



CAGEN: Critical Assessment of Genetically Engineered Networks

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National Academies Keck Futures Initiative: Synthetic Biology (Nov 2009)

Team 5: Why are human-designed biological circuits and devices fragile and inaccurate relative to their natural counterparts?

- A1: Inherent complexity of biological systems defies reliable engineering
- A2: Engineering needs iteration & debugging; it is too early to compare with nature

Idea #1: Understand sources of fragility and their impact on engineering

- Common features of natural circuits: crosstalk, redundancy, stochastic behavior
- Perhaps engineering approaches (eg, modularity) won't work in biological substrates

Idea #2: Biomolecular “wind tunnel”

- Develop carefully characterized test environment for measuring functionality
- Systematically test design(s) in presence of known perturbations; iterate as needed
- Test in cell. If it works, stop. If not, update environment to add in additional affects that matter; iterate

Idea #3: Synthetic biology competition

- iGEM is focused on innovation, not focused on robustness
- Alternative: make a circuit to given spec and send to organizers for robustness testing
- Tune challenge over the years as designs get better (ala DARPA Grand Challenge)

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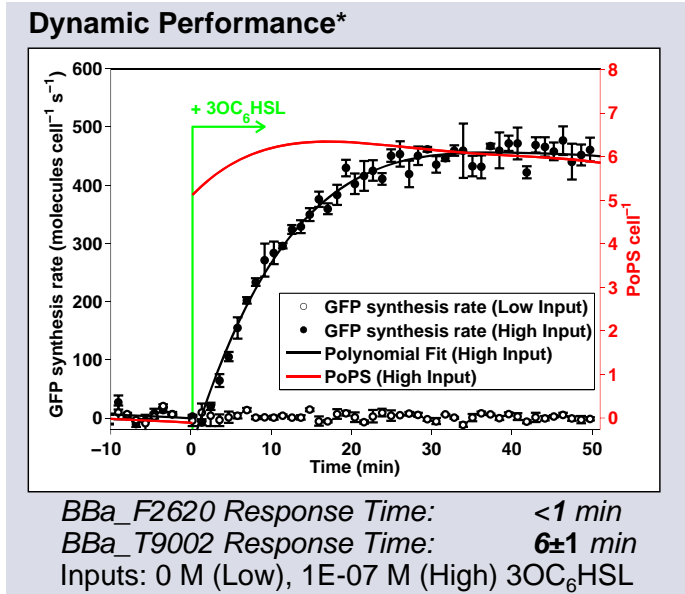
Approach: prototype competition to improve the robustness and performance of human-designed biological circuits and devices operating in cells

- Modeled after CASP (protein structure prediction)
- Specifications to set by steering committee (first slide)
- Metrics to be chosen to select for robust operation across a variety of operating contexts (species, media, temp., etc)
- Competition should be of interest to leading research groups

Timeline

- July 2010: first steering committee meeting; selection of draft competition specifications
- November 2010: refinement of specifications completed; call for participation released
- November 2011: submission deadline and selection of (3-5) finalists for full circuit characterization
- June 2012: Workshop for finalists; competition results announced

