אוניברסיטת בן-גוריון בנגב
Ben-Gurion University of the Negev

Importing ideas from systems biology

Tal Shay

Department of Life Sciences

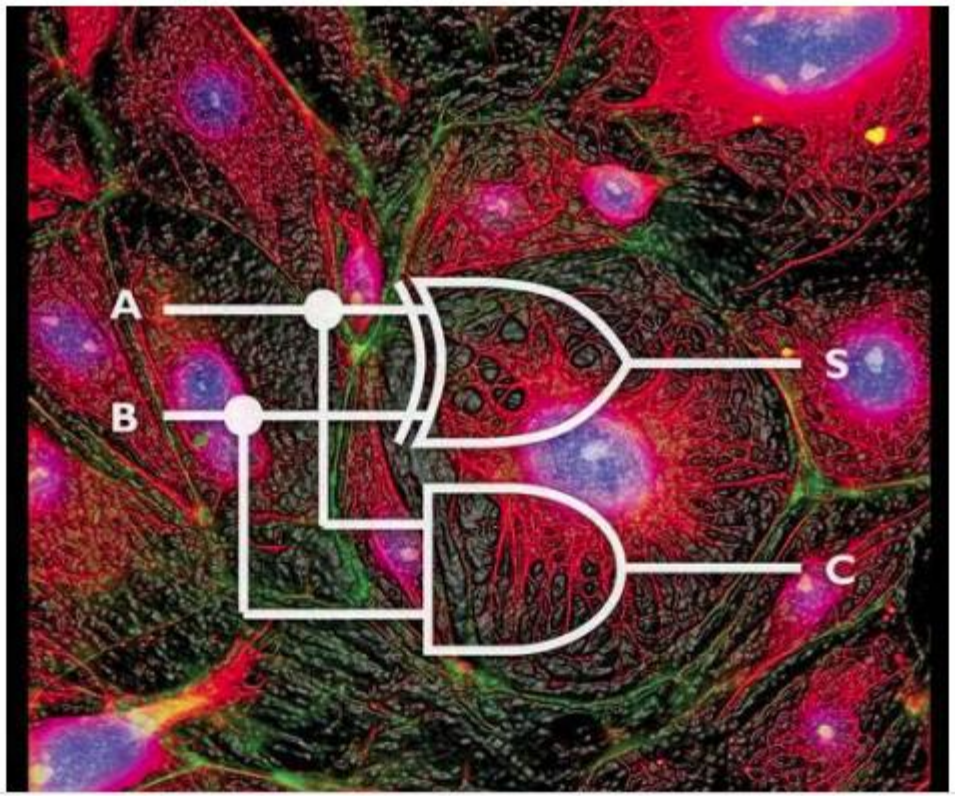
Ben-Gurion University of the Negev

Data science in cell imaging

Guest lecture

June 3, 2020

Systems biology, the study of the interactions and behaviour of the components of biological entities, including molecules, cells, organs, and organisms.



https://www.britannica.com/

Systems biology

Atom RSS Feed

Systems biology is the study of biological systems whose behaviour cannot be reduced to the linear sum of their parts' functions. Systems biology does not necessarily involve large numbers of components or vast datasets, as in genomics or connectomics, but often requires quantitative modelling methods borrowed from physics.

Systems biology is the computational and mathematical analysis and modeling of complex biological systems.

Biology-based interdisciplinary field of study that focuses on complex interactions within biological systems, using a holistic approach to biological research.

https://en.wikipedia.org/wiki/Systems_biology

- Ask two systems biologists for the definition of their discipline, and you will get three answers. This diversity reflects the youth of the field and its highly interdisciplinary nature, with the aims and approaches of the parent disciplines not yet fully integrated as a homogenous new discipline.

  Breitling 2010

- Diversity, simplicity, and complexity.

Systems biology

The study of the behavior of complex biological organization and processes in terms of the molecular constituents.

Built on:

- Molecular biology - in its special concern for information transfer
- Physiology - for its special concern with adaptive states of the cell and organism
- Developmental biology - for the importance of defining a succession of physiological states in that process
- Evolutionary biology and ecology - for the appreciation that all aspects of the organism are products of selection

The Meaning of Systems Biology, Kirschner, Cell 2005

Unrelated historical background

United States Supreme Court Justice Potter Stewart explaining why the material at issue in the case was not obscene under the law (1964)

“I shall not today attempt further to define the kinds of material I understand to be embraced within that shorthand description ["hard-core pornography"], and perhaps I could never succeed in intelligibly doing so. But **I know it when I see it**, and the motion picture involved in this case is not that.”

System biology - less formal definitions

[Like porn] I know it when I see it

Marc Kirschner, the founding chair of the Department of Systems Biology at Harvard Medical School.

Research described by biologists as “cool math, trivial biology”, and by mathematicians as “cool biology, trivial math”.

Shay Tal

Cool wow research

Tal Shay

Systems biology toolbox

- Quantitative measurement
- Modeling
- Reconstruction
- tweaking
- Theory

Systems biology is not a branch of physics, though it occupies many physicists

The Meaning of Systems Biology, Kirschner, Cell 2005

The Israeli angle

- Israel is a system biology empire!
- Many PHDs in physics migrated to biology in their postdocs and returned to the Israeli academy
- Several well established Israeli physicist migrated as well

Very partial list
Eytan Domany
Eshel Ben-Jacob
Elisha Moses
Uri Alon
Naama Barkai
Roi Kishoni
Aviv Regev progeny

Scales

- Reconstitution of complex processes from purified components and the study of the dynamical nature of those processes

