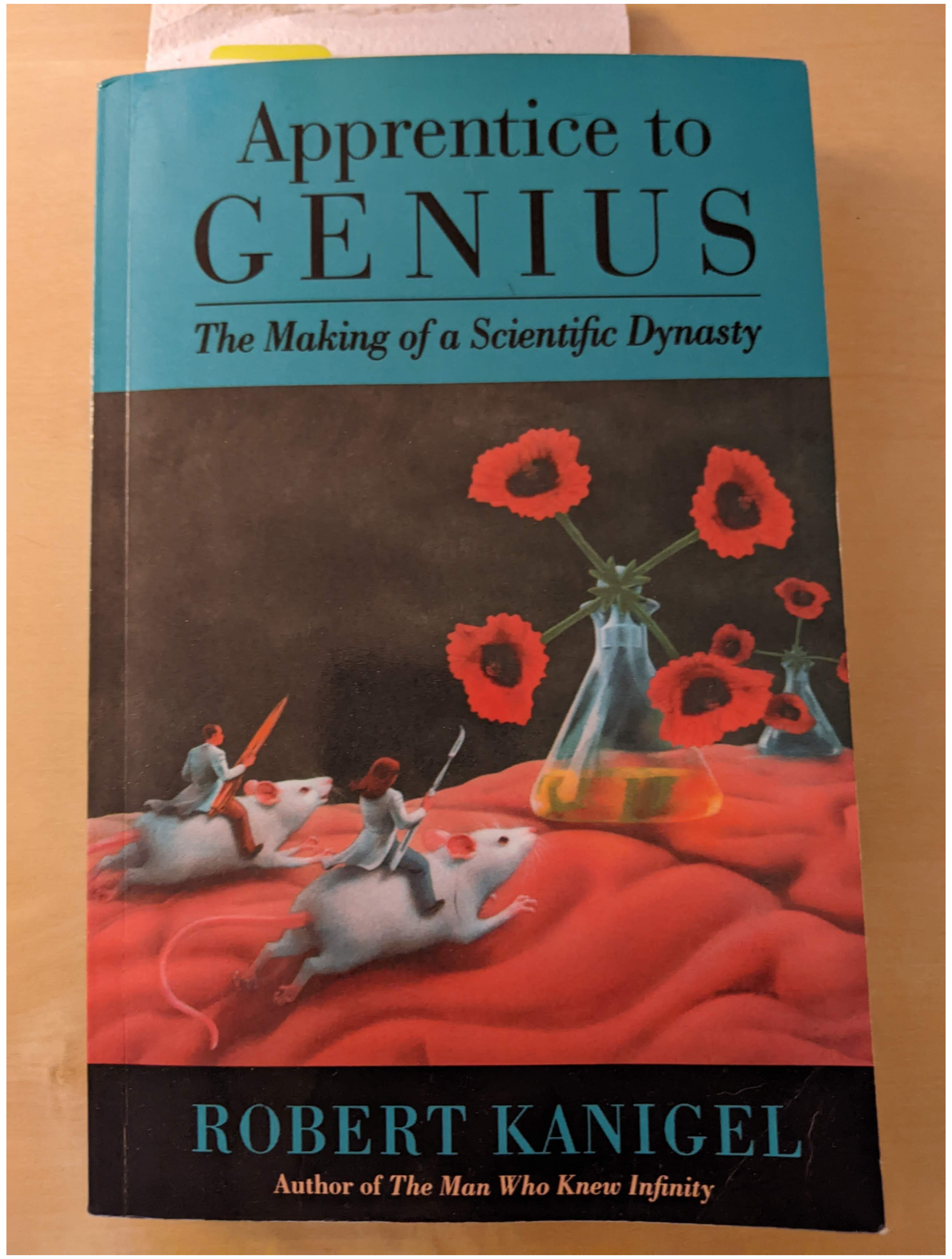
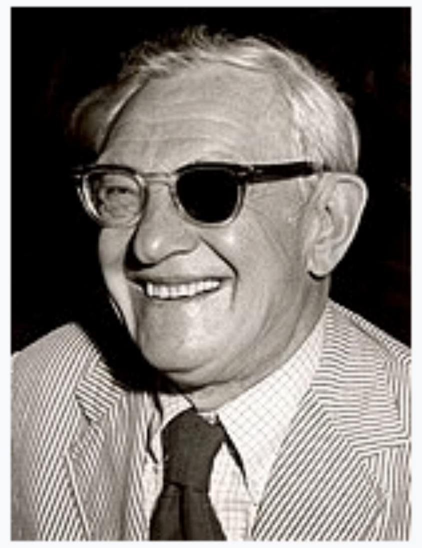
Introduction to mathematical modelling for molecular and cellular biologists

Jun Allard,
Department of Physics; Department of Mathematics,
UC Irvine



Julius Axelrod



Julius Axelrod (May 30, 1912 – December 29, 2004)[1] was an American biochemist. He won a share of the Nobel Prize in Physiology or Medicine in 1970 along with Bernard Katz and Ulf von Euler.[2][3][4][5] The Nobel Committee honored him for his work on the release and reuptake of catecholamine neurotransmitters, a class of chemicals in the brain that include epinephrine, norepinephrine, and, as was later discovered, dopamine. Axelrod also made major contributions to the understanding of the pineal gland and how it is regulated during the sleep-wake cycle.[6][7][8]

tamination. But he knew that a trace of contamination wouldn't mask the kind of results he'd set up the experiment to reveal with black-on-white crispness. By every account, he was a master at reducing complex questions to simple experiments with clear answers.

Roland D. Ciarnello, now at Stanford, tells how he can never see the *New York Times* without thinking of his mentor. They'd sit at Axelrod's desk going over the data and the moment Ciarnello got them bogged down in useless detail, Axelrod's attention would drift. "When you got to the differential equations, his eyes would wander to the *New York Times* on his desk. At that point I knew I had to simplify further."

"I don't like to do complex experiments. I'm not a complicated person," says Axelrod, as evenly as you could imagine, mildly, as a statement of neutral fact. But another time, extolling the virtues of simplicity in science, some of the modesty falls away. "Picasso," he says, "makes a single line—but it takes a lot of time and thought."

Axelrod's scientific articles were sometimes almost laughably simple. A few numbers, a few bar graphs that looked like they'd leapt intact from a sixth-grade arithmetic book. Axelrod had no use for statistics; resort to them, he felt, meant simply that the experiment was poorly designed. Better, re-

Outline

1. Main challenges of computational biology
2. Case study: Synthetic gene expression in bacteria
3. Simulation and differential equations
4. Common arrow diagrams
5. “Reverse” modeling

