

A Brief Look at the Ethical Debate of De-Extinction

Stanford-Brown iGEM 2013

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"If extinction is not forever, a lot changes."

-Dr. Stanley Temple, TEDx March 2013



Introduction

This year, the 2013 Stanford-Brown iGEM team stepped into uncharted territory. When we brainstormed projects back in April, a combined interest in ancient organisms generated questions on the origins of life and the nature of evolution itself. One screening of Steven Spielberg's *Jurassic Park* (1993) later and we developed iGEM's very first de-extinction project. Hollywood has taken advantage of exploiting scientific disasters. The following paper is meant to strip away the entertaining fiction and facilitate a discussion about the real consequences of de-extinction in the context of our project, both positive and negative.

We were still reviewing the task's objectives when we attended the San Mateo Maker's Faire in May. All four of our projects were met with enthusiasm. Amidst the excitement, however, were inquiries we had already begun to consider but had not completely explored. Many of the attendees expressed concern over the ethical issues of our de-extinction ideas. Some thought de-extinction had a lot of potential but most appeared weary of our desire to revive what is already "dead and buried."¹ Who are we to manipulate life so vigorously? With the benefit of education and discussion, we feel that the popular fear of de-extinction we encountered is more out of misinformation. The last thing we want to be guilty of is conducting a project without considering multiple perspectives, including the long-term consequences. Dr. Terry D. Johnson, the current UC Berkeley iGEM advisor, wrote on the nature of iGEM earlier this year in preparation for the Jamboree in October. Stanford-Brown 2013 paid special attention to his concluding remarks; "This project," or any project, for that matter, "should aim to do good with minimal risk of harm."²

We are not here to make incontrovertible conclusions, say that some thoughts are more important than others, or pass judgment values on insightful opinions. The purpose of this paper is to serve as a guide for future iGEM teams interested in ancestral reconstruction and show that Stanford-Brown 2013 has thought about these issues as we initiate a new area of study for iGEM.

Honing in on de-extinction

On May 31st the Stanford Law School held a forum titled "De-Extinction: Ethics, Law, and Politics." Speakers included Drs. Hank Greely, Stanley Temple, Stewart Brand, Kate Jones, and Jamie Rappaport Clark. They all defined true de-extinction as *when a complete organism from an extinct species is brought back to life*.

While clarifying definitions may seem like an elementary task, it is absolutely essential. To future iGEMers who are ready to enter a project under the heading of de-extinction, you need to understand how

¹ Isabel Rekow, personal interview, May 18 2013.

² Terry D. Johnson, "Biosensors and Blue Jeans," *Kinja*, Gawker Media, 13 June 2013, Web, 4 July 2013. <<http://tdj.kinja.com/biosensors-and-blue-jeans-berkeleys-2013-igem-projec-513187511>>

it falls under that category, which can actually be rather ambiguous. For instance, are you really just cloning something? What is the status of the species from which your subject comes? How authentic is the ancestral sequence you are using? Since resurrecting a living, viable organism from an extinct species has as of yet been unsuccessful (in 2003 a team in Spain managed to bring back a Pyrenean ibex, but the subject died nine minutes after birth), de-extinction projects at this time exist on a spectrum of successes and failures.³ Here are some questions we had to ask ourselves to understand where our project fits in this scheme:

1. What is your subject?

According to the very strict definition of de-extinction given above, a project can only be successful if a complete living organism is resurrected; the corpse of the nine-minute old ibex mocks this element. There are several plans underway across the world that fall under the category of ancestral reconstruction, they just deal with subjects of a different matter. Before we can bring back a full organism, they reason, aiming sights on single genes, proteins, even particular tissues, is more realistic. For instance, Dr. Joe Thornton at the University of Oregon has been working for over fifteen years on resurrecting a variety of ancient proteins; many of his amino acid chains in his Eugene lab reflect structures that are over 400 million years old. While he is not resurrecting organisms, he is still “raising the dead,” addressing pivotal questions on irreducible complexity and testing “hypotheses about evolution that would otherwise be just speculation.”⁴ De-extinction projects are not black-and-white, success-and-failure, organism-or-no-organism. Stanford-Brown 2013’s project, and others like it, exist under the wide umbrella of de-extinction, whose strict definition is more of an idealization than modern reality.

2. Is the subject that you’re bringing back really from an extinct species?

“Extinction” itself is relatively straightforward. According to the Environmental Protection Agency, a species is extinct when no member of that species is known to be alive, both in the wild and in captivity.⁵ It is those organisms that are at the center of the ideological definition and ultimate goal of de-extinction.