Published: 28 July 2005

Optimality and evolutionary tuning of the expression level of a protein

Erez Dekel & Uri Alon

Nature **436**, 588–592(2005) | Cite this article

The Meaning of Systems Biology, Kirschner, Cell 2005

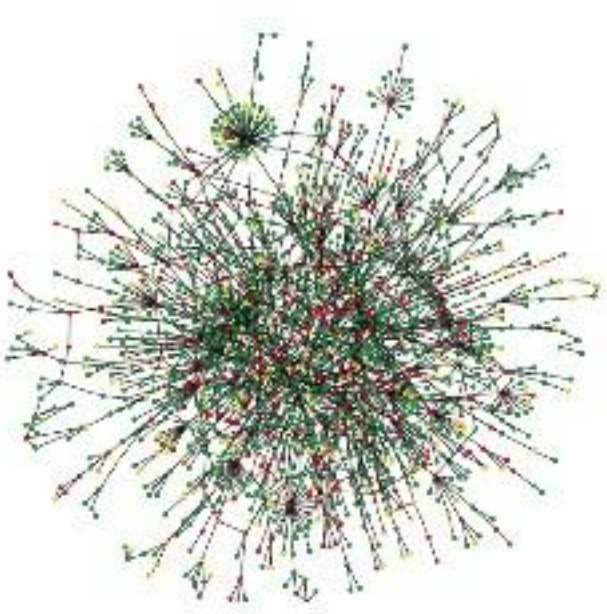
Scales

- Reconstitution of complex processes from purified components and the study of the dynamical nature of those processes
- The development and study of extract systems that recapitulate fairly faithfully cellular processes or explant systems that recapitulate developmental events
- Explicit reconstruction of circuits within cells or the deliberate modification of those circuits in order to describe the dynamical features of these synthetic or partially synthetic systems
- Global analysis of high throughput biology – measurement of the level/sequence/localization of a protein/RNA/DNA for all genes simultaneously.

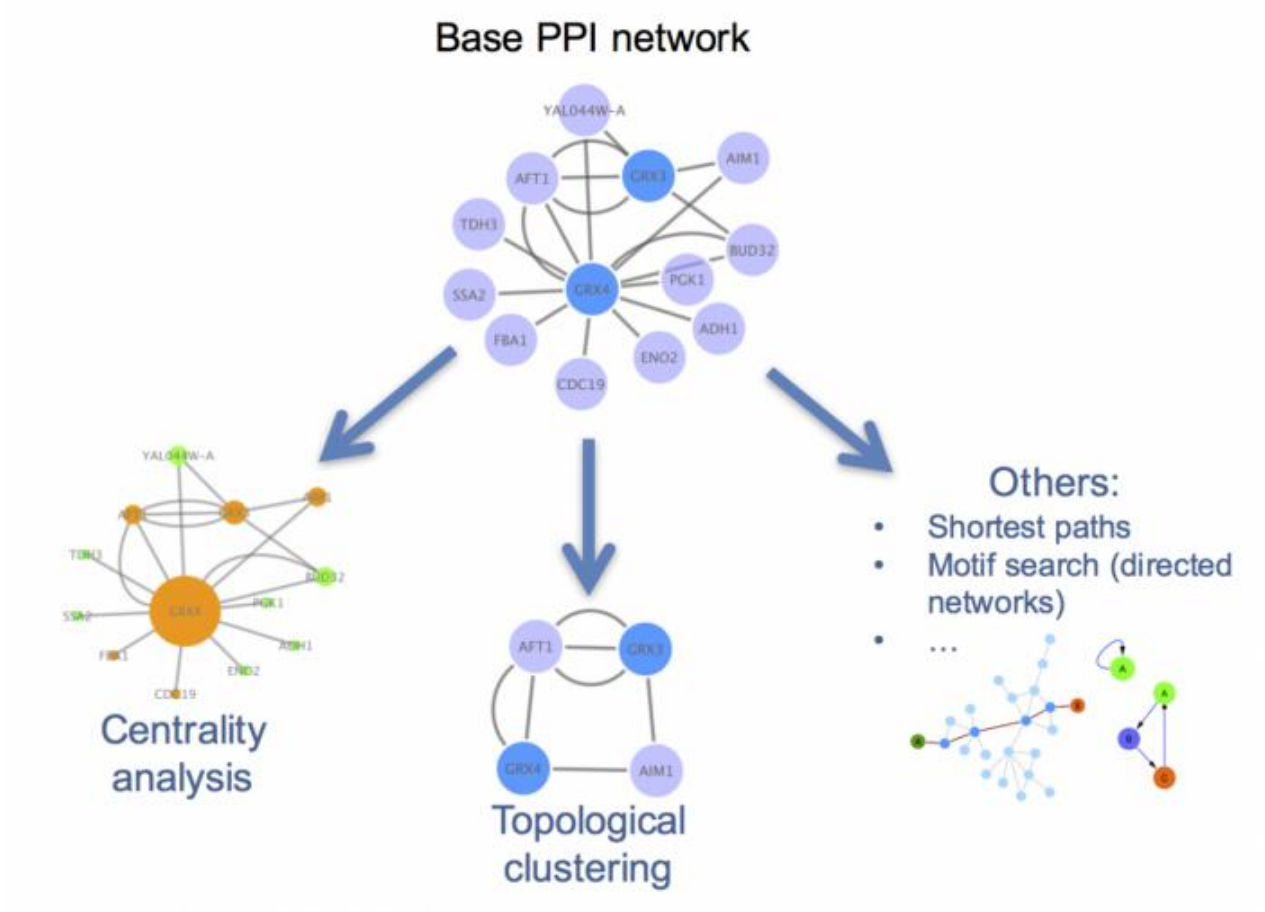
The Meaning of Systems Biology, Kirschner, Cell 2005

