Quantitative principles in biological systems

1. Chemotaxis and random walks

Spring 2025

What is surprising about biology?

$F = ma$

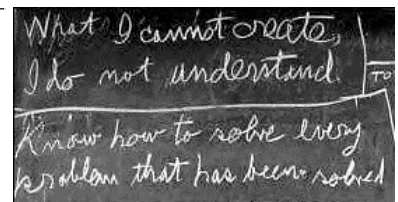Complex, diverse, evolved, functional, …

What are the quantitative principles governing biological systems?

Syllabus

Week	Topic
	Sensing molecules
1	Chemotaxis and random walks
2	Chemotaxis and chemical reaction networks
3	Problem solving session #1
	Optimizing growth
4	Bacterial growth and optimization
5	Gene regulation and statistical mechanics
6	Problem solving session #2
	Representing information
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15	Final project presentations
16	Searching for principles

→ Hopfield again –
Kinetic proofreading

→ Tools for predicting the next
pandemic strain

→ Hopfield networks –
2024 Nobel in physics

Syllabus

Week	Topic	Assignment
	Sensing molecules	Problem set #1
1	Chemotaxis and random walks	
2	Chemotaxis and chemical reaction networks	
3	Problem solving session #1	
	Optimizing growth	Problem set #2
4	Bacterial growth and optimization	
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	Representing information	Problem set #3
7	Morphogenesis and information theory	
8	Sequences and spin glass models	
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	Evolving diversity	Problem set #4
10	Evolution and evolutionary dynamics	&
11	Microbiomes and random matrix theory	Final project
12	Problem solving session #4	
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What I cannot create, I do not understand.
Know how to solve every problem that has been solved

Syllabus

Learning goals –

1. Biological systems follow quantitative principles.

2. Interdisciplinary research is more than mix and match.

3. We can *do* it!

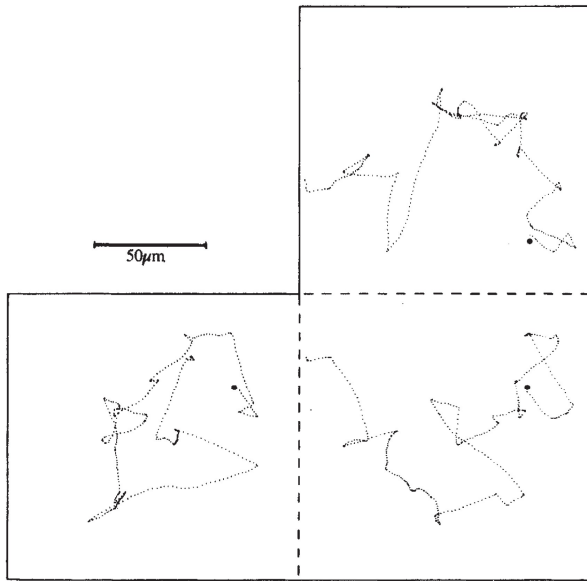## Bacterial chemotaxis will be our introduction to quantitative principles.

Numbers rule –

Size ~1 um

Speed ~20 um/s (!)

Lauga. *Annu Rev Fluid Mech* (2016)

Single-cell trajectories look like random walks.

The Problem of the Random Walk.

CAN any of your readers refer me to a work wherein I should find a solution of the following problem, or failing the knowledge of any existing solution provide me with an original one? I should be extremely grateful for aid in the matter.

A man starts from a point O and walks l yards in a straight line; he then turns through any angle whatever and walks another l yards in a second straight line. He repeats this process n times. I require the probability that after these n stretches he is at a distance between r and $r + \delta r$ from his starting point, O.

