Classical Systems Biology

MCSB Bootcamp — Mathematical and Computational Track

Jun Allard

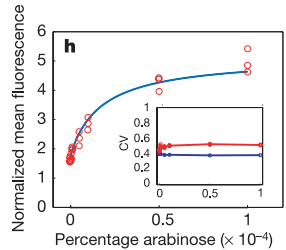
Early synthetic biology I

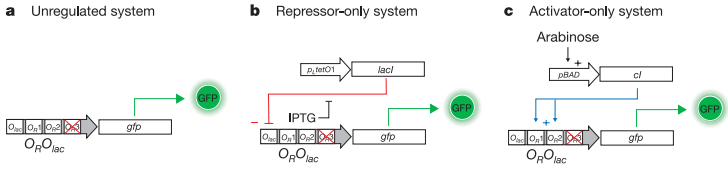
nature Vol 439|16 February 2006|doi:10.1038/nature04473

LETTERS

A bottom-up approach to gene regulation

Nicholas J. Guido[1]*, Xiao Wang[2]*, David Adalsteinsson[3], David McMillen[5], Jeff Hasty[6], Charles R. Cantor[1], Timothy C. Elston[4] & J. J. Collins[1]



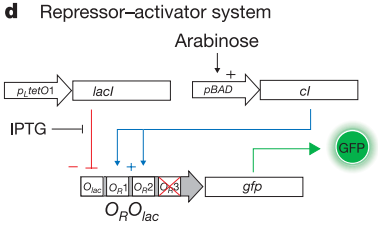


Early synthetic biology II

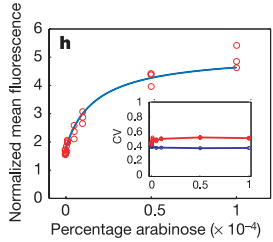
> *"The understanding of networks and pathways is really in its infancy and will be a challenge for decades," says James J. Collins, a biomedical engineer at Boston University. That hasn't stopped synthetic biologists from dreaming. "Grow a house" is on the to-do list of the M.I.T. Synthetic Biology Working Group...*

2007, MIT Synthetic Biology Working Group

What happens when you add positive feedback? I

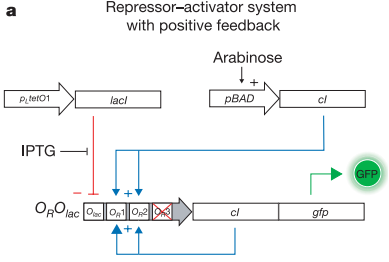


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What happens when you add positive feedback? II

"Computation drove the field of synthetic biology in its very early days."

Collins, 2020

"We didn't have those data sets. We didn't have a wet lab. We didn't have the capability. We had to rely on mathematical modeling."

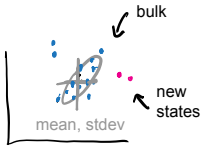
paraphrasing Collins, 2015

Complex systems and “systems thinking”

The goals, challenges, tools and approaches of today

Data and analytics

Keystone **goal**: discover the hidden — new states, cell types, disease classes, ...



Keystone **challenge**: biological data is not just big, it is **high-dimensional**.

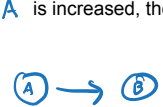
- 30000 genes, 1000 cells
- 10^4 microbial species, 20 patients



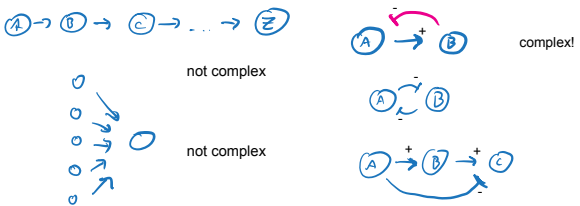
Keystone **tool**: clustering, regression, dimension-reduction ... coding.

Models and mechanism

Keystone **goal**: **prediction** — "what would happen if..."



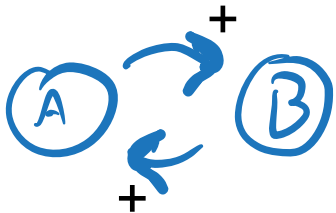
Keystone **challenge**: biological systems are **complex**, not just big.



Keystone **tool**: dynamical systems, control theory, (the differential equation,) ...

Most things in biology have feedback

stress

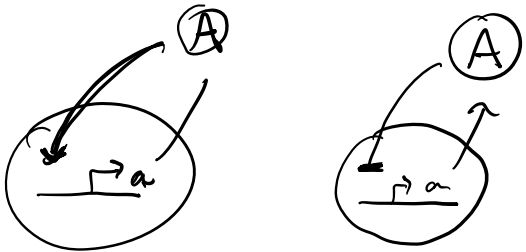


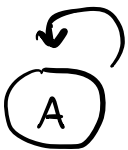
breathing rate

Complex biological systems and "systems thinking"

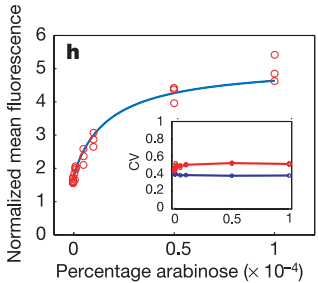
Activation

Repression





Positive feedback



With positive feedback, the curve showing steady-state protein as a function of activator TF should move up.

Does the curve move up by:

- shifting the EC50 to the left?
- moving up at high-C?
- moving up at low-C?
- a combination of all three?

Seven circuits

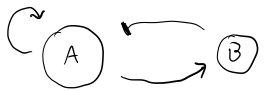


Activation

Repression

Positive feedback

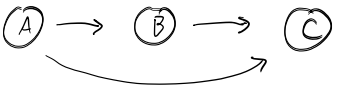
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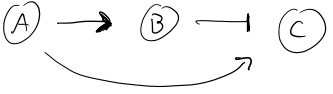
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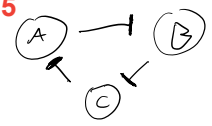
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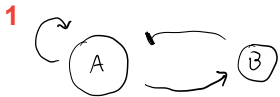
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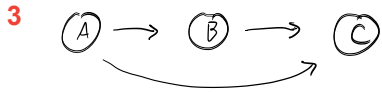
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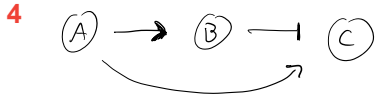


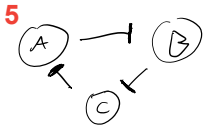
In-class activity: matching















Match each circuit to its name.

- Direct negative feedback
- Indirect negative feedback
- Double-negative feedback
- Fast positive and slow negative feedback
- Incoherent feedforward
- Coherent feedforward
- The Repressilator