Network motifs

The hairball



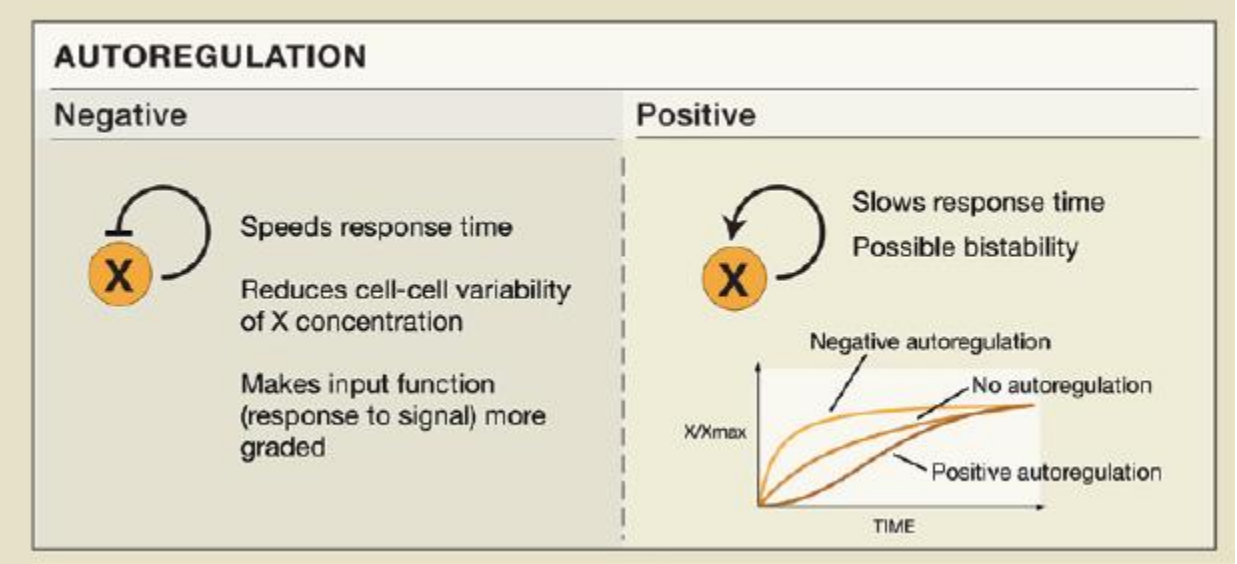
Analysing the topological features of a network is a useful way of identifying relevant participants and substructures that may be of biological significance



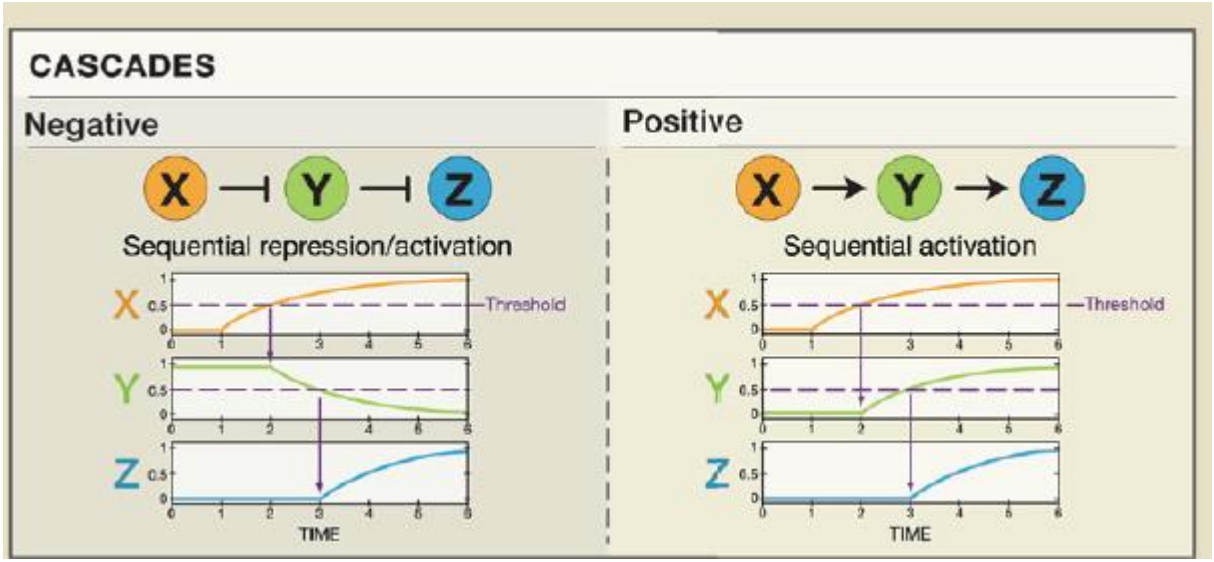
Network motif

- Statistically over-represented sub-graphs in a network.
- Motifs correspond with a pattern of connections that generates a characteristic dynamical response (e.g. a negative feedback loop).
- More useful in directed networks.
- The same small set of network motifs has been found in diverse organisms
- Experiments show that each network motif can carry out specific dynamic functions in the computation done by the cell.
- Next: classes of network motifs and their biological functions