The problem is one of considerable interest, but I have only succeeded in obtaining an integrated solution for *two* stretches. I think, however, that a solution ought to be found, if only in the form of a series in powers of $1/n$, when n is large.　　　　　　　KARL PEARSON.
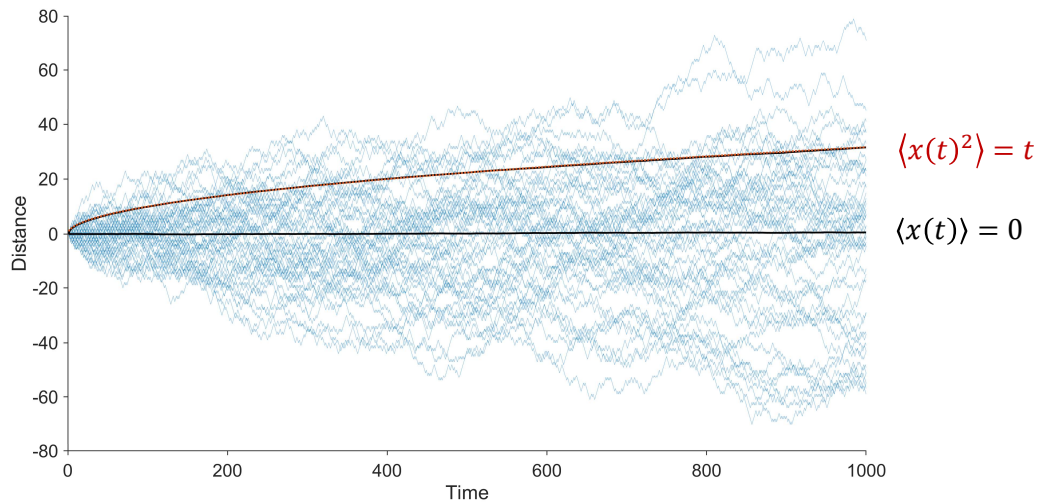
The Gables, East Ilsley, Berks.
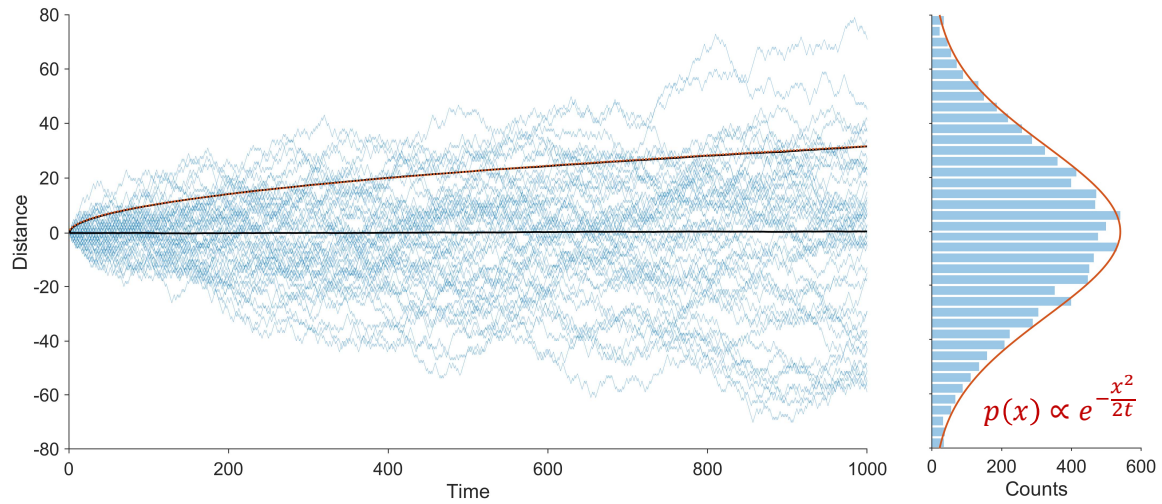
Pearson. *Nature* (1905)
Berg and Brown. *Nature* (1972)

Consider a simple 1D random walk.

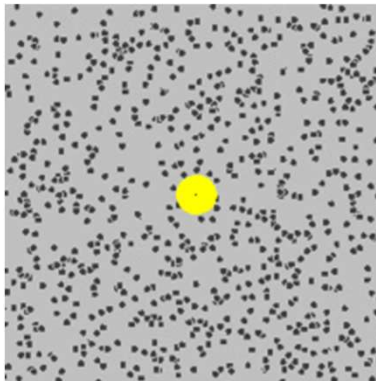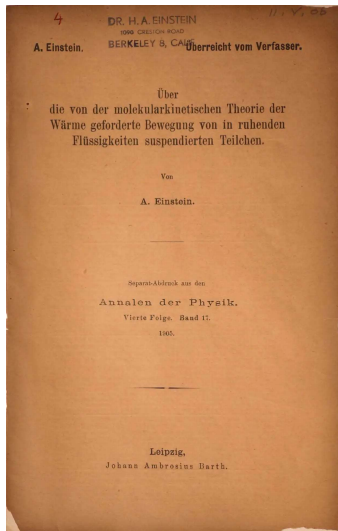At each time step, take a step left or right with equal probability.

$$\langle x(t)^2 \rangle = t$$

$$\langle x(t) \rangle = 0$$

Consider a simple 1D random walk.

