Mechanism and function of stochastic pulse regulation

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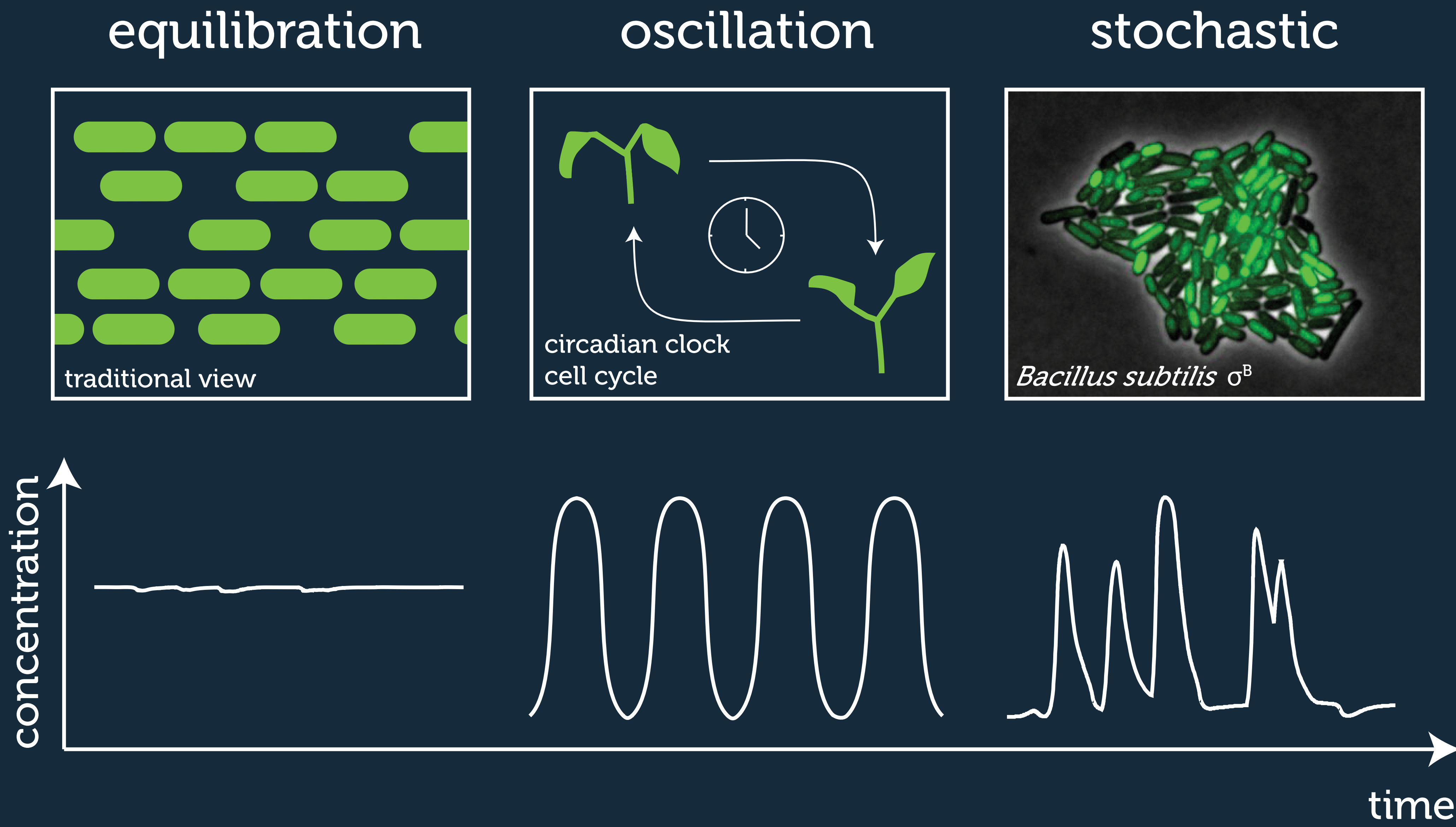
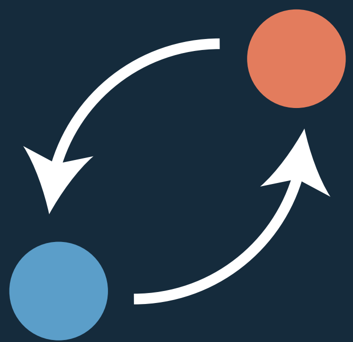
Gene expression is noisy

even under constant environmental conditions

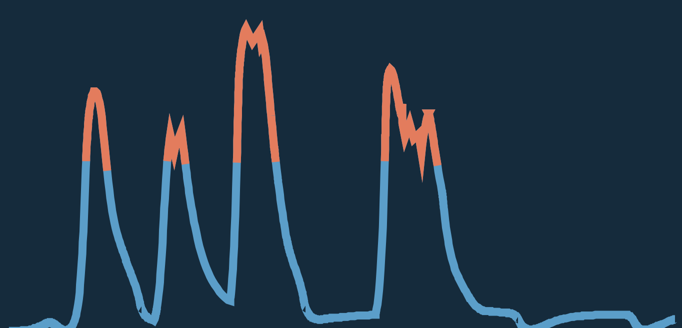


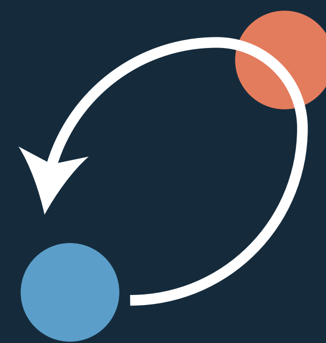
Noise is functionally important



bistable

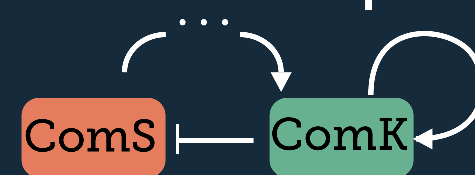
- Circuit
  - stochastic
  - threshold
  - positive feedback
- Persistence *E. coli*
  - HipBA toxin/antitoxin
  - antibiotic resistance

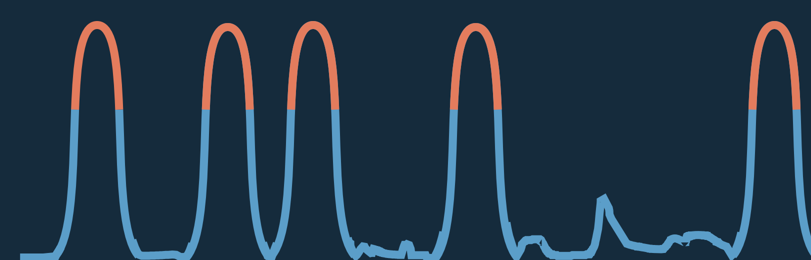




excitable

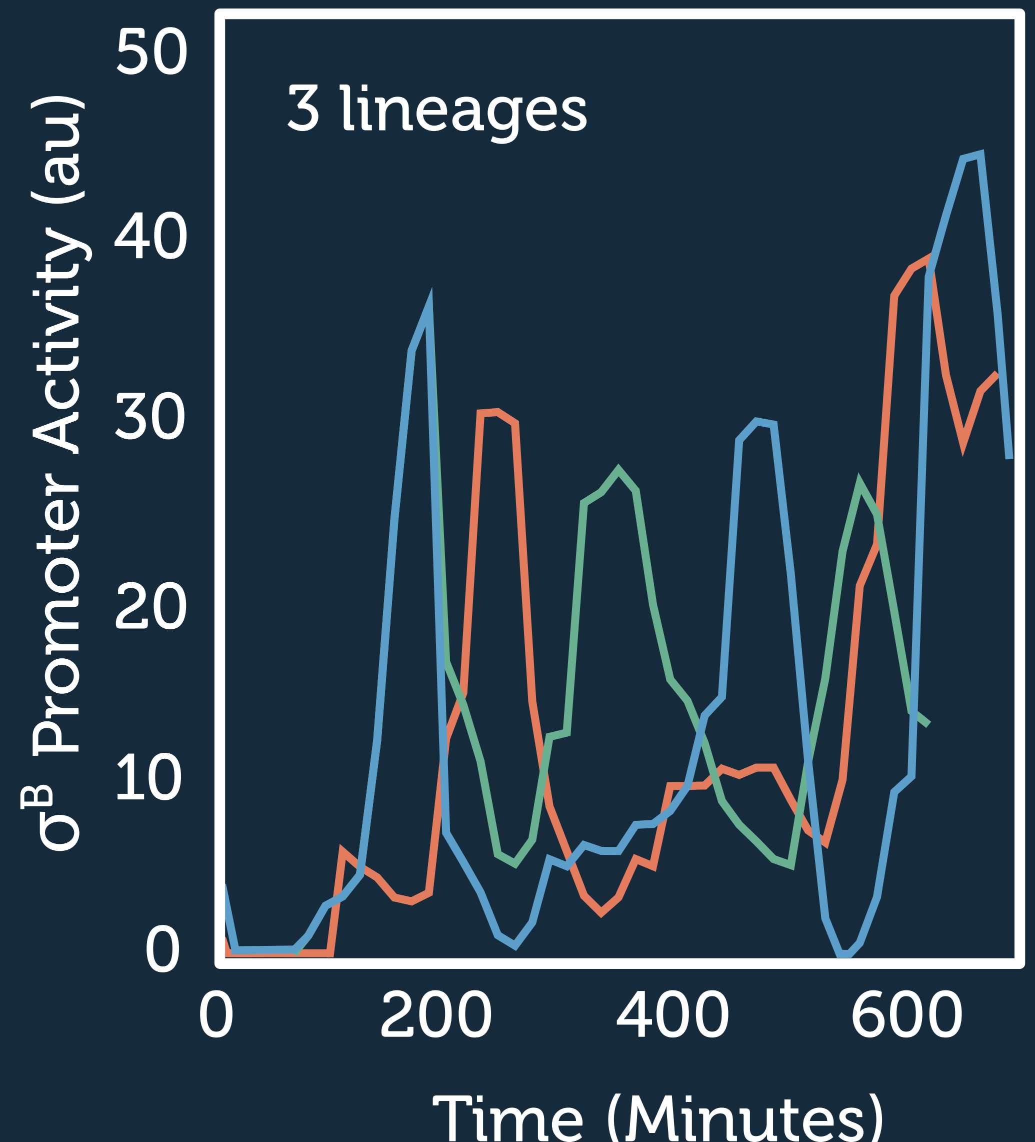
- Characteristic response
- Circuit:
  - stochastic process
  - threshold
  - fast/slow feedback
- Bacterial competence