Functional extinction, however, has more pragmatic potential in present ancestral reconstruction projects. A species is functionally extinct when there are so few individuals left that the species will inevitably die out from depleted mating opportunities, with a gene pool so small that diversity, essential for a population’s ability to adjust to environmental fluctuation, is next to impossible. Some conservation biologists suggest we ought to focus our de-extinction attentions on functionally extinct rather than extinct species. This way, we would still have access to living organisms with complete genomes and female bodies to carry the subjects to term. Such projects fall under the realm of de-extinction, with the initiative of restoring a once-thriving species, without following the strict impractical definition mentioned above.⁶

³ Carl Zimmer, “Bringing Them Back to Life,” *National Geographic*, National Geographic Magazine, April 2013, Web, 15 August 2013. <<http://ngm.nationalgeographic.com/2013/04/125-species-revival/zimmer-text>>

⁴ Helen Pearson, “Prehistoric Proteins: Raising the Dead,” *Nature* 483, 390-393 (22 March 2012).

⁵ <<http://www.nature.com/news/prehistoric-proteins-raising-the-dead-1.10261>>

⁶ “Threatened and Endangered Species,” U.S. Environmental Protection Agency, *EPA Online*, 9 May 2012, Web, 22 September 2013. <<http://www.epa.gov/espp/coloring/especies.htm>>

⁶ Zimmer, op. cit.

3. Is your sequence actually ancestral? How are you getting it?

There are a variety of ways this has been, or can be, done. The traditional method with regard to de-extinction is to extract as much original DNA from an extinct organism's remains as possible, sequence it, and fill in the gaps with codes from modern descendants. Another more recent approach has been to mathematically reconstruct the desired sequences using statistics and by comparing phylogenetic trees of genomes using bioinformatics software. The Stanford-Brown 2013 team is using the latter technique. Both methods are simply different approaches, one more organic than the other. It is up to interpretation and personal opinion about which is superior to the other; it ultimately depends on what the project itself is aiming to accomplish.

4. How our project fits in the category of de-extinction:

Stanford-Brown 2013 is working on a component of de-extinction. We are not resurrecting a whole organism, let alone an organism that is a member of an extinct species. We, like Dr. Thornton, are not working on the scale of an entire organism, but on the scale of individual proteins. Our sequences are not original codes, but mathematical reconstructions from a careful manipulation of bioinformatics software. Our project poses little to no risk of manifesting something that can contaminate the environment or destroy the system into which we are inserting it. Yet the questions surrounding de-extinction apply to us just as they should to scientists who want to bring back woolly mammoths or, more realistically, passenger pigeons and thylacines, also known as the Tasmanian tiger. Improving and building upon genetic reconstruction techniques could facilitate more controversial de-extinction projects in the future.

WHY?

Why are we focusing on de-extinction at all?

For iGEM, the project is about the process and the learning experience. Stanford-Brown 2013's ancestral reconstructions can be used to make inferences on how proteins operated in the past, where they might have come from, which amino acids may have been the most common, how they were conserved, their mutation rates, their approximate age, the list goes on. What we stand to learn from de-extinction addresses the heart of the nature of evolution itself.

What is one specific reason that could justify a long-term investment in de-extinction?

De-extinction has been proposed as the next futuristic tool to revitalize biodiversity. Dr. Stewart Brand and his wife Dr. Ryan Phelan are a power-couple when it comes to combining synthetic and conservation biology. Dr. Brand, the founder of the Whole Earth Catalogue, and Dr. Phelan, who began the genetics company DNA Direct, believe de-extinction is "absolutely" a way to "undo serious damage" and "restore lost genetic diversity."⁷

For instance, there are many extinct organisms that played singular roles in maintaining their respective ecosystems, ecosystems "which might benefit from their return." For instance, 12,000 years ago Siberia was a wildly diverse grassland, home to woolly mammoths and other mega fauna that maintained the landscape. Not long after the beasts vanished, the terrain was overwhelmed by moss that has since suffocated its diversity and rendered Siberia the wasted tundra it is today. Dr. Sergey Zimov, a Russian ecologist and director of the Northeast Science Station in Cherskiy in the Republic of Sakha, "has long

⁷ Kate Torgovnick, "Everything You Need to Know about TEDxDeExtinction," *TED Blog*, TED Conferences LCC, 13 March 2013, Web, 11 September 2013.
<<http://blog.ted.com/2013/03/13/everything-you-need-to-know-about-tedxdeextinction/>>

argued that this (abrupt shift in ecosystem) (is) no coincidence: The (now extinct) mammoths and numerous herbivores maintained the grassland by breaking up the soil and fertilizing it with their manure. Once they were gone, moss took over and transformed the grassland into less productive tundra.” While Dr. Zimov does not think it feasible, or even wise, to reintroduce woolly mammoths to Siberia, his theory is an example of how we could use de-extinction technology to repair modern ecosystems.⁸

