Power and responsibility

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The introduction

Peter Parker and Uncle Ben are on my mind. The reason is that is that a month ago I was jumped by Craig Venter. There were TV cameras around. The live audience was an interesting, edgy mix, on the interface between "technology", meaning computer technology, and culture/ media/ journalism; I had just given a closely prepared talk on the history, promises, and perils of biology, 20 minutes from solar system formation to origin of life to photosynthesis to agriculture to Asilomar to now; and I had paid particular attention to the existing threat from remade and lightly engineered viruses, and the various technology-empowered approaches that could contribute to a defense against unpredictable viral and bacterial pathogens. The whole set of ways the defense strategy needs to shift.

For whatever reasons, Craig came prepared to take the talk as an attack on himself and his agendas. As if review of human use of biology in historical context, and talk about real risks, somehow threatened his ability to mobilize resources toward his goals: removing nonessential genes from *Mycoplasma genitalium*, synthesizing hydrogen and methane, cruising around the world in boats, etc. The word "fearmonger" came up, multiple times. "Chicken Little" came up too, afterwards. And one terrific sound bite, which is that more people were killed by lightning last year than by anthrax attacks during the past 50 (see below).

Of course, nobody likes being jumped, but being jumped happens, I think I held my own, and when it's up on YouTube under Creative Commons, I hope it at least makes decent television. More to the point, Craig happens. Complaining that the man can go off half-cocked, or that he can conflate attempts at analysis with personal attacks...isn't relevant. Might as well complain that hurricanes are wet and full of wind. Because Craig is a force of nature, and, what's more, he's one of those forces of nature who is usually a force for good. It is very largely due to him that we had large-scale shotgun sequencing as soon as we did. And it's very largely due to his efforts and those of the extraordinary people he attracted that the fly genome, and then the human genome, were delivered so fast; had Craig not acted, it might have taken years more. Craig's sense of scientific celebrity and his adroit use of it bespeak a deep intuitive understanding of our culture. His current work to focus attention on the genomic analysis of microbial ecologies and energy production is igniting imaginations and no doubt helping recruit the next generation of genomic scientists and engineers all over the world. So this isn't about Craig. Still less about the anomie of the US scientific intelligentsia (misunderstood... yet again... shall we cry?).

Rather, this is about asking people who identify as members of a synthetic biology community to take a few next steps toward coming of age.

The facts on the ground

The first starting point is that certain kinds of biological engineering, including making pathogens drug resistant, and recovering live viruses from transfected recombinant DNA, are technically feasible and have been so for a very long time. The recovery of poliovirus from cDNA was accomplished by Baltimore and coworkers in 1982. To restate that, a generation ago, a lab (albeit one of the best virology and recombinant DNA labs in the world at the time) made infectious virus from DNA. If one needed a demonstration that one could remake viruses, this was it. Nowadays, remaking viruses is a matter of making appropriate DNA constructions that encode the viral genome and that provide any other functions needed to get live virus out. Polio is one of the simple ones. To remake many other DNA and RNA viruses requires helper functions-- for example, protein hardware to make negative RNA strands into positive RNA strands, or to start viral transcription going. So, to remake viruses, one transfects with DNA that is the viral genome or (for RNA viruses) directs the synthesis of the viral genome, together with DNA that directs the synthesis of the helper functions. You don't need to provide the helper functions from DNA constructs, you can also co-transfect genome-encoding DNA into cells co-infected with a related "helper virus" that you have screwed up so that it cannot replicate. Depending on the virus one is re-making, the ways one goes about getting live virus from DNA used to construct it range from really simple (mix 12 things, wait 24 hours) to relatively gnarly (some classes of viruses have not even been done yet, so would require new construction work and troubleshooting). To calibrate "gnarly", I mean "would take one of the 5,000 most skilled research groups in the world a year at least a year to carry out". For any given family of virus, I (or any of more than a thousand scientists) can be a great deal more specific about how one would perform any given construction job, and what technical hurdles might still exist and how one would overcome them. But given that this page will be crawled by Google within a week after it goes up, this is as specific as I'm now going to get.