A different kind of noise

stochastic pulsing



Bacillus subtilis $P_{\sigma B}$-yfp

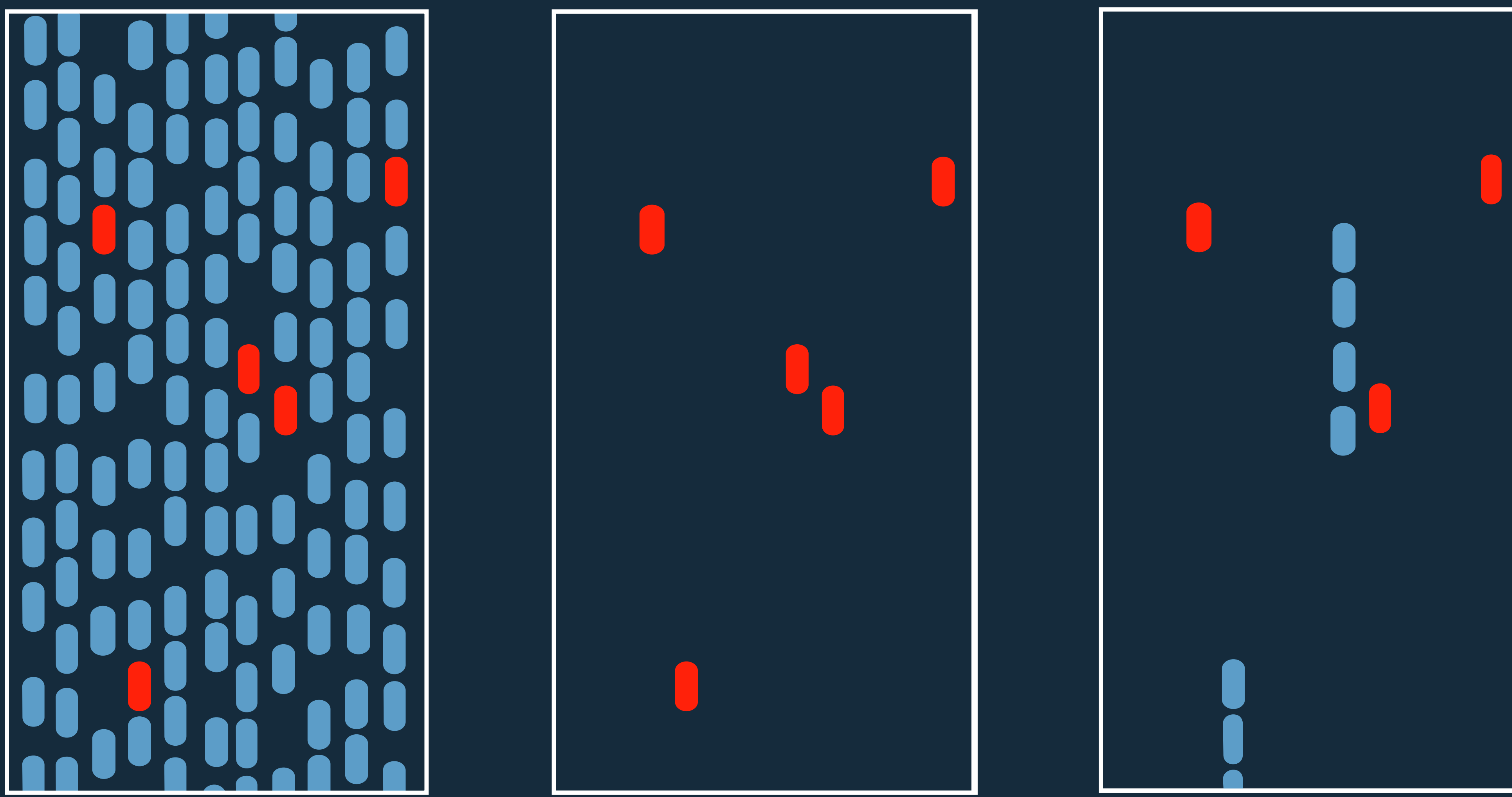
energy stress

40µg/L MPA

Locke et al. Science, 2011

What is the role of stochastic pulsing?

