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Defining An Algorithm For Inventing From Nature

The pipeline linking ecological discovery to bioengineering insight.

By Edward Boyden and Brian Y. Chow

"Time after time we have rushed back to nature's cupboard for cures to illnesses," noted the United Nations in declaring 2010 the International Year of Biodiversity. Billions of years of evolution have equipped natural organisms with an incredible diversity of genetically encoded wealth, which, given our biological nature as humans, presents great potential when it comes to understanding our physiology and advancing our medicine. Natural products such as penicillin and aspirin are used daily to treat disease, yeast and corn yield biofuels, and viruses can deliver therapeutic genes into the body. Some of the most powerful tools for understanding biology, such as the PCR reaction, which enables DNA to be amplified and analyzed starting from tiny samples, or the green fluorescent protein (GFP), which glows green and thus enables proteins and processes to be visualized in living cells, are bioengineering applications of genes that occur in specialized organisms in specific ecological niches. But how exactly do these tools make it from the wild to benchtop or bedside?

Many bioengineering applications of natural products take place long after the basic science discovery of the product itself. For example, Osamu Shimomura, who first isolated GFP from jellyfish in the 1960s, and who won a share of the 2008 Nobel Prize in Chemistry, once explained: "I don't do my research for application, or any benefit. I just do my research to understand why jellyfish luminesce." Around 30 years later, Douglas Prasher, Martin Chalfie, and Roger Tsien and their colleagues isolated the gene for GFP, expressed it, and began altering the gene, enabling countless new kinds of study. Bioengineering can emerge from the conscious exploration of nature, although sometimes with long latency. Every gene product is a potential tool for perturbing or observing a biological process, as long as bioengineers proactively imagine and explore the significance of each finding in order to convert natural products into tools.

Conversely, many bioengineering needs are probably satisfied, at least in part, by a process found somewhere in nature--whether it's making magnetic nanoparticles, or sensing heat, or synthesizing structural polymers, or implementing complex computations. The question in basic science often boils down to how generally important a process is across ecological diversity, but a bioengineer only needs one

example of something to begin copying, utilizing, and modifying it.

If we can build more direct connections between bioengineering and the fields of ecology and basic organismal sciences--converging at a place you might call "econeering"--we could together meet urgent bioengineering needs more quickly, and direct resources toward basic science discovery. Scientists could deploy these basic science discoveries more rapidly for human bioengineering benefit.

Recently we've begun to examine some of the emerging principles of econeering, as we and others pioneer a new area--the use of natural reagents to mediate control of biological processes using light, sometimes called "optogenetics."

As an example: Opsins are light-sensitive proteins that can, among other things, naturally alter the voltage of cells when they're illuminated with light. They're almost like tiny, genetically encoded solar cells. Many opsins are found in organisms that live in extreme environments, like salty ponds. The opsins help these organisms sense light and convert it into biologically useful forms of energy, an evolutionarily early sort of photosynthesis.

Plant biologists, bacteriologists, protein biochemists, and other scientists have widely studied opsins at the basic science level since the 1970s. Their goal has been to find out how these compact light-powered machines work. It was clear to one of us (Boyden) around a decade ago that opsins could, if genetically expressed in cells that signal via electricity (such as neurons or heart cells), be used to alter the electrical activity of those cells in response to pulses of light.

Such tools could thus be a huge benefit to neuroscience. They could enable scientists to assess the causal role of a specific cell type or neural activity pattern in a behavior or pathology, and make it easier to study how other excitable cells, such as heart, immune, and muscle cells, play roles in organ and organism function. Furthermore, given the emerging importance of neuromodulation therapy tools, such as deep brain stimulation (DBS), opsins could enable novel therapies for correcting aberrant activity in the nervous system.

What might be called the "example phase" of this econeering field began about 10 years ago, when several papers suggested that these molecules might be used safely and efficaciously in mammalian cells. For example, foundational papers in 1999 (by Okuno and colleagues) and 2003 (by Nagel and colleagues) revealed and characterized opsins from archaebacteria and algae with properties appropriate for expression and operation in electrically excitable mammalian cells. Even within these papers, basic science examples began to lead directly to bioengineering insights, demonstrating in the case of the Nagel paper that an opsin could be expressed and successfully operate in a mammalian cell line. In 2005 and 2007, we and our colleagues, in a collaboration

between basic scientists and bioengineers, showed that these molecules, when genetically expressed in neurons, could be used to mediate [light-driven activation of neurons](http://syntheticneurobiology.org/publications/publicationdetail/42/25) (<http://syntheticneurobiology.org/publications/publicationdetail/42/25>) and [light-driven quieting of neurons](http://syntheticneurobiology.org/publications/publicationdetail/45/25) (<http://syntheticneurobiology.org/publications/publicationdetail/45/25>). In the few years since, these tools have found use in activities ranging from accelerating drug screening, to investigating how neural circuits implement sensation, movement, cognition, and emotion, to analyzing the pathological circuitry of, and development of novel therapies for, neural disorders.

Now this econeering quest is entering what could be called the "classification phase," as we acquire enough data to predict the ecological resources that will yield tools optimal for specific bioengineering goals. For example, in a paper from our research group [published in *Nature* on January 7, 2010](http://syntheticneurobiology.org/publications/publicationdetail/97/25) (<http://syntheticneurobiology.org/publications/publicationdetail/97/25>), we screened natural opsins from species from every kingdom of living organism except for animals. With enough examples in hand, distinct classes of opsins emerged, with different functional properties.

