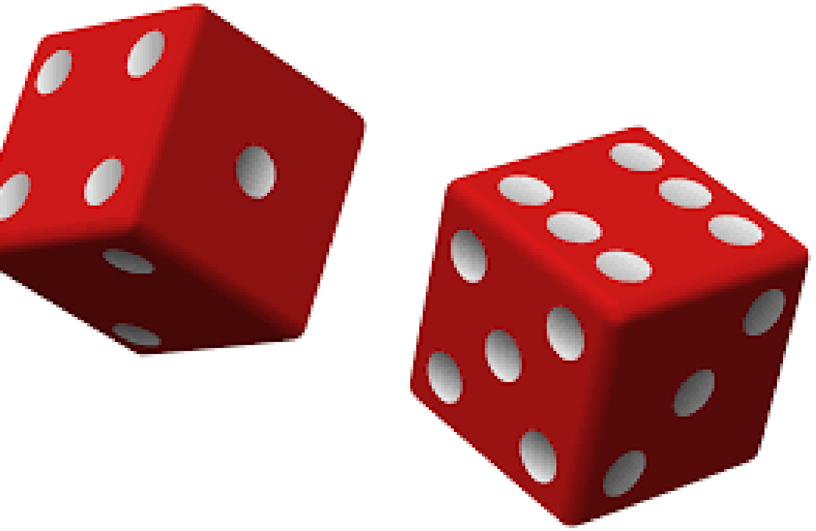
Stochastic processes in biology



SYMPOSIUM "CONNECTING MATHEMATICAL METHODS ACROSS UTRECHT UNIVERSITY"

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Why does biology need stochastic models?

Many biological systems are plagued by “noise”. They have often evolved ways to cope with it.
We may need stochastic models to understand their design.

Noise can qualitatively changing a system’s dynamics.
We may need stochastic models to reproduce their features.

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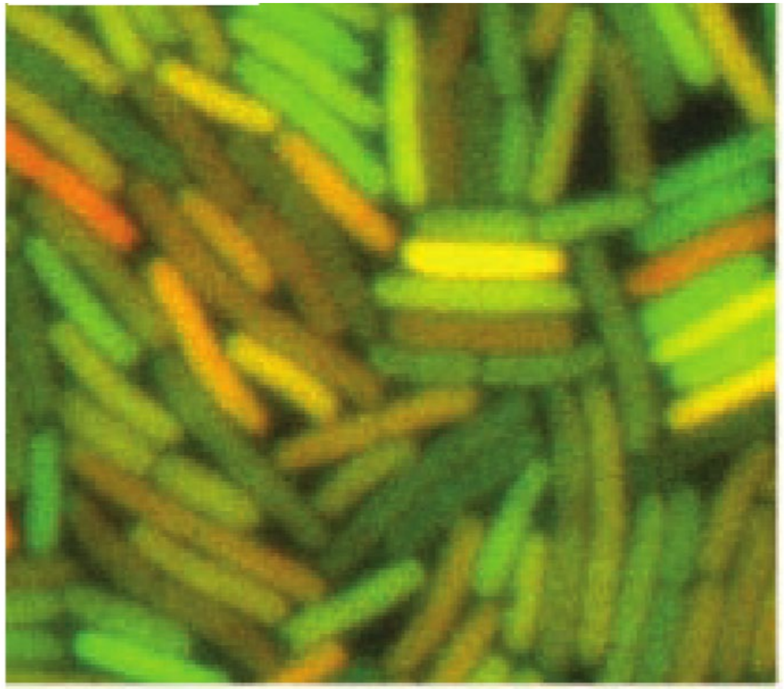
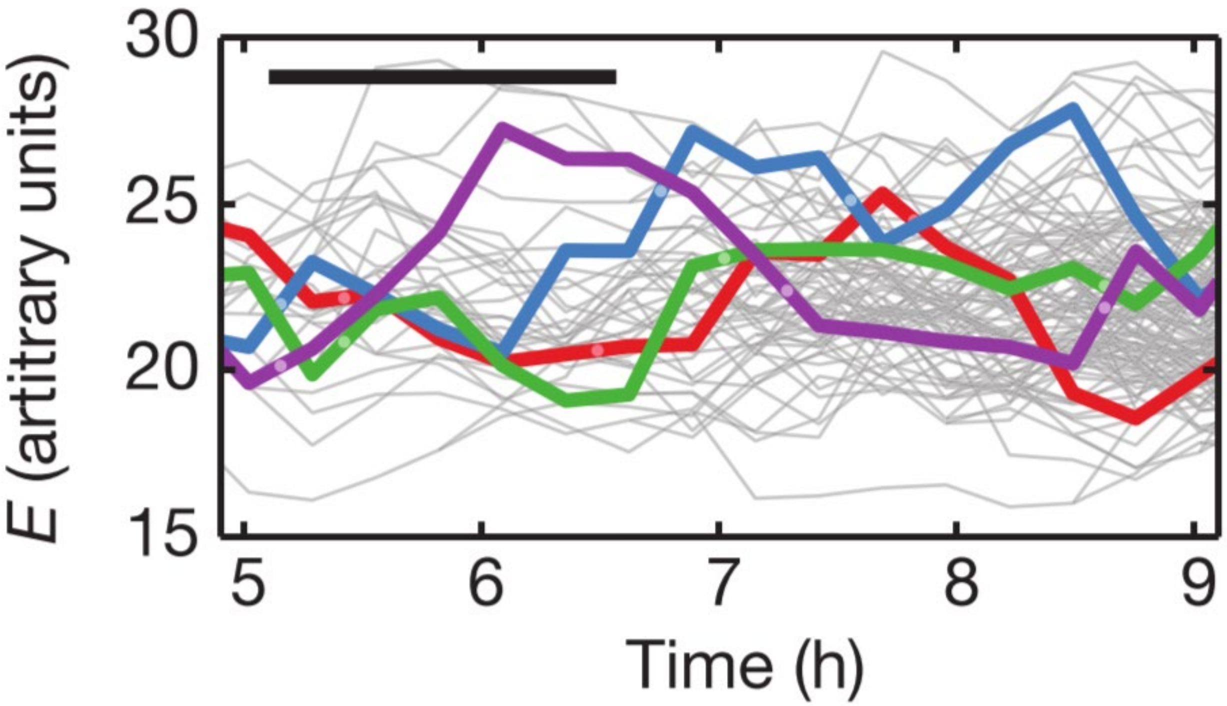
Genetically identical bacteria show large fluctuations in protein concentrations





