities to have people learn and encourage the communities that develop around important technologies to be constructive in what they are doing and the applications that are derived from them.

I moved to MIT in January 2002, thanks to Doug Loughlinberger the head of biological engineering. My goal was to go make biological engineering happen. By that I mean make biology simple to engineer. A specific reason I went to MIT was to work with Tom Knight who was already there. As we mentioned before, he has done things like the BioBricks standard supporting physical composition.

We were sitting around MIT and we were looking at the fact that we are going to have to teach people to be biological engineers. If you can imagine that you are 17 years old and you are showing up at MIT and you want to major in biological engineering, what do you expect to learn? Our students, we got a lot of them, and they are pretty smart and they go "I expect to learn how to engineer biology. I want to be able to design and build living organisms that behave as I expect. In the same way that my friends who are studying electronic engineering are going to be able to design and build computers and programs and the programs and the computers themselves will behave as I expect. So that is what I expect you to teach me. And biology is pretty cool so this will be a really great major."

As we were sort of anticipating these appropriate conversations with our future student, the next notion that pops into your head is "Oh, no! We don't know how to teach them." We are pretty inept when it comes to engineering biology. So the first thing that we did, we didn't go into our labs or into our library and try to figure it all out. We said the only way we are going to learn how to teach this, is to start teaching.

That sounds a little funny but that is how it works. I didn't teach a semester long course the first time, we taught a month long course in January 2003, called the Synthetic Biology Lab, with Tom Knight and Jerry Susman and Randy Redberg and myself.

We were inspired by past examples of this type. So for example, Lynn Conway, who came to MIT around 1978 to teach one of the first courses on very large scale integrated electronics systems design. Getting students educated on how to build complicated integrated circuits without being overwhelmed by the complexity, leading to advanced microprocessor design eventually.

So we went and talked to her and learned about her experiences 25 years earlier with something like this, and then we had our own ideas and combined them and adapted them to what would become synthetic biology. We asked the students that January in 2003 to design, not build, the DNA sequences that would program cells to oscillate, drawing inspiration from Michael Elowitz's work on the repressilator system. We figured electrical engineers oscillators fairly easily through standardized parts, so surely we could teach our students to design genetically coded oscillators in a month.

I went out and I raised $80,000 to pay for DNA synthesis so students at the end of the month would have their design and at the end of the month we could test it out. At the end of the month, the added cost of the DNA synthesis would have cost $120,000. So we were 50% over budget, we were sort of like," Oh no!" But then somebody notices that the teams of students were using a similar type of function as another team, and if they could just get it together and share the knowledge of the functions they were trying to use then maybe we could not have to synthesize everything. We could reuse some of the components. In response to this educational pressure, this financial constraint, Randy Redberg started giving out more parts numbers and from this experience came the Registry of Standard Biological Parts.

The registry is a public resource that lets people define and share different standard genetic functions that you can use to program stuff. So it sort of immediately confirmed this hypothesis that if you don't know how to do something in engineering you just start teaching people how to do it and they will help you figure out what it is that you should be doing.

That was really terrific so we taught the course again in 2004. We had a similar experience on the level of more powerful objects we call devices. Devices are harder to make and it became important for us to figure out how to share them. We developed some frameworks for doing that, specifically, what resulted from that course was a very crisp specification of what we call PPS, polymerase per second, which is a common signal carrier for hooking up devices derived from regulational gene expression.

This was sufficiently great that we immediately decided to teach the course again. This time we taught it as a competition, the 2004 Synthetic Biology competition. The NSF chipped in $400,000 to pay for it. We had Princeton, MIT, Caltech, Boston University and UT- Austin as the five teams. A bunch of people came up in the fall and presented their designs.

The team from Texas had worked with some friends from UC –San Francisco, and they programmed bacteria to change colors in response to the light. They had bacterial photography systems working, they called it Coliroid. This became a paper that they eventually published in *Nature*, so that was pretty terrific. We taught it again next year, called iGEM, which was an acronym I came up with the goal being to be purposefully dorky, to avoid things like Bug Wars. That seems like a bad thing to celebrate.

We started that and we had 13 schools, three from outside the US, and that was terrific. So we did it again in 2006 and we had I think 36 schools, 20 from outside the US and that was more terrific. We did it again last year and we had almost 60 schools, 600 students, 20 some countries. When all the students got together last month at MIT to present their projects, it was actually the best scientific meeting I've been to. So that's iGEM.

MICHAEL: While you are talking about this, I realize a lot of is based on the theories of open-source and you seem to be a big advocate of open source biology. Why do you feel open-source is so important?