Bet-hedging in an uncertain environment

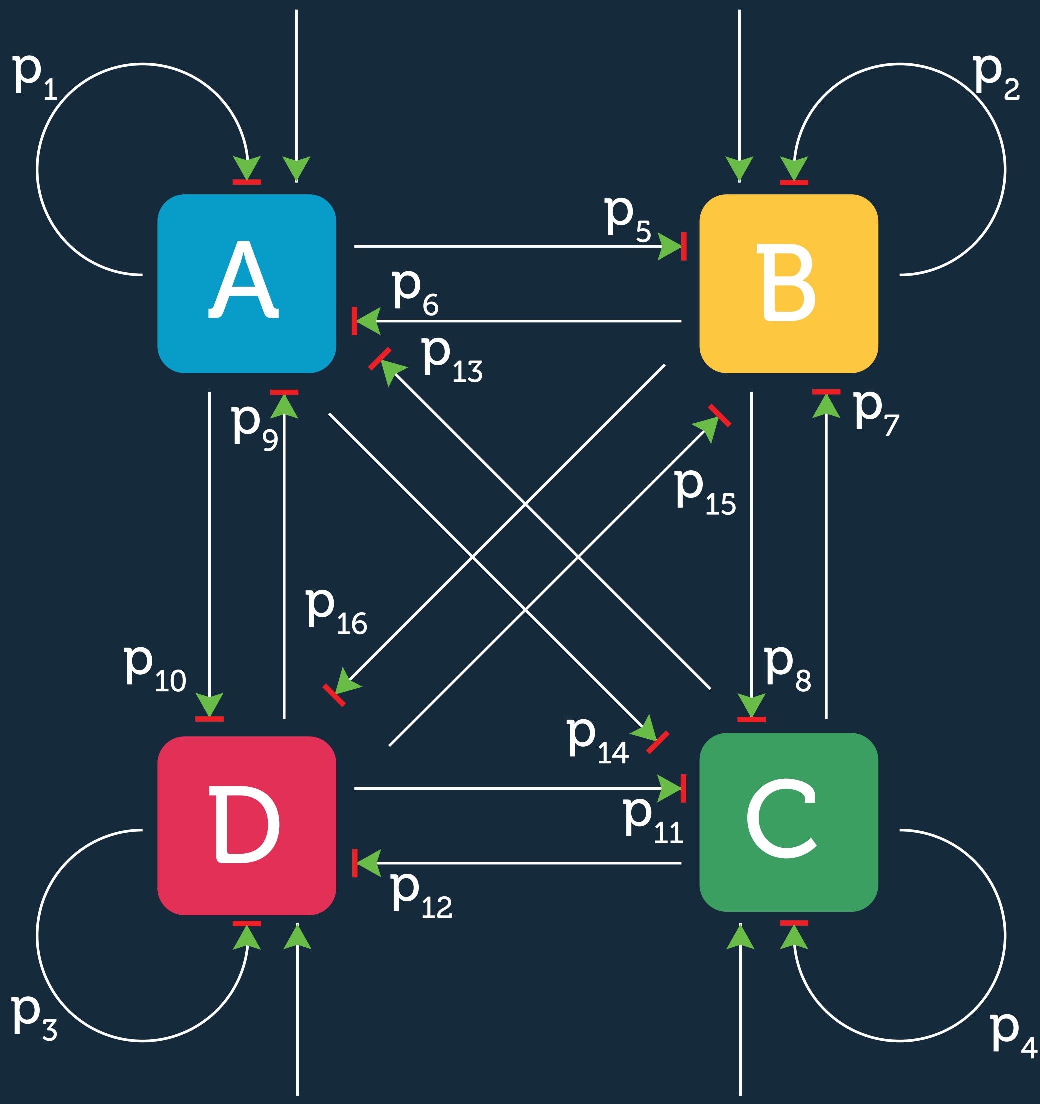


Optimal growth conditions

Catastrophic event

Optimal growth conditions

Modelling a gene regulatory network



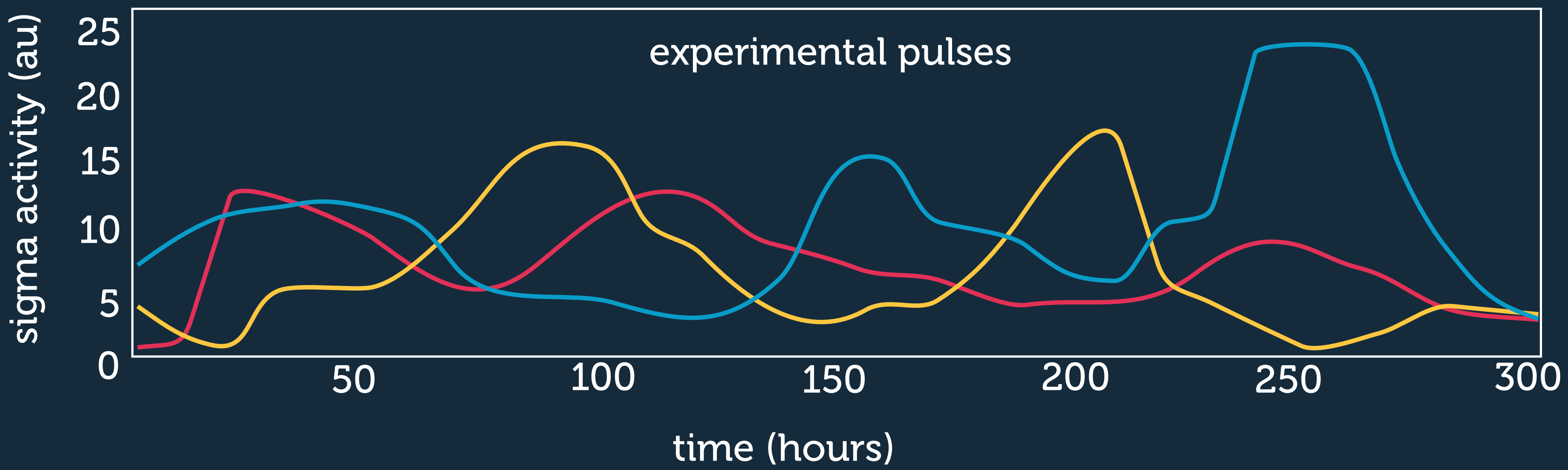
Interactions between genes define network

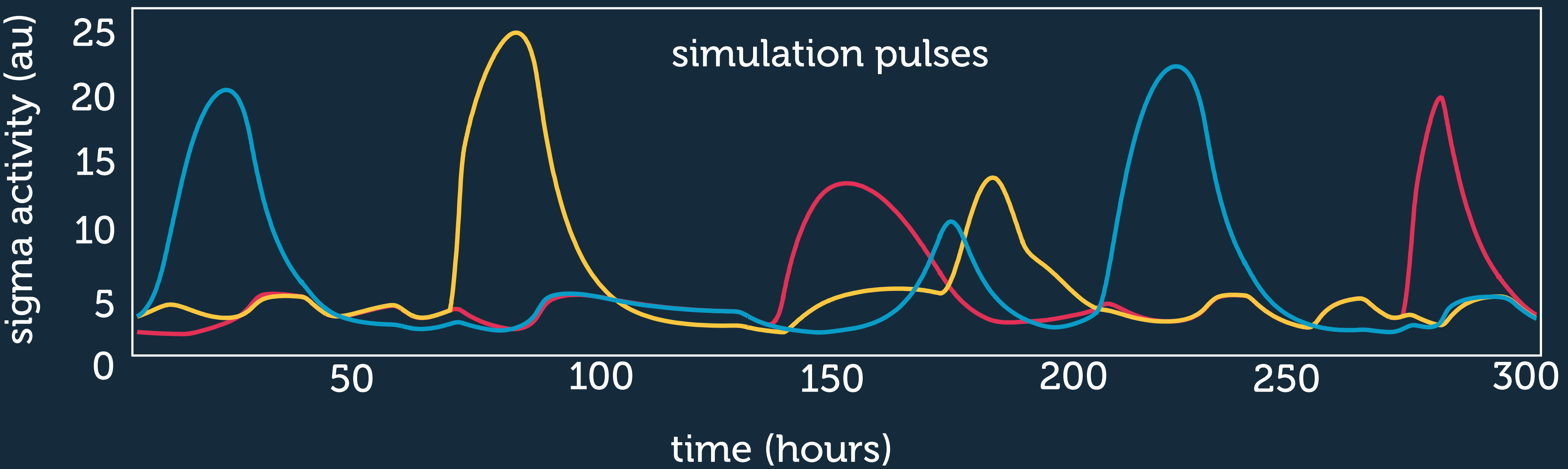
$$N = \{p_1 p_2 p_3 p_4 \ldots p_{16}\}$$

For each path, p:

• present / absent	{bool.}
• activation / repression	{bool.}
• response curve	{real}
• lag	{real}

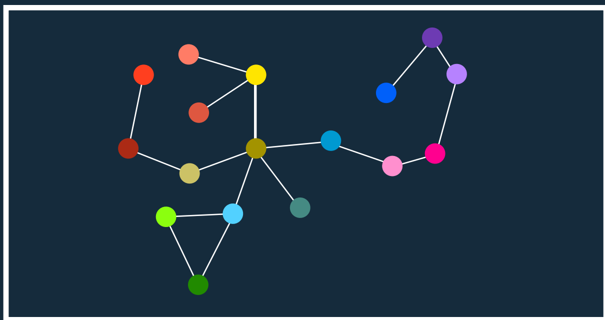
Simulating network interactions





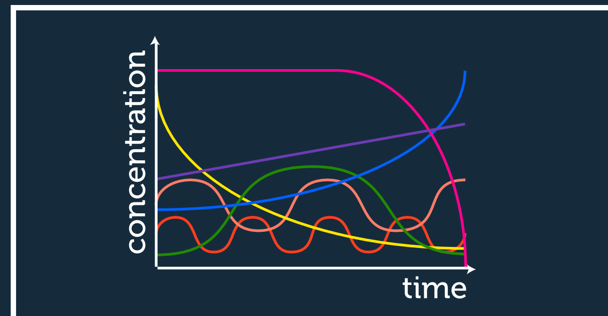
Emulating biological evolution

1. Initiation



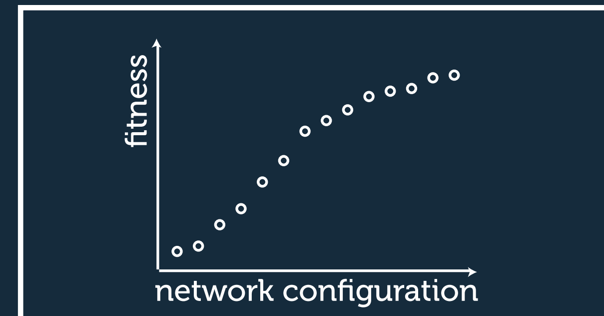
generate random networks

2. Simulation



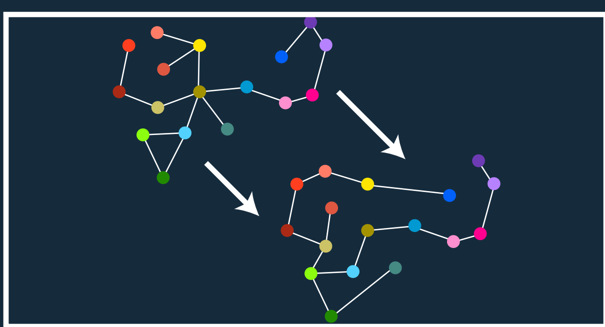
run simulations to get timeseries of gene concentrations