The second starting point is to imagine two circles in a Venn diagram. One circle is the set of people who know how to perform various manipulations and pieces of construction work, who could for example make the DNA, or troubleshoot what was wrong in a co-transfection setup as above. The second circle is the set of people who might be motivated to build and release a self-replicating organism that hurts people. The number of people in the first circle has been growing steadily, at a guess at around 10% per year, for many decades. At the moment, the number in the second circle is large, and is sensitive to international attitudes (I am guessing that it has grown significantly in the past 5 years). If we are in luck, there might now be no people in the intersection of those two circles. But even if we are lucky now, there is no reason to think we will be lucky in the future, because the number of people in the first circle will continue to grow.

To run the calculation for the first circle, let's ask, if there are 20,000 undergraduates at UC Berkeley, how many possess the technical skills and access to labs to make a gram positive organism, anthrax, resistant to the first line fluoroquinilone antibiotic, ciprofloxin? Let's guess that one tenth of them do. 2,000 UC Berkeley undergraduates. Now, let's try to guess how many UC Berkeley undergraduates have the DNA manipulating skills needed to construct the plasmids and perform the transfections needed to follow recipes to recover animal viruses? Surely more than 20? Maybe 200? Now, given that techniques keep getting easier, and more people keep getting trained in their use, how many past and present UC Berkeley undergraduates will have those skills in 2016?

How synthetic biology interacts impacts this existing strategic situation

Now, the group of people who call themselves synthetic biologists did not make this situation. But up to now, the community of synthetic biologists has been poorly defined and has staked out boundaries, that, from outside, seem weird and artificial. To be provocative, I am going to call the community a self-made ghetto, with an arbitrary line drawn to wall off a group from a much greater community of related activities (I am imagining the sacred cord, the *eruv*, that the faithful can place at the perimeter of orthodox Jewish neighborhoods, thus enabling those within the cord to perform certain activities on the Sabbath). Inside the ghetto, good work on fabrication, abstraction hierarchies and (in the US but not in Europe where it is considered to be chemical engineering) on microbe-powered chemical synthesis. At the same time, the overwhelming majority of the real genetic engineering work of the world, such as engineering of crop plants, the applications of genetic engineering to scientific research, to pharmaceuticals, and to medicine, and most of the complex applications of recombinant DNA to microbial synthesis of organic chemicals, has been going on for 3 decades, outside the boundaries and largely unaware of ghetto activities.

So I would like to stipulate some things. I believe that most reasonable people can agree with Venter that the applications of synthetic biology within the current ghetto boundaries pose no significant risk. Hold a gun to my head, and I say: "zero risk". Zero, zip, nada, none. To say this again, there is no reason anyone should fear a minimal *Mycoplasma* genome, or a bug that makes plastic, or methane, or artemisinin. Period. Full stop.

But I also submit that most reasonable people *can* fear drug resistant anthrax, or smallpox, or a revenant 1918 flu that carries a point mutation that makes it resistant to the first line antiviral, tamiflu.

I also submit that the increased attention, capital investment, and technical ingenuity now being deployed to further develop chemical synthesis of long pieces of double-stranded DNA provides another path to making DNA constructions. It joins other schemes, ligation *in vitro* and PCR and various methods perform homologous recombination *in vivo*, but, yes, it definitely adds yet another path. For that reason, the widening capability to synthesize long pieces of DNA directly, increases the incremental

risk for biological attack. I can't quantify that incremental risk but suspect that it this is low.

I further submit that developing an additional class of DNA hackers via high school and undergraduate engineering routes (as opposed to the existing scientific or biomedical communities) also provides some increment of risk. I can't quantify that risk, either, although I suspect it is not high, but it will become very much higher if we permit an outlaw hacker culture to come into being and are foolish enough to glamorize it.

Finally, I submit that the synthetic biology community has been extremely proactive in recognizing those incremental risks introduced by large-scale synthesis of double stranded DNA and attempting to address them. The general approach has been to identify those activities specific to self-identified Synthetic Biology, then, to the extent possible, seek to zero them out. This ghetto will police itself, at least a little. Call it a "Hippocratic" approach: within the *eruv*, the boundary defined by the consecrated string, we will address our risks, we will not add to the potential for harm.

