Growth modulation turns a non-cooperative positive feedback bistable

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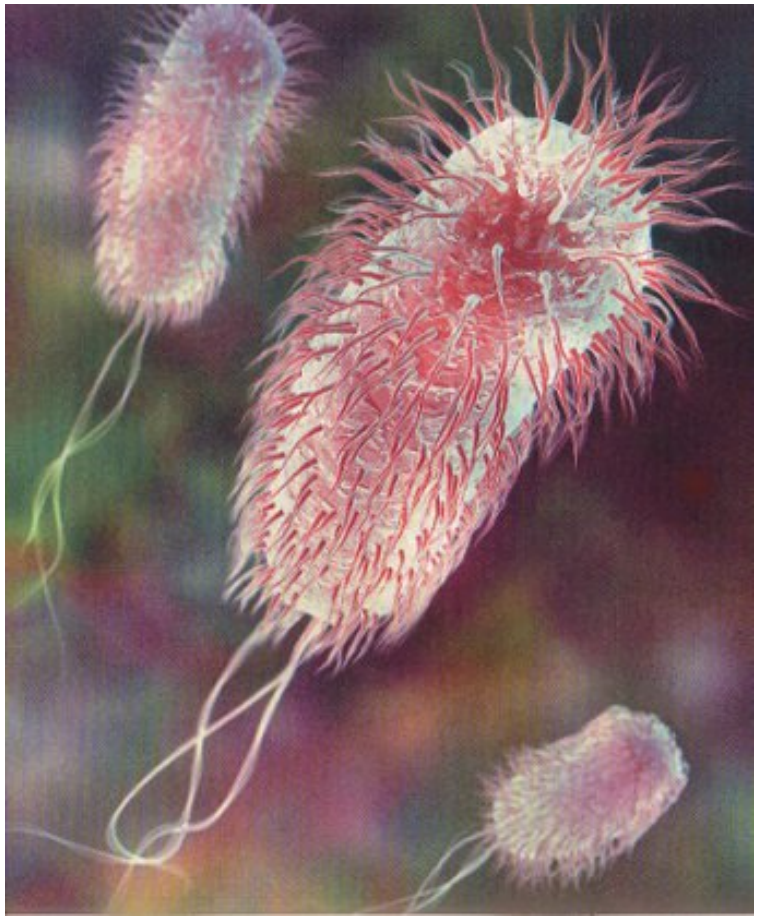
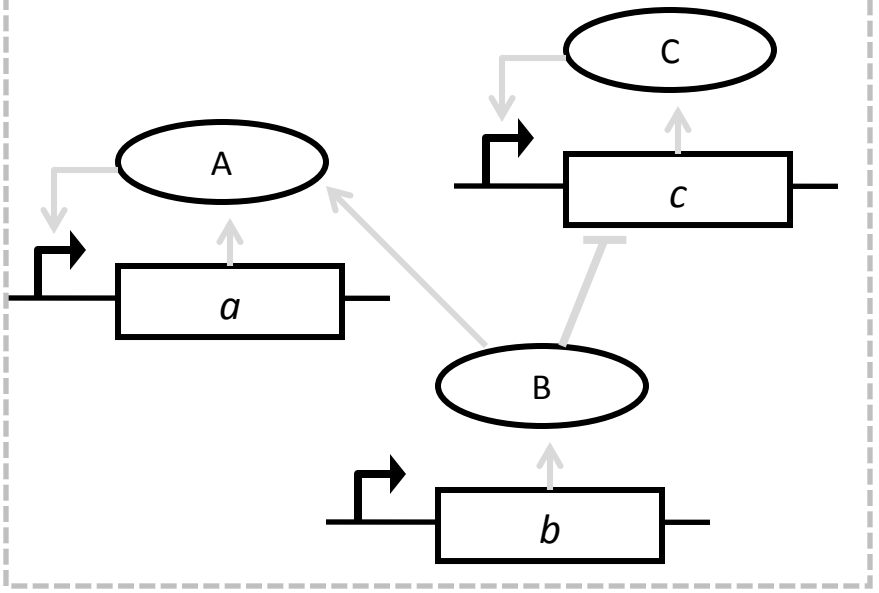
A bioengineer's goal/dream: Modularity