We found that opsins from species of fungi were more easily driven by blue light than opsins from species of archaeobacteria, which were more easily driven by yellow or red light. The two classes, together, enable perturbation of two sets of neurons by two different colors of light. This finding not only enables very powerful perturbation of two intermeshed neural populations separately-- important for determining how they work together--but also opens up the possibility of altering activity in two different cell types, opening up new clinical possibilities for correcting aberrant brain activity. Building off of data from and conversations with many basic scientists, we then began mutating these genes to explore the classes more thoroughly, creating artificial opsins to help us identify the boundary between the classes. Understanding these boundaries not only gave us clarity about the space of bioengineering possibility, but told us where to look further in nature if we wanted to augment a specific bioengineering property.

In the current model of econeering, the "example phase" and the "classification phase" both provide opportunities for productive interactions between bioengineers and ecologists or organismal scientists. During the example phase described above, both basic scientists and bioengineers tested out candidate reagents to see what was useful, and later many groups initiated hunts for new examples. During the classification phase, more systematic synthetic biology and genomic strategies enabled more thorough assessment of the properties of classes of reagents.

Interestingly, something similar has been happening recently with GFP, as classes of fluorescent protein emerge with distinct properties: for a while, it's been known that mutating the original jellyfish GFP can yield blue and yellow fluorescent proteins, but not red ones. A decade ago, an example of a red fluorescent protein from coral was revealed-- now this example has yielded, through bioengineering, a new class of

fluorescent molecules with colors such as tomato and plum. So it is possible that the cycle described here --find an example, define a class, repeat--might represent a generally useful econeering process, one of luck optimization intermeshed with scientific and engineering skill.

Did the opsin community do "better" than the fluorescent protein community, in speeding up the conversion of basic science insight into bioengineering application? Well, one of the opsins that we screened in this month's paper was first characterized in the early 1970s, and it was better at changing the voltage of a mammalian cell than perhaps half of the other opsins we screened. So one could argue that a decent candidate reagent had hidden in plain sight for almost 40 years!

Although these two specific fields have benefited from basic scientists and bioengineers working together, a more general way to speed up the process of econeering would be to have working summits to bring together ecology minded and organismal scientists and bioengineers at a much larger scale, to explore what natural resources could be more deeply investigated, or what bioengineering needs could be probed further. Then interfaces, both monetary and intellectual, could facilitate the active flow of insights and reagents between these fields. The next step could involve teaching people in each field the skills of their counterparts: how many bioengineers would relish the ability to hunt down and characterize species in the ocean or desert? How many organismal biologists and ecologists would benefit from trying out applications in specific areas of medical need?

To fulfill the vision of econeering, we should devise technologies for assessing the functions of biological subsystems fully and quickly, perhaps even enabling rapid basic science and bioengineering assessments to be done in one fell swoop. Devices for point-of-discovery phenotyping that allow for gene or gene pathway cloning, heterologous expression, and functional screening--and maybe even downstream methodologies such as in-the-field directed evolution--would allow the rapid assessment of the physiology of the products of genes or interacting sets of gene products. (Note well: the gene sequence is important, but only the beginning; gene sequences are not sufficient by themselves to fully understand the function of a gene product in a complex natural or bioengineering context.)

Bioinformatic visualization tools could be useful: can we scan ecology with a bioengineering lens, revealing areas of evolutionary space that haven't been investigated (at either the example or class level)? What are the areas of bioengineering need where examples from nature might be useful in inspiring solutions?

Ideally, an econeering toolbox will emerge that will let us confront some of our greatest unmet needs--not just brain disorders, but needs in complex spaces such as energy, antibiotic resistance, desalination, and climate. If we can better understand, invent

from, and improve the preservation of our natural resources, we'll be poised to equip ourselves with a billion years of natural bioengineering. This will give us a great advantage in tackling the big problems of our time--and help future generations tackle theirs.

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Upcoming Events

[SXSW Interactive \(http://www.sxsw.com/\)](http://www.sxsw.com/)

Austin, TX

Friday, March 12, 2010 - Tuesday, March 16, 2010

<http://www.sxsw.com/> (<http://www.sxsw.com/>)

[FEI 2010 – The Annual Front End of Innovation Conference A New Front End: The Era of Collaboration \(http://www.iirusa.com/feiusa/fei-home.xml?registration=FEI2010TECHREV\)](http://www.iirusa.com/feiusa/fei-home.xml?registration=FEI2010TECHREV)

Boston, MA

Monday, May 03, 2010 - Wednesday, May 05, 2010

<http://www.iirusa.com/feiusa/fei-home.xml?registration=FEI2010TECHREV>
(<http://www.iirusa.com/feiusa/fei-home.xml?registration=FEI2010TECHREV>)

[2010 IEEE Conference on Innovative Technologies for an Efficient and Reliable Electricity Supply \(http://www.ieee-energy.org/\)](http://www.ieee-energy.org/)

Waltham, Massachusetts

Sunday, September 27, 2009 - Tuesday, September 28, 2010

<http://www.ieee-energy.org/> (<http://www.ieee-energy.org/>)

[MIT Sloan CIO Symposium \(http://www.mitcio.com\)](http://www.mitcio.com/)

MIT Campus, Cambridge, MA

Wednesday, May 19, 2010

<http://www.mitcio.com> (<http://www.mitcio.com>)

[BIO International Convention \(http://convention.bio.org\)](http://convention.bio.org/)

Chicago, IL

Monday, May 03, 2010 - Sunday, May 10, 2009

<http://convention.bio.org> (<http://convention.bio.org>)