At each time step, take a step left or right with equal probability.

$$p(x) \propto e^{-\frac{x^2}{2t}}$$

From random walks to diffusion.

$$\langle x^2 \rangle \propto Dt$$

$$D = \frac{kT}{6\pi\eta r}$$

Diffusion coefficient

Viscosity

Einstein. *Ann Phys* (1905)
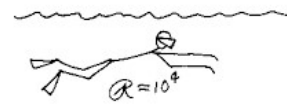Wikipedia

From random walks to diffusion.

$D \approx 100$ um^2/s
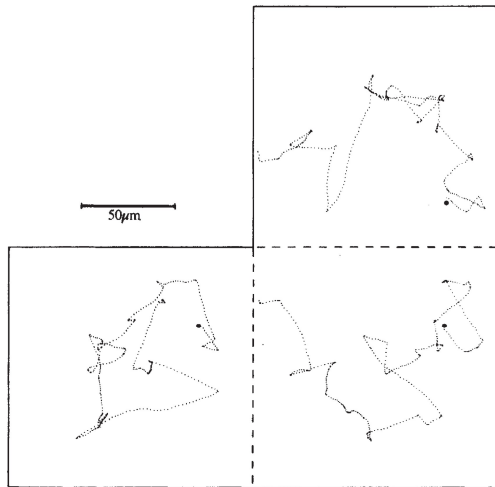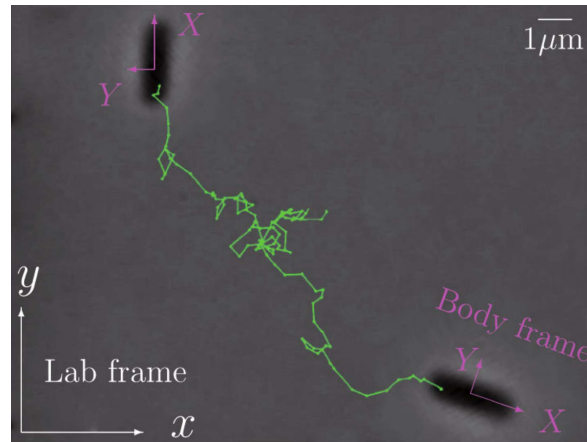
$D \approx 1$ um^2/s

Tavadodd et al. *Eur Phys J E* (2011)
Berg and Brown. *Nature* (1972)

Bacteria live in low Reynolds number.

Numbers rule –

Reynolds number Re =
(density*speed*length) / (viscosity η)

Bacteria can't coast!

Purcell. *Am J Phys* (1976)
Lauga. *Annu Rev Fluid Mech* (2016)
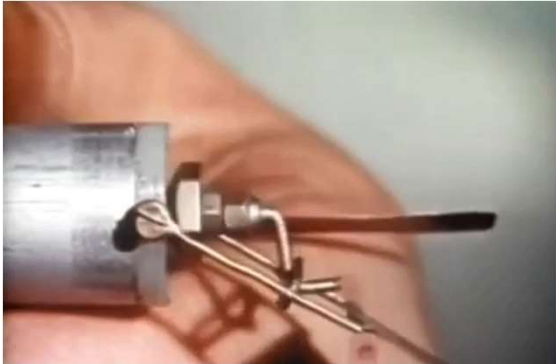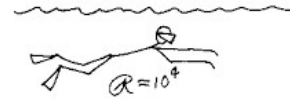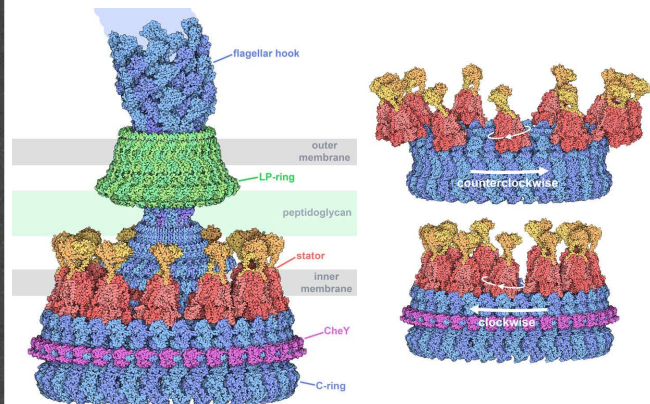
Bacteria live in low Reynolds number.