The goals, challenges and approaches of modern computational biology

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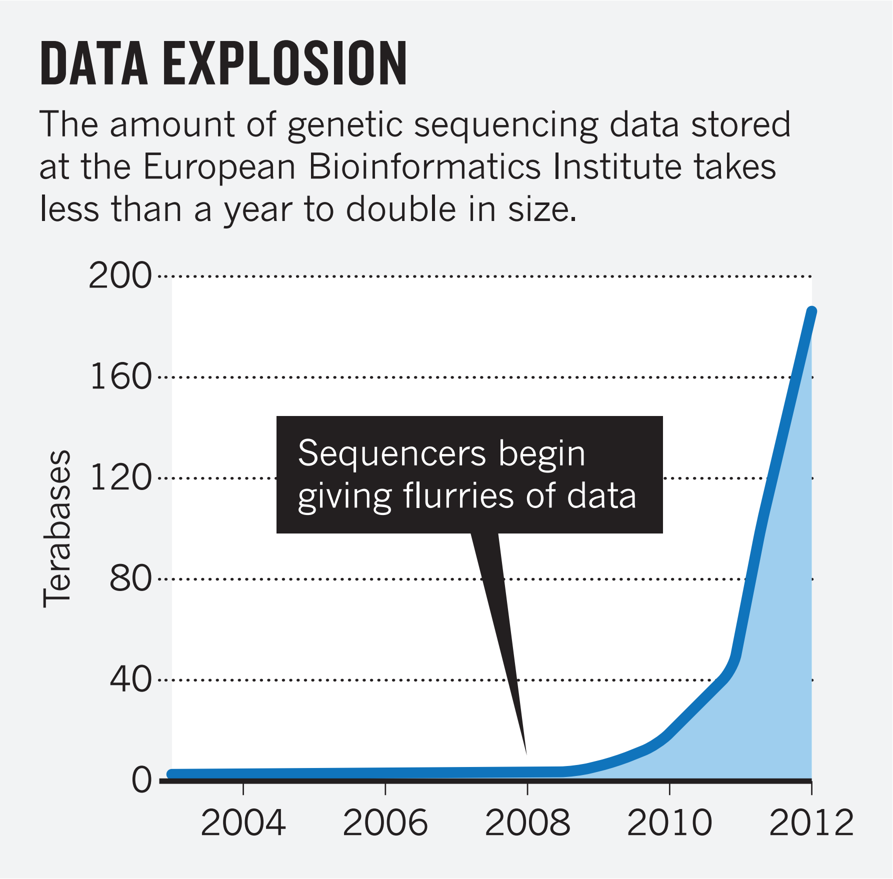
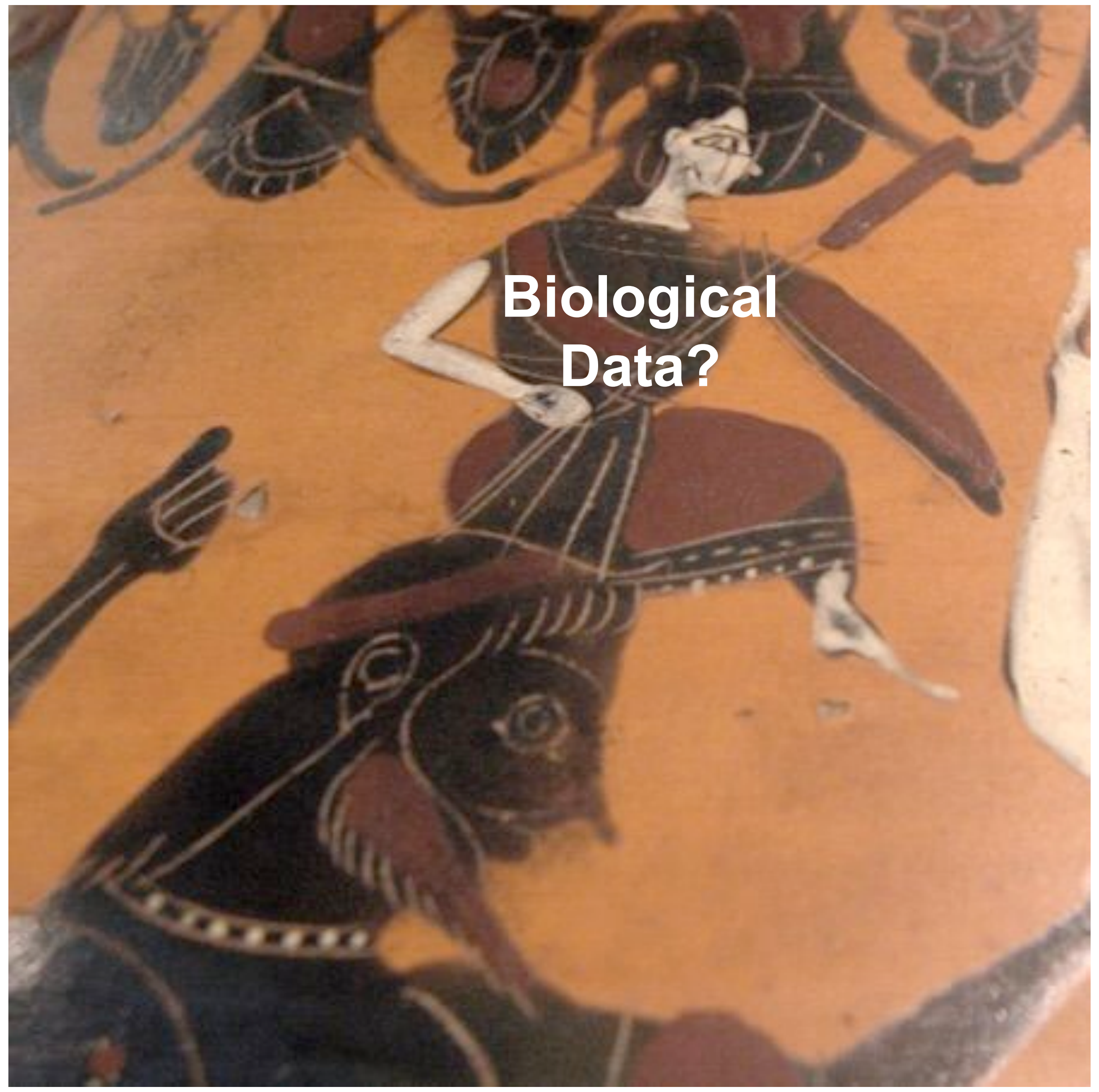
THE BIG CHALLENGES OF BIG DATA

As they grapple with increasingly large data sets, biologists and computer scientists uncork new bottlenecks.





Athena

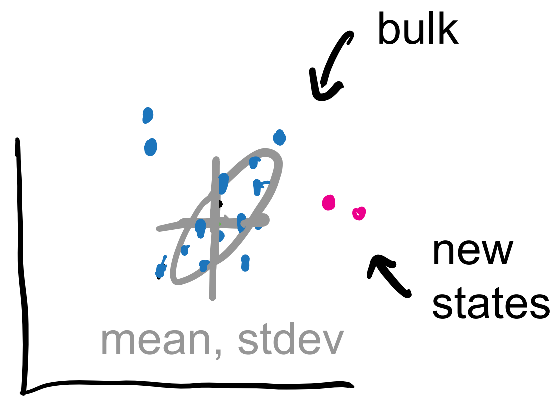
From Wikipedia, the free encyclopedia

She was the daughter of Zeus, produced without a mother, so that she emerged full-grown from his forehead. There was an alternative story that Zeus swallowed Metis, the goddess of counsel, while she was pregnant with Athena, so that Athena finally emerged from Zeus. Being the favourite child of Zeus, she had great power. In the classical Olympian pantheon, Athena was regarded as the favorite daughter of Zeus, born fully armed from his forehead.[89][90][91][h] The story of her birth comes in several versions.[92][93][94] The earliest mention is in Book V of the *Iliad*, when Ares accuses Zeus of being biased in favor of Athena because "*autos egeinao*" (literally "you fathered her", but probably intended as "you gave birth to her").[95][96] She was essentially urban

The goals, challenges and approaches of modern computational biology

Data and analytics

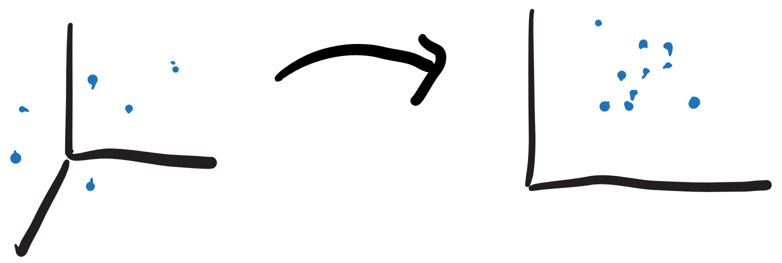
- Keystone goal: **Discover the hidden** (new states, cell types, disease classes,...)



- Keystone challenge: Biological data is not just big, it's **high-dimensional**.