Elowitz, M. B. *et al, Science* 297, no. 5584 (2002); Kiviet, D. J. et al, *Nature* 514, no. 7522 (2014)

This raises many questions:

- What are the main sources of noise in gene expression?
- What determines the distribution of protein copy numbers?
- What is the effect of all this noise on the functioning of the cell?
- What can and does the cell do to reduce noise or cope with it?
- …

Gene expression: from DNA via mRNA to Protein

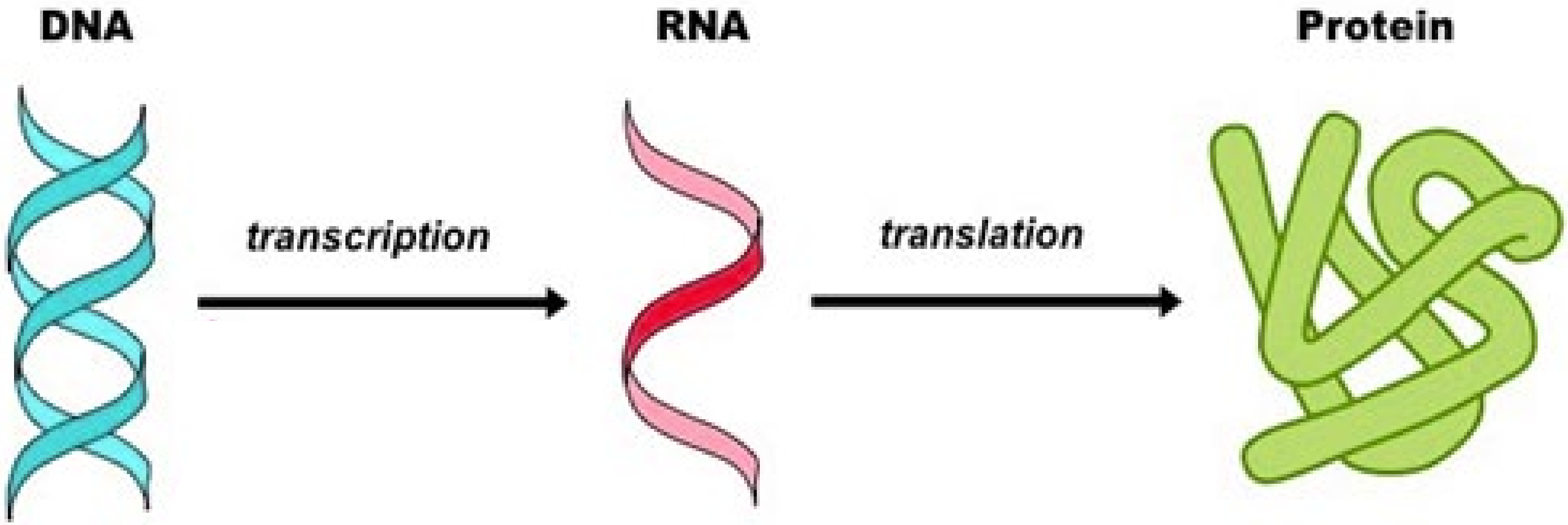
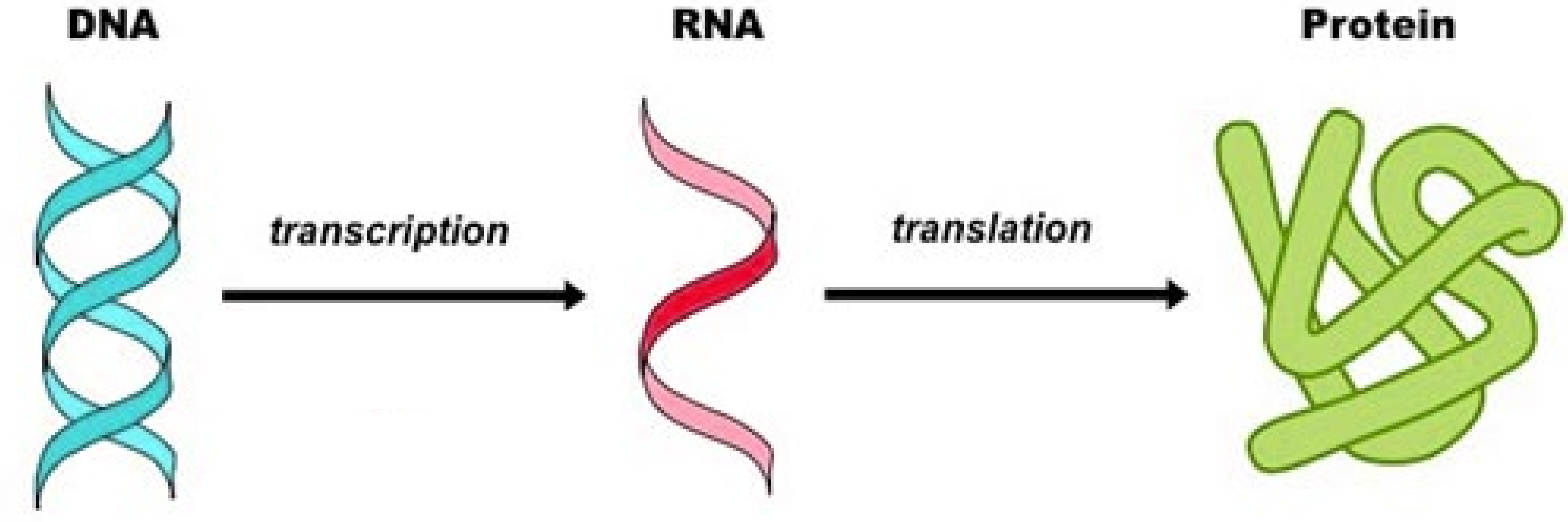