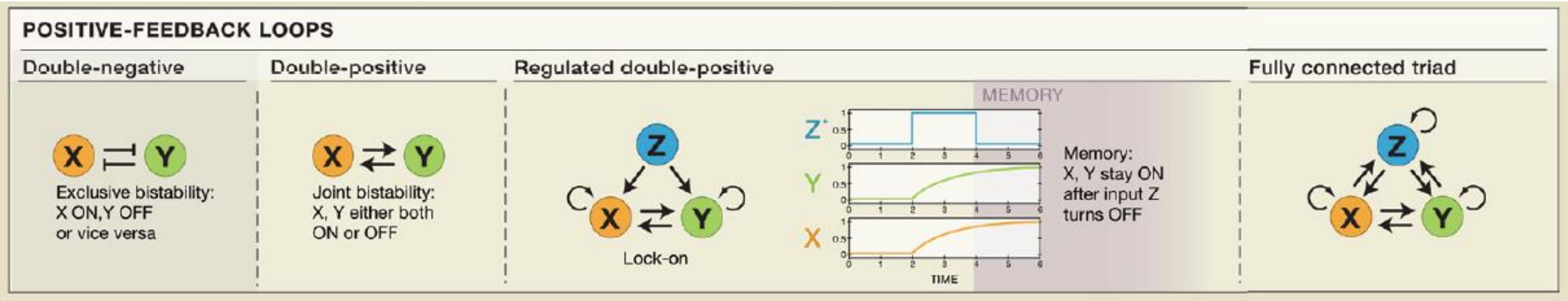
Shoval & Alon, Cell 2010 143(2):326



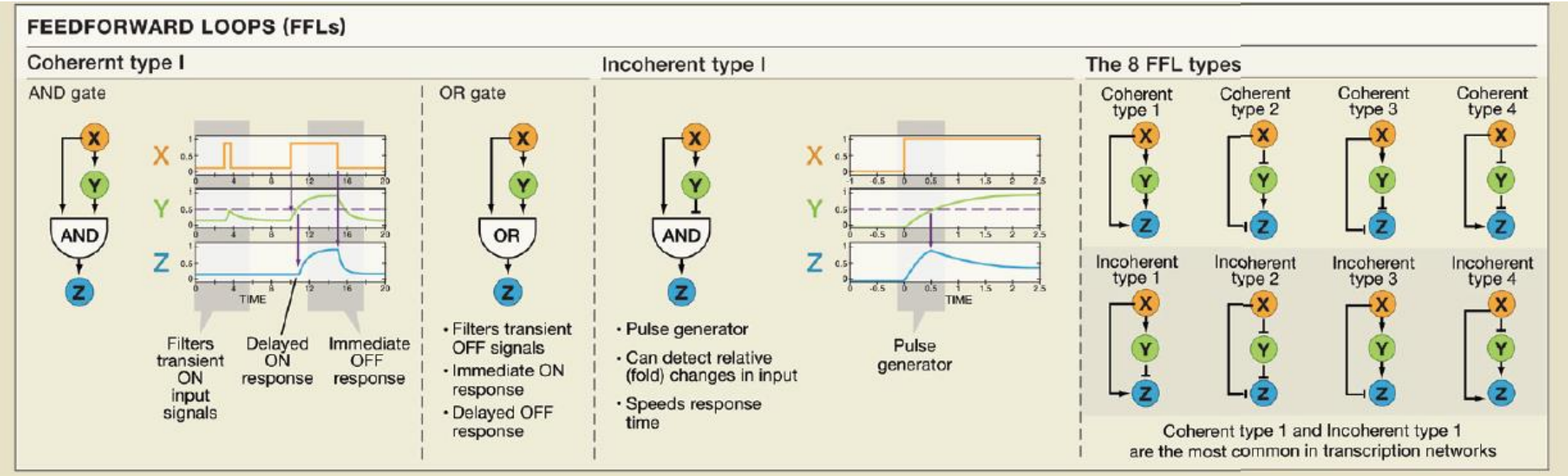
Shoval & Alon, Cell 2010 143(2):326



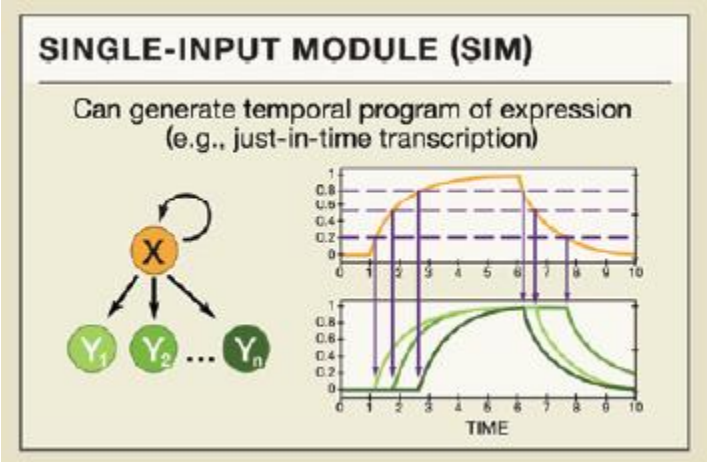
Shoval & Alon, Cell 2010 143(2):326



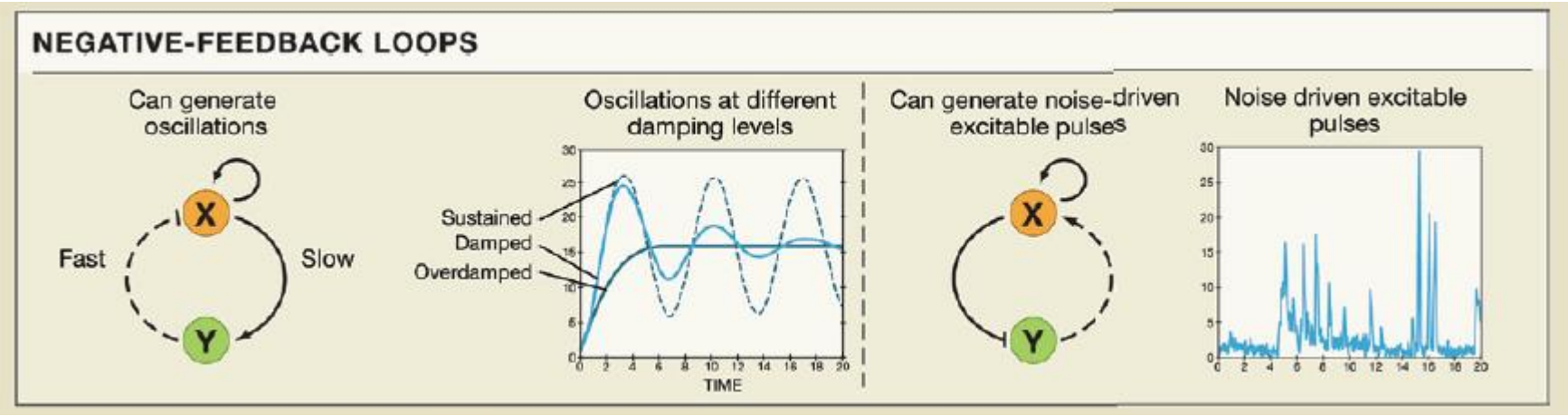
Shoval & Alon, Cell 2010 143(2):326