30000 genes
1000 cells

10^4 microbial species
20 patients



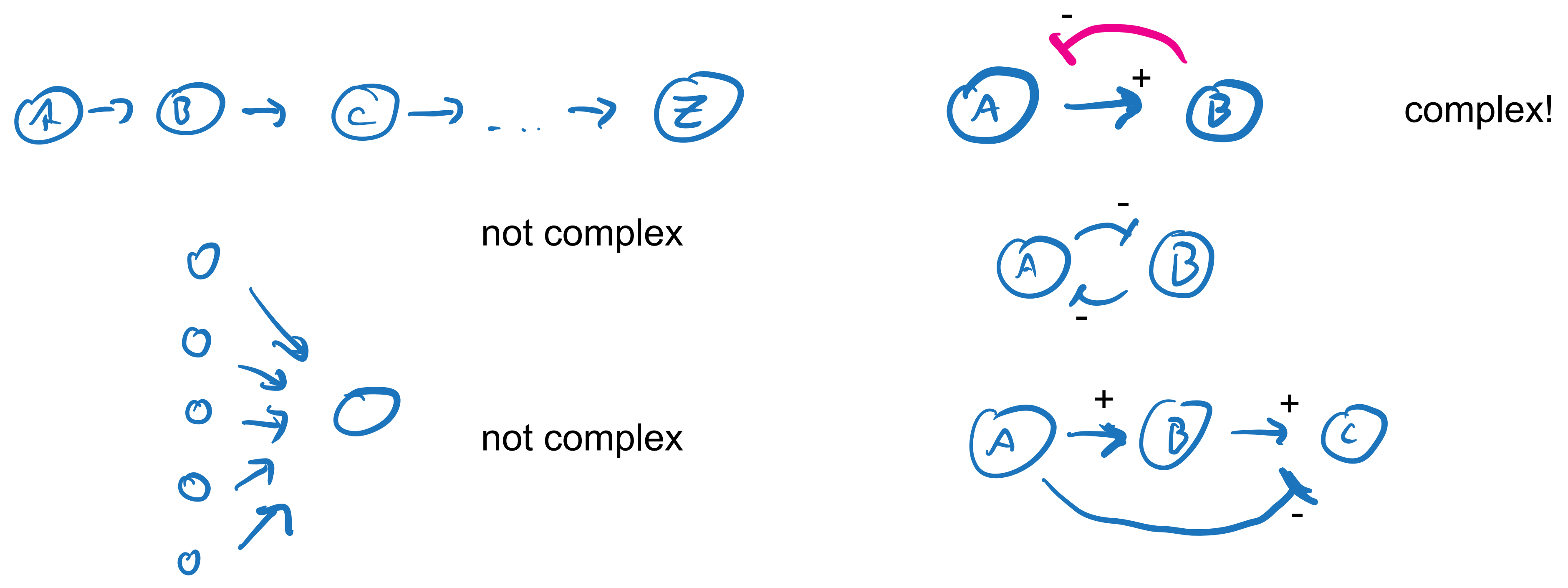
- Keystone tool: Clustering, regression, dimension-reduction… coding

Models and mechanism

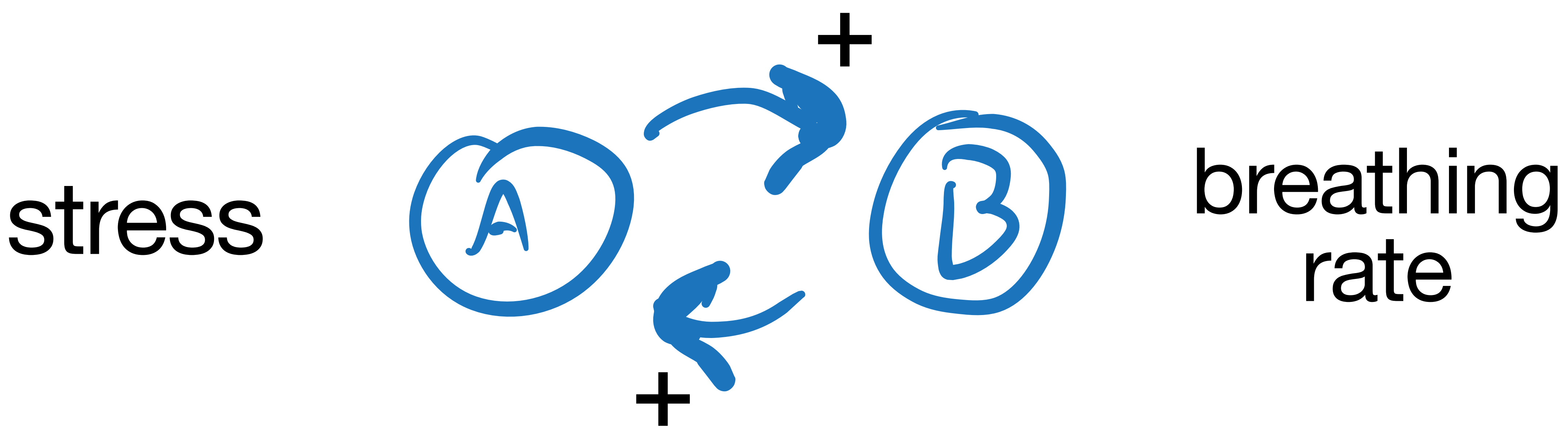
- Keystone goal: **Prediction** (“What would happen if…")

if A is increased, then...

- Keystone challenge: Biological systems are **complex** (not just big)



- Keystone tool: Dynamical systems, control theory, (the differential equation,) …


stress
A
+
+
B
breathing
rate

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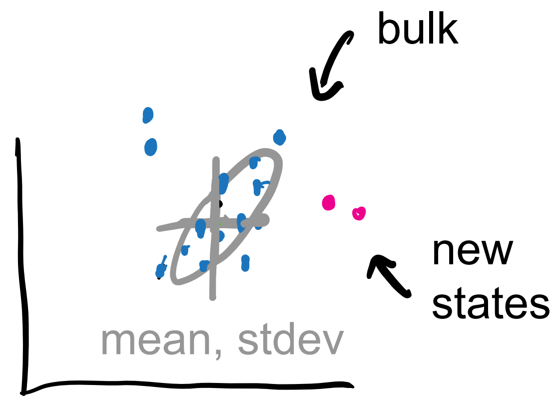

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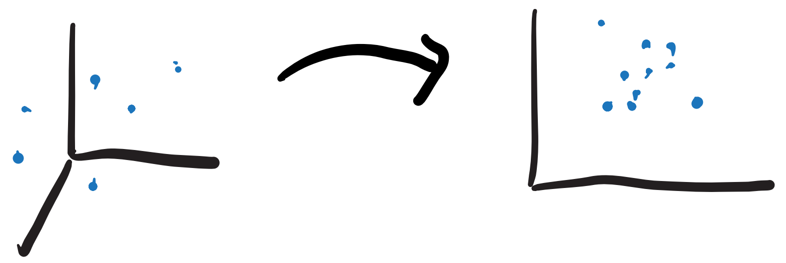

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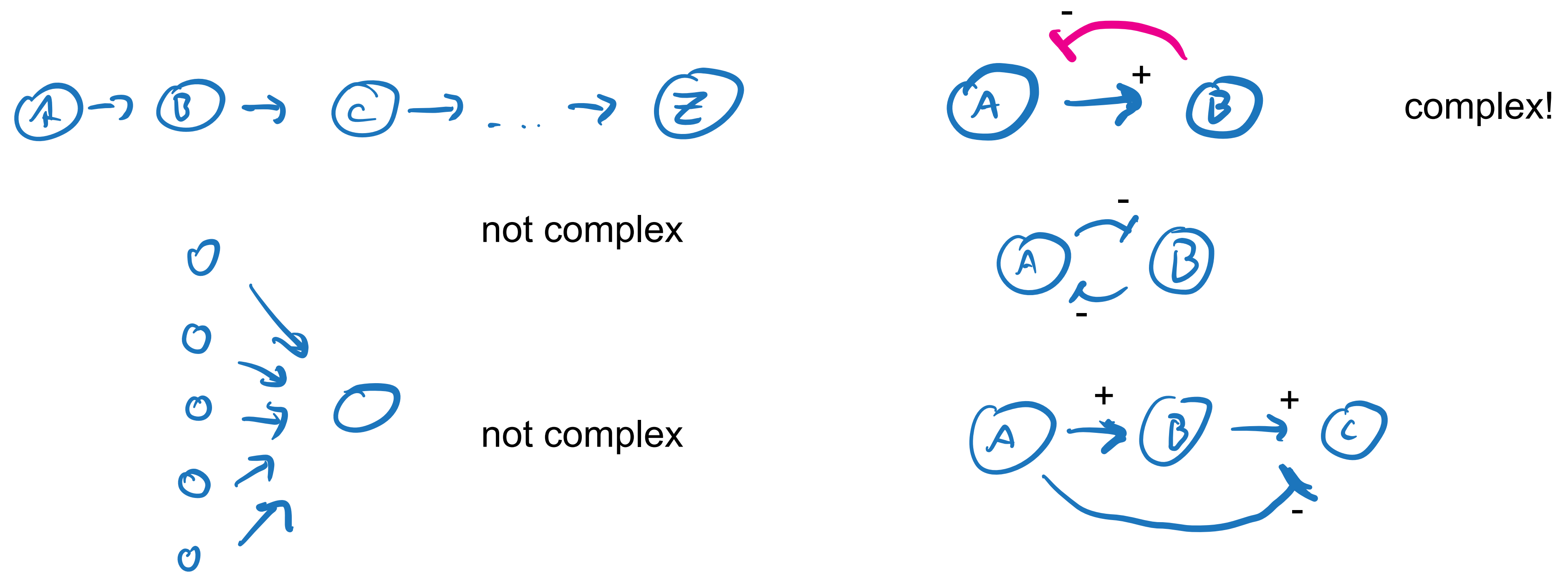