Escherichia coli

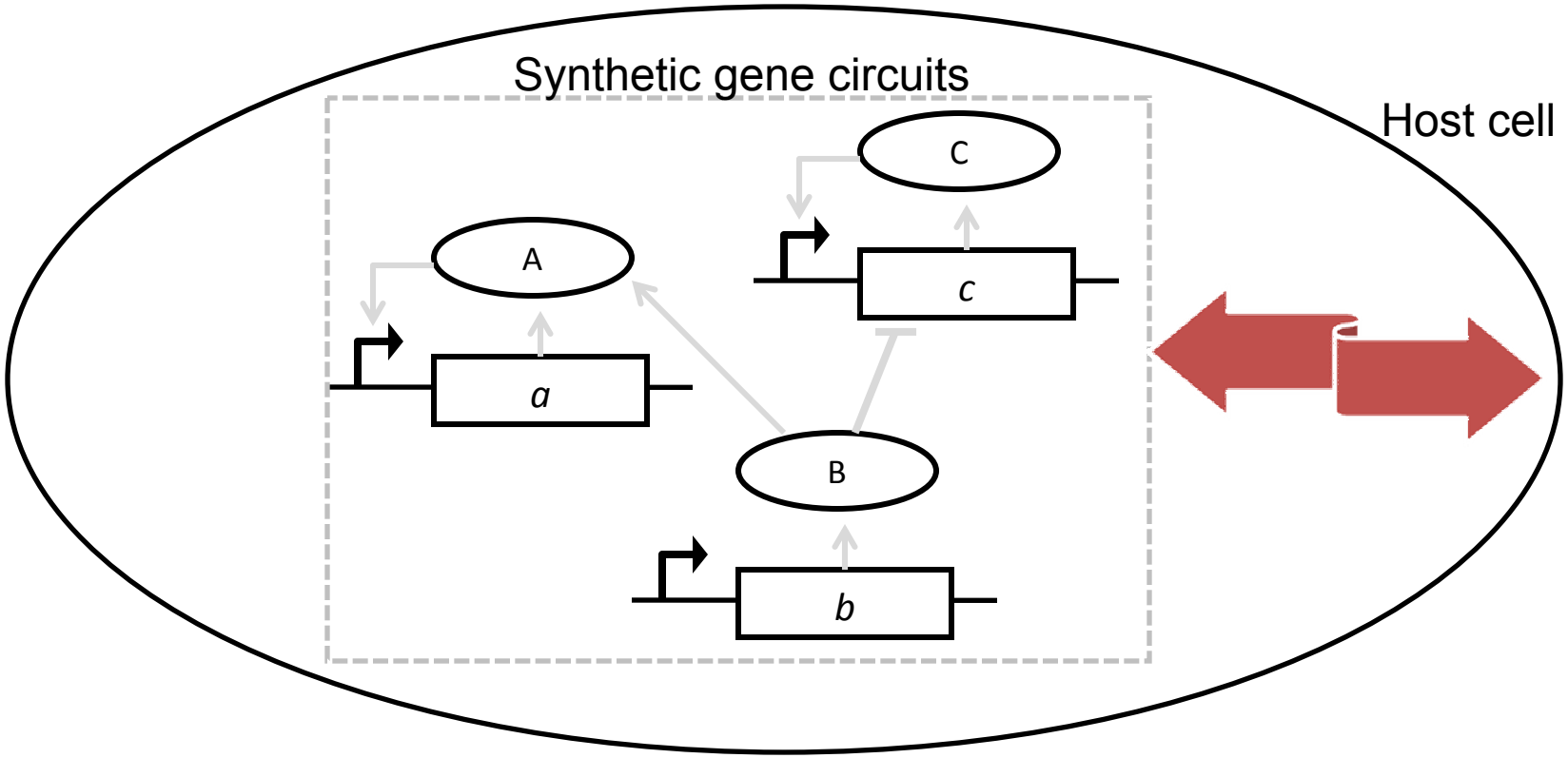


Synthetic gene circuits



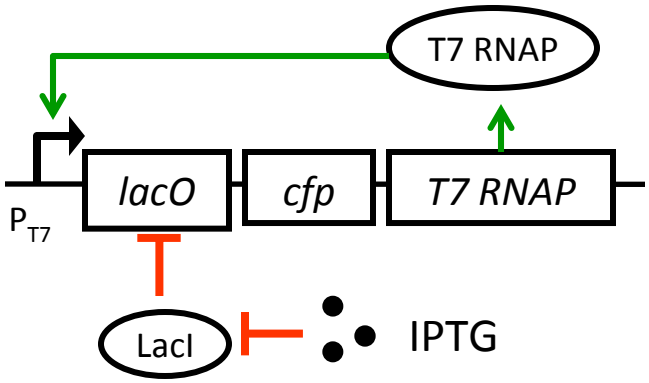
Perfectly modular?

