Genome Engineering

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Questions Introduced Last Time

D. What is a standard biological part?

E. What is reliable physical composition? And, reliable functional composition?

F. How does synthetic biology relate to genetic engineering?

Discussion for Today

F. How does synthetic biology relate to genetic engineering?

G. Can we implement reliable physical and functional composition via standard biological parts?

ANNOUNCEMENT

"Genetic control of the synthesis and assembly of materials for electronics and energy"

Angela Belcher, Mass Tech

4-5p today in 32-123 (food at 3:40p outside room)

34. How does synthetic biology relate to genetic engineering?

People have long been interested in using biology to solve problems, from food and shelter, to drug production and biofuels, and now a wider number of applications, including building electronics, environmental monitoring and remediation, and perhaps even growing large-scale structures, like houses. About 30 years ago researchers discovered restriction endonucleases and invented recombinant DNA technology (rDNA). rDNA allows people to intentionally cut and paste pre-existing fragments of genetic material (so long as the restriction sites are in the right places!). This marked the beginning of "genetic engineering." (**What does it mean to be an engineer?**)

35. About the same time the rDNA technology got invented, polymerase chain reaction (PCR) was figured out, with some of the foundational work being done here at MIT and then fully invented in the 1980s at Cetus, Inc. As important, by 1977, DNA sequencing was figured out by Fred Sanger at Harvard.

36. Taken together, rDNA, PCR, and DNA sequencing form a core set of underlying technologies that allow for the editing and reading out of genetic material. Since biological systems are encoded via genetic material, these are important technologies both biological science (e.g., change things and see what happens) and biological engineering (e.g., make something that does what you want, hopefully). **For whatever reasons, these three technologies form the basis of what has been called "genetic engineering." It doesn't really matter what you call it, so long as you appreciate what the technologies can do, and how to use them for constructive purposes.**

37. One important lesson across all of engineering is that, so much as it is possible, it is critically important to improve the tools that we use to solve problems. Building 32 was designed with computers, using computer aided design (CAD) software adapted from plane manufacture. For that matter, the Boeing 777 was designed entirely on computer (so I am told). Microprocessors can only be designed using CAD tools developed back in the 1970s. And, let's not forget the American System of Manufacturing, developed in Western Mass. and other places back in the early to mid 1800s (for producing guns). **So, as a question, could we get better at reading DNA (i.e., sequencing). And, could we get better at writing DNA (i.e., synthesis or construction)?**

38. The answer to this question is obviously yes. So, today, there are three new technologies being developed that aid in the process of engineering biological systems. These three technologies are (a) automated DNA construction, (b) physical and functional composition (and other) standards, and (c) abstraction. Automated DNA construction, based on DNA synthesis, lets us make DNA from scratch, in place of bashing DNA together in the lab w/ rDNA and PCR. Standards and abstraction help us manage the information going into the DNA synthesizers. Taken together, these three new technologies extend and improve the underlying foundations of both biological science and engineering. For whatever reasons, these three new technologies form the basis of what is now being called "synthetic biology." Again, it doesn't really matter (to me) what you call it, so long as you know what is going on and why. And, as a final comment, just like DNA sequencing (and PCR and rDNA) technology was fairly primitive in 1977 compared to today, many aspects of these three new foundational technologies are immature. We have to go make them happen if we want make biology easier to engineer.

Let's get back to composition, and standards that might support both reliable functional and physical composition.

39. As one example of functional composition, let's consider the engineered riboswitches described in the BE seminar last Thursday. For those who missed the talk (b/c of 20.109 lab), here's a quick link to the paper:

http://www.pnas.org/cgi/content/abstract/104/36/14283

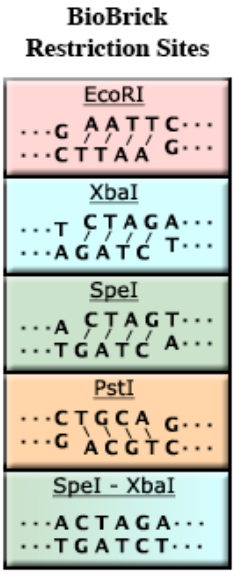
Basically, a riboswitch is made from three parts. A ribozyme, an aptamer, and a communication domain. A ribozyme is an RNA structure that has an enzymatic activity -- it can cut RNA (usually itself). An aptamer is an RNA structure that can interact with another chemical (e.g., a small molecule like caffeine). A communication domain links the ribozyme and the aptamer together, so that when the ligand and present, the ribozyme is either activated or inactivated.