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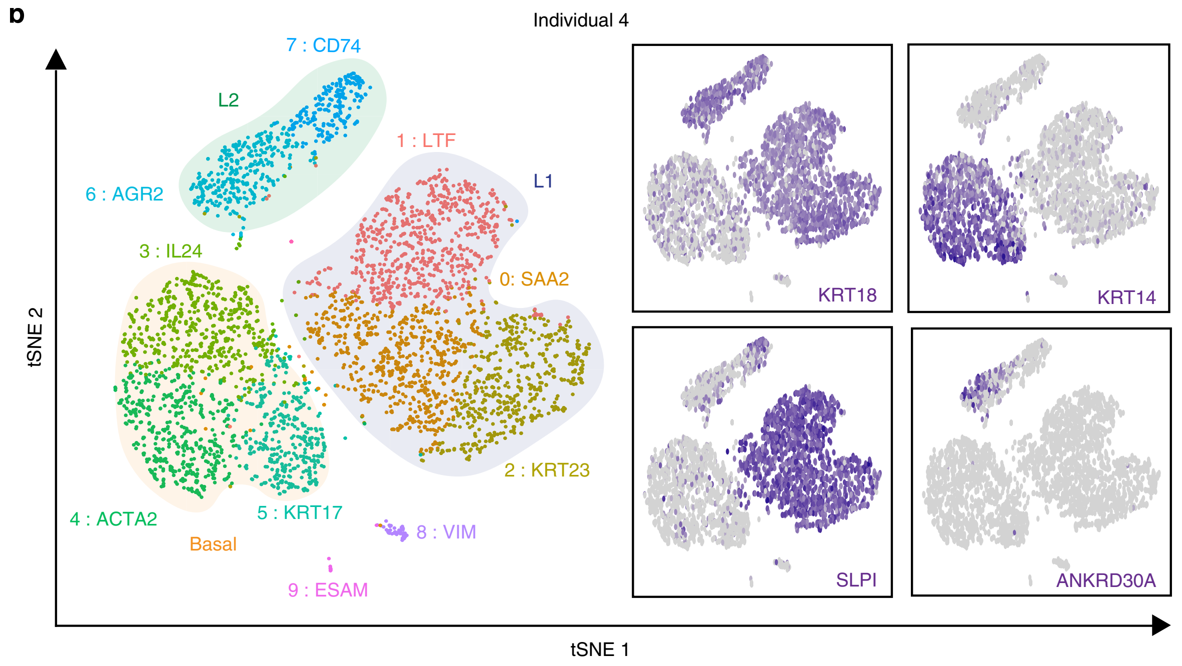
NATURE COMMUNICATIONS | (2018)9:2028

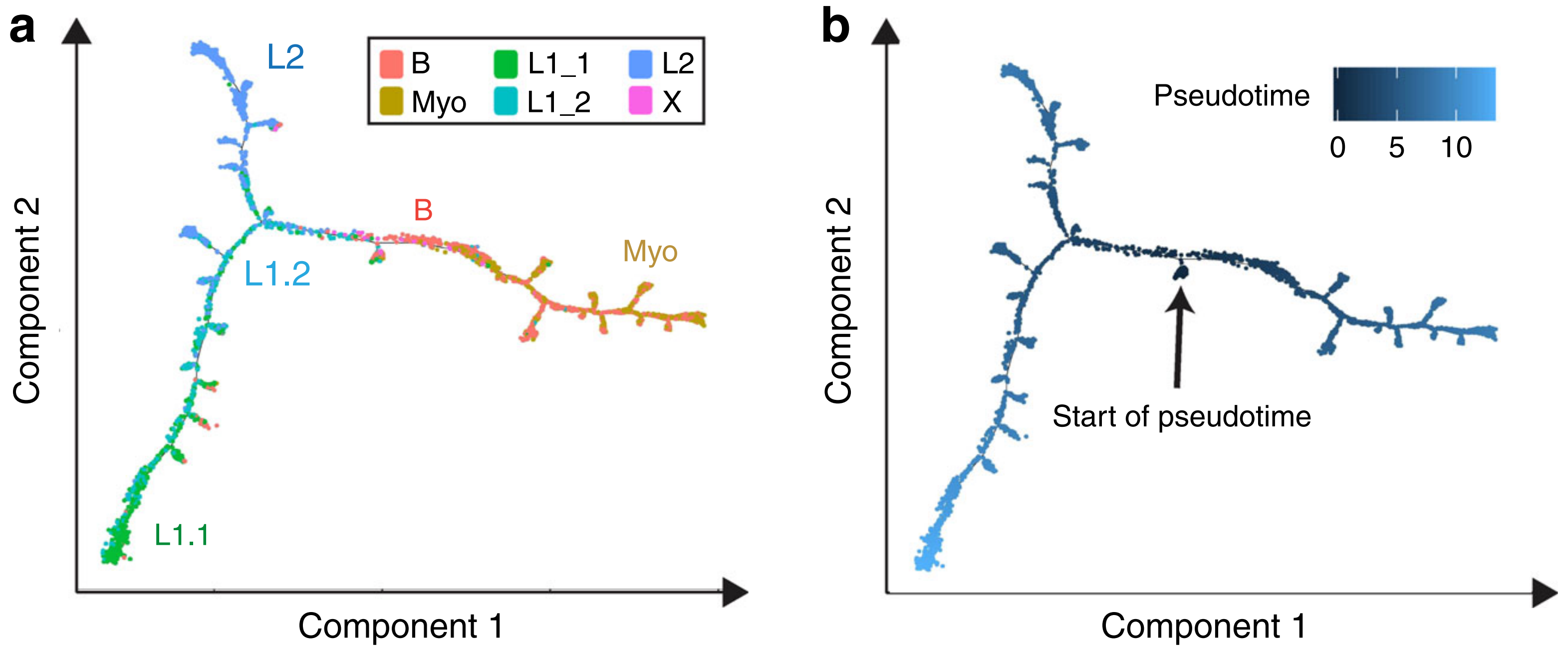
Profiling human breast epithelial cells using single cell RNA sequencing identifies cell diversity

Quy H. Nguyen[1], Nicholas Pervolarakis[2], Kerrigan Blake[2], Dennis Ma[1], Ryan Tevia Davis[3], Nathan James[1], Anh T. Phung[3], Elizabeth Willey[4], Raj Kumar[4], Eric Jabart[5], Ian Driver[4], Jason Rock[4], Andrei Goga[6], Seema A. Khan[7], Devon A. Lawson[3], Zena Werb[4] & Kai Kessenbrock[1]

and additional quality control filtering (see Methods section), we proceeded to analyze 703 single cell at ~4500 genes detected on average per cell, where the gene detection range was comparable between basal and luminal cells (Supplementary Fig. 1c).

indirect immunofluorescence analysis to validate our scRNAseq findings on the protein level and to spatially integrate newly discovered cell types and states into the anatomy of the breast. We first focused on the cell states detected within the basal