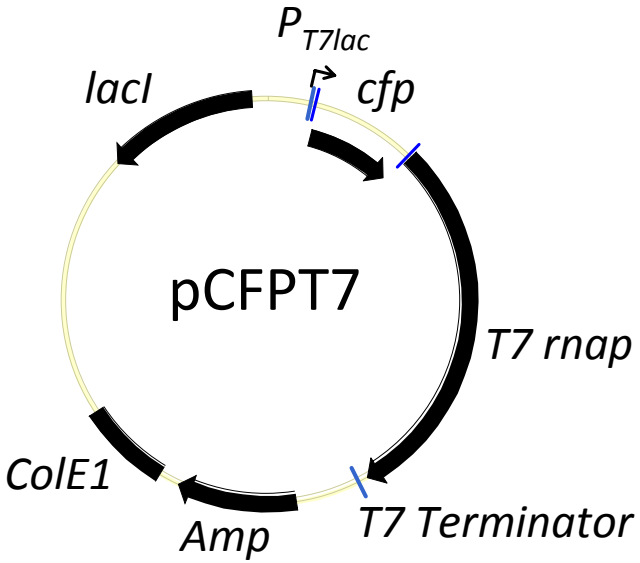
Emergent properties may arise due to circuit-host interaction



Can interaction between a synthetic gene circuit and cell physiology causes qualitative changes in the circuit behavior?