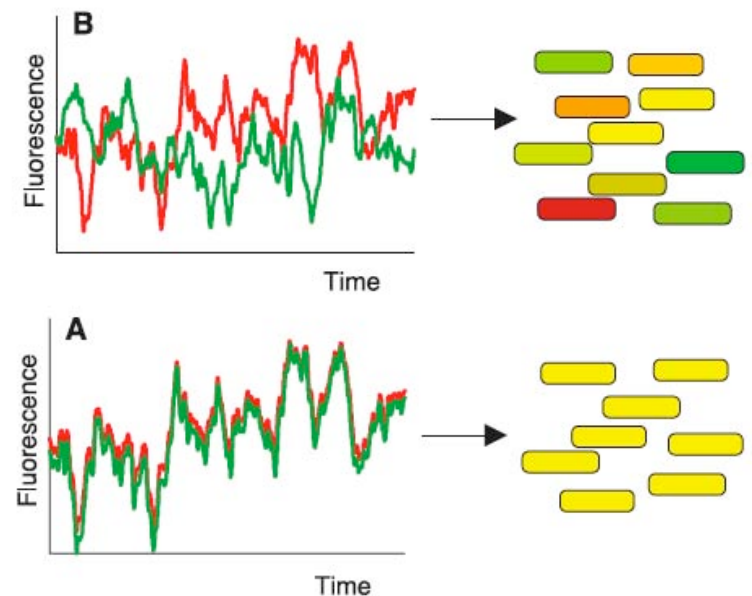
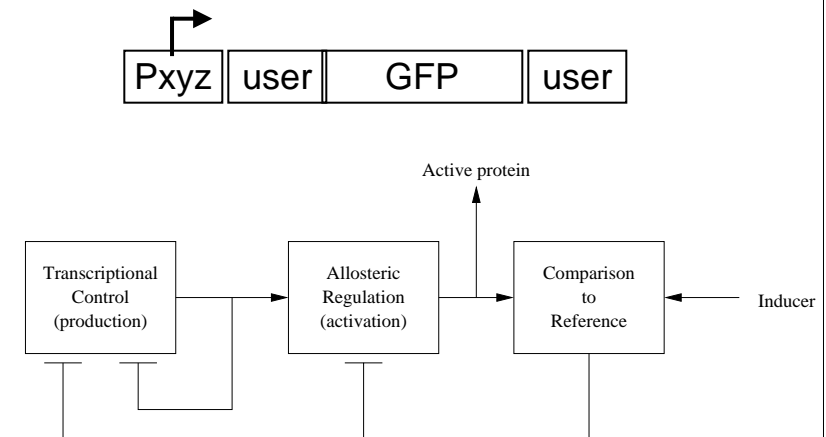
<http://www.openwetware.org/wiki/CAGEN>



Example CAGEN Competition

Design a circuit to accurately track a reference species driven by an inducer

- *Reference*: fluorescent protein under control of inducer (chemical, light, ...)
 - Teams can modify protein to provide sensing domain (fusion protein, 5' UTR, ...)
 - Inducer known ahead of time, but promoter for reference protein is unknown
- *Output*: second fluorescent protein, whose concentration tracks reference (single cell)
 - Best circuits will maintain a constant “color” (minimize effects of intrinsic noise)
- *Score*: integral square error between reference and outputs, averaged then summed
 - For a given condition, take the average L2 error, then sum across conditions
 - Lowest score wins



Summary and Topics for Discussion

CAGEN: Critical Assessment of Genetically Engineered Networks

- Promote methods to design and implement circuits that are as robust and accurate (?) as biological circuits
- Hope to choose a competition that leading groups and organizations participate in
 - What are the features that would make *you* want/not want to participate?
 - What “return on investment” is required (bragging rights, analysis data, cash)?
- What is the best way to submit the design: sequence-only? plasmid?

BIOFAB: what capabilities would be helpful to CAGEN?

- Ability to characterize a circuit’s performance across multiple operating conditions
- Well characterized parts, processes, measurement techniques that teams can use
- Reference designs that teams can use as a starting point (?)

More information:

- Competition web page: <http://www.openwetware.org/wiki/CAGEN>
- Mailing list coming soon: cagen-announce
- Steering committee: [Adam Arkin \(LBL/Berkeley\)](#), Barry Canton (Ginko Bioworks), [Peter Carr \(MIT\)](#), Jim Collins (BU), [Drew Endy \(Stanford\)](#), [Eric Klavins \(U. Wash\)](#), [Richard Murray \(Caltech\)](#), Maria Pellegrini (Keck), Georg Seelig (U. Wash), Pam Silver (Harvard), David Sprinzak (Caltech/Tel-Aviv U)