Shoval & Alon, Cell 2010 143(2):326



Shoval & Alon, Cell 2010 143(2):326

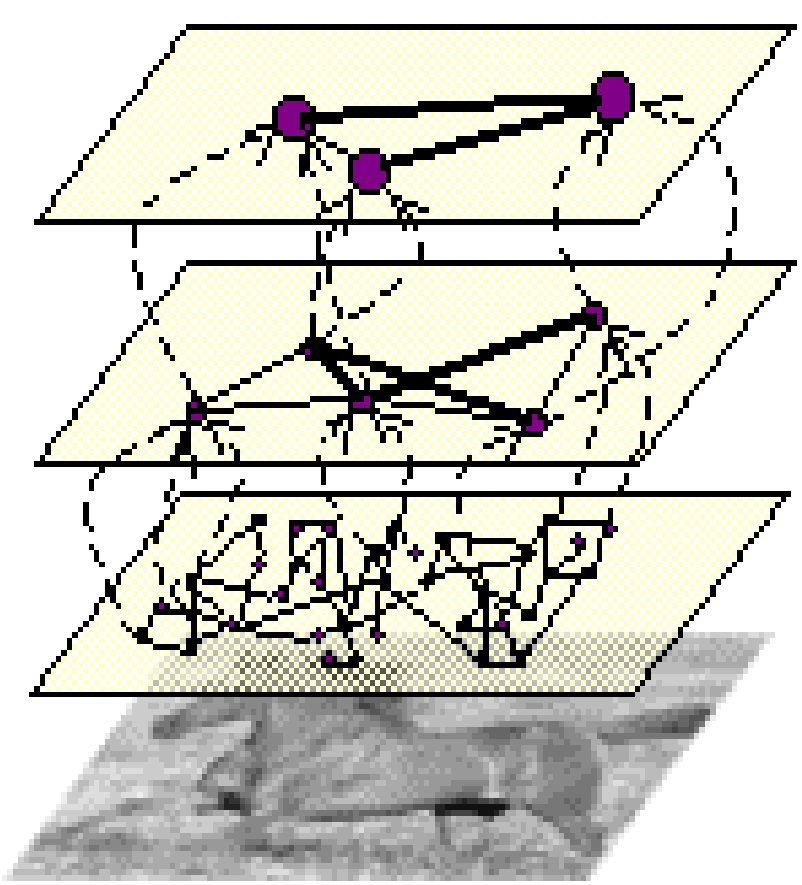


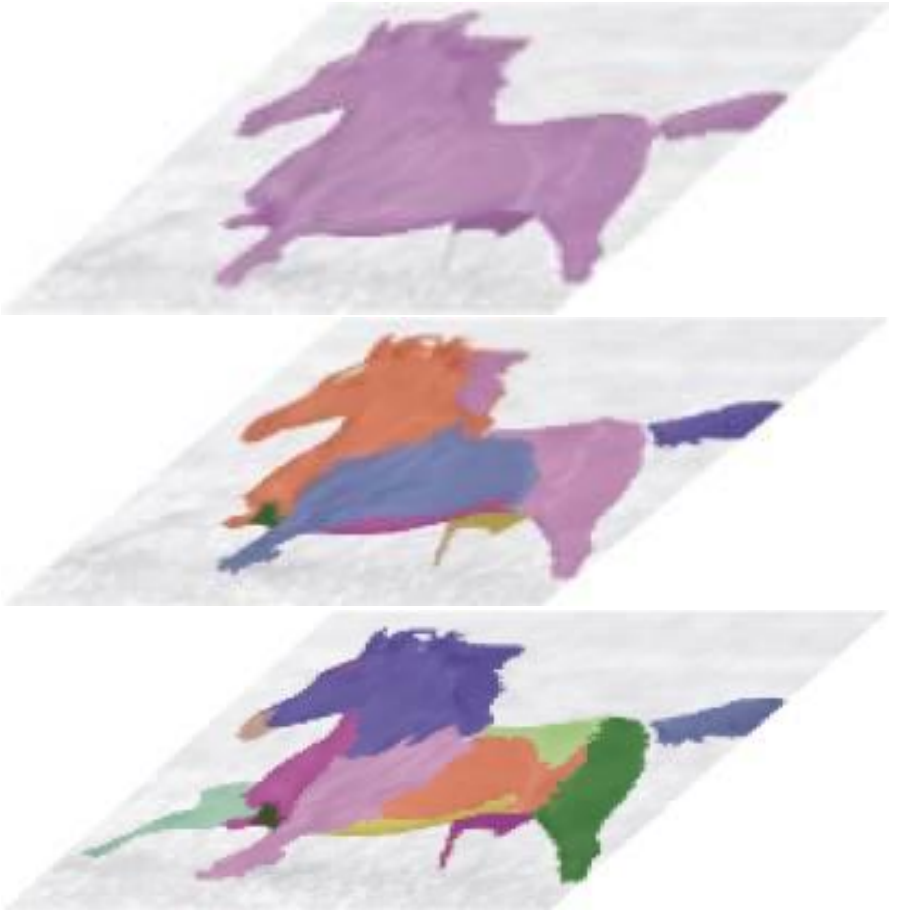
Shoval & Alon, Cell 2010 143(2):326

Summary

Network biology makes use of the tools provided by **graph theory** to represent and analyse complex biological systems.

