Genome Engineering

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Questions Introduced Last Time

A. What can we infer about the design of a genome by considering the physical problems that a biological systems solves?

B. How is genetic "real estate" divvied up?

C. What makes a good genetic "part"? What makes a good genome design?

Questions for Today

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?

ANNOUNCEMENT

"A framework for programming integrated RNA devices"

Christina Smolke, Small Western Trade School

4-5p today in 32-141

17. Last time we ended up considering the following sequence of DNA, the basic biological functions encoded on the DNA, and whether or not this particular genetic architecture might be "good" or "bad."

gc**[atg**cgcaa**agggagg**cgac**{ATG**gcaggttacggcgc**taa]**aggaatccgaaat**TGA}**aaa

18. It's hard for us to answer the question of good/bad architecture because we do not know (and perhaps, cannot know) the absolute purpose of this particular piece of DNA. **What is the objective that nature has evolved this sequence to perform? If efficiency of encoding more or less important than modularity? Is a greater sensitivity to mutations in the overlapping coding sequences good or bad?**

19. Because the living world we inhabit is encoded by natural sequences of DNA (including ourselves), it is a hugely important to improve our understanding of the architecture of genetic systems.

Too bad natural DNA code doesn t come with documentation!

20. What is the purpose of a natural sequence of DNA? What defines whether or not its architecture is good or bad?

21. Now, sometimes you can learn about how something works by building new things. When you take a car about, and scatter apart the parts across your lawn, that's one sort of understanding of a car. But, an entirely different level of understanding would be realized if you could take the parts and put them back together to make a car (one that runs, of course).

22. When we looked at DNA sequence before, we were starting with a system (e.g., a bacteriophage) and then "drilling down" to get to the primary DNA sequence. What if looked at things differently. What if we started with DNA sequences and began to build up higher order systems. Maybe we would look at the design and purpose of genetic parts differently.

23. To get started we are going to make something up. A computer scientist would call what we are about to make up an "abstraction hierarchy." That's a fine label so let's keep it. The purpose of an abstraction hierarchy is to organize functions and operations across levels, so that the more primitive components and functions are grouped together, and evermore sophisticated functions are built on top of the more basic functions. However, one key point in an abstraction hierarchy is to hide, or at least manage complexity. We can't be considering really sophisticated functions while, at the same time, pay attention to every low level detail. This will be more clear once we get specific.

24. So, let's consider an abstraction hierarchy that supports the design and construction of DNA-based systems.

The lowest level in our hierarchy might be DNA:

- DNA is a string of dinucleotides encoding genetic information.

Note that this is an information layer, that is itself an abstraction of a physical layer below, which is defined by the physics an chemistry of DNA itself.

25. However, we don't want to stop here. Otherwise we would have to memorize sequences of DNA. For example:

TAATACGACTCACTATAGGGAGA

What's this sequence do? It turns out to be a consensus promoter for a T7 RNA polymerase. **It would be a lot of work to memorize the sequence of every DNA molecule that you might want to engineer with. There's too much complexity (although, if you do need to memorize DNA sequences, using them as the root password for your computer is a handy learning device).**

26. So, the next level in our hierarchy might be Parts (I'm using "might" because you might choose to invent a different hierarchy). Now, we need to define parts:

- Parts are basic biological functions that can be encoded as DNA

Examples of types of parts might include promoters, RBSs, operators, CDSs, docking sites, phosphorylation motifs, and so on, and so on.

You can imagine that we are going to have a lot of parts, more than we want to memorize.

27. So, the next level in our hierarchy might be Devices:

- Devices are combinations of one or more parts that encode a human-defined function

Examples of types of devices might be protein generators, senders, receivers, banana smell generating, wintergreen smell generating, swim, invade, make spider silk protein, and so on, and so on.

25. OK. Let's stop here (although the current hierarchy goes up one more level to systems, which you could guess because we are going to have lots of Devices). **Looking at the Parts and Devices levels, what can we say about Parts? That is, what are we going to want to do with Parts?**

We are going to want to put Parts together to make Devices

(and, we would like our Devices to work!)

26. Ah ha! Now that we know what we want to be able to do with Parts, we can evaluate the designs of parts. **What makes a good or a bad part?**

27. Within our invented framework... **A good part is a part that can be easily combined with other parts. A good part is a part that, when combined with other parts, behaves as expected.**

28. Let's take a look at a historical example (nuts and bolts demo):

ON A SYSTEM OF

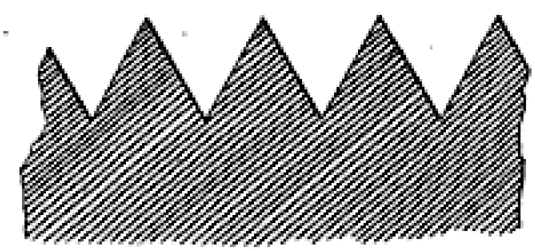
SCREW THREADS AND NUTS.

By WILLIAM SELLERS.

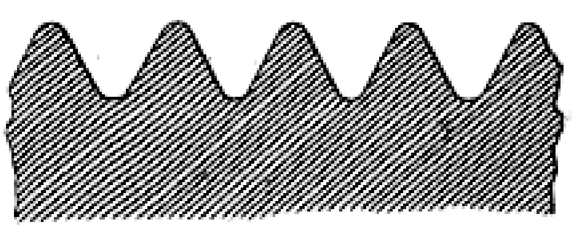
[Read before the Franklin Institute, April 21, 1864.]

The importance of a uniform system of screw threads and nuts is so generally acknowledged by the engineering profession, that it needs no argument to set forth its advantages; and in offering any plan for their acceptance, it remains only to demonstrate its practicability and its superiority over any of the numerous special proportions now used by the different manufacturers. In this country no organized attempt

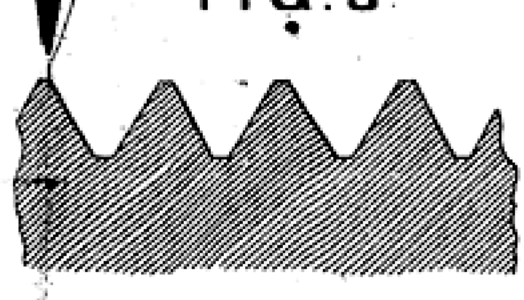
— FIG. 1 —



— FIG. 2 —



— FIG. 3 —



29. The significance of the Seller's screw thread standard is that each of us can go to a hardware store today, purchase nuts and bolts, and put them together. We don't need to take a Fundamentals of Mechanical Engineering Laboratory to put nuts and bolts together. It just works.

30. Nuts and bolts go together w/o requiring further experimentation because they are designed to support reliable physical and functional composition.

31. Do natural genetic parts support reliable physical and functional composition?

32. Can we engineer synthetic genetic parts that more readily support reliable physical and functional composition?

33. How does our M13 work related to making synthetic parts? Well, maybe we can redesign the parts of M13 to make them easier for us to work with them, to enable more reliable physical and functional composition.

34. If time, relate synthetic biology to genetic engineering