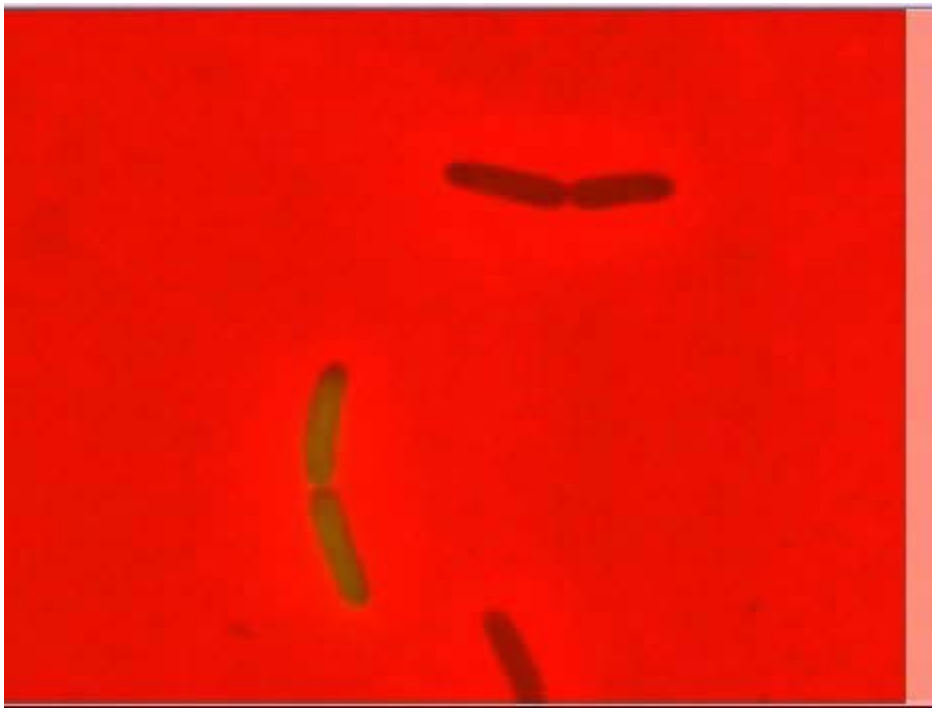
We started with a “simple” circuit

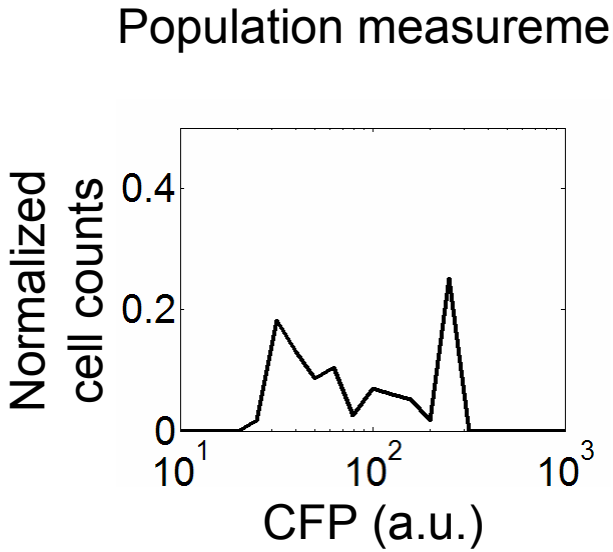




A minimal positive feedback without cooperativity

The circuit give rise to a bimodal population

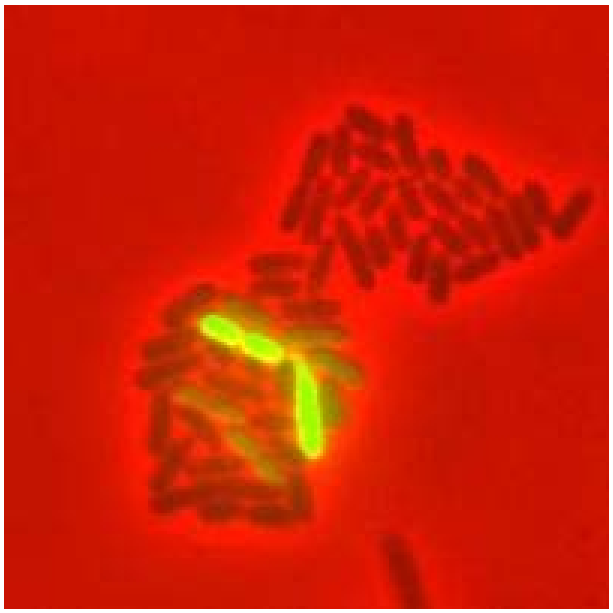




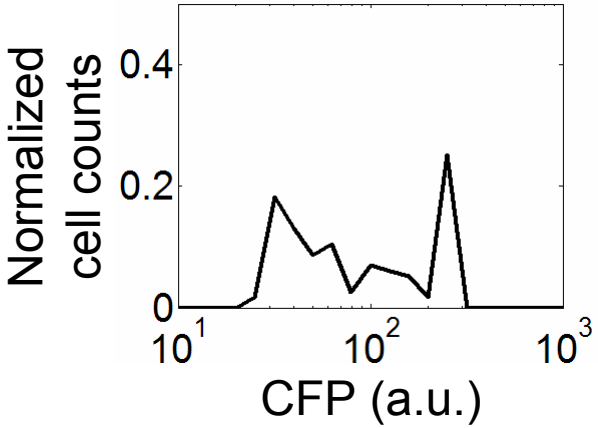
OFF cells : Cells with no CFP
ON cells : Cells with CFP