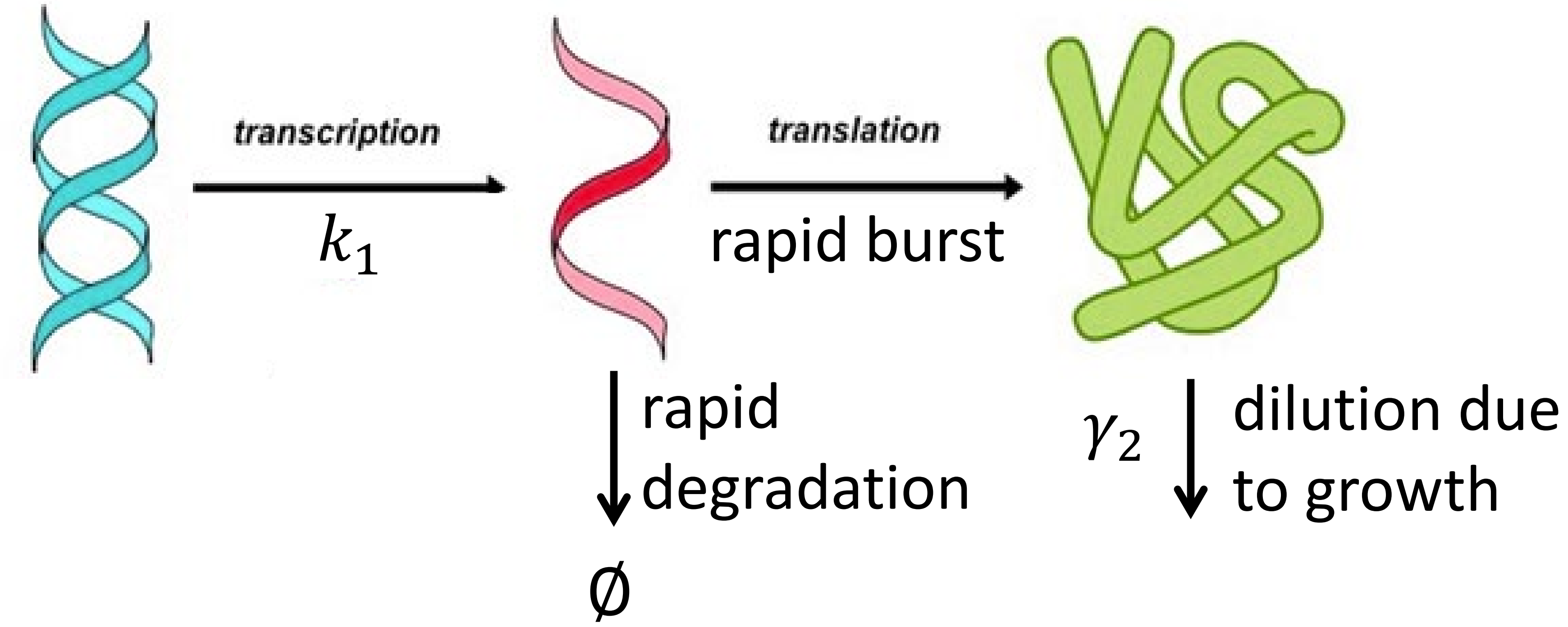
Figure adapted from https://byjus.com/biology/central-dogma/

Bacteria are small; hence copy numbers and reaction rates are often small



Copies:	1—4 per cell	0—20 per gene per cell	0 to 10000 per gene per cell
Produced:	1—3 per hour	0—5 per minute	0—5 bursts per minute

Example of a stochastic model of gene expression

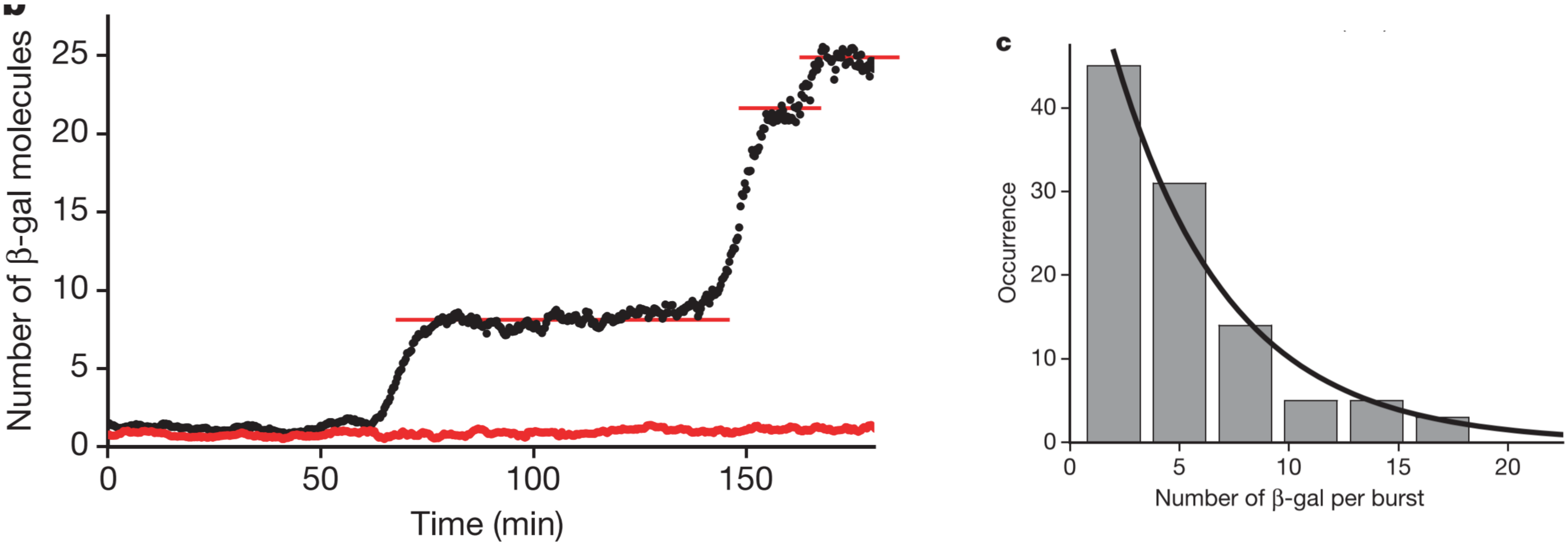


Master equation:

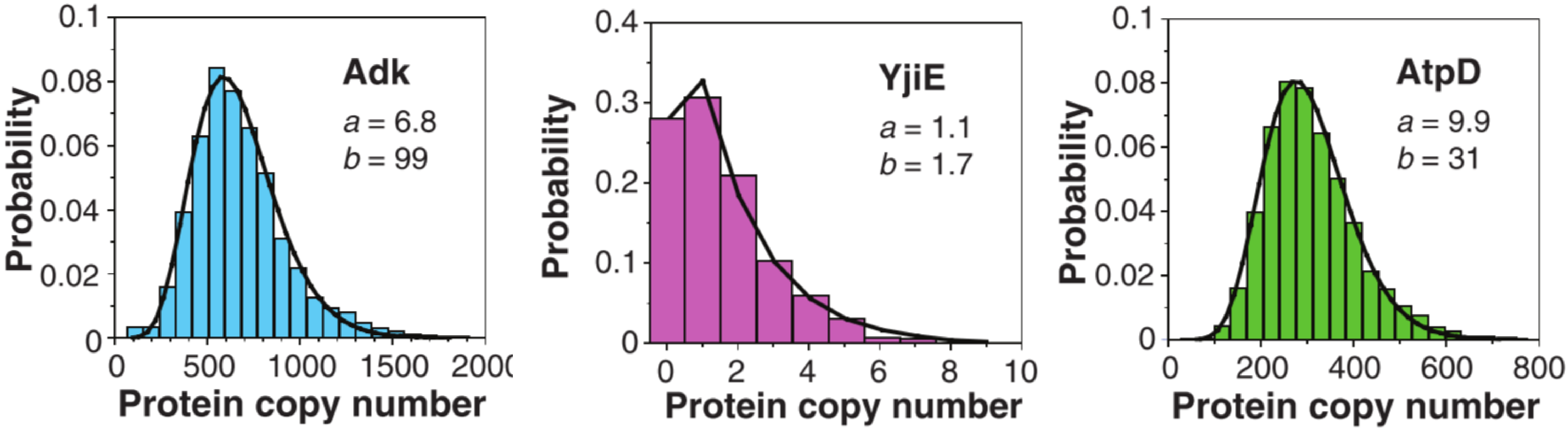
$$\frac{\partial p(x)}{\partial t} = \frac{\partial}{\partial x}[\gamma_2 x p(x)] + k_1 \int_0^x dx' w(x, x') p(x')$$

Friedman, N. *et al*, *Physical Review Letters* 97, no. 16 (2006)

Data suggest exponential burst-size distribution



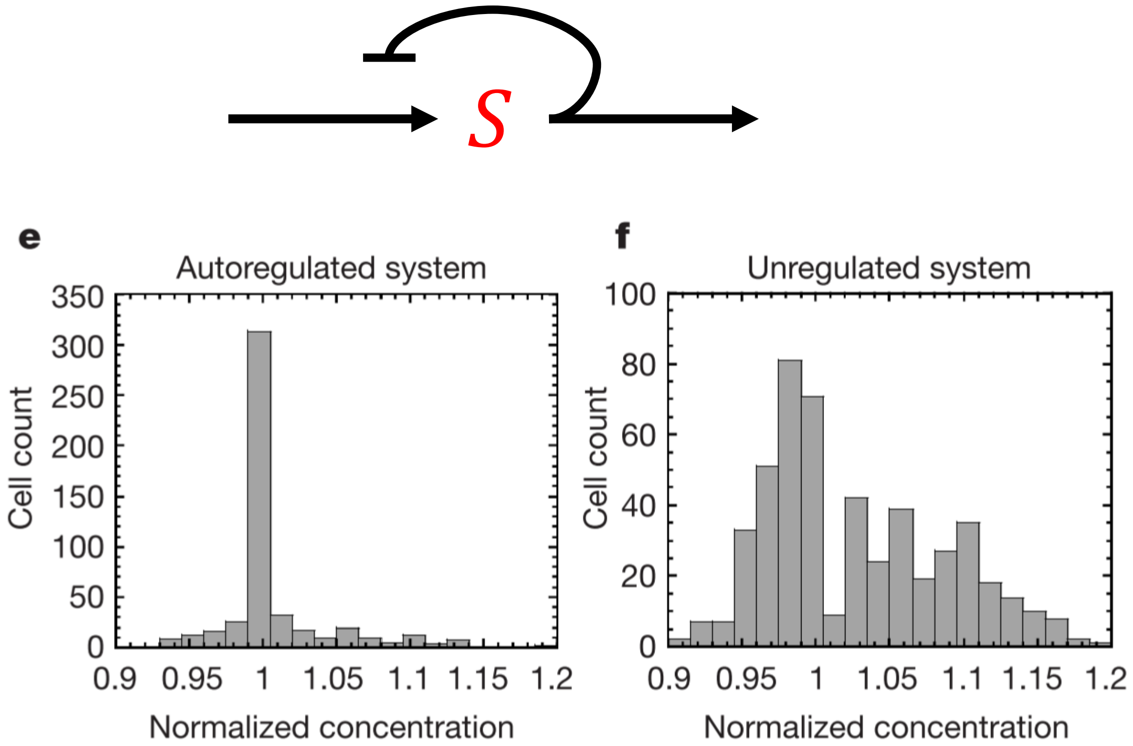
Prediction:
Steady-state probability distribution is a Gamma distribution



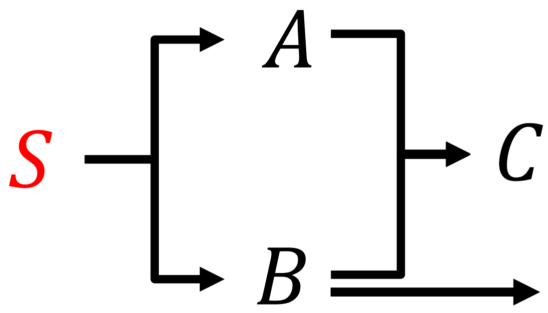
Taniguchi, Y. et al. *Science* 329, no. 5991 (2010)