So much do ecologists like Dr. Zimov and conservation biologists like Drs. Brand and Phelan believe in the potential of de-extinction that they are generating a new era of private organizations to fund de-extinction endeavors in the name of environmental protection. In early 2012, Drs. Brand and Phelan started the Revive and Restore Project. Stationed in San Francisco, the group of carefully assembled scientists, bioinformatics specialists, students, and curious entrepreneurs, promote “ecological enrichment through extinct species revival” and are in “constant contact” with Dr. Zimov’s Pleistocene Park in the Sakha Republic. The Project has already set work on plans to resurrect the passenger pigeon, a protocol developed in conjunction with Dr. George Church at Harvard’s Wyss Institute.⁹ This last March Dr. Church himself announced the foundation of his own de-extinction company with the Chief Scientific Officer of Advanced Cell Technology, Dr. Robert Lanza. Tentatively titled the Ark Corporation in honor of Noah’s Ark, Dr. Church hopes the corporation will not only “revive some extinct species” but “combine cutting-edge cell biology and genome engineering in order to breed livestock and maybe even create DNA-altered pets that live much longer than usual.”¹⁰ The novelty never dies.

Common Ethical Questions Concerning De-Extinction

Does humanity have a moral obligation to bring back species we are responsible for eliminating?

In truth, there is no right or wrong answer to this. Of course many argue that as the most intelligent species on the planet (some say), it is our obligation to protect it; anything we destroy we are responsible for.

And humans have caused an alarming number of species to go extinct. Revive and Restore’s favorite subject, the passenger pigeon, died out in 1914 due to deforestation and careless overhunting. The North American sea mink vanished by the end of the 19th Century in conjunction with the fur trade. The Chinese baiji dolphin was declared “functionally extinct” in 2006 due to the industrialization of the Yangtze River and illegal fishing. Many individuals, either of the scientific community or part of the wider public, insist that we are compelled to act on behalf of these wronged species. Dr. Michael Archer, an Australian paleontologist, is one of these individuals; “If it’s clear that we exterminated (a) species, then I think we have not only a moral obligation to bring it back, but a moral imperative... We have to do something. If we can.”¹¹

But extinction is also a natural occurrence. In fact, the most catastrophic exterminations Earth has seen occurred millions of years before human beings even existed; 99.9% of all species that ever lived on

⁸ Zimmer op. cit.

⁹ “Forward to the Past,” *longnow.org*, Revive and Restore, March 2013, Web, 24 September 2013.

¹⁰ Antonio Regalado, “A Stealthy De-Extinction Start-Up,” *Technology Review*, MIT Technology Review, 19 March 2013, Web, 18 September 2013. <<http://www.technologyreview.com/view/512671/a-stealthy-de-extinction-startup/>>

¹¹ Michael Archer, “Second Chance for Tasmanian Tigers and Fantastic Frogs,” *www.ted.com*, TEDxDeExtinction, March 2013, Lecture. <http://www.ted.com/talks/michael_archer_how_we_ll_resurrect_the_gastric_brooding_frog_the_tasmanian_tiger.html>

Earth are now extinct, and the majority of those species died out with absolutely no human involvement.¹² Why bother with species that went extinct because of humans? After all, human beings are nature. If something dies because of us, it is still being selected against by nature because we are a part of that grander system. In fact, opponents to de-extinction claim that by trying to resurrect a species we are trying to “play God.” To this, Dr. Archer simply replies, “I think we played God when we exterminated these animals (in the first place).”¹³

What does de-extinction compromise?

Conservation biologists are also very wary of de-extinction, whether it be that of single genes or entire organisms. If we allocate all of our funds to bringing back the past, they argue, then who is taking care of the present? Aren’t there more pressing matters to deal with than re-creating what nature has already selected for destruction?¹⁴

Dr. Temple, in a TEDx talk as part of a special series on de-extinction last March, warned that “de-extinction might indeed undermine conservation biology” by “diverting resources” away from current ecological preservation undertakings.¹⁵ Dr. Elizabeth Hadly of Stanford University also laments the increasing focus on de-extinction. Dr. Hadly believes the self-interest of industrial laboratories stuck on de-extinction depletes funding for preserving endangered species; the funding allocated to environmental preservation, she argues, “pales compared to the big grants (for) genomics and synthetic biology.” Dr. Jamie Rappaport Clark reiterates Dr. Hadly’s sentiments; “We need to do a better job of stewarding what we have before we go rushing off after cool science experiments.”¹⁶ We cannot focus on what is already lost if it means ignoring current problems. We should not put ourselves in the position to compromise one dead or dying species for the other. And, if we have to choose between the two, it makes more sense to take care of what we are losing now rather than bringing back what is already gone.