3. Fitness



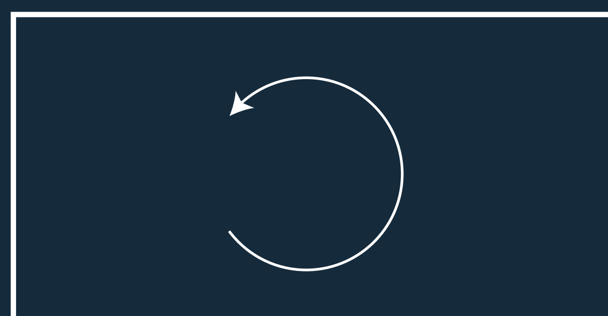
rank all networks according to fitness of output (choose function)

4. Reproduction



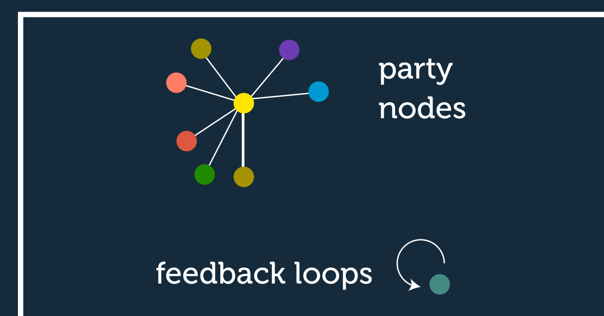
mutations, recombination and clonal reproduction

5. Evolve



repeat steps 2 - 4 over many generations

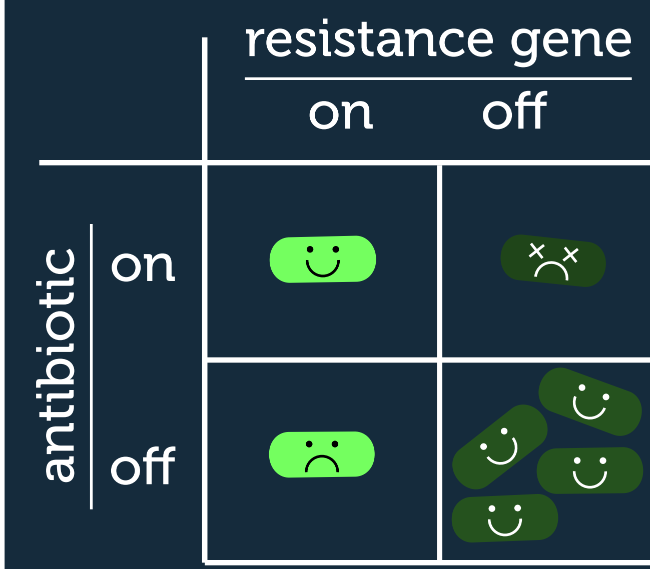
6. Analysis



look for common themes in evolved networks

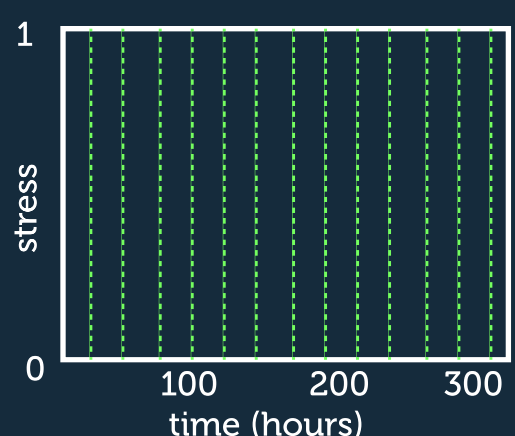
Testing for bet-hedging

population
size of
K cells
in colony
(not to scale)



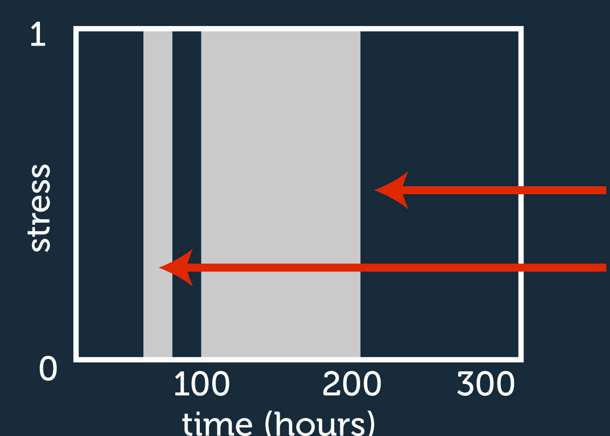
four
possible
scenarios
for
phenotype
and
environment

Cell divisions



all cells
expressing gene
1 during
cell division will
not reproduce
(but will survive)

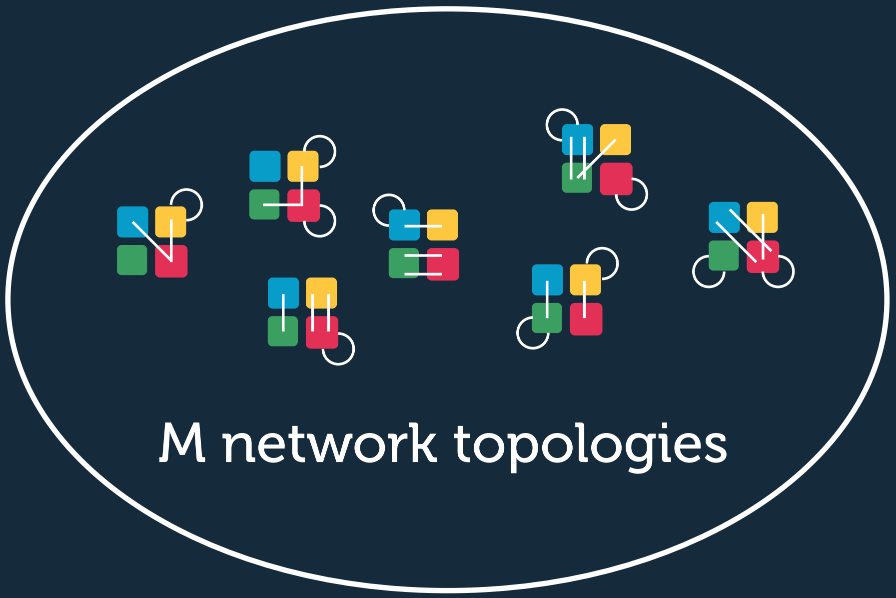
Antibiotic windows



all cells not
expressing
gene 1 in
these
windows
will die

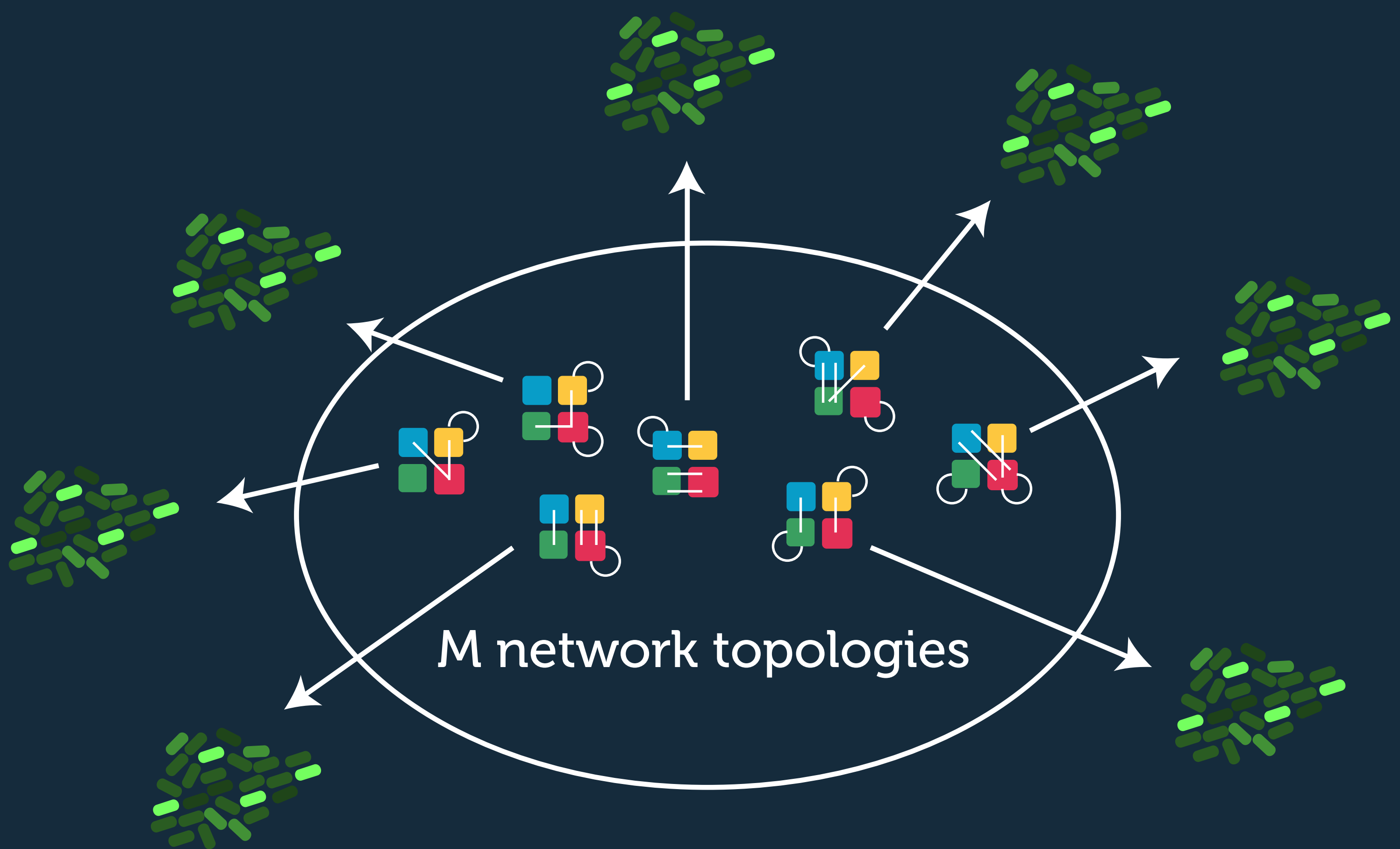
This is all very slow

For each generation:



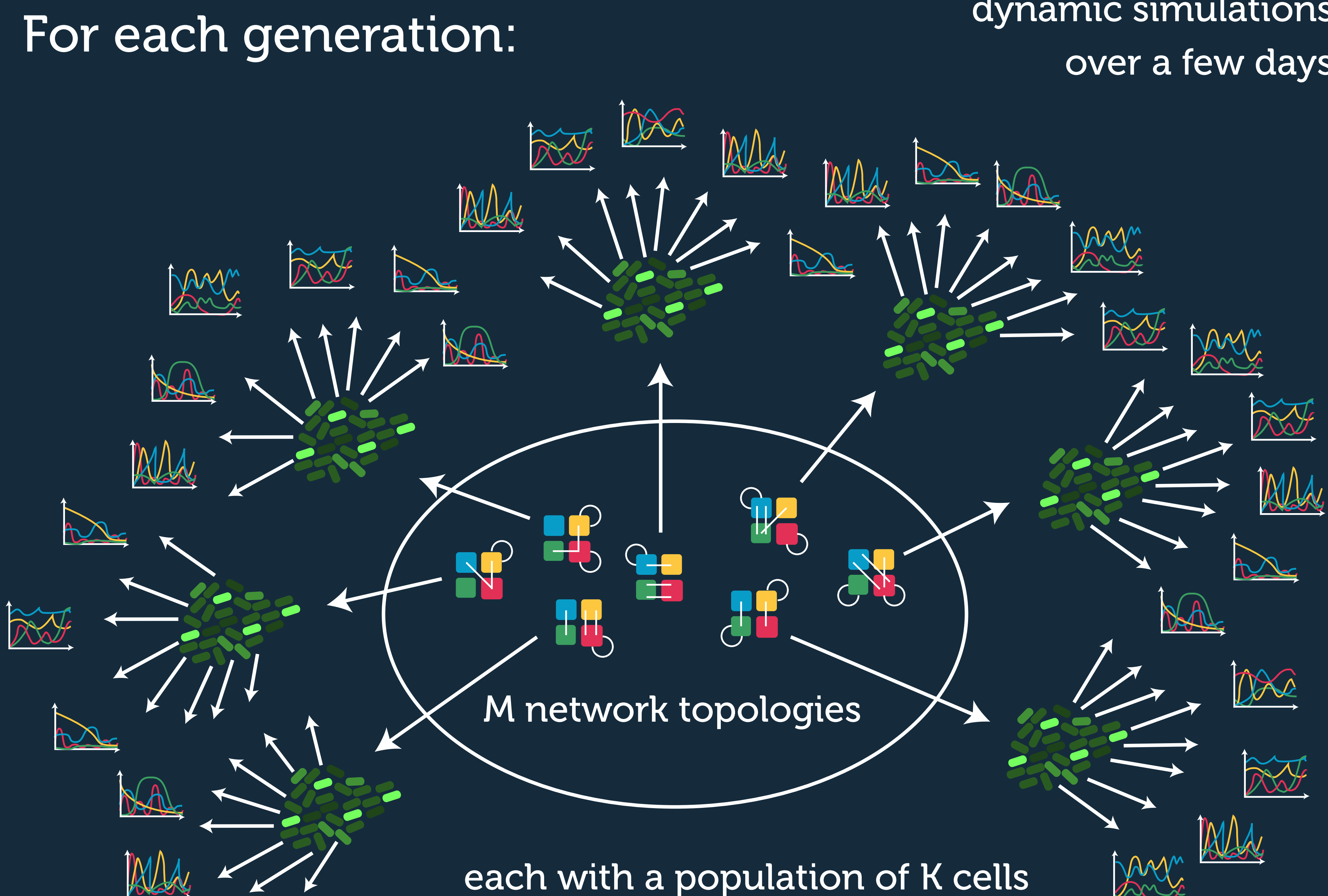
This is all very slow

For each generation:



each with a population of K cells

This is all very slow

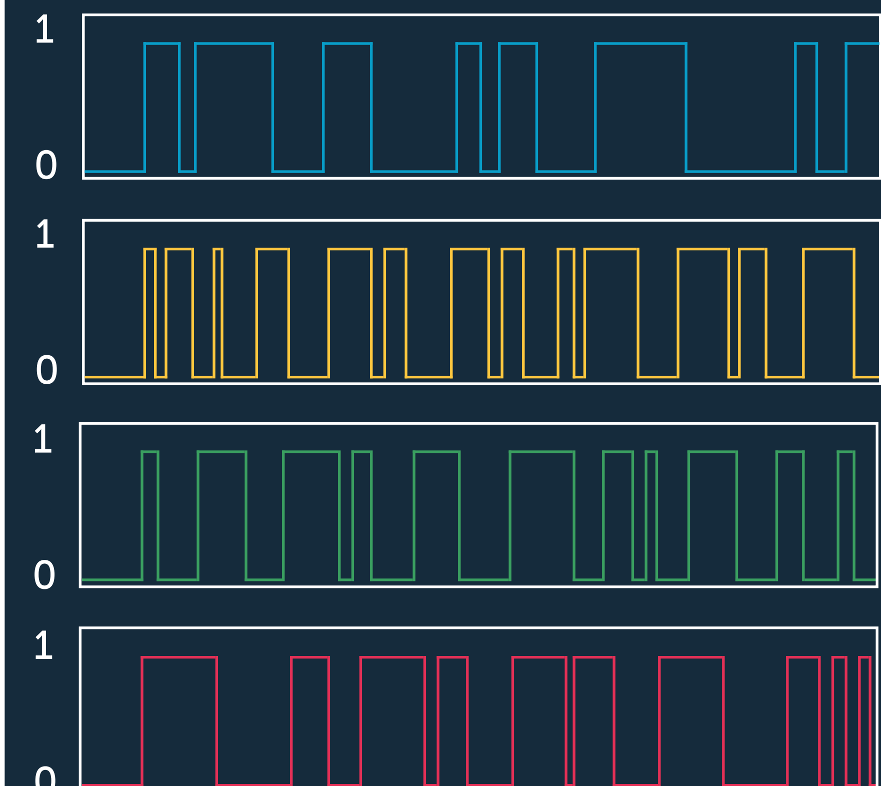


Boolean Approach

off (0) on (1)

Gene concentrations

Dynamic simulation:



paths 0 or -1 or 1

logic gates

or and

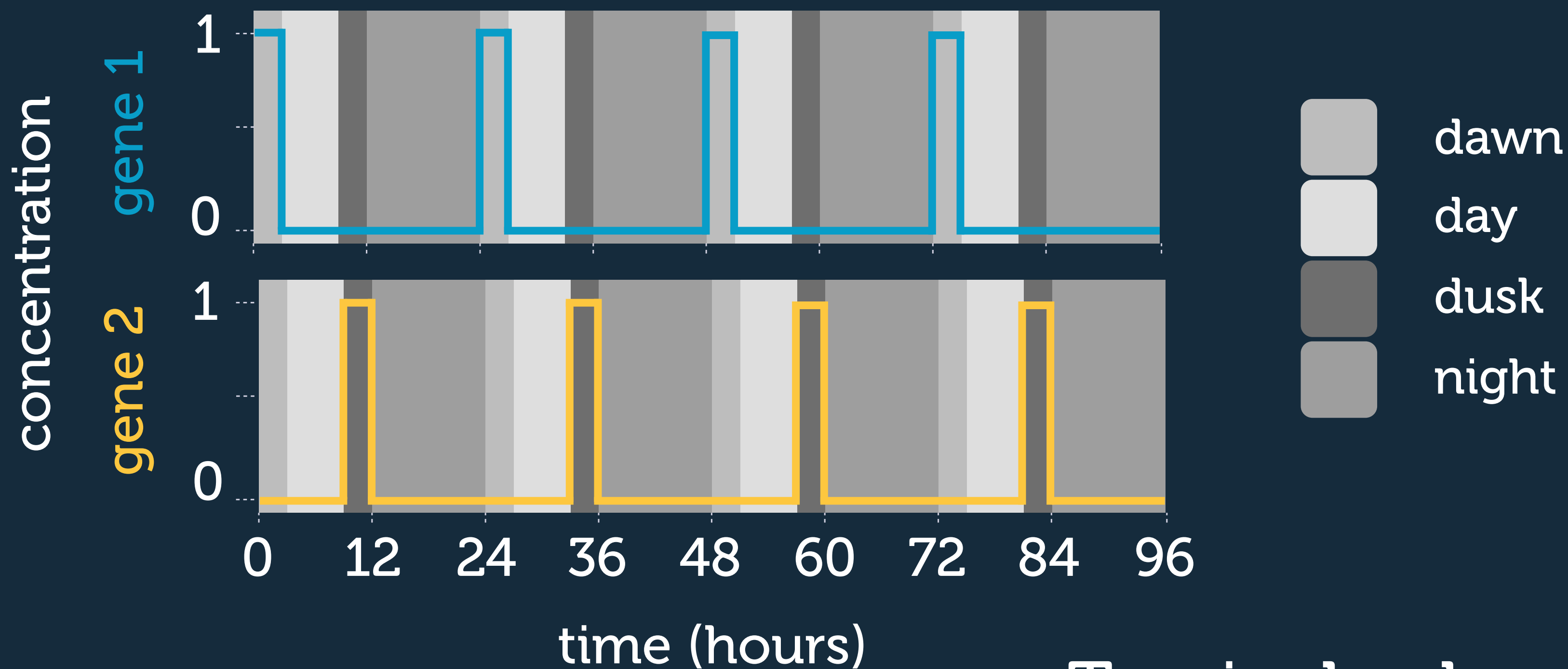
0 < lag < 60 minutes

environmental signal and response

Validating the boolean approach

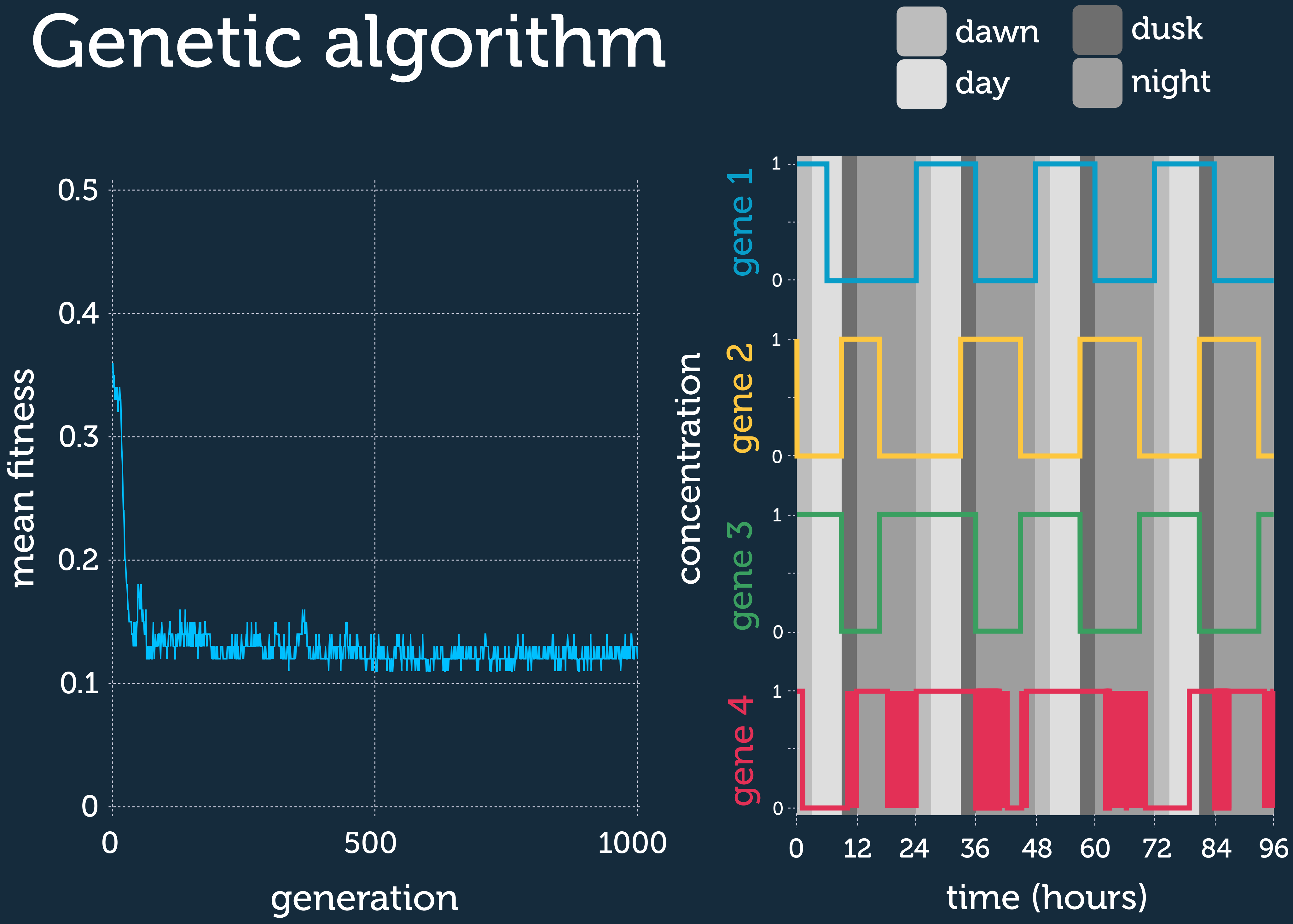
can we evolve a clock?

$$\sum_{\text{dawn}} G_1 + \sum_{\text{dusk}} G_2 - \sum_{\text{not dawn}} G_1 - \sum_{\text{not dusk}} G_2$$



Troein, Locke et al., 2009

Genetic algorithm



Summary and next steps

Done

- Constructed a generic frame-work for network evolution
- Established novel boolean network evolution system
- Written GA and fitness functions
- Evolved a clock (sort of)

Doing

- Try starting with networks that are already clocks
- Try starting with networks that evolved in the clock evolution paper

To do

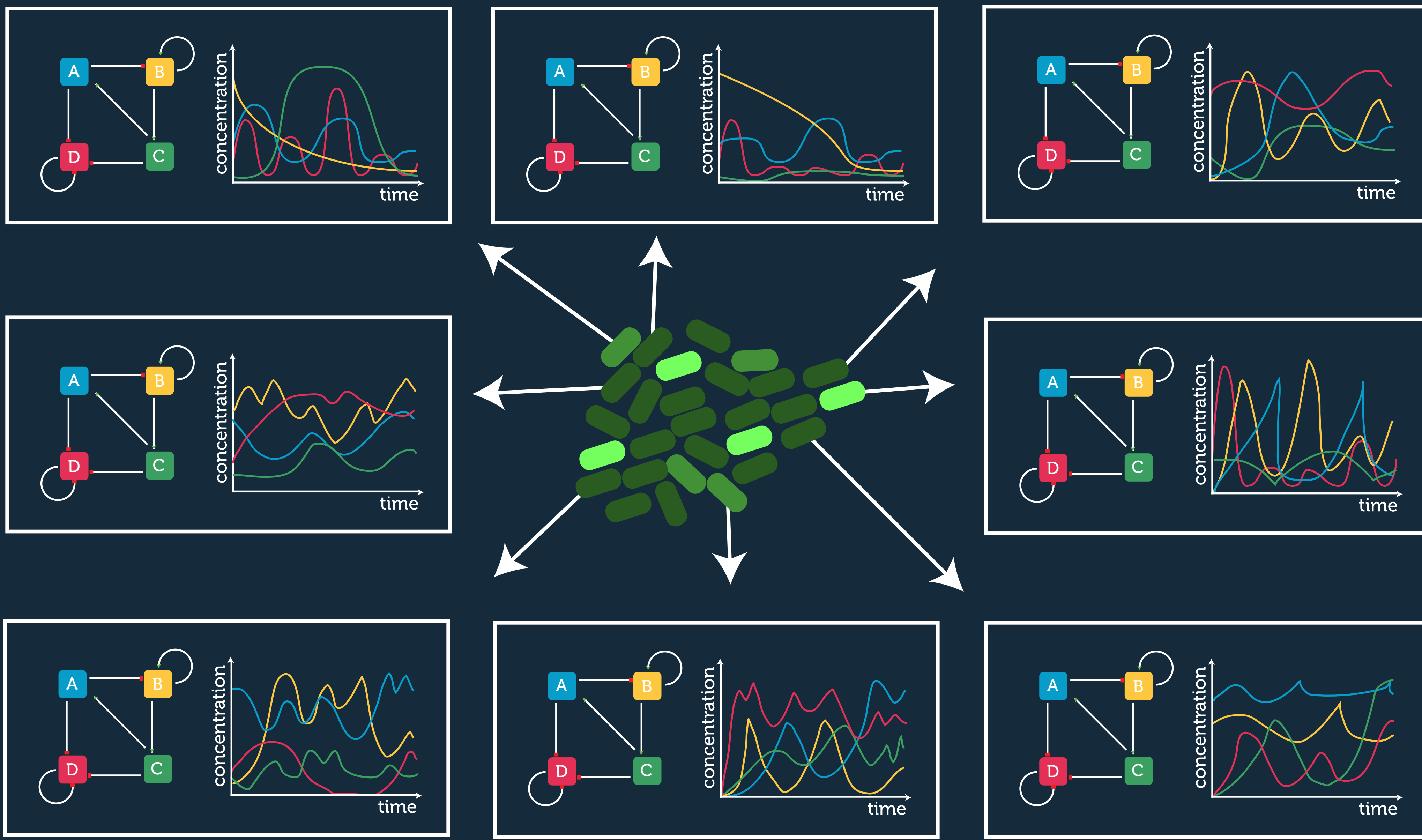
- Change the environmental input pattern
- Look at the interplay between sensory and anticipatory pathways