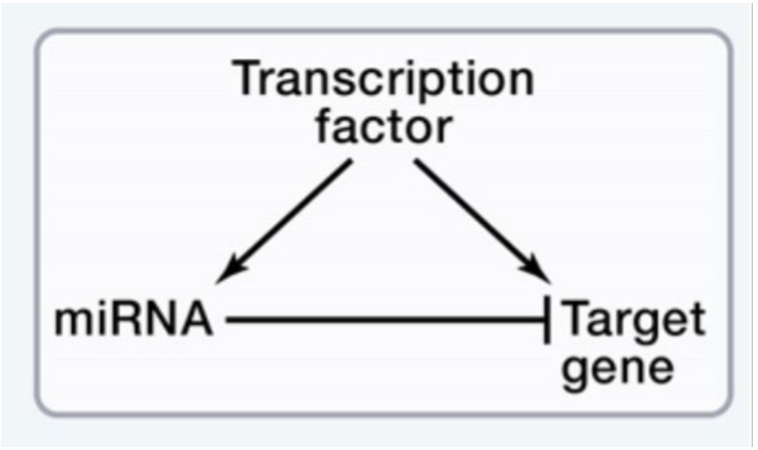
Molecular networks can filter noise; examples:

Negative feedback



Annihilation module:





Laurenti *et al*. *Biophys. J.* 114, no. 12 (2018); Becskei and Serrano. *Nature* 405, no. 6786 (2000); Ebert *et al*, *Cell* 149, no. 3 (2012)

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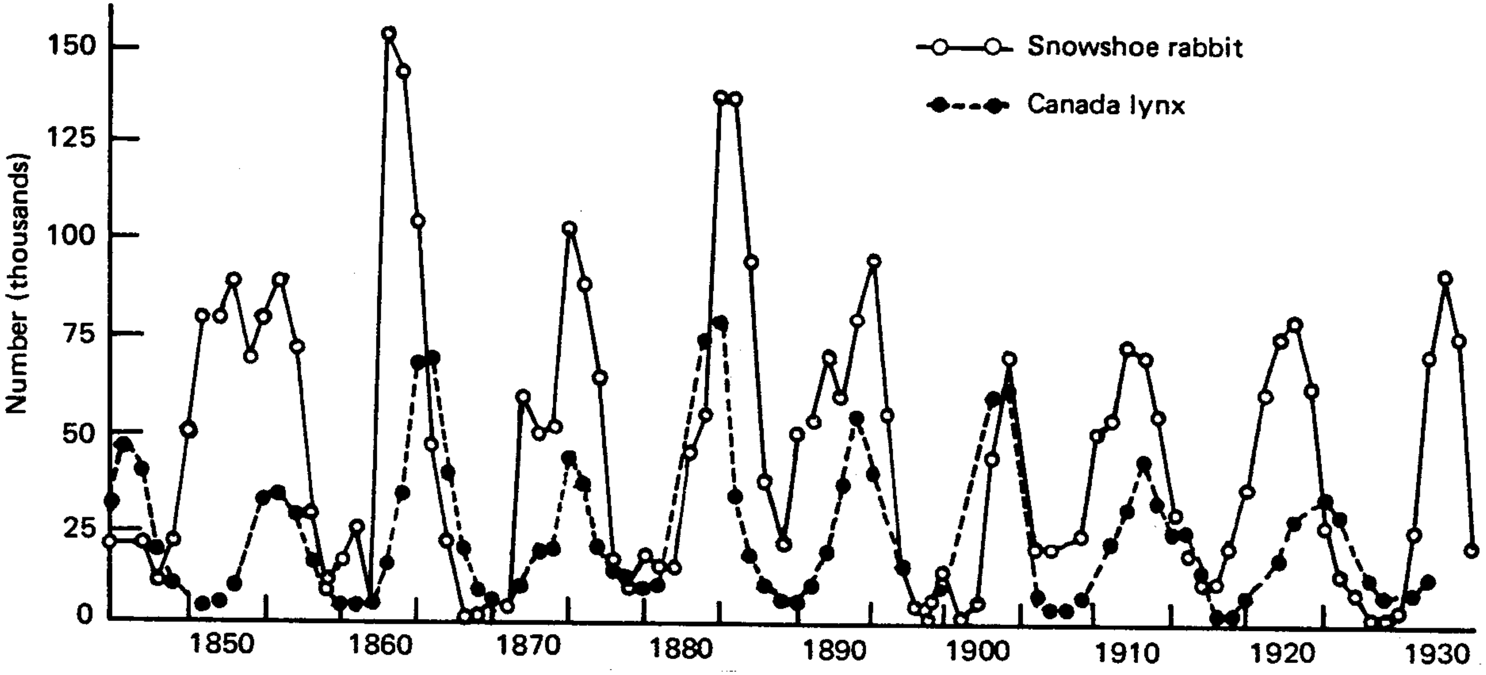
Classical topic in ecology: predator-prey cycles



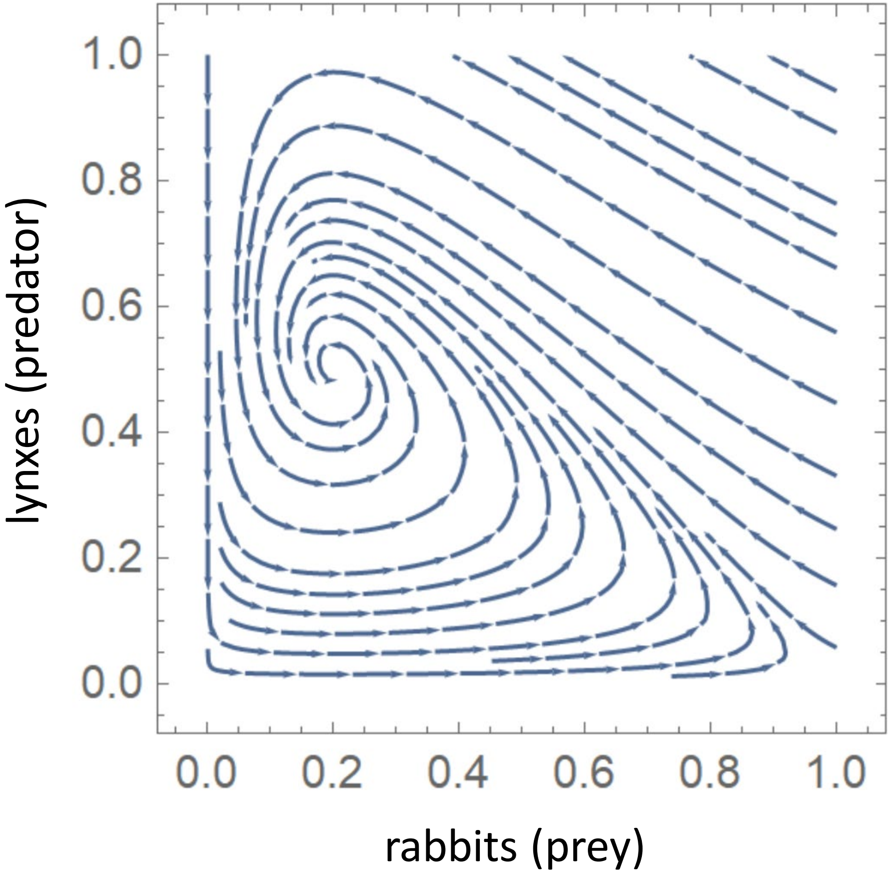
Volterra equations for predator-prey interactions, with logistic growth for prey: no stable oscillations

rabbits (prey)