The issue

The trouble is, that if one doesn't understand or recognize the boundaries defined by the sacred string, things immediately start seeming a little, um, Talmudic. Asking for help in screening long double stranded pieces of chemically synthesized DNA to see they don't encode pathogens? Look at how responsible we ghetto members are! The fact that this screen won't apply to shorter, single stranded synthetic DNA, the fact that ligation *in vitro*, PCR and serial recombination in yeast and *E. coli* all provide perfectly good alternative ways to make any DNA construction? Not our problem! We synthetic biologists only police our own ghetto -- and we reserve the right to move the string that defines the boundary whenever we like. Even though nobody else even understands the string, or insofar as they do understand it, takes the string with any seriousness.

The reason the boundaries and self-policing can't work anymore is that the multiple and reasonable connotations of the term "synthetic biology" naturally mean that anybody not of the ghetto will immediately associate it with the entirety of recombinant DNA work in general. And this is a time when discussions about recombinant DNA powered work are breaking surface again. For all sorts of reasons, including the ones above (On November 18th, Kofi Annan called for international discussion about the dangers arising from the ability to resynthesize viruses). In the US, visibility is only likely to increase, because the country is in a runup to elections in 2008 that will probably drag both energy policy and climate change into political discourse. In fact, it's not too far a stretch to imagine we might hear about hemicellulose and lignin, microbial fermentation of higher alcohols and hydrogen, during the 2008 US Presidential debates. So, for biology, we may once again be coming into an "Asilomar moment". If this is true, then people who know how to make DNA constructions, from the very top of the celebrity chain (ie, Craig), all the way down to the 11th grade student who has just finished a high school science fair project, are going to be asked for their opinions as to whether and how organisms created by recombinant DNA work should be regulated.

And I guess this is the place to recall the postmodern mythology. Long ago, there was a time when Peter Parker was a freshly minted (as opposed to veteran) adolescent superhero. Parker's Uncle, Ben, told him that "with great powers come great responsibilities". Soon after that helpful pronouncement, Ben was killed by a criminal. The same miscreant whom Parker, as Spiderman, who had been tearning money as a wrestler, had refused to help the police apprehend. Because collaring perps wasn't Spiderman's job.

The responsibilities

So I am urging members of the synthetic biology community to acknowledge three responsibilities.

Responsibility to not screw up the defense. The argument that more people are killed by lightning than anthrax will get every bit of the respect it deserves. But it isn't enough to let fatuousness collapse under its own weight. Much of what needs doing requires complex and thoughtful action. In particular, the "Maginot line problem", that an attacker will want to outflank fixed defenses, means that we will need to move to agile detection and response to pathogens we cannot now predict. Development and deployment of the needed technical measures constitutes a set of hard problems that will take brains, money, and time to solve. Synthetic biologists can help with these problems if they are willing to learn enough to contribute to their solution. The complementary need to invent and implement appropriate social controls, be those criminal penalties, stigmatization, or licensing regimes, constitutes a set of equally hard problems that again will require creative brainpower to address. Synthetic biologists can at least help explain these issues to other stakeholders, and can help input into these schemes to make sure that they do more good than harm. The US and Europe being as they are, it now seems unlikely that the world will get adequate defenses into place before an attack, but some of us feel duty to act as if that is possible and prepare the ground for the needed work. Evasion and denial are not our friends here. People who claim that there is no risk while other people are working to envision 21st century public health systems... those people are just not helping Uncle Ben.

Responsibility to tell the truth. I admit that "truth" here can be slippery, especially for those of us whose jobs involve helping bring the future into being through our dreams. But when synthetic biologists step outside their ghetto, the people on the outside tend to ask questions on topics other than the oscillators, switches, minimal bacterial genomes and synthesis of fine chemicals by fermentation that the synthetic biologists dream about. This is the place where it's easy to slip up.