Multiscale segmentation





Sharon, Brandt, Basri (2000)

The evolution of antibiotic resistance – MEGA plate

- https://youtu.be/plVk4NVIUh8

- Display a simple way to observe how bacteria move as they become resistant to drugs.
- Takes complex, often obscure, concepts in evolution, such as mutation selection, lineages, parallel evolution, and clonal interference, and provides a visual, seeing-is-believing demonstration of these otherwise vague ideas.

Roi Kishoni

https://science.sciencemag.org/content/353/6304/1147/tab-figures-data

equilibrium with intermediate **B** lies far to the left. The chemoselectivity might be explained by the more electrophilic nature of intermediate **A** versus nitrenoid **B**. This preliminary hypothesis is consistent with the observation that moderate-to-strong bases such as K_2CO_3, Et_3N, and pyridine completely inhibit amination, but not aziridination. Moreover, addition of TsOH (1.5 equiv.) to the reaction of **1** with 2,4-DNPONHMe (**12**) produced only the arene amination adduct **5** and no aziridine. As an additional control, it was shown that the presence of 2,4-DNP-OH (1.5 equiv.) did not alter the reaction manifold in favor of aziridination when **4a** was used as the aminating reagent and only **5** was observed.

It was also instructive to compare our methodology with the intermolecular Rh-catalyzed amination procedure of Du Bois to gain a perspective on their respective complementary chemoselectivities (Fig. 4) (*42*). Both have similar efficiency using *p*-ethylanisole (**13**), but the Du Bois procedure leads to benzylic C-H insertion only, whereas our methodology gives arene amination exclusively, providing **15** and **16** in a combined 67% yield.

The influence of ligands and counterions on the reactivity of organometallics is well precedented (*43*, *44*). However, examples of such dramatic bifurcation of the reaction manifold are rare and warrant closer study to understand the energetics and full synthetic potential of this metalloid-nitrogen umpolung for direct arene aminations.

ANTIBIOTIC RESISTANCE

Spatiotemporal microbial evolution on antibiotic landscapes

Michael Baym,[1] Tami D. Lieberman,[1]* Eric D. Kelsic,[1] Remy Chait,[1]† Rotem Gross,[2] Idan Yelin,[2] Roy Kishony[1,2,3]‡

A key aspect of bacterial survival is the ability to evolve while migrating across spatially varying environmental challenges. Laboratory experiments, however, often study evolution in well-mixed systems. Here, we introduce an experimental device, the microbial evolution and growth arena (MEGA)–plate, in which bacteria spread and evolved on a large antibiotic landscape (120 × 60 centimeters) that allowed visual observation of mutation and selection in a migrating bacterial front. While resistance increased consistently, multiple coexisting lineages diversified both phenotypically and genotypically. Analyzing mutants at and behind the propagating front, we found that evolution is not always led by the most resistant mutants; highly resistant mutants may be trapped behind more sensitive lineages. The MEGA-plate provides a versatile platform for studying microbial adaption and directly visualizing evolutionary dynamics.