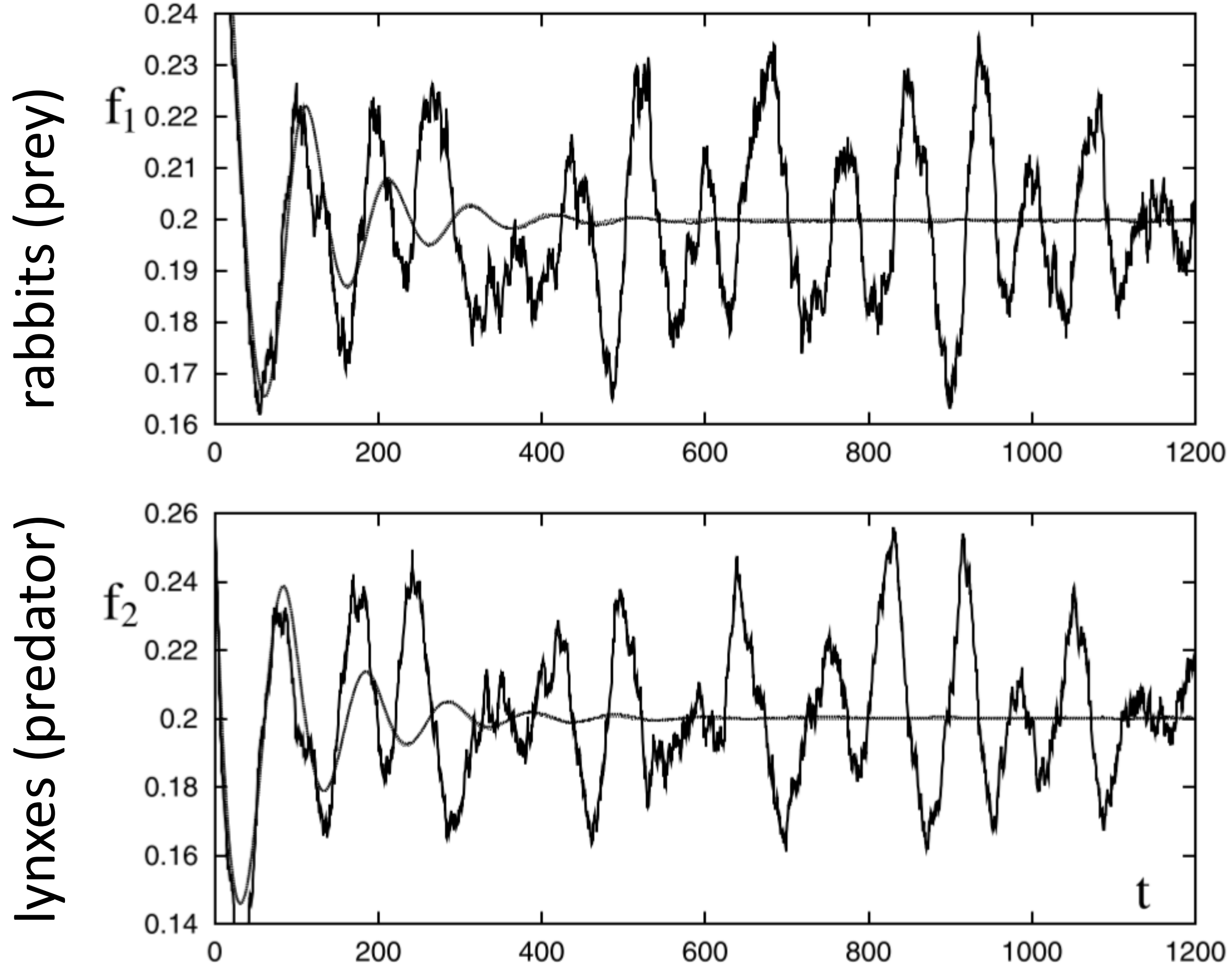
$$\frac{\mathrm{d}\,r}{\mathrm{d}\,t} = a\,r\left(1 - \frac{r}{K}\right) - b_1\,r\,l$$

lynxes (predator)