For example, journalists ask: what's new? (and they will ask this, that question being such a large part of their jobs). Now, suppose a journalist asks a synthetic biologist what distinguishes her field from previous genetic engineering, and our synthetic biologist replies that in the past genetic engineers did not create assemblies of multiple parts to carry out desired functions, whereas synthetic biologists do. That statement is utterly

counterfactual, but your basic science or business journalist cannot be expected to vett it, and in fact it appeared in all over print media in 2005 and 2006. Which alienated numerous of scientists outside the community who would otherwise have been supporters. Better to make the case for standardized parts and attention to abstraction hierarchies than to speak falsehood with authority.

Responsibility to the truth can also take on other forms. If Craig, in order to help advance the idea that building synthetic bacterial genomes is safe, says that more people were killed by lightning in the last year than by anthrax attack in the last 50, it's of course true, just as it is true for people killed by exploding hydrogen warheads. But even though it's true, it's just not especially relevant. Call that... a "designed to distract" kind of true, an "Exxon-Mobil" kind of true. Now imagine that, to decouple fears of microbial fermentation from fears of biological attack, a synthetic biologist finds herself asserting that it's not easy to remake measles, or influenza with synthetic DNA. Or simply that there is a legitimate scientific uncertainty around that point, so that the prudent next step is... further study. Plead uncertainty, or assert that there is a controversy, where none exists, and there we are back at Exxon-Mobil again. Unless perhaps some readers believe that governments, foundations, and corporations should be staging scientific meetings in 2010 to address an alleged lack of consensus as to whether human generated CO_2 emissions are contributing to a rise in average planetary temperature?

Finally, responsibility to the truth can take the form of admitting ignorance. This summer there were interviews in which self-identified synthetic biologists were asked, among other things, about "experiments of concern". Now, "experiments of concern" is what one calls a "term of art". It was coined in the Fink report, where it refers to 7 highly specific classes of activities (for example, deliberately making a pathogen resistant to a therapeutic drug). Reading the transcripts, it is hard to shake the impression that, in some of the interviews, neither the graduate student interviewers (public policy students) nor the young leaders being interviewed (often, engineers, and in any case not infectious disease researchers) had any idea that the term had a specific meaning, much less what it did mean. Is it too much to ask that at least one of the parties in these conversations have admitted that they didn't know exactly what they were discussing?

Responsibility to articulate and help bring about positive consequences. I suspect that most people who read this will share the belief that biological engineering, recombinant DNA work, and synthetic biology have a great deal to contribute to a better human future. And that the current ghetto boundaries, the focus on devices, minimal bacterial genomes, microbial chemical synthesis, and ability to make long pieces of double stranded DNA, do not capture all the good that needs to be done. But, although I am very sympathetic to the ideas that hacking and playfulness are good for their own sake, I'm pretty sure that, for hacking in biology the public is not going to buy into this without a positive vision. So, I suspect that to give the field traction, it will be necessary articulating and working toward achievable positive goals.

I've already mentioned defense. There is a lot to do here, and of course I'd like to see students of biological engineering make more contributions than they have to problems of

disease detection, diagnosis, prophylaxis, and treatment. But defense isn't the half of it. There are tremendous human needs during this century, including but not limited to food, energy, health, housing, water, cleanup, and, for all we know, emergency fixation of carbon. Why should the next election not feature a proposal to spend 50 million dollars by 2010 on open source standard parts, genes encoding enzymes relevant to anabolism (carbon fixation, alcohol synthesis, energy storage materials, plant derived materials and functions) and catabolism (chemical remediation, recycling)? Couple this with strong technical defenses and social norms including condign punishment of pathogen-makers, and you have a bridge you might be able to sell.

Protecting Uncle Ben

Precisely because it has attained a measure of prominence, synthetic biology has attained a measure of power. At the very least, it has increased its power to influence people's thoughts and opinions, and so affect public debate. At the same time, technical trends that predate synthetic biology but will inevitably be associated with it have brought about the risky current landscape. The consequences are pretty clear. On some day in the future, they are going to hit us. Fill in your own "they"; remember that "they" in 2006 may not be the same "they" as in 2016; remember that "they" in 2006 could be "he" or "she" in 2016; and fill in your own "us". On the day that they hit us, significant numbers of Uncle Bens are going to die. Fill in your own "Uncle Bens"

With greater powers come greater responsibilities.

Technical publication information

DOI not yet assigned