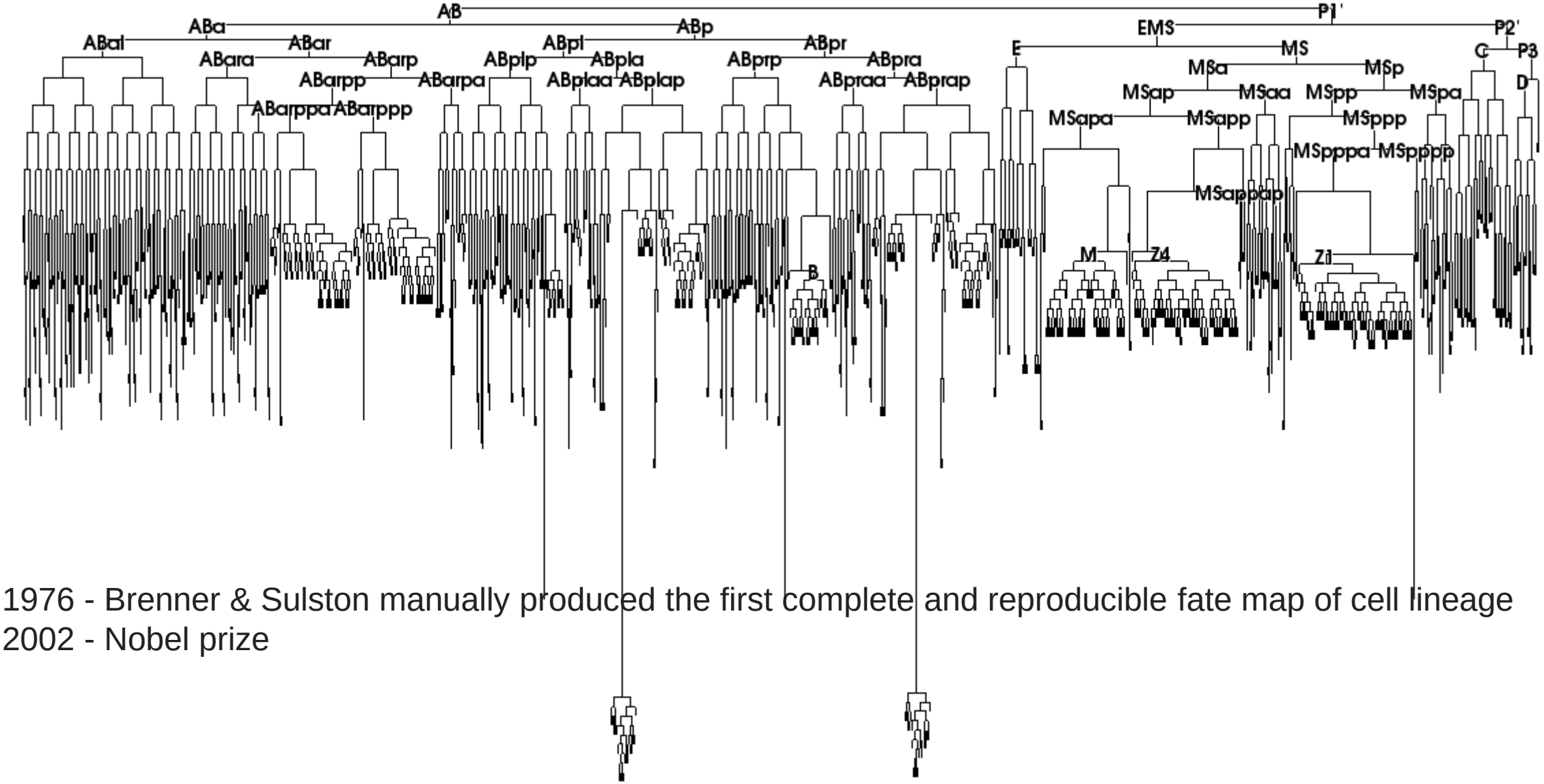
The worldwide increase in antibiotic resistance has motivated numerous studies aimed at understanding the phenotypic and genotypic evolution of antibiotic resistance (*1*–*7*). These experiments have shed light on the trade-offs constraining adaptive evolution in single- and multidrug environments (*5*, *6*, *8*, *9*). However, most of our current knowledge about the evolution of resistance is based on laboratory setups with well-mixed environments (*1*–*7*, *10*, *11*).

In natural and clinical settings, bacteria migrate between spatially distinct regions of selection

The C. elegans cell fate lineage

- ~ 1 mm long nematode
- Patterns of cell lineage are the same between individuals
- The embryo consists of 558 cells, adult hermaphrodite 959, male 1031
- Transparent eggshell & animal - cell divisions & migrations can be followed by microscope

The C. elegans cell fate lineage



1976 - Brenner & Sulston manually produced the first complete and reproducible fate map of cell lineage
2002 - Nobel prize

Zebrafish lineage tree

- https://youtu.be/RQ6vkDr_Dec

Scales

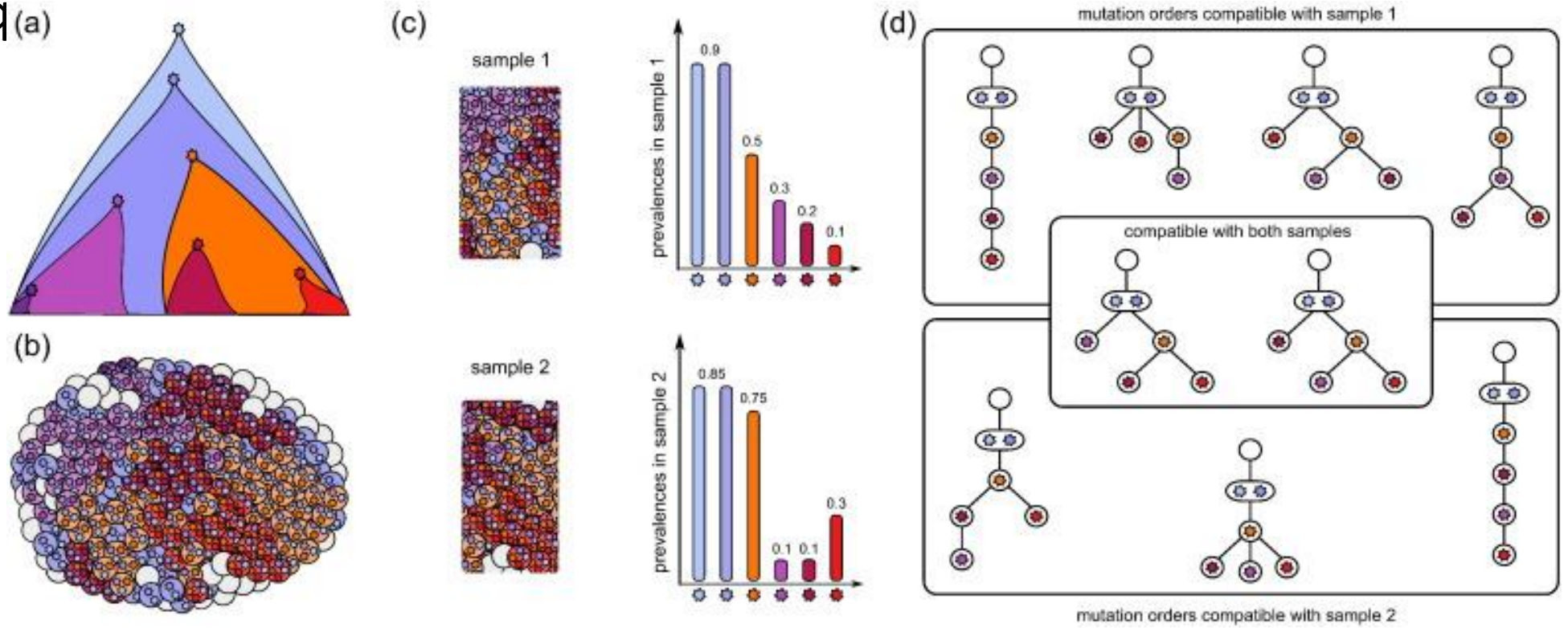
- Reconstitution of complex processes from purified components and the study of the dynamical nature of those processes
- The development and study of extract systems that recapitulate fairly faithfully cellular processes or explant systems that recapitulate developmental events
- Explicit reconstruction of circuits within cells or the deliberate modification of those circuits in order to describe the dynamical features of these synthetic or partially synthetic systems
- Global analysis of high throughput biology – measurement of the level/sequence/localization of a protein/RNA/DNA for all genes simultaneously.