There is an additional issue of contamination, on the scale of the single gene and the entire organism. For instance, what if a de-extinct subject were to be let loose, unmonitored? How destructive could it be to already-present ecologies? Our group’s background research on other ancestral reconstruction projects revealed that ancestral components are normally more virulent and more thermostable than their modern counterparts.¹⁷ Whose responsibility is it to monitor and safeguard these ancient proteins? Where and how should they be stored? Should the proteins and the cells they are inserted into simply be destroyed once the project is completed?

¹² “The Five Worst Mass Extinctions,” *Endangered Species International*, Endangered Species International Inc., 2011, Web, 23 September 2013.

<<http://www.endangeredspeciesinternational.org/overview.html>>

¹³ Zimmer, op. cit.

¹⁴ George Church, “Hybridizing with Extinct Species,” *www.ted.com*, TEDxDeExtinction, March 2013, Lecture. <http://www.youtube.com/watch?v=oTH_fmQo3Ok>

¹⁵ Stanley Temple, “De-Extinction: A Game-Changer for Conservation Biology,” *www.ted.com*, TEDxDeExtinction, March 2013, Lecture. <<http://www.youtube.com/watch?v=DCnhQzwgP-A>>

¹⁶ Liza Gross, “De-Extinction Debate: Should Extinct Species Be Revived?” *KQED Science Inc*, Public Media for Northern California, 5 June 2013, Web, 13 July 2013.

<<http://blogs.kqed.org/science/2013/06/05/deextinction-debate-should-extinct-species-be-revived/>>

¹⁷ Bastien Boussau et al, “Parallel Adaptations to High Temperatures in the Archean Eon,” *Nature*, Nature Online, 24 September 2008, Web, 24 July 2013.

<<http://hal.inria.fr/docs/00/32/41/59/PDF/boussau-blanquart-et-al2008.pdf>>

For Stanford-Brown 2013, our ancestral proteins do not, and probably cannot, exist in the wild. They have only ever known plates swimming in nutrient-rich LB and have been spoiled by our stocks of antibiotics. From what we have seen, the knockout cells that receive the ancestral inserts certainly express the protein, but have a difficult time passing it on to their offspring. Still, there is always the risk, however small, that they will mutate and adapt into something stronger, even destructive. As our project comes to a close, our cells will certainly be destroyed as we move on to future work. But the information to re-create our ancestral protein mock-ups will be readily available. Worrying about the environmental impact, past, present, and future, is a huge, if not the central, concern when it comes to any de-extinction project.

Finally, according to Dr. Temple, the reason why a reluctant public endorses conservation biology at all is the finality of extinction. If de-extinction makes extinction no longer permanent, then even fewer will care about ecological preservation. Dr. Temple worries that success in de-extinction will generate insurmountable complacency, feeding a new popular attitude arguing; “Can’t we just let them go extinct and bring them back later?” The net loss of biodiversity resulting from such a stance would be tragic.

What might de-extinction offer for the field of synthetic biology? What do we stand to learn that can outbalance ethical concerns?

There is a reason the Presidential Commission for the Study of Bioethical Issues was the first science-based Commission endorsed by the new Obama Administration in 2009. The Commission was created working off a 2009 statement from the Lloyds of London's Emerging Risk Group; “Biology will be one of the transformative technologies necessary to combat climate change, energy shortages, food security issues and water deficits.”¹⁸

The process of resurrecting an ancient protein has an array of practical applications. With further experimentation of bioinformatics software, for instance, the software may not only become more sophisticated, but cheaper. Lowering cost increases accessibility, thereby increasing the aptitude for more research. The corresponding amalgamation of new data could contribute to remarkable advances in the fields of bioengineering, medicine, pharmacogenomics, and personalized human genomics, to name a few.

