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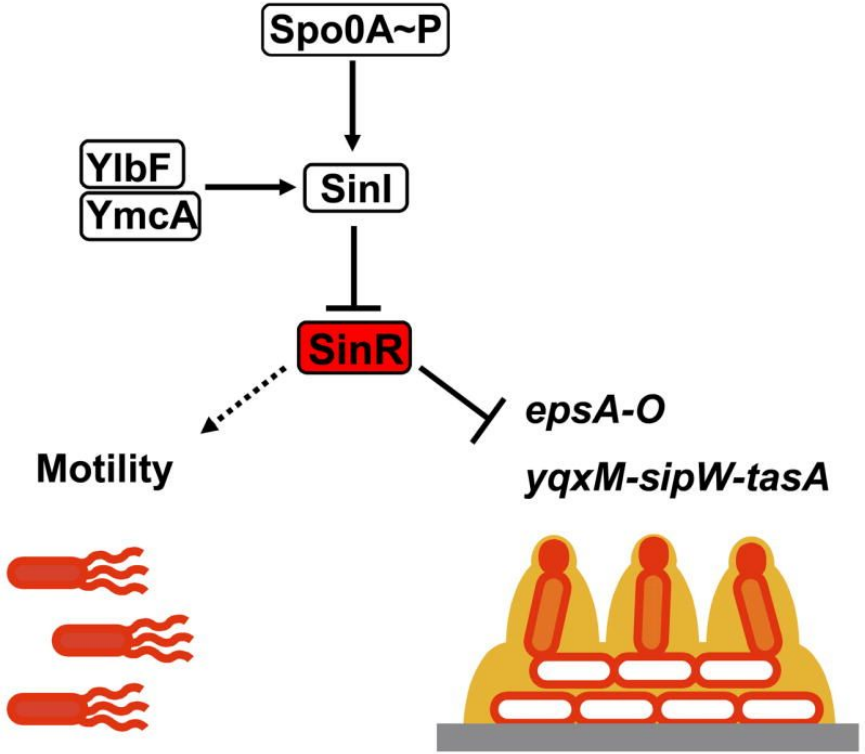
# Stochastic Antagonism between two proteins governs a bacterial cell fate switch (Lord et al. 2019, Science)

Flavio Rump, Computational Biology and Bioinformatics Seminar, 07.05.2020

# Background

# Bacillus Subtilis can be both sessile-multicellular or motile-unicellular



# Why do cells switch fates randomly?

Sensing the environment comes at a cost (building and maintaining sensory machinery), and isn't that beneficial when

- environment generally changes slowly
- cells can not respond in time with sudden change

Enter Stochastics

- Bet Hedging
- Catastrophe prevention
- Altruism

**Requirement for cell fate switches**

Cell fate decision circuits must be variable so that cells can adopt a multitude of fates. Yet also these states must be distinct, stable and coordinated with neighboring cells.

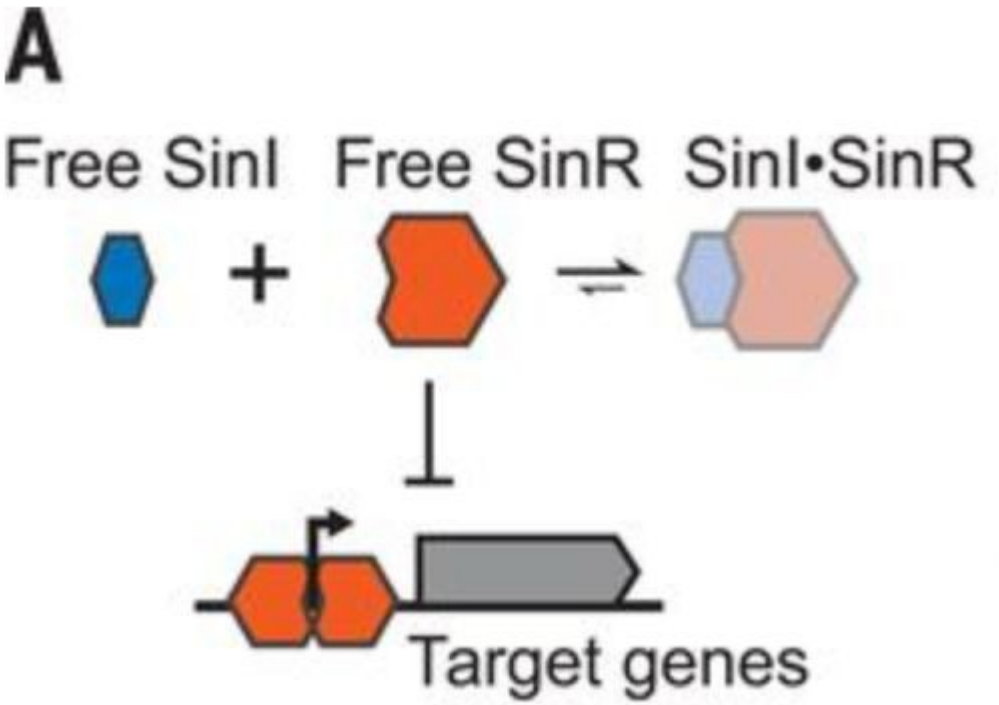
**How is this cell fate switch achieved?**

