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By Alla Katsnelson

Standardize What?

What is a "part," anyway? And how can I compare yours to mine?

The original assembly standard developed by MIT researcher Tom Knight laid the groundwork for the notion of mix-and-match biological parts. But technical protocols for assembling DNA are far from the only element of synthetic biology that needs to be standardized for the idea of parts sharing to take off. Once you make a part, you need to specify its characteristics — how strongly it expresses a particular gene, for example — for others to use it.

So far, such characterization is not a strong suit of the parts in the BioBricks Foundation's Registry of Standard Biological Parts. "If you look through the Registry, you'll find there are lots of parts available," says Jason Kelly, who finished his PhD in Drew Endy's lab at MIT last year and cofounded Ginkgo Bioworks, a synthetic biology services provider. "A smaller fraction, marked with a 'W', are listed as working. And then there's an extremely small fraction that have some information about the characterization of the component in some quantitative way."

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Last summer, Endy, now at Stanford University, published a first for the field in terms of characterization — a "data sheet" similar to those widely used in engineering which quantifies the performance of a BioBrick part that activates a transcription factor in the presence of a cell-cell communication molecule (Nat Biotech, 26:787—93; 2008).

Using the idea of PoPs, or polymerases per second, the data sheet quantifies the part's inputs and outputs. Just as current measures the flow of electricity, PoPs measures the absolute number of polymerases produced upon gene expression. One problem: A researcher can indirectly gauge PoPs by measuring gene expression, but there's no clear way to measure this directly. Another problem: Measuring the performance of the specific BioBrick part Endy chose

was very time-consuming. Still, to create an incentive for such efforts, the journal Synthetic Biology announced it will publish data sheets.

Meanwhile, Kelly is refining a kit he developed that lets researchers measure the relative strength of gene expression promoters under different lab conditions. The idea is simple — by comparing the strength of a promoter of interest to some reference promoter (both measured by the intensity of a GFP signal), you get a ratio that expresses the strength of the promoter in standard units.

There's also the question of computational standards. While the Registry is in one sense a physical repository of DNA, it's also an online catalogue. Many argue that creating a shared computer-based language for exchanging parts is becoming key, especially as DNA sequencing becomes more affordable, and researchers begin to consider sending out their proposed sequences to companies such as GeneArt for assembly rather than going through the messy, old-fashioned molecular biology protocols which most labs now use.

Different computer tools might be good at different things, for example, analyzing circuits, assembling sequences or simply tracking where in the freezer your clones are stored. Mackenzie Cowell, who worked for the Registry after catching the iGEM bug as an undergraduate and left in April 2008 to start up an effort called DIYbio (short for do-it-yourself biology), compares the potential scenario to the plethora of social networking programs like Facebook, Youtube, and Twitter: A single program (called friendfeed) now lets you update just one application, and have that update transmitted to the others as well. For that to happen in synthetic biology, he says, each application would have to share the same definition of a "part."

Last April, at a meeting organized by Herbert Sauro at the University of Washington, Cowell and others came up with the idea of PoBoL, which stands for Provisional BioBricks Language, and provides a computational definition of a part; it's also the Welsh word for "people" — an allusion to its community-defined role. "Basically, it provides a standardized way to explicitly say, 'This is a sequence. This sequence belongs to BioBrick number such and such. This BioBrick was written by so-and-so'," Cowell says. But the fact that PoBoL started outside the iGEM inner circle is raising some hackles in the synthetic biology community.

Randy Rettberg, iGEM's organizer and director of the Registry, says he's working on his own solution, and he's not sure the two systems will be compatible. PoBoL aims to establish the minimum amount of information needed to define a part, but the Registry wants such a definition to include more information -- as much as is available. He worries that if the PoBoL developers get it wrong, it will constrain the way parts are henceforth defined. What's more, he says, the program simply needs more work. PoBoL proponents, however, argue that any compatibility issues between PoBoL and the Registry are fixable. "I think the technical issues are probably fairly minor," says Sauro, adding that the way to solve them is not by boycott. "[The MIT crew] just need to come on board to provide their input, then the community will adjust," he says. "The idea of putting forward a proposed standard is for people to start criticizing it," he adds, but without such engagement, the effort will stall. "We've really got to sit down and thrash things out."