For example, during a TEDx de-extinction colloquium last March Dr. Church noted how the field could help us fight deadly viruses. If we are to resurrect viruses and place them in the coevolutionary context of the human immunological response, the understanding of how viruses change could help our medicinal munitions against them. On October 5, 2005 the Center for Disease Control sent out a press release stating that they had successfully revived the Spanish influenza virus. Understandably so, the public was very concerned. Why resurrect a virus that was responsible for the death of nearly 50 million people barely a century before? CDC Director Dr. Julie Gerberding defended the project; “We need to know much more about pandemic influenza viruses (in order to combat them). Research such as this helps us understand what makes some influenza viruses more harmful than others... (and) help us identify, early on, influenza viruses that could cause a pandemic.” The microbiologist who resurrected the final gene sequences of the virus, Dr. Terrence Tumpey, noted how resurrecting the Spanish flu may help us “develop new vaccines and treatments” that are cheaper and more effective. He concluded, “influenza viruses are constantly evolving, and that means science needs to evolve if we want to protect as many

¹⁸ Kate Redford et al, “Synthetic Biology and Conservation of Nature,” *PLOS Biology* 11(4) (April 2013): n. pg, Web, 24 August 2013.
<<http://www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.1001530>>

people as possible.”¹⁹ According to Dr. Church, the very nature of de-extinction research is ultimately to “excite people about science,” promote biological conservation, and perfect “medical advancements,” that will “save millions of lives in the future.”²⁰

De-extinction even has applications in space exploration. Stanford-Brown has the unique opportunity to work in a laboratory at NASA Ames’ Research Center. With regard to synthetic biology, one of NASA’s goals is to engineer microorganisms to be astronauts on our behalf. What if we could use tiny life forms, rather than very large, heavy, and expensive machines, to build for us in space? Or clean for us in space? Or even send back data? There are a variety of microorganisms with exceptional qualities that could provide some of these functions. They, at least, have characteristics that allow them to survive better in space than human beings and could be manipulated by directed evolution, with input from de-extinction research, to do extraterrestrial work for us. Dr. Lynn Rothschild, Chief Scientist for Synthetic Biology at NASA Ames, insists that one of the most pivotal reasons to pursue de-extinction is to understand these organisms’ genetic origins. Under what evolutionary circumstances did *Deinococcus radiodurans* become so resistant to radiation? What about the extremophiles in Yellowstone National Park who thrive in high-acidity environments? And then there are the tardigrades, eukaryotic “water-bears” that can withstand temperatures just above absolute zero and survive the vacuum of outer space.²¹ Looking at the genetic history of these organisms, a number of which are among the oldest species on the planet, could provide vital information about the potential for space exploration, not to mention the possibility of finding life in the universe or understanding the nature of life itself.

How does this apply to our project?

One of the proteins reconstructed in our own project is CasA, the first protein in the CRISPR cascade defense response inherent in most modern prokaryotes. Dr. Church was one of the original researchers on the CRISPR complex, and he believes that understanding its immunological components may help our own attempts to distill certain illnesses, including HIV/AIDS.²² What if we were successful at generating a sort of inherent immune system reminiscent of the CRISPR cascade? One that can recognize particular viruses and eliminate them before their genetic information is even taken up by the host? One way we can do this is to de-construct the evolutionary history of CRISPR to better understand its function. In the case of our particular project, our results have the potential to feed Dr. Church’s goal that de-extinction may contribute to a better quality of life for human beings

Conclusion

In an address to NASA Ames faculty, students, and summer interns on July 18th 2013, Director Dr. Pete Worden announced that the whole purpose of science, synthetic biology in particular, is to “make science fiction a reality.”²³ Who wouldn’t want a chance to see a real living dinosaur? Or witness a woolly

¹⁹ “Researchers Reconstruct 1918 Pandemic Influenza Virus; Effort Designed to Advance Preparedness,” CDC Media Relations Immediate Press Release, 5 October 2005, Web, 5 August 2013.

<<http://www.cdc.gov/media/pressrel/r051005.htm>>

²⁰ Church, op. cit.

²¹ Lynn Rothschild, “Pushing the Envelop For Life,” Stanford University, Building 20 Main Quad, CA. 26 Jan 2013, Lecture.

²² Church, op. cit.

²³ Pete Worden, “The Curiosity of NASA Ames Research Center,” Nasa Ames Rsearch Center, Building N201 Auditorium, Moffett Field CA, 18 July 2013, summer lecture series.

mammoth roam Siberian grasslands once again? De-extinction has great potential; if we can resurrect functional proteins now, how far are we, really, from generating complete organisms? Curiosity is the ultimate fuel for science, particularly the more elaborate goals like bringing back a species. But such endeavors should always be pursued with caution. How do we defend what is natural, how do we define what is natural, especially when capable of manipulating nature to such a degree? For Stanford-Brown 2013, de-extinction represents one of the best available learning opportunities for young scientists; it forces us to remind each other, the leaders of the next generation of bioengineers, that the question of “should we?” rather than “could we?” is always the most important.

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