Established view is that only regulatory networks with (complex) self stabilizing feedback loops can achieve stability.

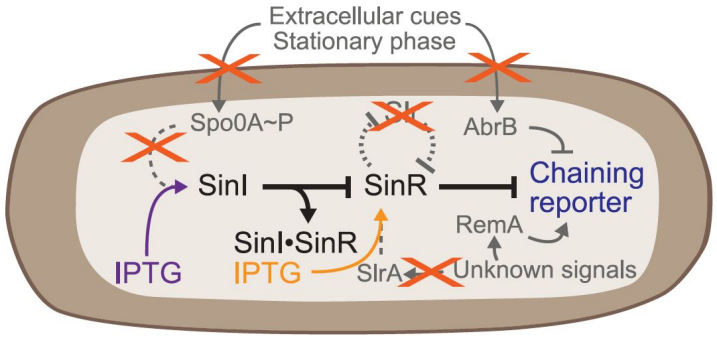
However, the authors here find something different...

# How Bacillus Subtilis stochastically determines cell fate

# SinI binds SinR to derepress target genes



# Reduced *Bacillus subtilis* circuit



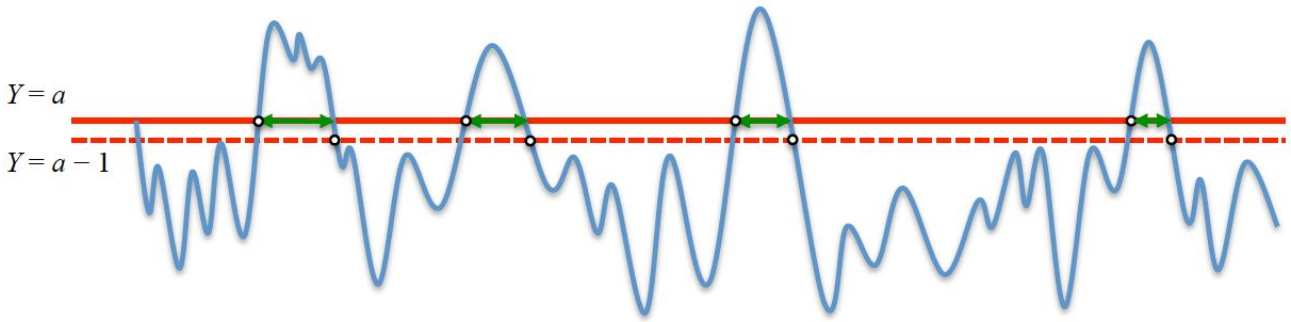
# **MODEL** Memoryless motile state, calibrated sessile state

Let X denote $[SinR]_{free}$, Y denote $[SinI]_{free}$.