$$\frac{\mathrm{d}\,l}{\mathrm{d}\,t} = b_2\,r\,l - d\,l$$

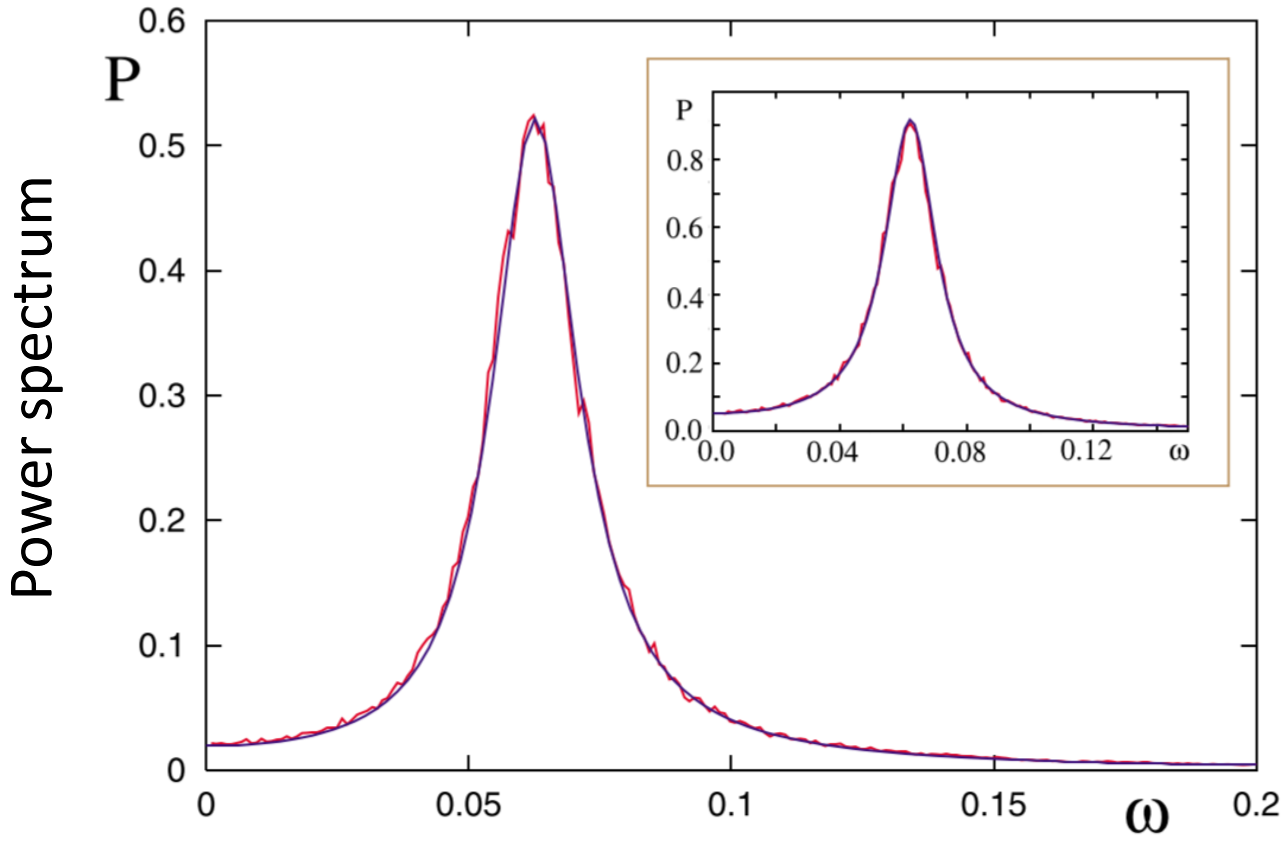


The stochastic equivalent does show oscillations



- Simulations (Gillespie) based on a Master Equation
- Sustained oscillations found
- Amplitude much larger than expected based on Poisson noise

Power spectrum of fluctuations reveals a resonance



- Approximate the Master equation by a Langevin equation.
- Fourier transform equation, solve

Result:

- Intrinsic noise amplified near the resonance frequency.

Conclusion:

- Some oscillations observed in nature may require stochastic models to be explained.

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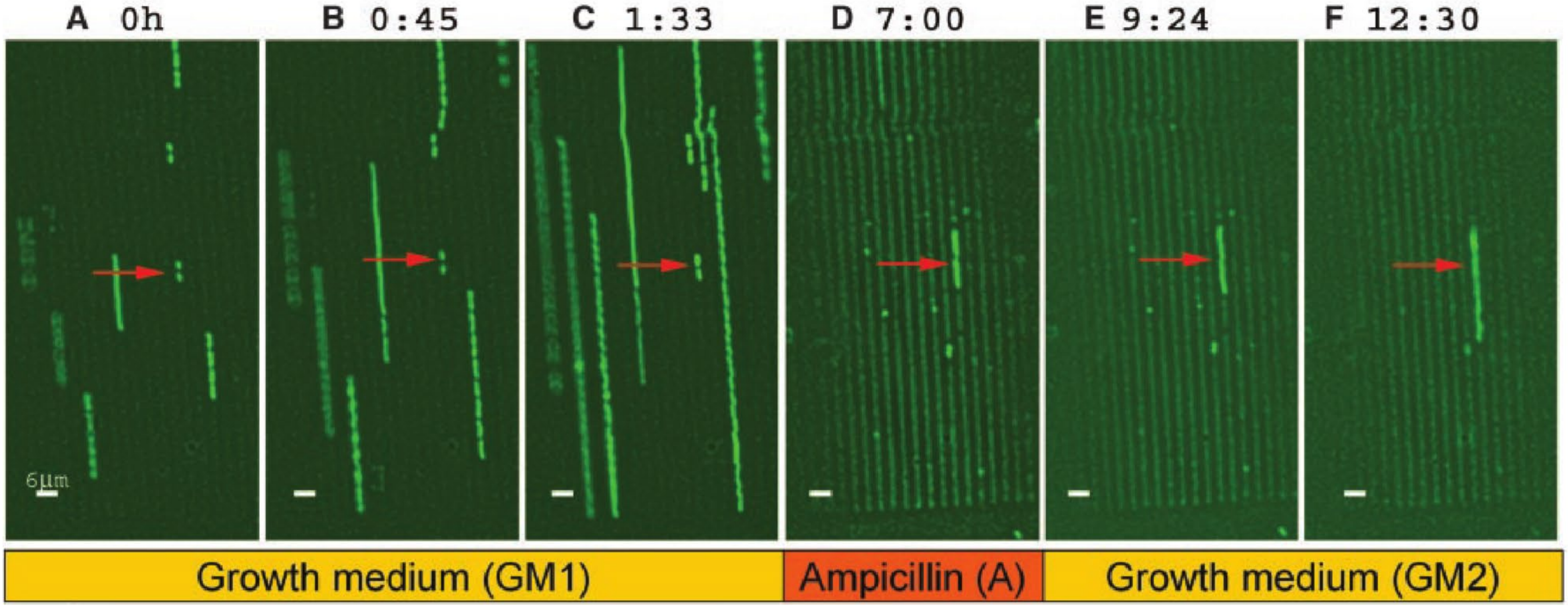
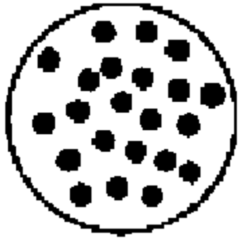
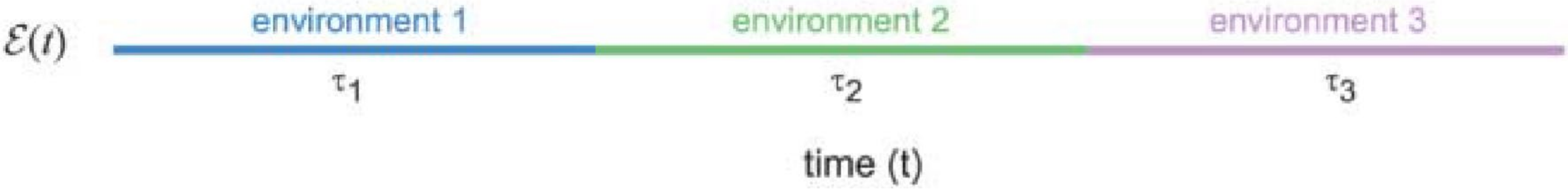
Bacterial persistence may be a bet-hedging strategy