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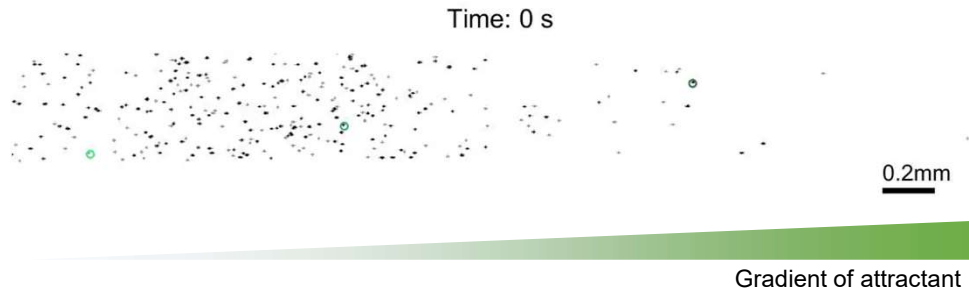
Bacteria can't coast!

Purcell. *Am J Phys* (1976)
Lauga. *Annu Rev Fluid Mech* (2016)

Run and tumble, counterclockwise and clockwise

David Goodsell. PDB (2024)
Lauga. *Annu Rev Fluid Mech* (2016)

Bacterial chemotaxis will be our model system for sensing.

Time: 0 s

0.2mm

Gradient of attractant

- How to measure gradients?
- Control which components of the process?

Yang Bai et al. *eLife* (2021)

Statistics of runs and tumbles

How random is the motion?
They are Poisson processes:
Constant rate of events
Independent events

From calculations of autocorrelation functions of sequences of twiddles and of sequences of runs we conclude that twiddles and runs of different length occur at random. The statistics are

$p(t) \propto e^{-\lambda t}$

Runs

Tumbles

Speed (µm/s)

Time (s)

Fraction of twiddles or runs of length greater than a given length

Twiddle length or run length(s)
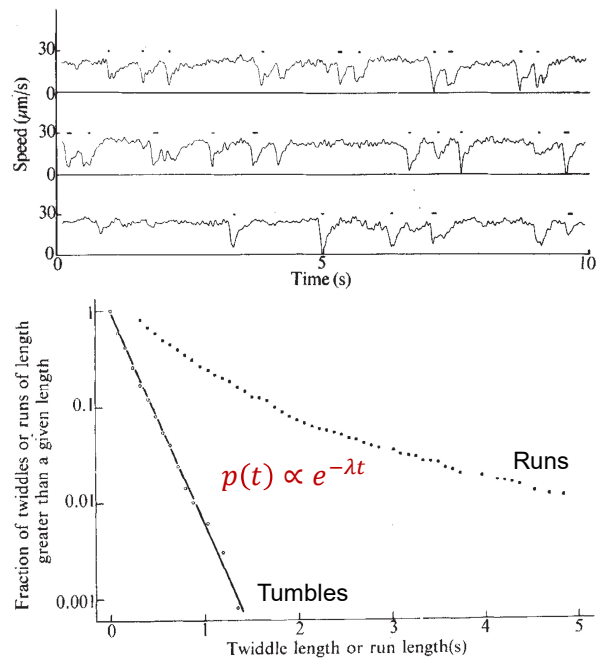
Berg and Brown. *Nature* (1972)

How precise can cells sense concentration levels?

Concentration c

Random walks with diffusion constant D

Equilibration time $\tau_d = a^2/D$

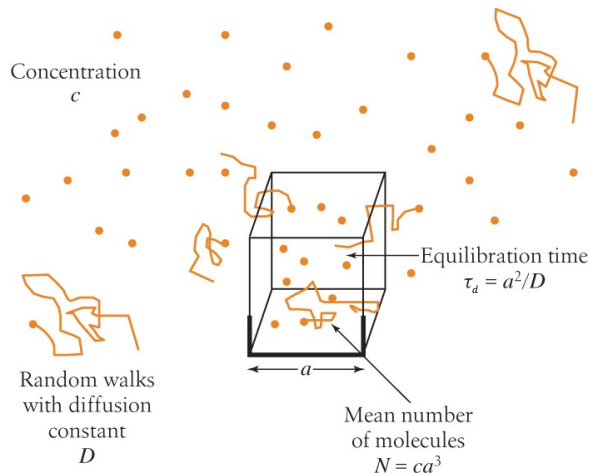Mean number of molecules $N = ca^3$

What are typical values of c and D?