At the single cell resolution!

The Meaning of Systems Biology, Kirschner, Cell 2005

Single cell measurements

- DNA sequencing
- RNA sequencing
- ATAC-seq

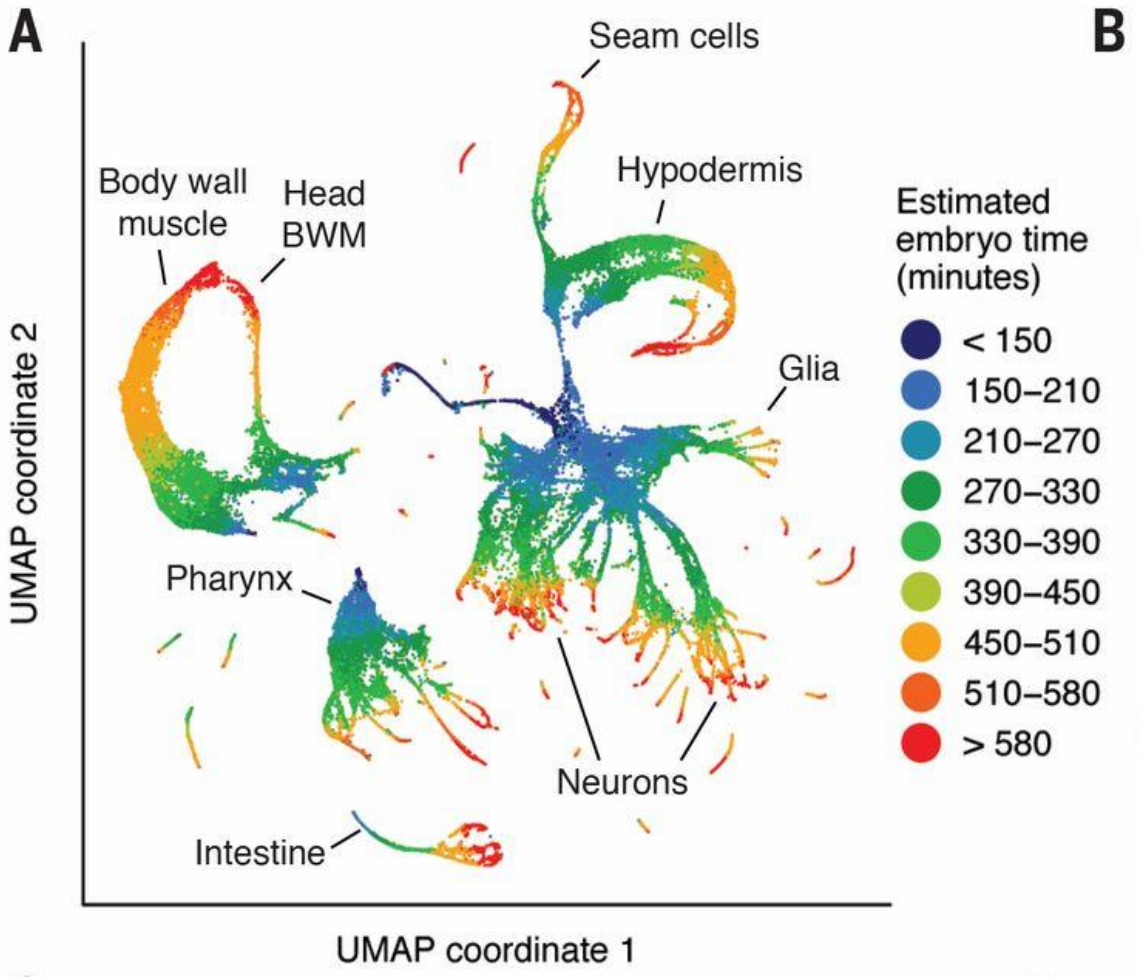


Kuipers et al. 2017

Single cell measurements

- DNA sequencing
- RNA sequencing
- ATAC-seq

The C. elegans cell lineage



RNA sequencing of 86,024 single embryonic cells
Identified 502 terminal and pre-terminal cell types
Mapped most single-cell transcriptomes to their exact position in *C. elegans*' invariant lineage.

Findings:

1) The correlation between a cell's lineage and its transcriptome increases from mid to late gastrulation, then falls dramatically as cells adopt their terminal fates
2) Multilineage priming contributes to the differentiation of sister cells at dozens of lineage branches
3) Most distinct lineages that produce the same anatomical cell type converge to a homogenous transcriptomic state

Packer et al. Science (2019)

Single cell measurements computational challenges

- Sparse, high dropout -> Imputation, coverage correction
- Visualization of cellular landscape -> Dimension reduction
- Clustering and classification of cells
- Trajectory analysis