ENDY: I am being very selfish which sounds funny, but it's not. It comes back to a comment that I made earlier. Biotechnology in its modern form is only years old. It is a young adult. We have so much more work to do. I would like all of biotechnology to come true, sooner rather than later, and if it comes true during my lifetime that is terrific. In all of biotechnology I don't mean stem cells and bioenergy I mean everything you can imagine. Let's get really good at engineering biology over the next one, two, three decades. That is why I think it is important to make it easier to engineer biology.

Good engineers don't just solve problems by delivering specific applications. They develop tools that make the work of engineering much, much easier. It is important often times to give away the tools so that other people can do stuff. My hope is that by giving things away I will get more back in the long run, and that is obviously true in this case.

If you look specifically at something like the BioBrick part, you know we exist in a world where the ownership of the uses of biological functions tend to be balkanized. Split up from one function to the next. Now all of a sudden synthetic biologists come along and we're programmers of DNA or poets of DNA. We want to design and build many component synthetic biological systems. Which means we need unfettered access to the basic functions. We are going to want to reuse them over and over and over again.

I can't afford to pay a lawyer to license 20 different functions every time I want to make a 20 part biological circuit. That will cost me hundreds of thousands of dollars. And if I can't do that then most people in the world can't do that. Practically everybody can't do that. What happens when I want to go make a 1000 component system? No one can afford that except for a very small number of people. In the same way that Oxford University hundreds of years ago thought it would be a good idea to come up with the Oxford English dictionary, I think that we are going to need some compendium of standard genetic functions that people can draw upon to write new genetic program. Or essays or poems whatever you want to call them.

MICHAEL: That is the idea behind the registry I guess?

ENDY: That's the idea behind the BioBrick Foundation.

MICHAEL: I saw a talk you gave for IT conversations… you said a couple of solutions to solving the open source issues would be the Registry as well as open DNA, "Many Eyes, Fewer Bugs."

ENDY: If that is true. If those clichés are true from the software world.

MICHAEL: You made a point to say that this has to be right. What happens if we are wrong?

ENDY: Well if an open model in biotechnology is not correct, if many eyes lead to more bugs, or if many eyes lead to more viruses, then that is going to cause a lot of problems. If we make biology easier to engineer, what are people going to use it for? If more people start using it and that leads to more bugs, that means there are going to be more accidents. That doesn't sound good. It is bad enough when computer programs fail. I'm not going to like a world where genetic programs fail.

Another thing is if we make biology easy to engineer and people begin to purposefully misapply it, either because they think it is funny or they actually want to hurt somebody. That is going to be really bad too. It becomes very important to be clear about whether or not an open model leads to fewer bugs in biotechnology, because we can't afford accidents largely, and its also going to be very important to develop a constructive culture around the technology that the number of people who might choose to misapply it in the future are as few as possible. That's coupled into many other things, like why we call iGEM iGEM instead of Bug Wars.

MICHAEL: I looked at all the papers and most people want to talk about ethics in the end. It seems like everyone that is not a scientist seems very pessimistic. They're worried that they are going to make a pathogen that humans aren't ready for or there is no resistance to and it's just going to take people out. I found a quote from your Esquire article separated from all the other paragraphs, and it simply said, "'People will die.' Says Drew Endy." I found that interesting that you would put it that way.

ENDY: It's not my article. It's Chris Jones' article and I had no control over the formatting.

MICHAEL: Definitely, I found it funny that's the way he would represent that. It just seems that everyone is pessimistic, so worried that something horrible is going to happen.

ENDY: By definition we aren't pessimistic. By definition we're optimistic. Otherwise we wouldn't be doing this. In the same way that if you were doing a history of computing or computer programming, and you were talking to a computer security expert, and he said that in the future no one will make computer viruses, it will be impossible, you would be scratching your head thinking how could they possibly believe what they were saying? If I looked forward to a world where we succeeded in making biology easy to engineer, then I think it would be irresponsible for me to present this possibility that nobody will design and build pathogens, human, plant, animal, or

otherwise that will hurt people, or plants or animals, or hurt people indirectly. I don't see that as being a believable position to hold. So, the context around that quote got separated as a one-liner, or a zinger, in that copy. That's why he's in a different business than I am.

MICHAEL: What I was trying to get at is, obviously, scientists are very optimistic about this.

ENDY: I'm an engineer. But scientists are optimistic, too.

MICHAEL: The people in the field are optimistic and that's why they do it because they see all the good that it can bring. But why do you feel that people who aren't in the field but who are becoming aware of it, why do they immediately jump to "look what happened in Jurassic Park" kind of thing.

ENDY: I don't think everybody immediately jumps to that. I think people who are in the business of drawing attention to things and getting paid to draw attention to things are under a selective pressure to jump to things that catch attention. I think a lot of people find new things to be scary until you figure out what they are all about. There are reasons for that.