Bimodal CFP distribution

Single cell experiments

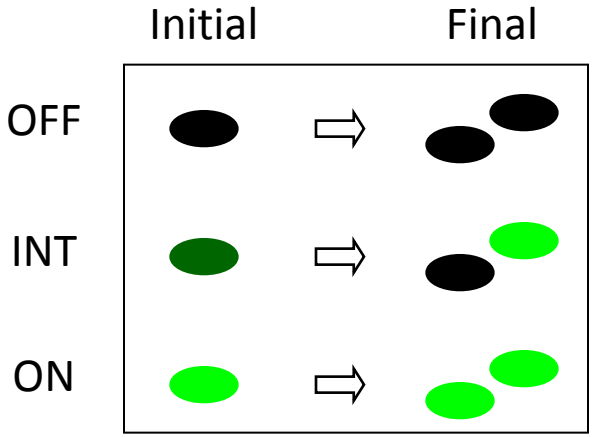


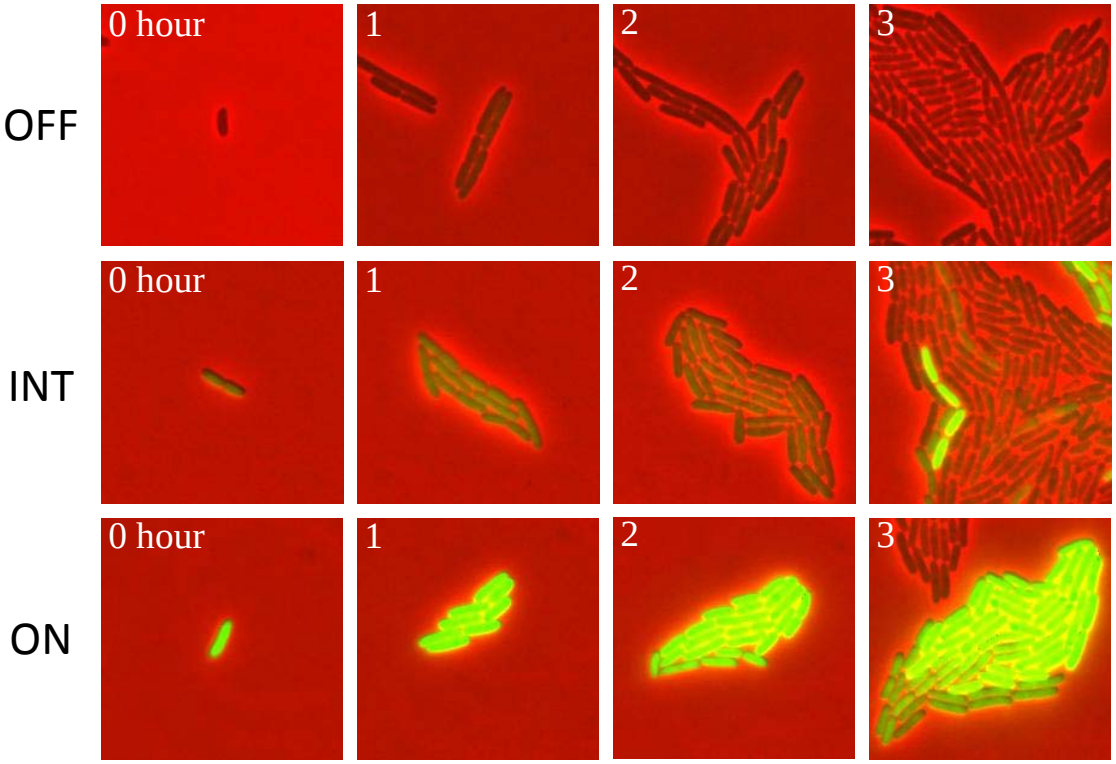
Population measurements



OFF cells : Cells with no CFP
ON cells : Cells with CFP

The circuit exhibits hysteresis

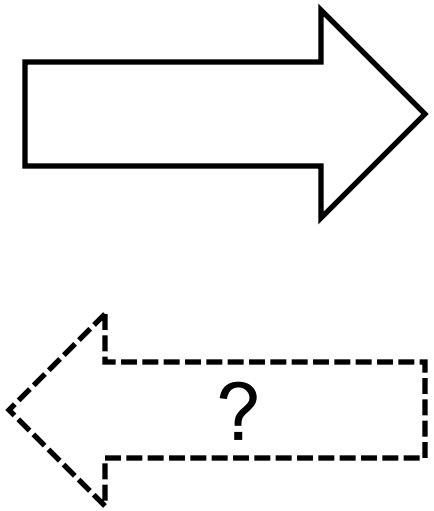




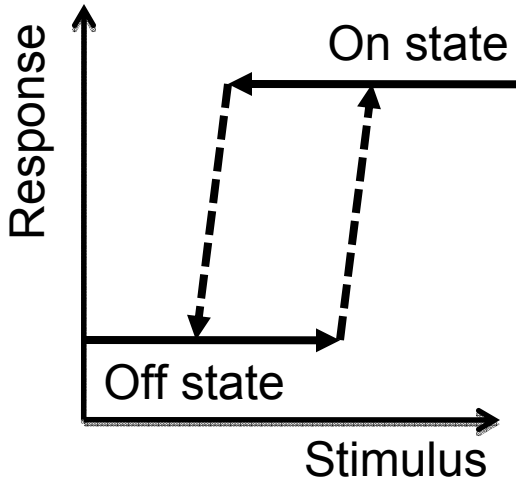
Single cell measurements show history dependant behavior (hysteresis).

Are the observations caused by a bistable switch?