Acknowledgements

James Locke Carl Troein Locke Lab

Thanks for listening

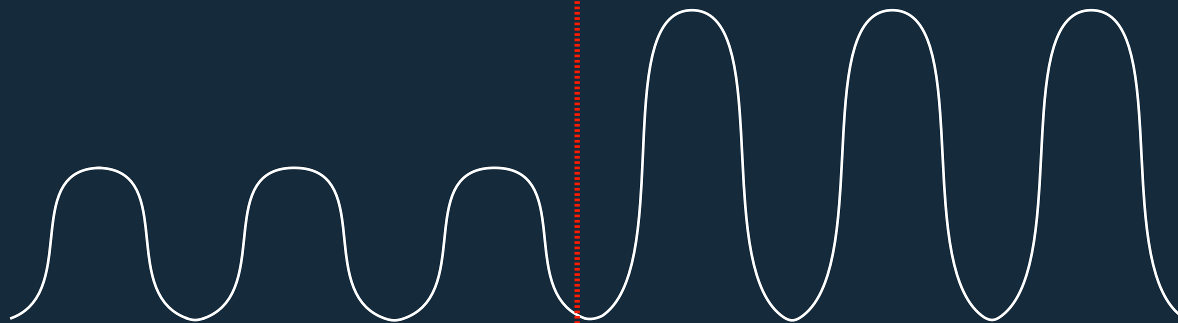
Bet-hedging requires whole colony



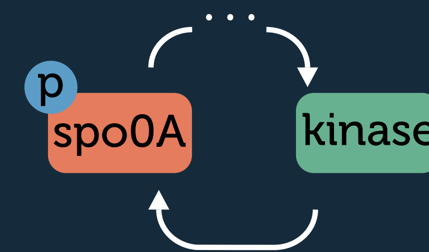
Multiple stochastic simulations for every generation (slow)

Pulse modulation

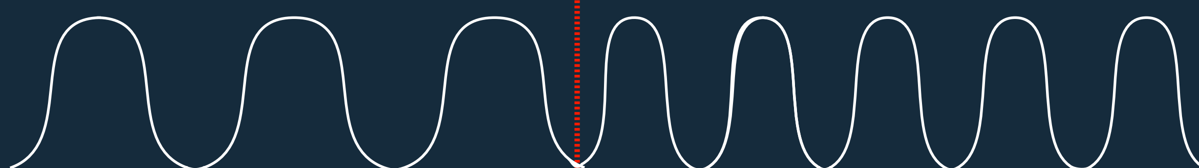
Amplitude modulated (AM)



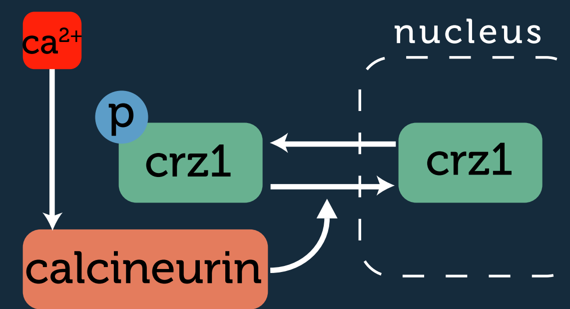
Bacillus subtilis spo0A



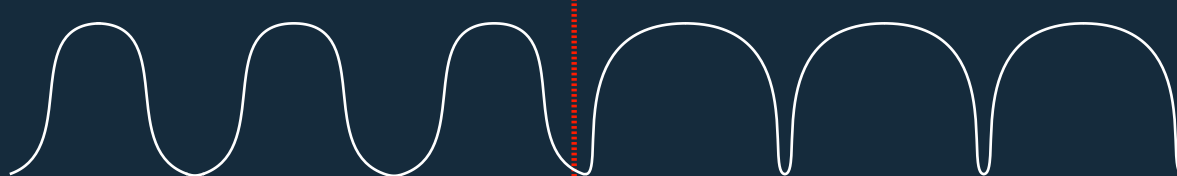
Frequency modulated (FM)



Yeast Crz1



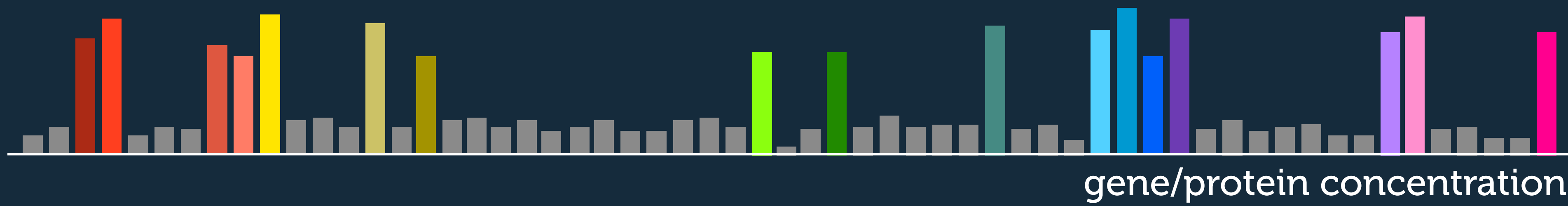
Duration modulated (DM)

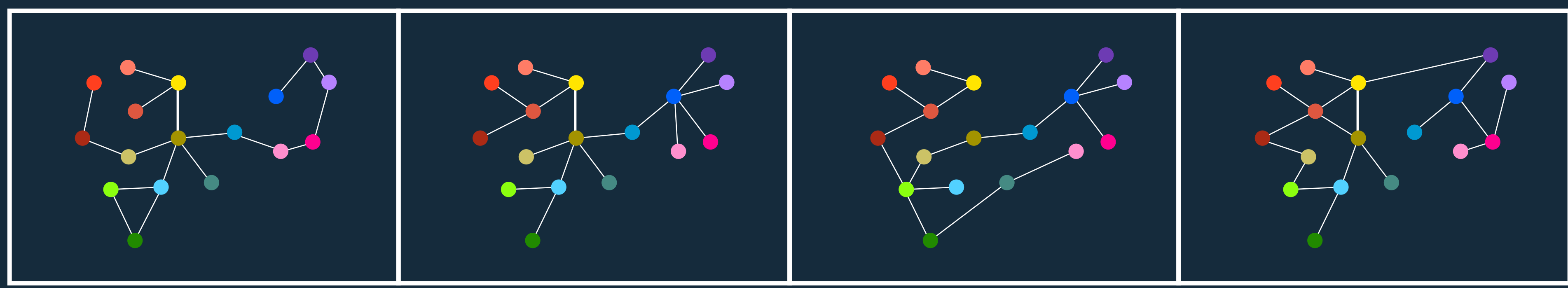


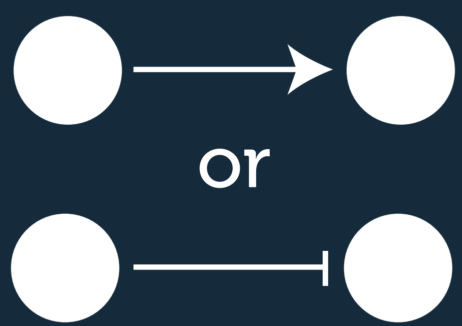
?