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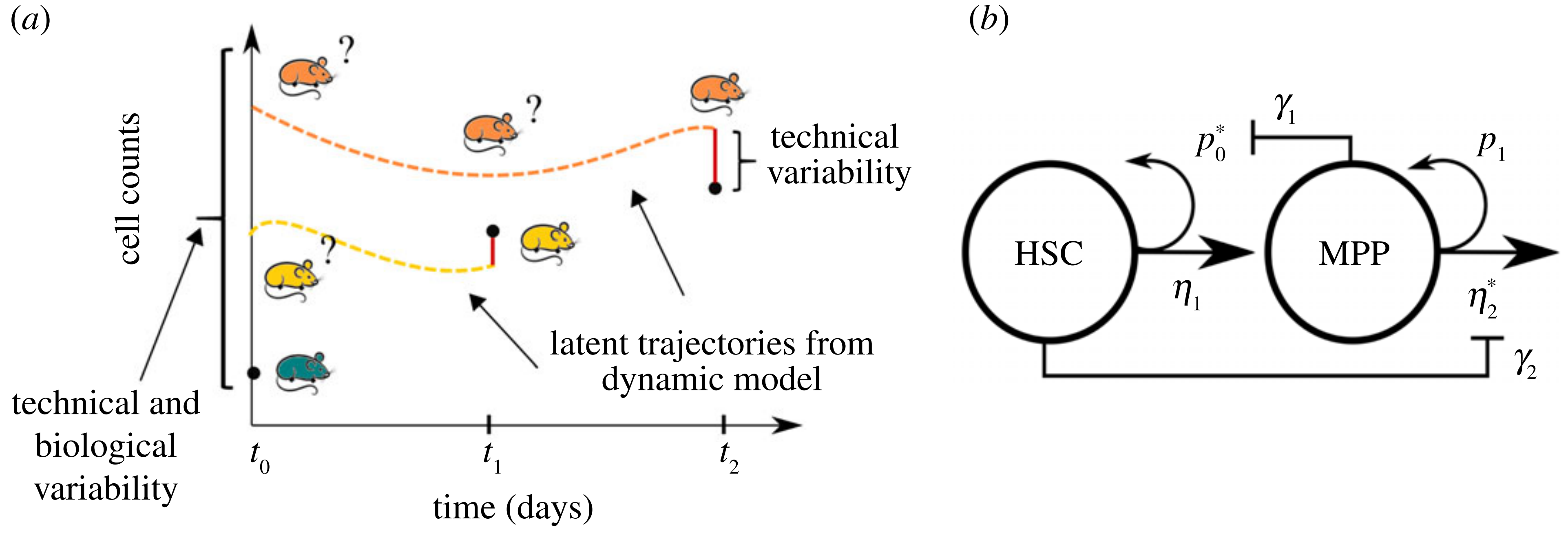
Optimal experimental design for mathematical models of haematopoiesis

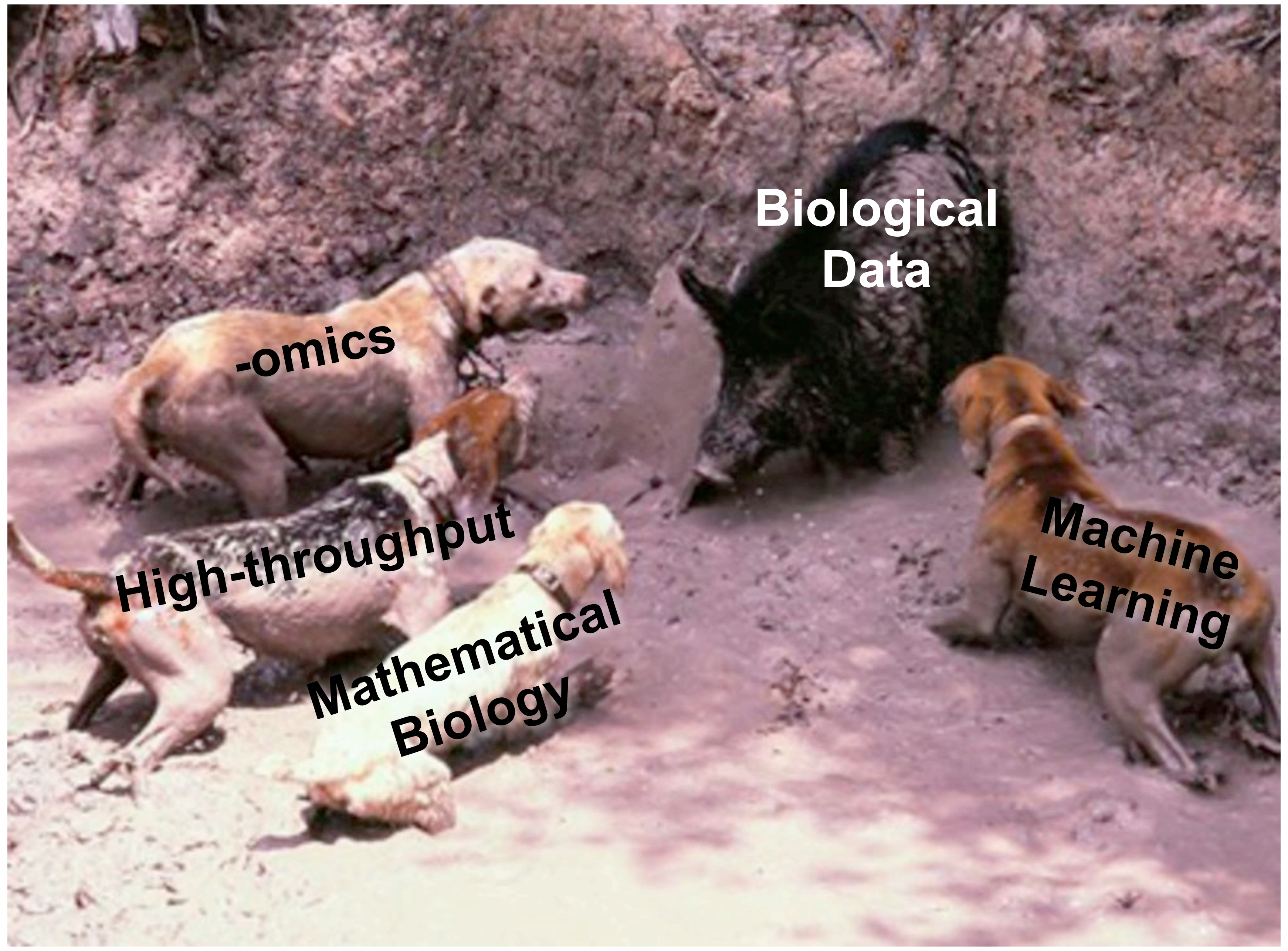
Luis Martinez Lomeli[1,†], Abdon Iniguez[1,†], Prasanthi Tata[2], Nilamani Jena[2], Zhong-Ying Liu[2], Richard Van Etten[1,2,3,4,5], Arthur D. Lander[1,4,5,6,7], Babak Shahbaba[1,4,8], John S. Lowengrub[1,4,5,7,9] and Vladimir N. Minin[1,4,8]

royalsocietypublishing.org/journal/rsif *J. R. Soc. Interface* **18**: 20200729

that accounts for feedback and feedforward regulation on cell division rates and self-renewal probabilities. A significant obstacle is that the experimental data are not longitudinal, rather each data point corresponds to a different animal. We overcome this difficulty by modelling the unobserved cellular levels as latent variables. We then use principles of Bayesian experimental design to optimally distribute time points at which the haematopoietic cells are quantified. We evaluate our approach using synthetic and real experimental data and show that an optimal design can lead to better estimates of model parameters.



The goals, challenges and approaches of modern computational biology



… require multiple approaches.