I would contend that what you're saying might not be true. That if you actually sampled – it would be an experiment to do, I don't know what the data would show, but if you actually went out and talked to people on the street, "Hey a bunch of researchers are going to make biology easy to engineer! What do you think about that?" What fraction of the people would go "Huh?" and what fraction would go "that sounds really bad."? I just don't know. You'd get, "that sounds like a good idea" or "I don't know what you're talking about" or "that sounds like a really bad idea." It would be interesting to collect that data. Just to know. But I'm not convinced that most people are pessimistic. I think most people would be optimistic. Actually, optimistic isn't the right word. I think by definition most people are "constructed" meaning they do things to make more things because if that weren't true then we wouldn't have civilization.

MICHAEL: Life has a tendency to move towards order, right?

ENDY: errr yeah

MICHAEL: You mentioned that, for this technology that's highly relevant to the public, you find it important that the public becomes educated and aware of what goes on behind it. How do you propose that's going to happen, that people are going to understand what's going on behind this genetic program?

ENDY: I think what you're doing is important, sharing the results of these types of conversations with the public is important. I think talking about it with whoever wants to talk about it is important. I think educational programs like iGEM are important. Presumably most of the iGEM students will go off and do something else, but at least

when they look back on iGEM they'll have this experience where they can think, "I competed with the best in the world in genetic engineering competition, and I saw what people were able to do, I saw what we tried to do, and I have this sense of reality here." So the more constructive interactions one can participate in around questions -- call them questions of human practice something I learned from Paul Rabinow -- an anthropologist from Berkeley -- what happens when people start getting involved in stuff , the more interactions that are constructive interactions the better.

As a comment around this, if you look at where we are today and where things are going, it is the same way that the personal computing revolution that started 25 years after the early days of centralized computers, the next 25 years, from 1975 to 2000 and going forward, are even more interesting. The conversations are becoming even more important. And so if people are interested in issues of human practice around biotechnology then something to keep in mind is we need to figure out how to have really constructive conversations around these issues, whether its safety or security or ownership or sharing or community building or whatever. We need to have these conversations for many, many years to come. These aren't conversations that get figured out in six months and then we move on and get back to watching football.

Technologies around this area are going to improve so dramatically, they already are, that the conversations need to happen for decades, probably, in response to the improvements in the technology. What that means is that it's really worth building a good knowledge base and a solid education in the area so that the conversations are as constructive as possible and as friendly as possible. It becomes important to become friends with the people who are disagreeing with you, as appropriate because that's how you can really learn from one another and figure out what the answers are. I'm not going to talk on the phone here you and tell you I understand how to solve the bio-security framework . I don't think anybody does know. Which means that we really have to have some good conversations about this.

MICHAEL: Sure. Finally, what do you see becoming of this technology in the ideal situation? Will we have bacteria that eat the plaque off our arteries and things like that?

ENDY: If that's possible, sure. I don't know if that's possible, right? But I do know that what is possible is more than I can now imagine. This is why we want to make it easier and why we want to try to get more people to come in and work on building constructive things. And we'll see what comes out. There's a trap that some of the early computer people fell into. It was, like, "What are you going to do with computers?" said somebody in 1955. The answers were oftentimes very funny whereas the real answer was, "I have no idea but let's make these things and see what people can do with them. And let's set up a world where people are supposed to do useful constructive things."

MICHAEL: Nice.

ENDY: And that's what gets you this amazing transition from, "Yes, we're building computers to design hydrogen bombs" to, "Oh wow! We have the early Internet. We have the personal computer." And now we have, what, the iPhone or something.

MICHAEL: Yes, the iPhone.

ENDY: You know, we have consumer electronics today? What does the world look like when we have consumer biologics? And as that world gets filled out, how do we replace that with something that's more beautiful?

MICHAEL: Whenever my friends ask me what I do at school and study, I tell them that some day I want to be able to, for example, for a girl I want to design her a flower with a special scent and color and named after her.

ENDY: You're going to be able to do that pretty soon.

MICHAEL: You think so?

ENDY: Yes.Changing the scent of smell wintergreen and bananas. Fragrances will happen pretty fast.

MICHAEL: Do you think it will someday be that accessible that a person could make something fun like that?

ENDY: It's already being done by teenagers. How much more accessible do you want?

MICHAEL: I guess you're right. So it is.

ENDY: It's not very easy. It could be a lot easier, but it's not rocket science. And oh by the way, consider the history on the folks who are doing personal rocketry and the private space launching effort.

MICHAEL: Thank you. Is there anything else you'd like to talk about?