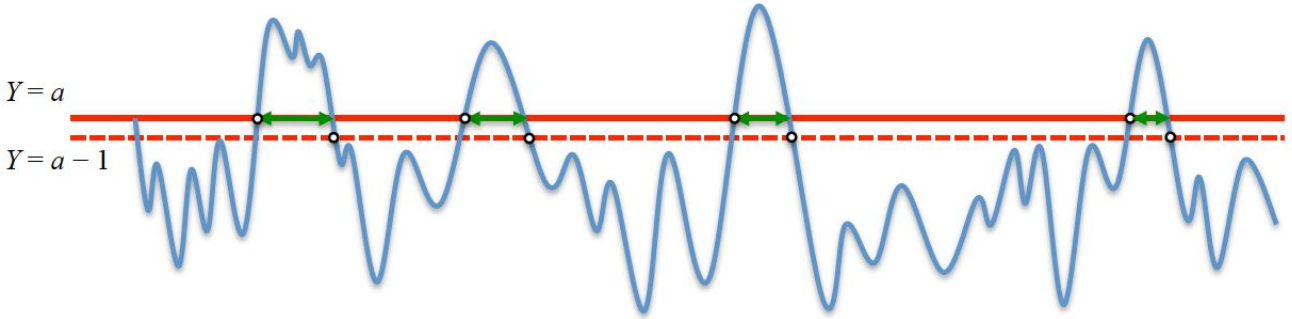
$$X \xrightarrow{\lambda_X} X+1 \qquad Y \xrightarrow{\lambda_Y} Y+b$$

$$X \xrightarrow{X/\tau_X} X-1 \qquad Y \xrightarrow{Y/\tau_Y} Y-1$$

$$(X,Y) \xrightarrow{cXY} (X-1,Y-1)$$




x-axis: generations, y-axis: concentration of SinI




## How long are the SinI dominant peaks (green arrows)?

## Assumptions of the simplistic model

Free species degrade and dilute at the same rate ($\tau_x$=$\tau_y$)

Species that form complex SinI:SinR happens instantaneously (c is very large)

$$X \xrightarrow{\lambda_X} X+1 \qquad Y \xrightarrow{\lambda_Y} Y+b$$

$$X \xrightarrow{X/\tau_X} X-1 \qquad Y \xrightarrow{Y/\tau_Y} Y-1$$

$$(X,Y) \xrightarrow{cXY} (X-1,Y-1)$$

## Approach

1. Derive Chemical Master Equation PDE:
2. Derive Probability to stay in state y>=a
3. Derive expected time of peak

$$\partial_t P(y,t|y_0)$$

$$G(y_0,t) \equiv \sum_{y=a}^{\infty} P(y,t|y_0,0) = \text{Prob}\{T_{y_0 \to a-1} \geq t\}$$

$$\langle T_{1\to 0} \rangle =$$

# Key results of the model

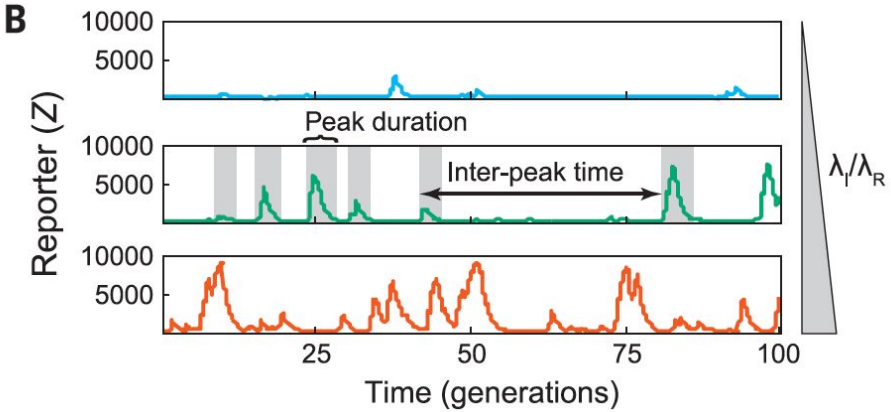
$$\mathrm{CV} = \frac{\sqrt{\mathrm{Var}[T_{1\to 0}]}}{\langle T_{1\to 0}\rangle} = \frac{\sqrt{\langle T_{1\to 0}^2\rangle - \langle T_{1\to 0}\rangle^2}}{\langle T_{1\to 0}\rangle} > \frac{\sqrt{2\langle T_{1\to 0}\rangle^2 - \langle T_{1\to 0}\rangle^2}}{\langle T_{1\to 0}\rangle} = 1$$