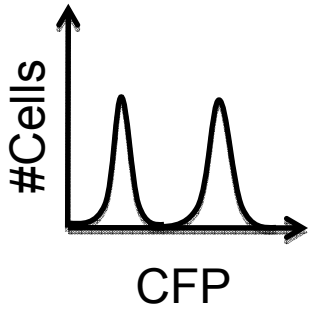
Bistable Switch



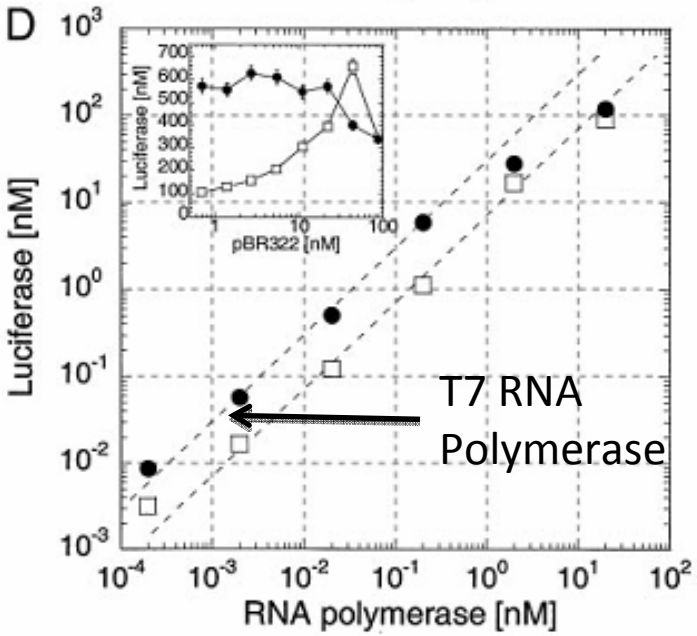
Hysteresis



Bimodality



There is a problem: We did not expect a bistable switch

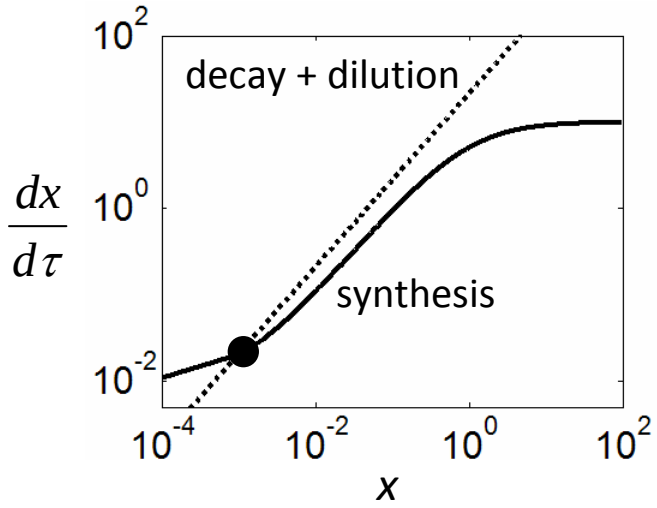


Noireaux, PNAS 2003

$$\frac{dx}{d\tau} = \frac{\delta + \alpha x}{1 + x} - (\varphi + 1)x$$

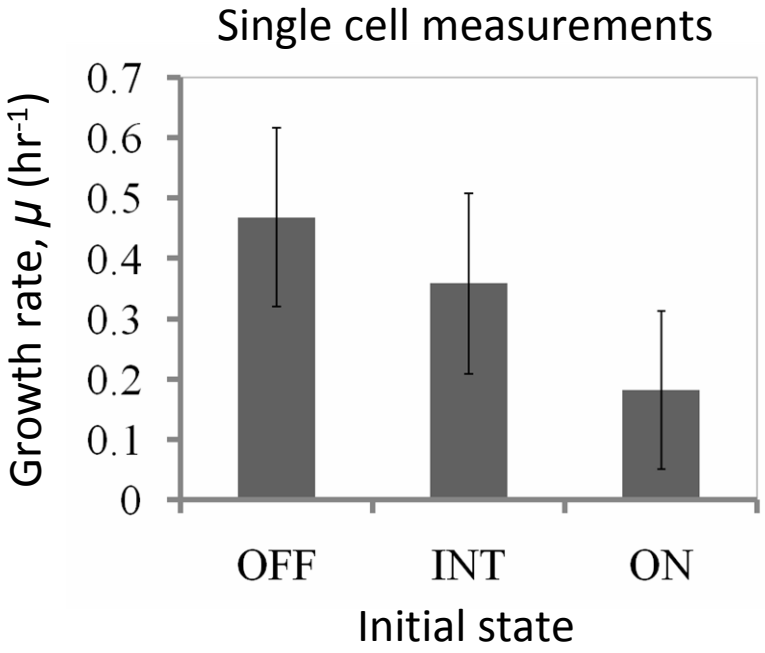
Synthesis

Decay + dilution



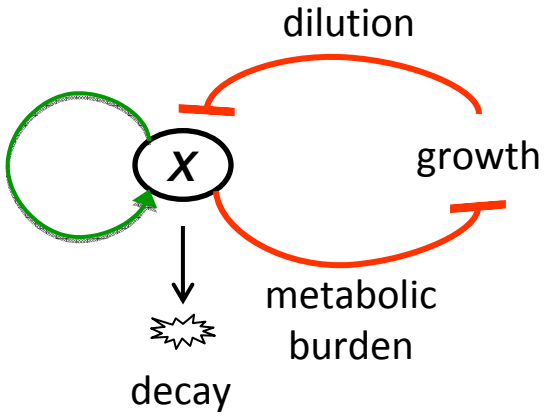
The circuit alone can not generate bistability.