$c \approx 1$ nM $\quad \to$ 1 molecule per cell
$D \approx 10$ um²/s $\to 10^{-1}$ second per cell

What is the precision of counting n molecules?
Poisson process again!
$$\langle n \rangle = N$$
$$\langle n^2 \rangle = N$$
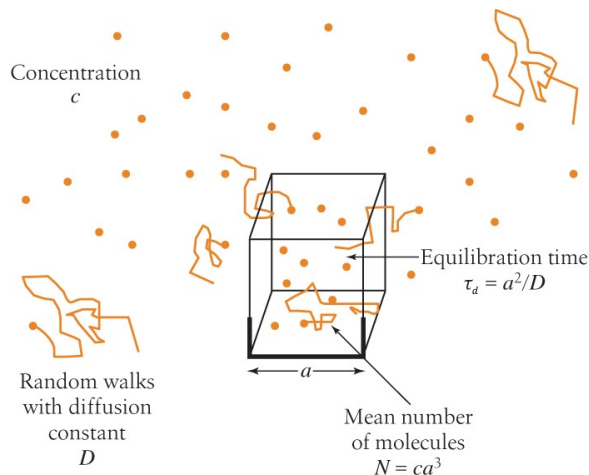$$n \approx N \pm \sqrt{N}$$

How many molecules are counted over time?
(counting time τ) / τ_d * $N \sim Dac\tau$
τ_d: time to "renew" sampled volume

Relative error $\dfrac{\Delta c}{c} = \dfrac{1}{\sqrt{Dac\tau}}$

Bialek

How precise can cells sense concentration levels?

Concentration c

Random walks with diffusion constant D

Equilibration time $\tau_d = a^2/D$

Mean number of molecules $N = ca^3$

Numbers rule –

Diffusion limited rate $Dac \approx 500$ s⁻¹
$\to$ Relative error $\dfrac{\Delta c}{c} \geq 3\%$ after 1 s.

Measurable gradient across the length of a cell cannot be smaller than $\dfrac{1}{c}\dfrac{\Delta c}{\Delta x} \approx 30$ mm⁻¹
… but actual gradients much shallower

Must measure temporal gradients!
Runs last 1 s at 20 um/s
... measurable gradient is now ≈ 1 mm⁻¹.

Why not measure even longer?

Bialek

How precise can cells sense concentration levels?

CheC497
Nonchemotactic mutant
7.2s
1 run
Mean speed 31.3 $\mu m/s$

50μm

Berg and Brown. *Nature* (1972)

Numbers rule –

Diffusion limited rate $Dac \approx 500$ s^{-1}
   → Relative error $\frac{\Delta c}{c} \geq 3\%$ after 1 s.

Measurable gradient across the length of a cell
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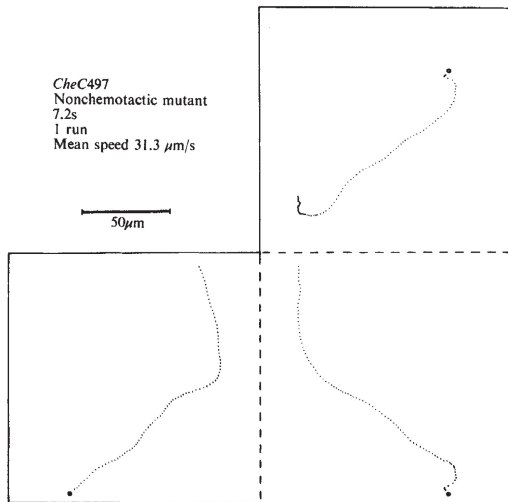   … but actual gradients much shallower