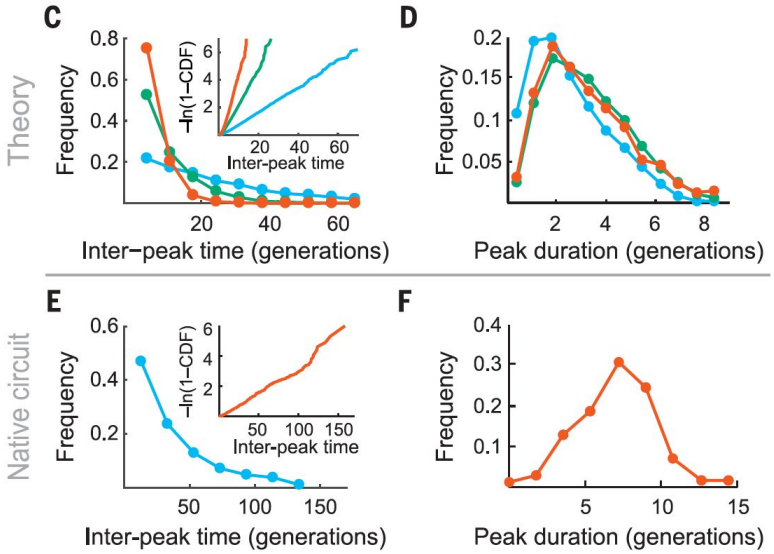
$$\langle T_{a\to a-1}\rangle = \frac{1}{a + \lambda_X - \lambda_Y}$$

With bursting, we can then achieve longer peaks of dominance (since we now burst above *a* number of *y* molecules..)

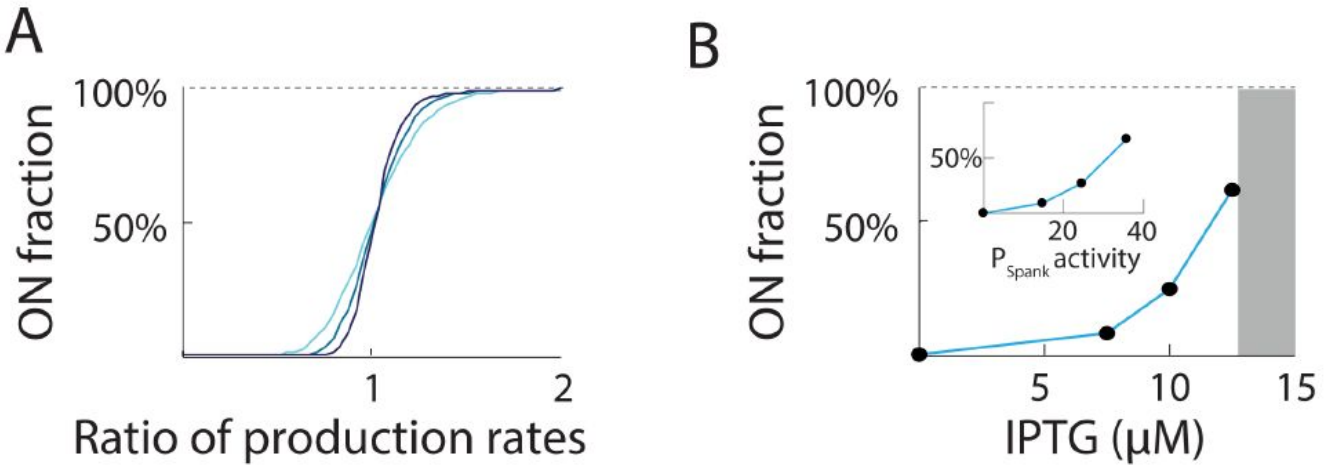
# Minimal model with target genes either on or off

Simplistic Model where the target genes are either expressed or not
Expression depends on the difference in concentrations (i.e. the difference between two random variables)
**ON = max([SinR]-[SinI],0)**