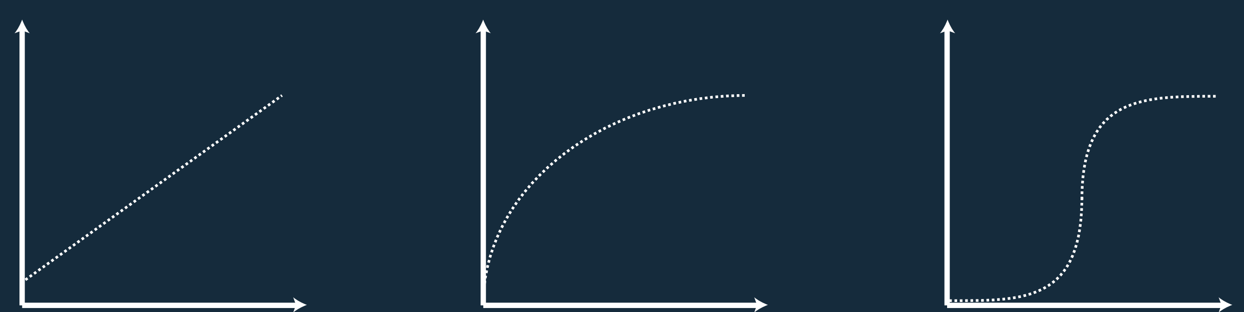
Approach

inferring networks from data





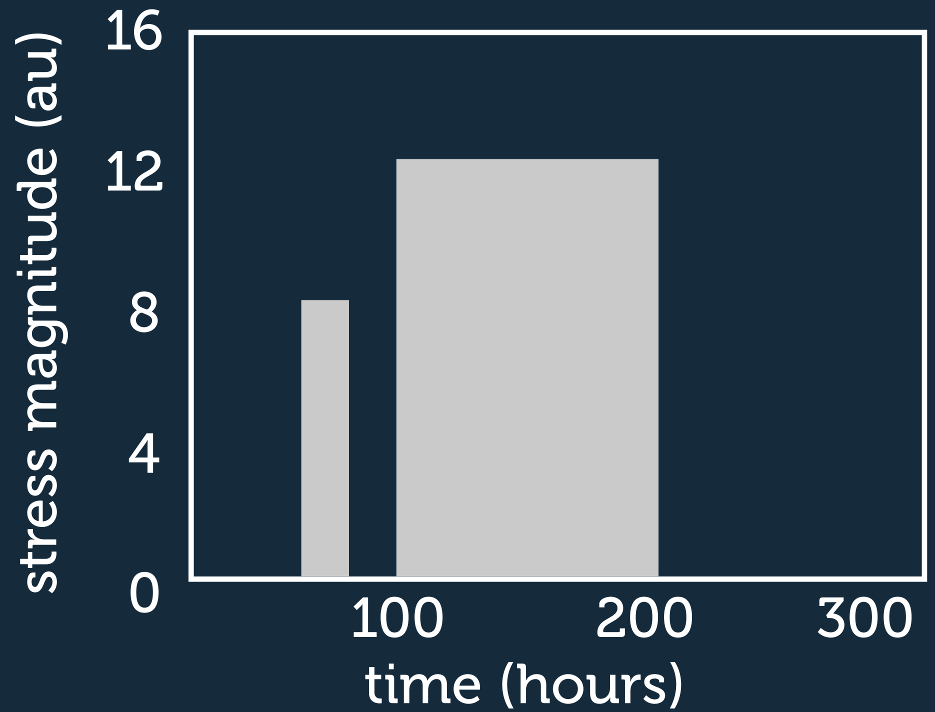




response curves

Testing for bet-hedging

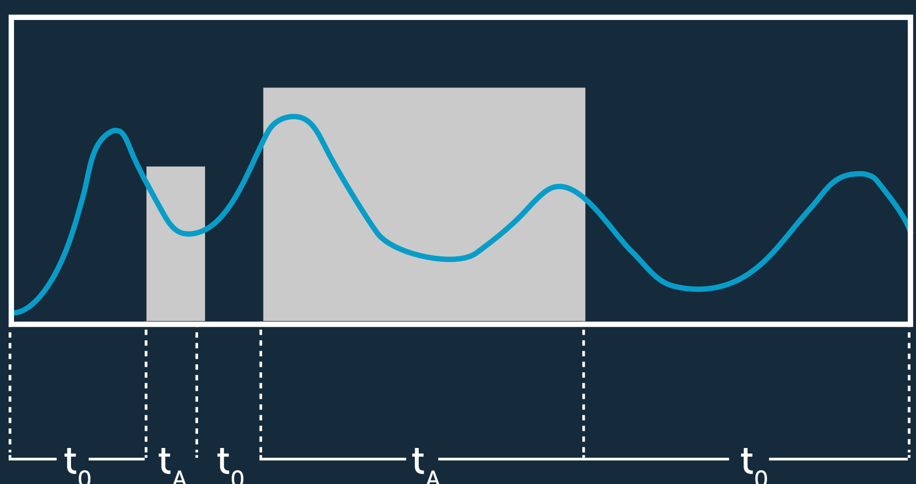
A B D C



A antibiotic resistance gene

(a) severe cost for no/low expression during stress

(b) slight cost for expression otherwise (slowed growth)



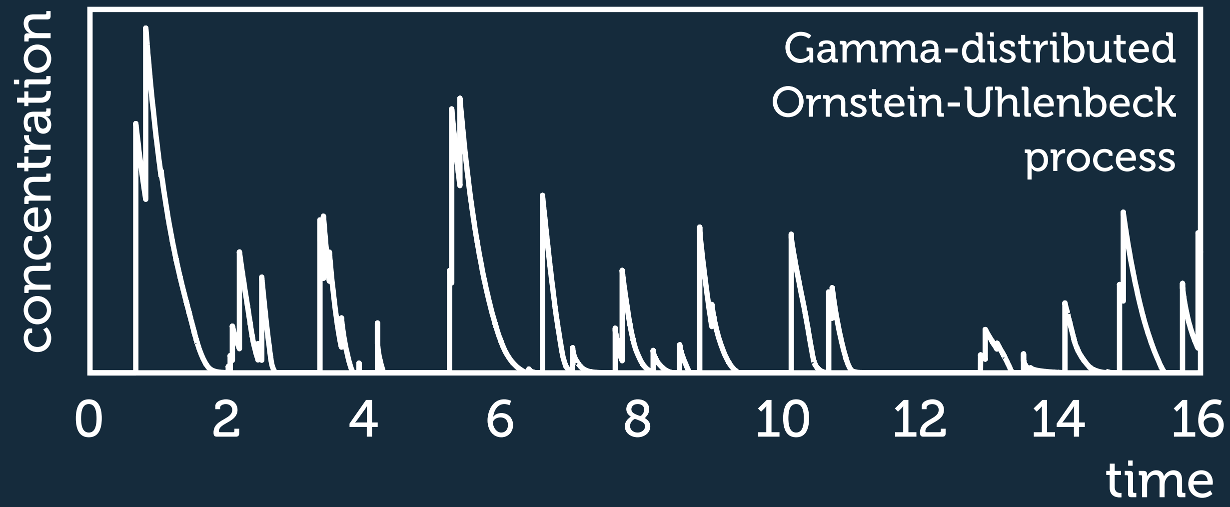
Fitness will be proportional to:

(a) $\int_{t_A} G_1$

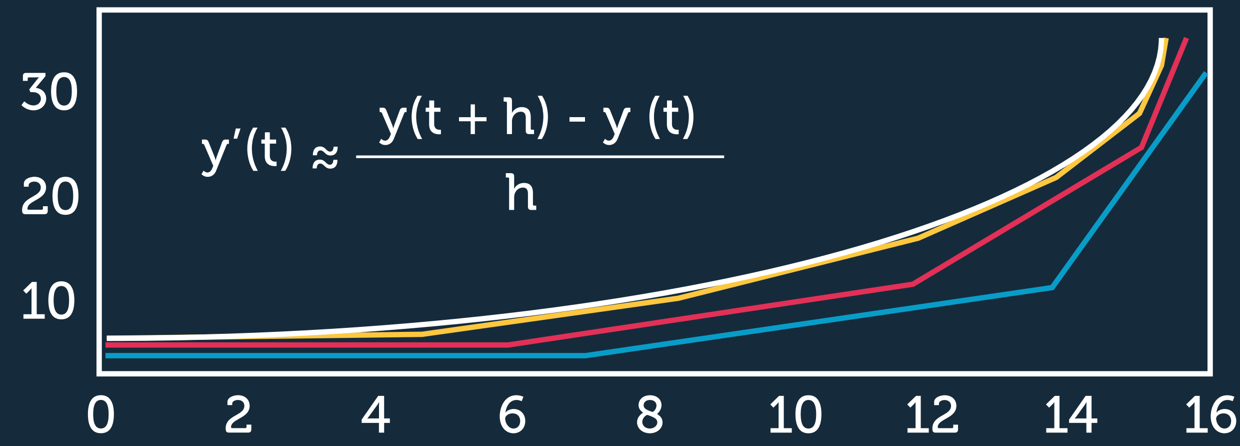
(b) $-\int_{t_0} G_1$

Bet-hedging requires stochasticity

Option 1:
Discretise and solve piecewise



Option 2:
Create an SDDE solver



Option 3:
Simulate transcription and translation using SDE solver with no lag.