The goals, challenges and approaches of modern computational biology

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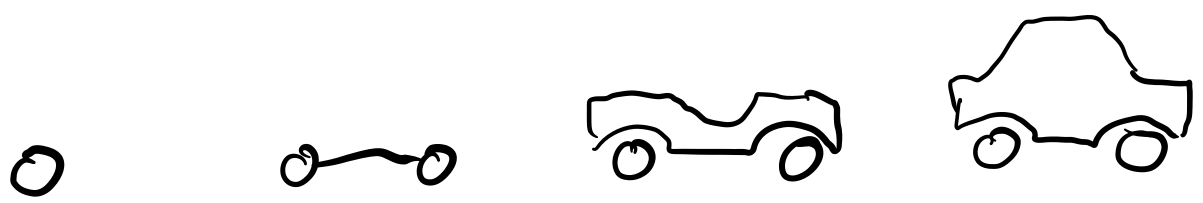
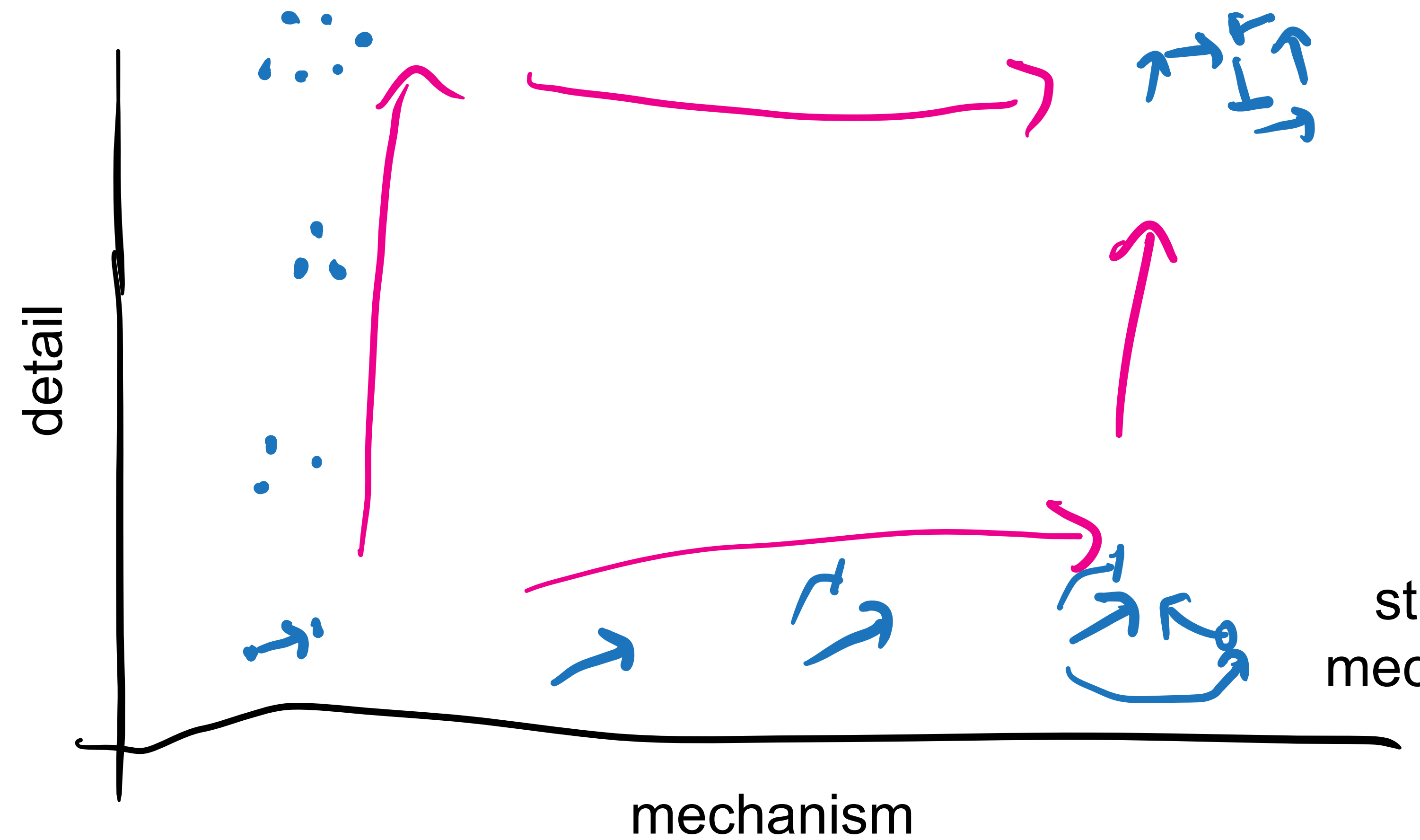
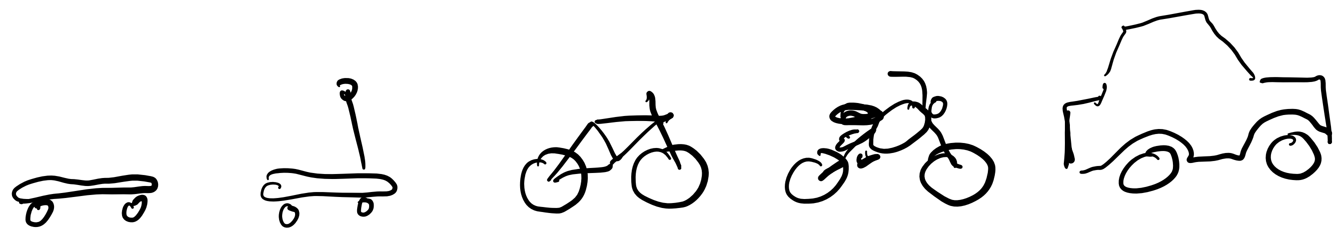


strategy: discover everything first (predictive understanding later)



strategy: get approximate mechanism first (details later)



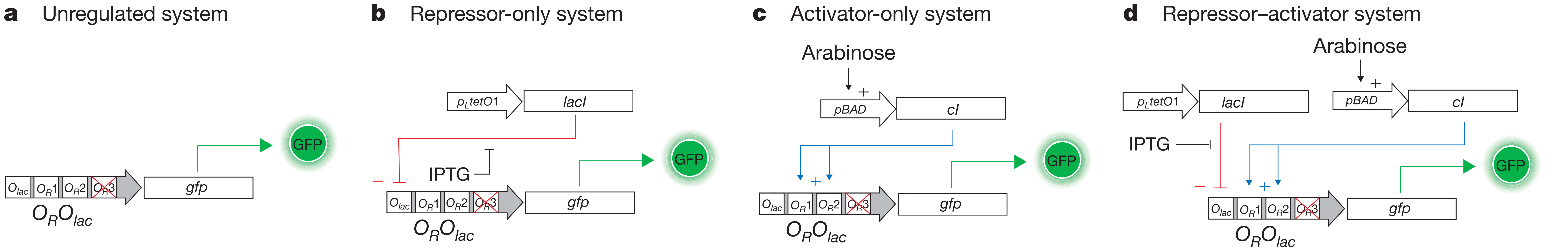
Case study: Synthetic gene expression in engineered bacterium

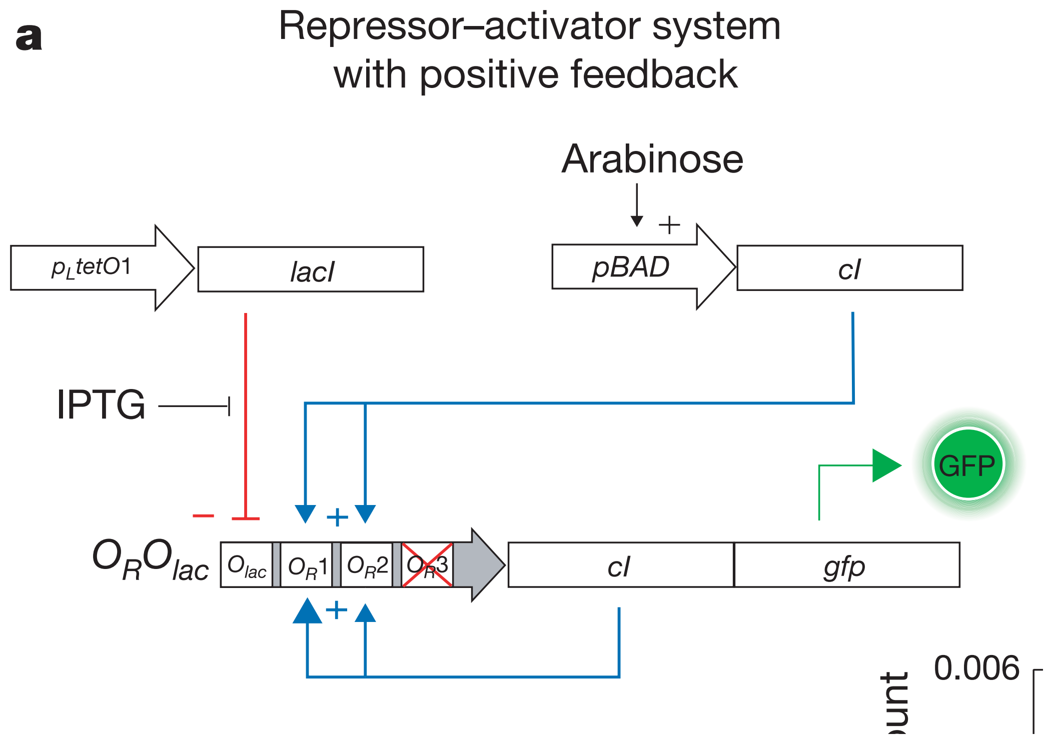
nature Vol 439|16 February 2006|**doi:10.1038/nature04473**