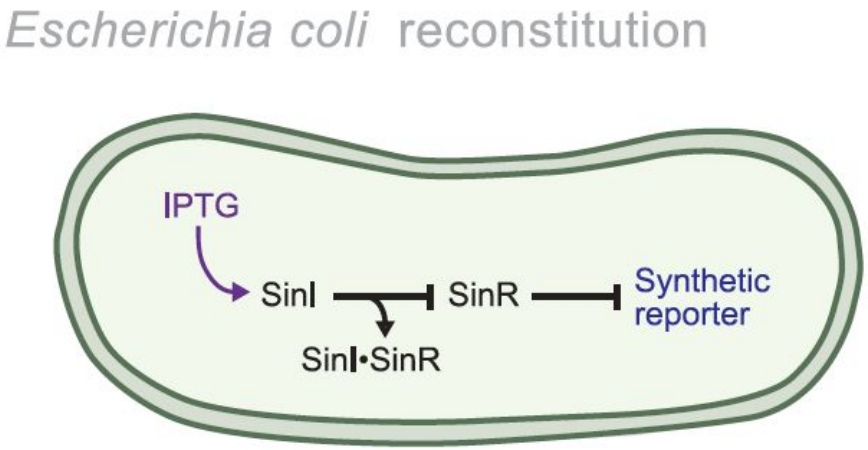



# Model predicts and experiments confirm ultrasensitivity



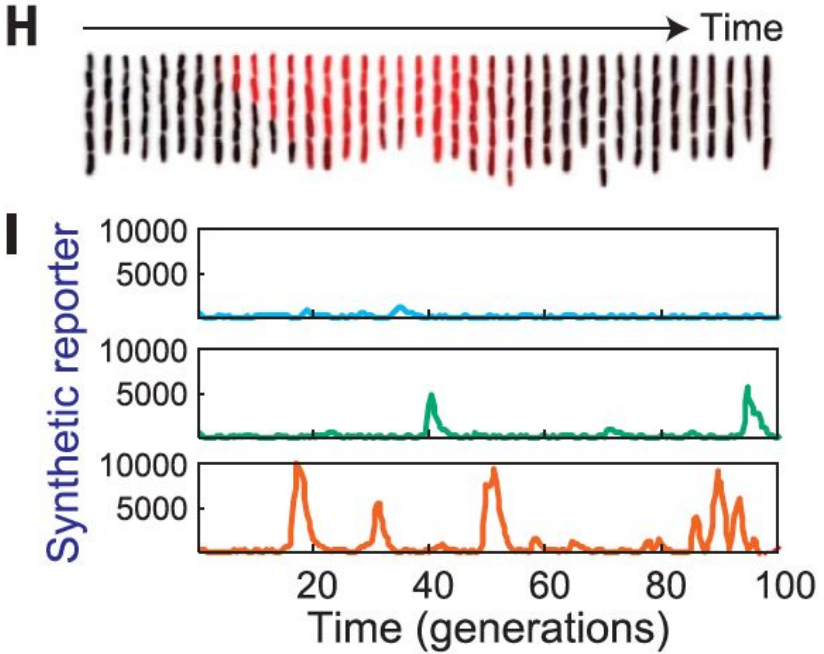
# How do we know SinI and SinR aren't just tracking another mechanism that is actually responsible for the cell fate switch?

Idea: Synthetic circuit with only SinI and SinR!