40. The key advance in this engineered riboswitch work appears to be that the authors have figured out how to combine any aptamer with a ribozyme, in order to control ribozyme activity (although they have only shown that two different aptamers work -- what could be some of the problems that might come up). They've also figure out how to integrate their riboswitches into transcripts in order to control gene expression, and claim to be able to control the level of most any mRNA. **So, this work is an example of reliable functional composition. Because functional composition appears to be working, you could be switches against most anything you can find an aptamer for. Question. Do these authors present any results on reliable physical composition? (Not that I can see).**

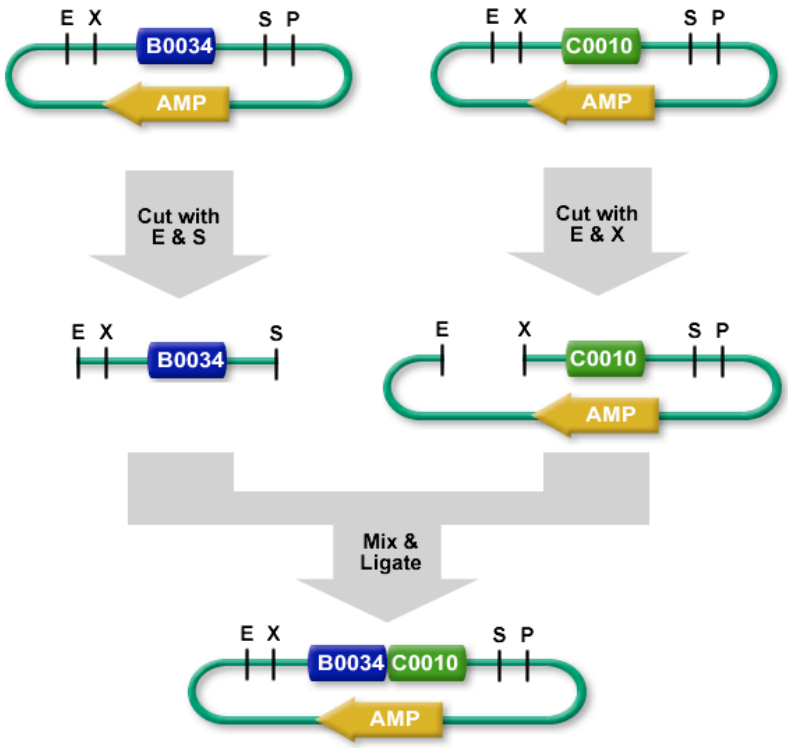
41. Now, as an example of physical composition, Let's take a look at the parts in the Registry of Standard Biological Parts (note that it is not called the Registry of Biological Parts, so there must be something different about Standard Biological Parts, right?). It turns out that the parts currently in the Registry are called BioBrick parts (one "brand" of standard biological parts, although there are not yet any competing brands of standard biological parts). **The BioBrick parts follow a particular scheme** (invented by Tom Knight here at MIT) **that supports physical composition. How does this scheme work?**

42. Each BioBrick part is bracketed by the same four restriction endonuclease sites:

EcoRI-XbaI [PART] SpeI-PstI



43. As a result of bracketing each part with these four sites, you can put any two parts together, and the resulting composite part is bracketed with the same four sites (i.e., you have a new part!).



44. So, the BioBricks standard assembly scheme is an example of reliable **physical composition**. But, note, this says nothing about functional composition, per se.

Questions

Which would you rather have, reliable physical composition, or functional composition?

What sort of functional composition issues can we begin to think about with the parts that make up phage M13?