T7 RNAP expression reduces cell division rates



Can this circuit-host interaction lead to bistability?

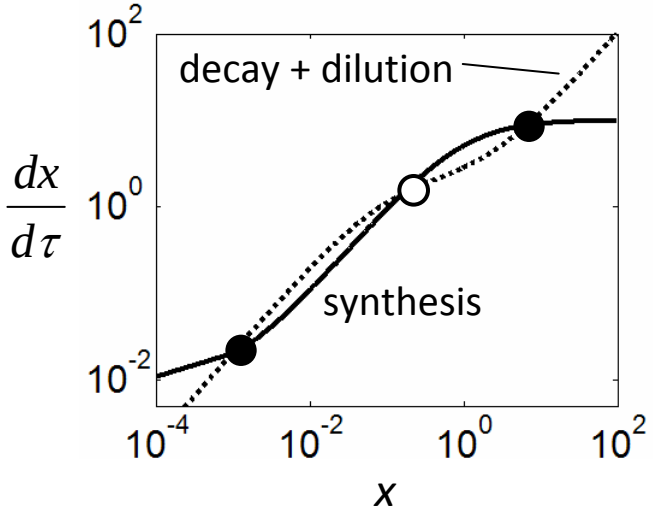
Bistability is due to circuit-host interaction



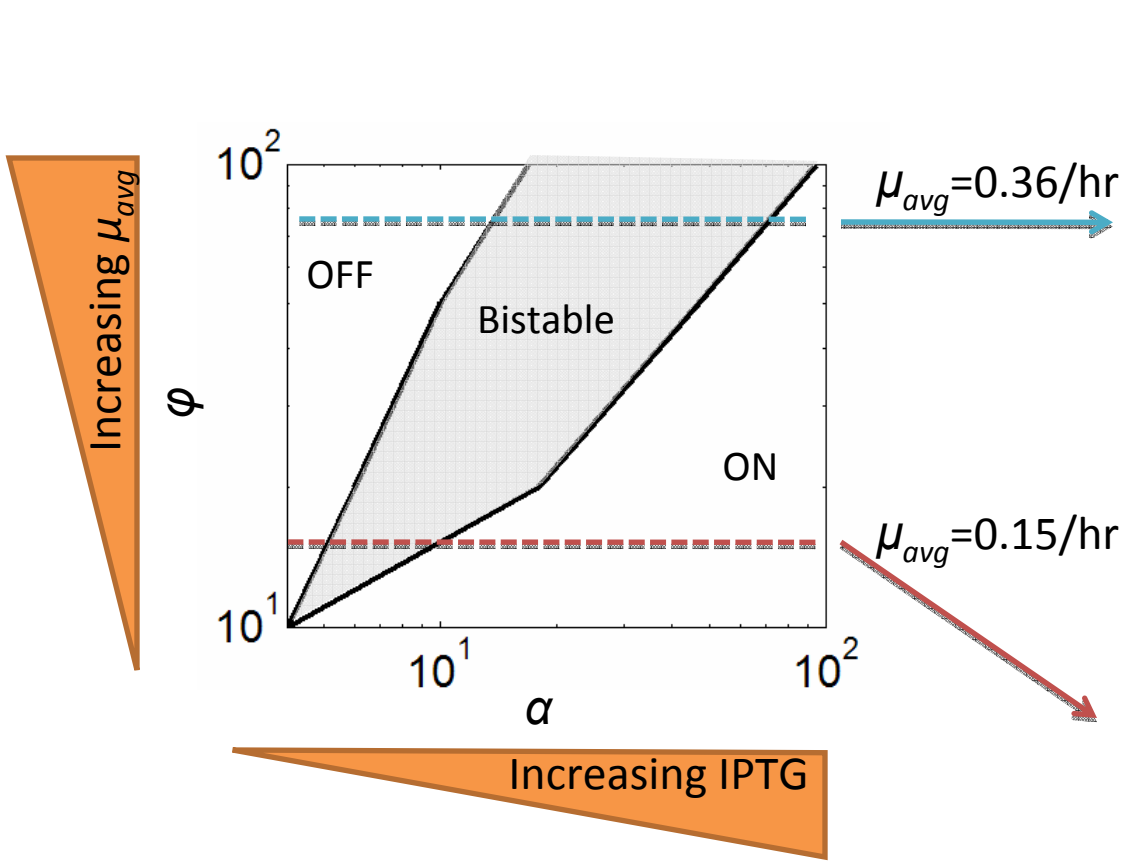
$$\frac{dx}{d\tau} = \boxed{\frac{\delta + \alpha x}{1+x}} - \boxed{\frac{\varphi x}{1+\gamma x} - x}$$