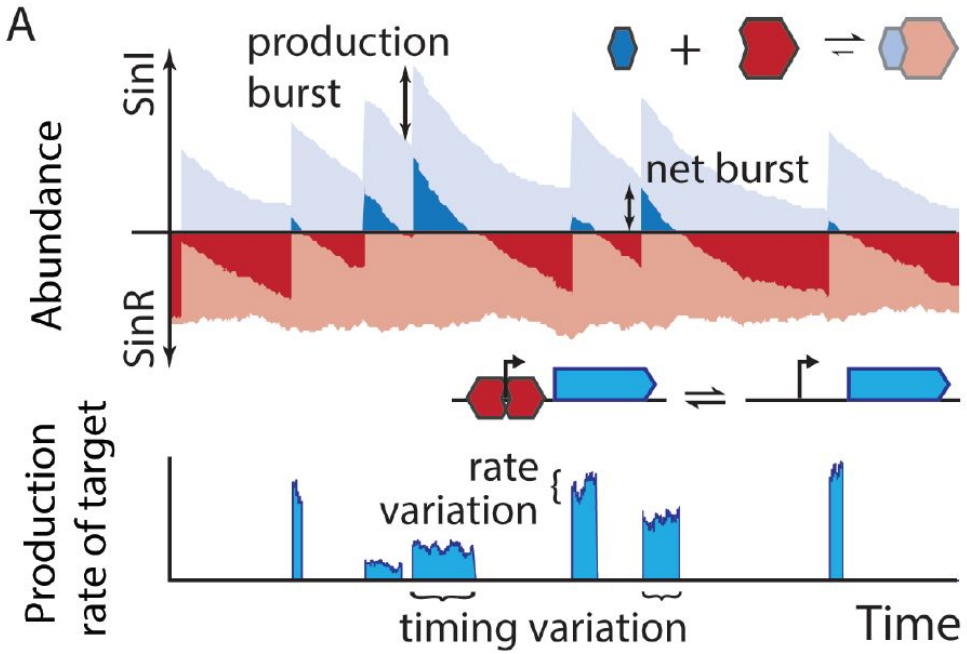


# Experiment: Synthetic cells behave exactly the same

Experimental data with synthetic circuit confirms the predicted behavior

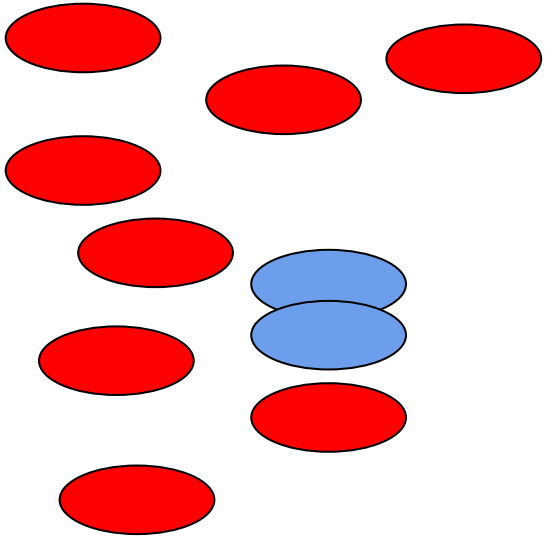


# Bringing it all together

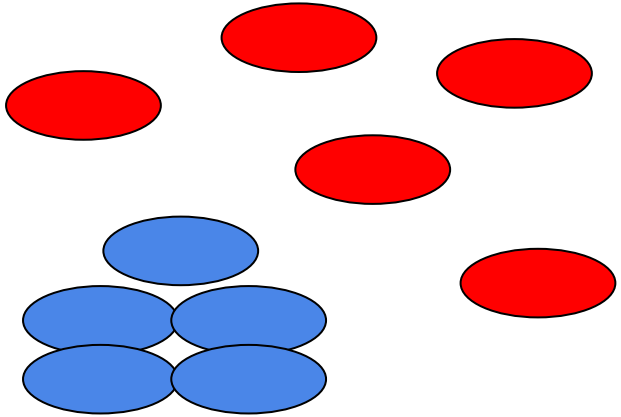


# Switch helps colonies manage risk by turning signal strength into cell fate on population level(!)

low Spo0A / weak bursts of SinI



high Spo0A / strong bursts of SinI



# Summary

- Cell fate switch in Bacillus S. depends only on stochastics of protein production
- Bursts of SinI lead to multigenerational pulses of sessile-multicellular state
- Mutual antagonism of Slr and SinR key mechanism to prolong the pulse, but Slr not needed for the inital cell fate switch
- **Key:** Bacillus S. can convert a signal into cell fates in an adaptive manner on a population scale: **fate distribution of cells correlates with signal strength!**

# More generally

- stochastic competition is commonplace is cells and could explain cell fate decisions in other organisms (and may have been hiding because not as visible as positive feedback loops)

- knockout experiments can give function, but not role in control. See how cells can still maintain fate switch without Slr, by increasing SinI production.

# My thoughts about the paper

**Pros:**

Very solid mathematical underpinning

Simple, well designed experiments to prove points in a powerful way

Reduction to a simple model which explains most of the behavior

**Cons**

lacked introduction as to why B. Subtilis would do this

lacked context around how this fits with known signalling pathways, morphological/coordination behavior of the cells

# Appendix

# How can cells stay in the pulse for longer?