Must measure temporal gradients!
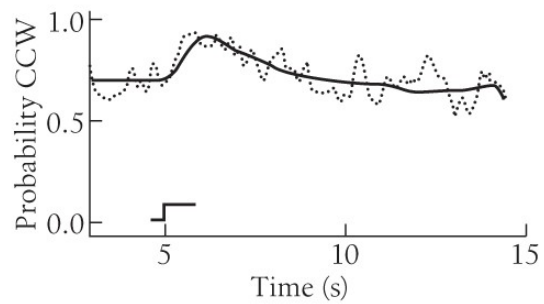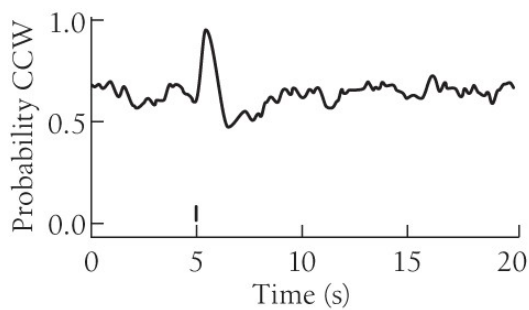   Runs last 1 s at 20 um/s
   ... measurable gradient is now ≈ 1 mm^{-1}.

Why not measure even longer?
   Rotational diffusion.
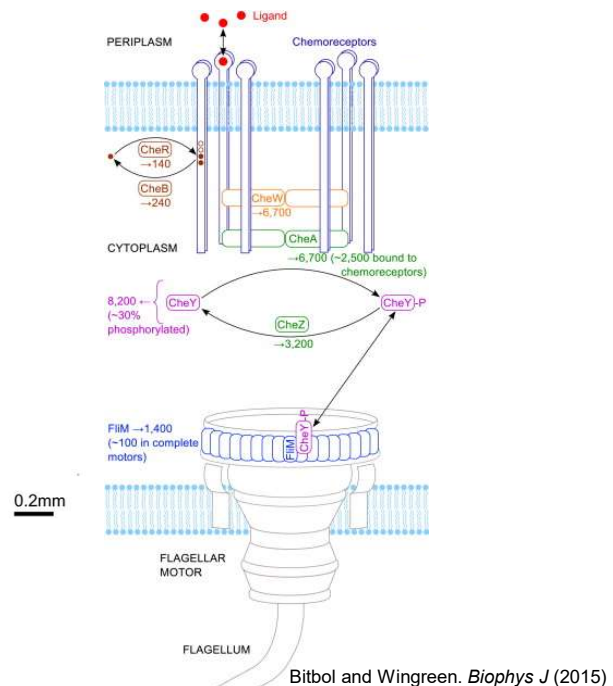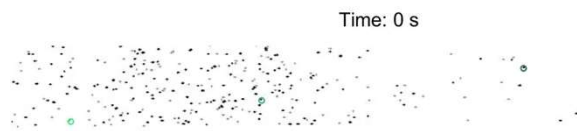

Bacteria measure temporal gradients.

Adaptation

Block et al. *Cell* (1982)

Summary

- Numbers provide intuitions for understanding biological systems.

- Bacterial chemotaxis is a stochastic process that senses and adapts to single molecules.

Time: 0 s

0.2mm

Bitbol and Wingreen. *Biophys J* (2015)

Themes and perspectives

A personal take on science and society

World view

Biology must generate ideas as well as data

By Paul Nurse

Data should be a means to knowledge, not an end in themselves.

Accepting a Nobel prize nearly two decades ago, my old friend Sydney Brenner had a warning for biology. "We are drowning in a sea of data and starving for knowledge," he said. That admonishment, from one of the founders of molecular biology, who established the nematode worm *Caenorhabditis elegans* as a model organism, is even more relevant to biology today.

Rather often, I go to a research talk and feel drowned in data. Some speakers seem to think they must unleash a tsunami of data if they are to be taken seriously. The framing is neglected, along with why the data are being

"It would have been a pity if Darwin had stopped thinking after describing the shapes and sizes of finch beaks."

To refocus on that goal, we must improve our working processes, placing a greater emphasis on theory and shifting our research culture.

How? Embed engineers and experimentalists who are developing new technologies and methods deeply into the biological problems. It is through deep familiarity with the biology – not simply a drive to collect more and more data – that important questions will be asked. Such questions will sustain the investigators' passion to keep probing data until patterns and knowledge emerge, and will also influence the data that are gathered.

There are other necessary steps. Develop appropriate analytical tools, including programs for data mining and machine learning. Make certain that data are usable, properly annotated and openly shared. Model the molecular and cellular components involved in a biological

Themes and perspectives

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→ What problems are biological systems trying to solve and how?

→ How do biological systems navigate parameter space?

→ How do biological systems represent information?

→ How does biological diversity emerge and persist?