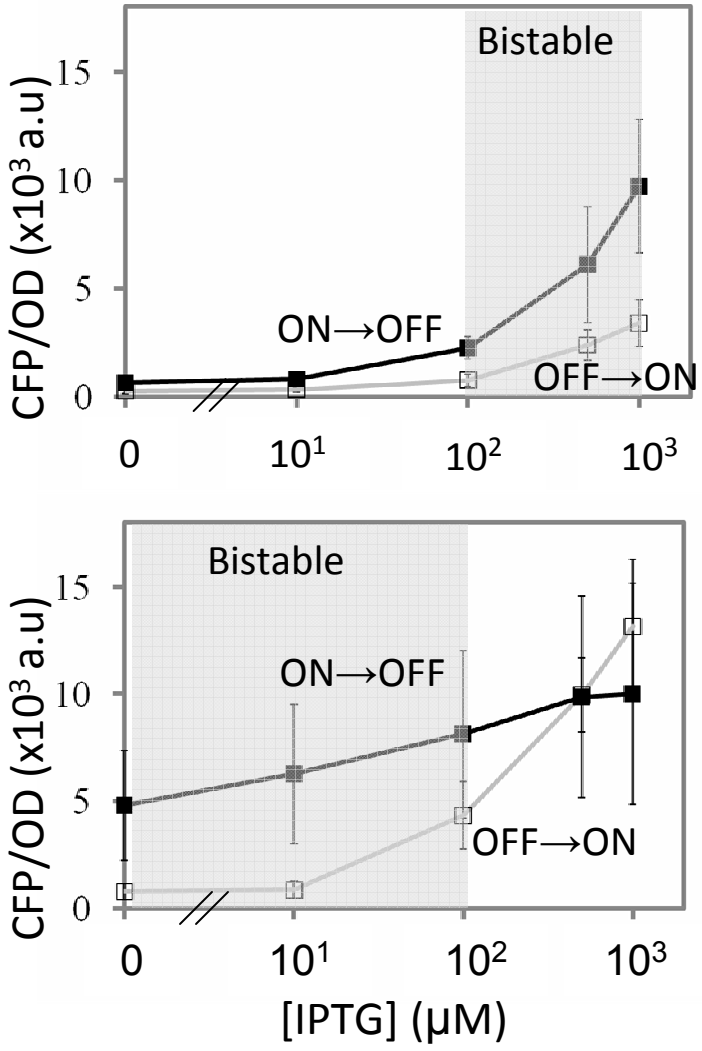
Synthesis

Decay + dilution



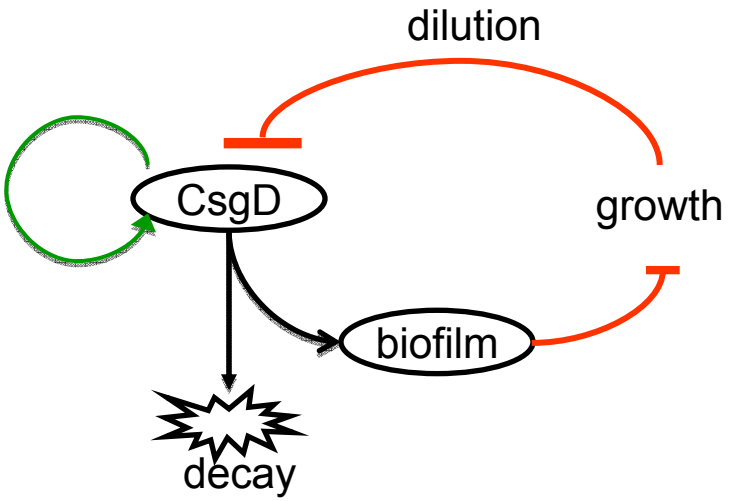
Bistable region can be shifted





Conclusions

- Natural biological systems might use similar design.



Conclusions

- The growth modulation might have contributed to bistability of natural or synthetic switches previously characterized.
- A significant challenge to synthetic biology. Host-circuit interactions can lead to complex circuit dynamics.

Acknowledgments

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