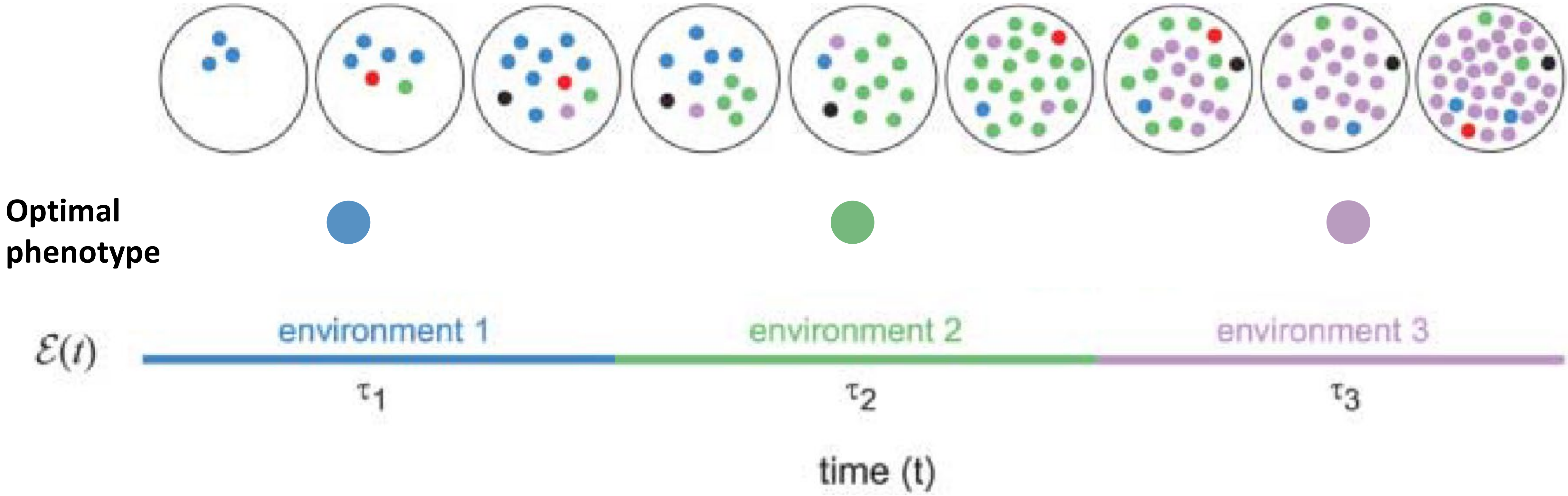
Fluctuating environments:
Fixed or random phenotype?

Fixed phenotype   Bet hedging

Optimal phenotype



Optimal behavior is a clever bet-hedging strategy



Bet-hedging can even outcompete sensing, if sensing carries a cost

- Would an organism that senses its environment and switches phenotype accordingly do better?
- This depends on
  - the cost of the machinery involved (larger favors bet-hedging)
  - the speed of the response (lower favors bet-hedging)
  - the frequency of switching (lower favors bet-hedging)
  - the uncertainty in the environment, quantified by environmental entropy (lower favors bet-hedging):

$$I_{\mathrm{env}} = -\sum_{ij} p_j b_{ij} \log b_{ij}$$

Random behavior can also evolve as a mixed evolutionary stable strategy

The New York Times

GLOBAL HEALTH

Measles Outbreak Infects 695, Highest Number Since 2000

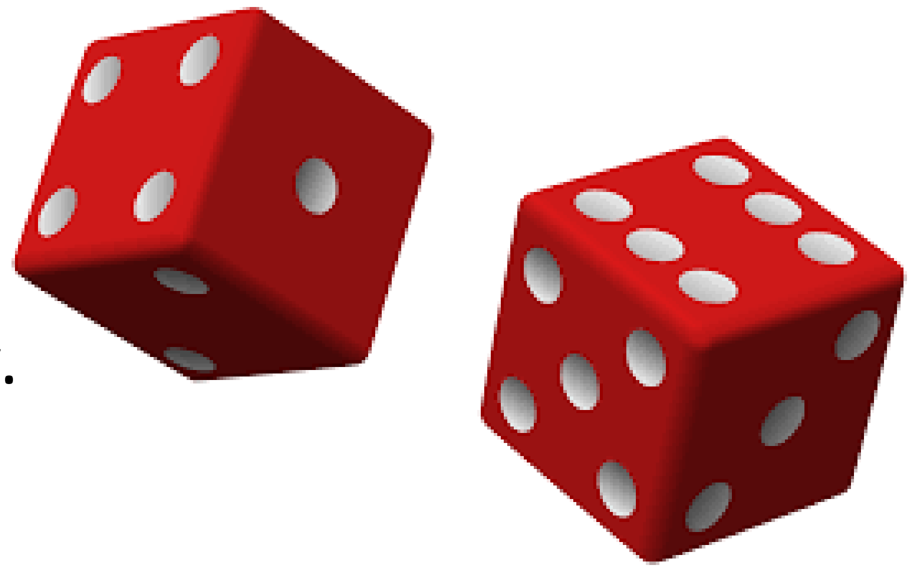
The outbreak, linked to skepticism about vaccines, has led to extraordinary measures, including $1,000 fines and bans on unvaccinated children in public.

No pure strategy is *stable*:

- If everyone takes the vaccine, individuals have an incentive to stop doing so.
- If nobody takes the vaccine, risk increases, individuals have an incentive to get a vaccine.

A mixed ("random") strategy could be stable

If everyone has the vaccine with probability p
such that the expected payoff of getting the vaccine
or not getting the vaccine are *equal*,
no other strategy can invade.



This would be the *evolutionary stable strategy*.

Not optimal in any way,
but could nevertheless be selected.

Conclusion:

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