# Contextualizing context for synthetic biology – identifying causes of failure of synthetic biological systems

Stefano Cardinale and Adam Paul Arkin
Biotechnology Journal (2012) 7(7):856-66.

Presented by Ryan

17 April 2013

20.385

# Genetic programs constructed from layered logic gates in single cells

Moon Ts, Lou C, Tamsir A, Stanton BC, Voigt CA.

| Source | Transcription Factor | Chaperone | Promoter |
| --- | --- | --- | --- |
| Salmonella | InvF (100%) | SicA (100%) | P(sicA) |
| Shigella | MxiE (27%) | IpgC (54%) | P(ipaH) |
| ~~Yersinia~~ | ~~YsaE (15%)~~ | ~~SycB (50%)~~ | ~~P(syc)~~ |
| Pseudomonas | ExsA (10%) | ExsC (13%) | P(exsC) |

"Yesinia parts were non-functional and were not pursued further."

Paula and Natalie, 02/20/13

# Learning from Failures

- Goal: to make synthetic biology efficient, safe, understandable and predictable

- Problem: divergence between design and actual function of synthetic system

- What can we learn from our mistakes?

- "A much cited barrier to predictability in design is context."

# Context

- The environment in which a system finds itself

    – Compositional Context

    – Host Context

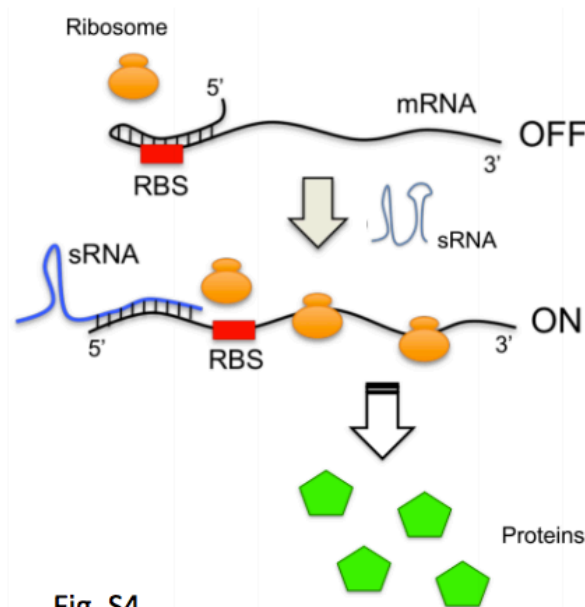    – Environmental Context

CONTEXT

DESIGN　　　　　　*IN VIVO*

# Compositional Context

- Functional composition of devices leading to unexpected circuit failure

- Approximate knowledge of RNA folding and *cis/trans* regulation



**De novo automated design of small RNA circuits for engineering synthetic riboregulation in living cells.**
Rodrigo et al. A. *PNAS* (2012) 109(38):15271-6.

Fig. S4

# Host Context

- Reliance on limited host resources can impact host homeostasis
  - Nucleotides, tRNAs, polymerases and ribosomes
- Devices are subjected to growth, replication and partitioning
- Non-specific binding and crosstalk
  - Positive vs. negative selection in evolution -> orthogonality

# Host Context

- Strain specific results
  - Issues between circuit and host genetic background

# Environmental Context

- Can directly affect physical chemical properties of biological parts and thus their function
  - Temperature, especially for RNA parts, can affect predictable functioning
  - pH, tune population density by changing pH to affect quorum-sensing signal acyl homoserine lactone
- Host-mediated cross-feeding and cross-protection
- Availability of external nutrients

# Relation to 20.020 Projects

- Host chassis choices
- Ocean environment – changes in temperature and pressure
- Implementation of multiple devices in a host
- Chauffeur – pH of stomach

# Discussion

Strengths and Limitations

- Clear review of failures in synthetic biology

- Broad range of context effects covered

- Current lack of knowledge to predict unwanted intra- or intermolecular interactions

Summary and Relation to Today's Topic

- Learn from failures to make designing successes easier

- Kristine's paper: creating an *E. coli* platform to make designing and debugging easier

# Questions

- What kind of compositional, host, or environmental context effects might arise in your 20.020 group project?

- How does knowing about these context effects change how you go about planning your projects (not specifically this class!)?

# Context



A – compositional

B – host

C – environmental