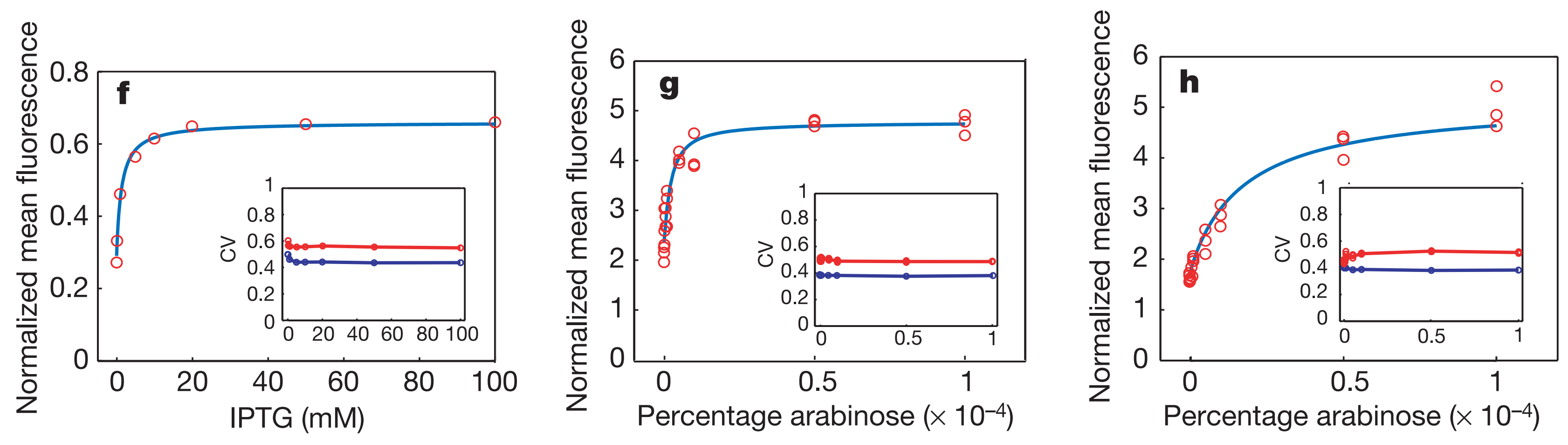
LETTERS

A bottom-up approach to gene regulation

Nicholas J. Guido[1]*, Xiao Wang[2]*, David Adalsteinsson[3], David McMillen[5], Jeff Hasty[6], Charles R. Cantor[1], Timothy C. Elston[4] & J. J. Collins[1]







pseudocode

A transcription factor binding and unbinding to its locus

```
% parameters
kon = 0.01; % attachment rate, s^-1 uM^-1
koff = 0.005; % unbinding rate s^-1
C = 1.0; % microMolar, concentration of transcription factor

% initial conditions
u_bound = 0;
u_unbound = 100; % the total number of times this promotor occurs in the system

dt = 1.0; % second. EVERY SECOND, update the number of bound and unbound promotors
ntmax = 1000;

for nt=1:ntmax

    u_bound   = u_bound   + (+ kon*C*u_unbound - koff*u_bound)*dt;
    u_unbound = u_unbound + (- kon*C*u_unbound + koff*u_bound)*dt;

end
```

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end
```

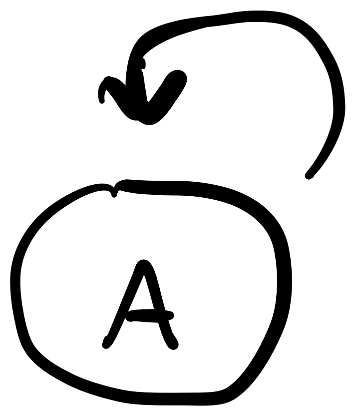
Ordinary differential equation

```
du_bound/dt   = + kon*C*u_unbound - koff*u_bound;
du_unbound/dt = - kon*C*u_unbound + koff*u_bound;
```

Complex biological systems and “systems thinking”

$\rightarrow$ Activation

$\dashv$ Repression



Positive feedback

- With positive feedback, the curve showing steady-state protein as a function of activator TF should move up.

- Does the curve move up by:
  - Shifting the EC50 to the left?
  - Moving up at high-C?
  - Moving up at low-C?
  - Combination of all 3?

Complex biological systems and “systems thinking”

Andreessen Horowitz (also called **a16z**, legal name **AH Capital Management, LLC**) is a private American venture capital firm, founded in 2009 by Marc Andreessen and Ben Horowitz. The company is headquartered in Menlo Park, California.

Andreessen Horowitz invests in both early-stage start-ups and established growth companies.[1] Its investments span the mobile, cryptocurrency, gaming, social, e-commerce, education and enterprise IT (including cloud computing, security, and software as a service) industries.[2]

Contents [hide]

AH Capital Management, LLC

andreessen. horowitz

Type	Private
Industry	Venture capital
Founded	July 6, 2009; 12 years ago
Founders	Marc Andreessen Ben Horowitz
Headquarters	Menlo Park, California, U.S.
AUM	18.8 billion (as of August 31, 2021)
Website	www.a16z.com

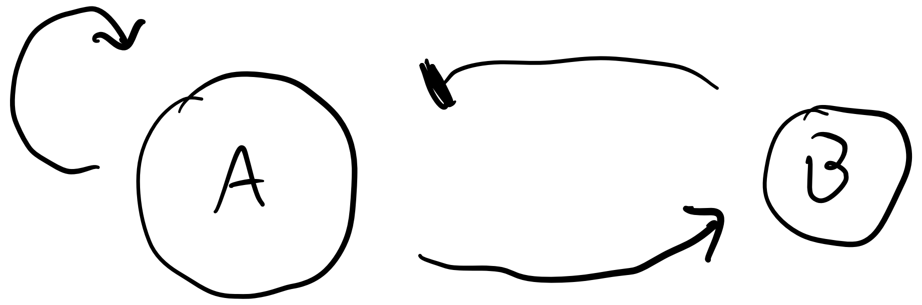
"It’s two skills that normally don’t go together.

[First,] it’s systems thinking. Most people are not systems thinkers meaning they cannot think about, ‘OK if I change this here then it’s gonna affect that over there’. You know, as an economist, [you hear] people always make these dumb mistakes, like 'Move the minimum wage, and nothing else will change'. But it's a system, and you have to think about it as a system.

“The second is: Can you actually see the people in your organization? ... Do you understand their motivation? ... And can you understand the implications through the eyes of [other people]?”

Common arrow diagrams

1



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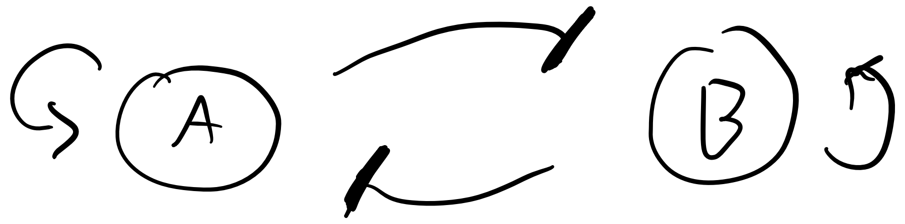

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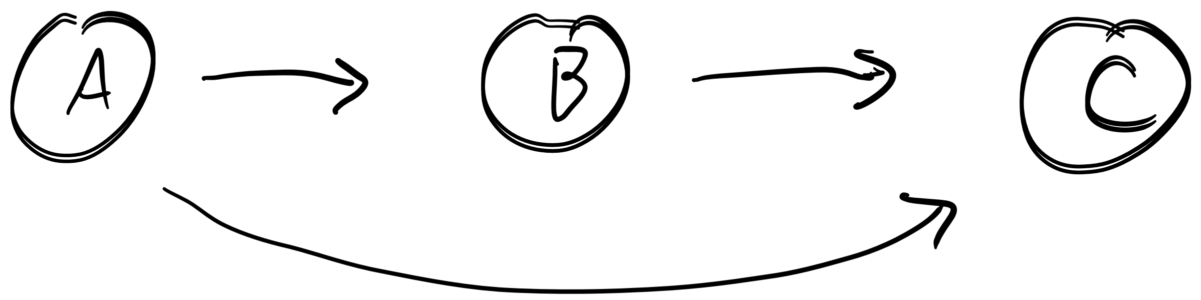

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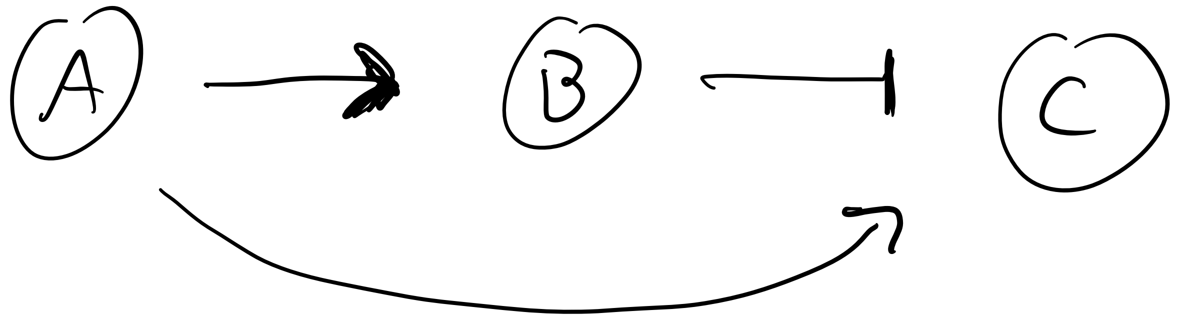

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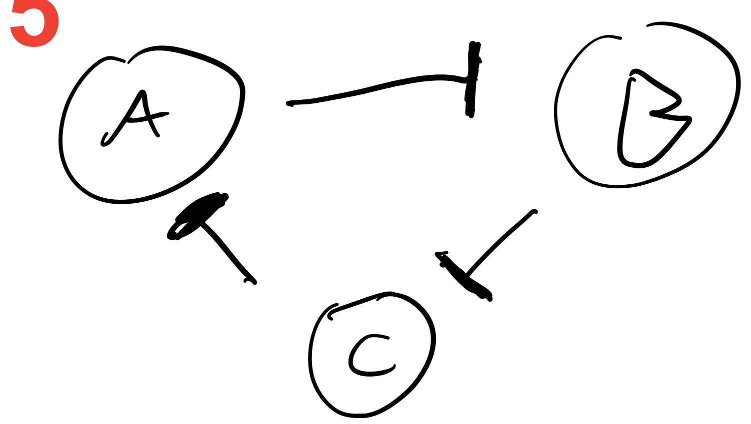

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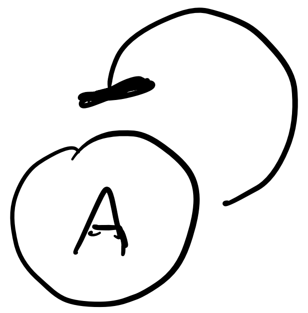

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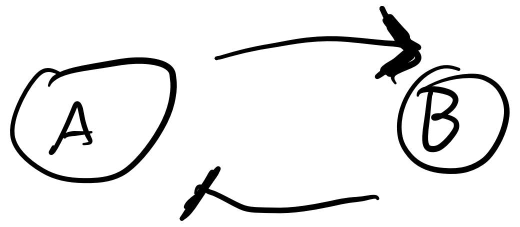


- Direct negative feedback
- Indirect negative feedback
- Double-negative feedback
- Fast positive and slow negative feedback
- Incoherent feedforward
- Coherent feedforward
- The Repressilator

Problem #1

The probability of rain in California is 5%.

It rains on your 1st visit.

It rains on your 2nd visit.

What is the probability it will rain on your 3rd visit?

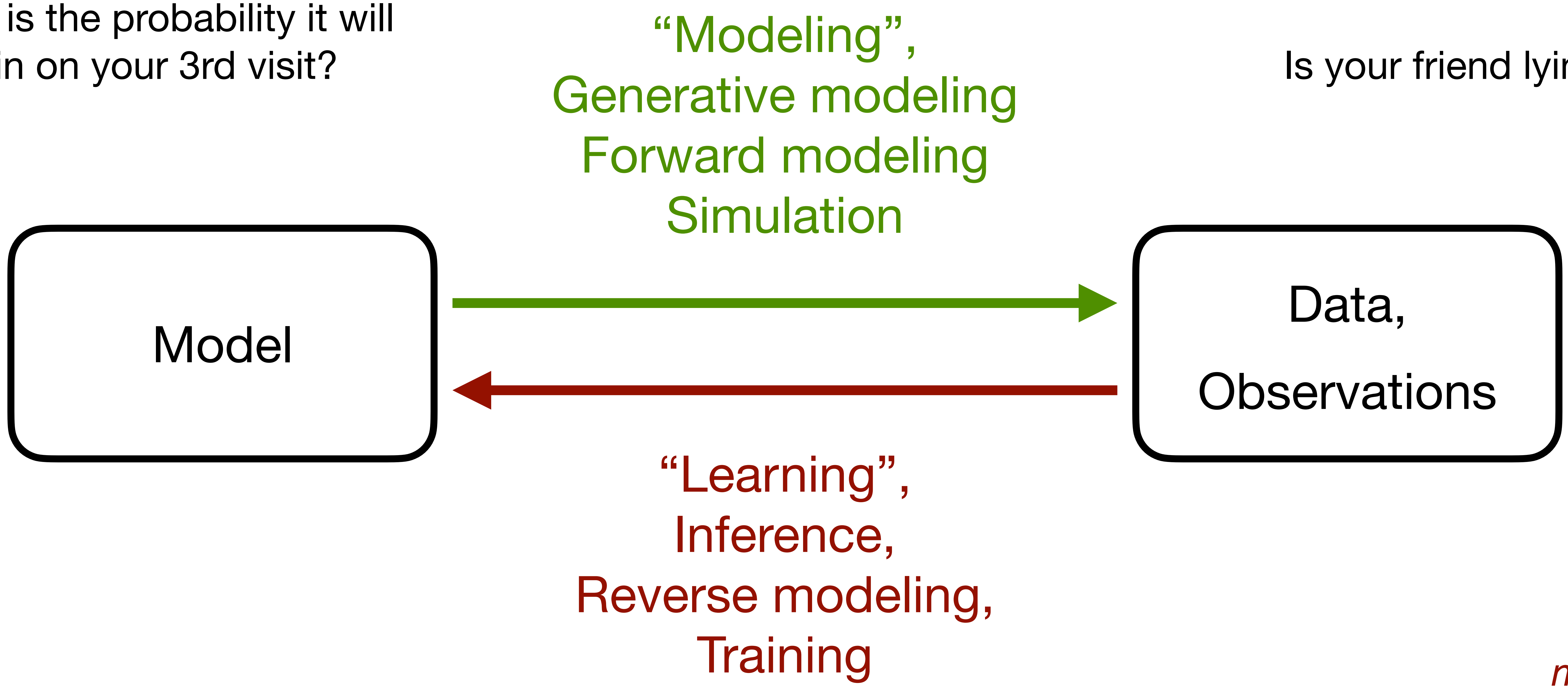
Problem #2

Your friend tells you, “The probability of rain in California is 5%.”

It rains on your 1st visit.

It rains on your 2nd visit.

Is your friend lying?



All reverse modeling methods involve 1) trying many models and “forward simulation” them, plus 2) clever tricks.