

Biological networks

18.S995 - L25

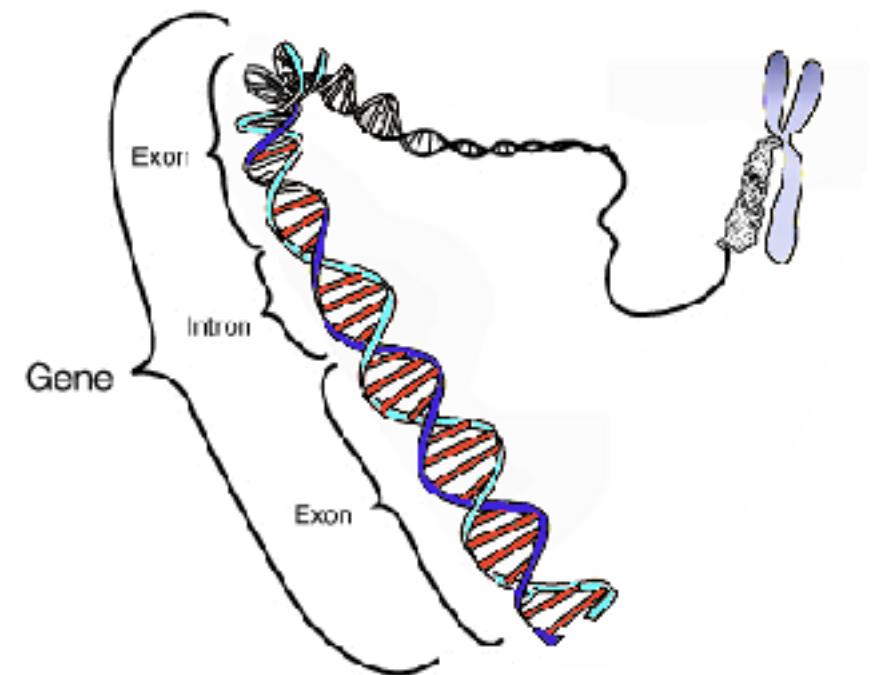
Examples

- gene regulatory networks
- neur(on)al networks
- structural networks (cytoskeleton, gels, ...)
- hydrodynamic transport networks (blood vessels, slime molds, leaves, trees)
- tree structures (phylogenetic, cell lineages)
- ecological networks

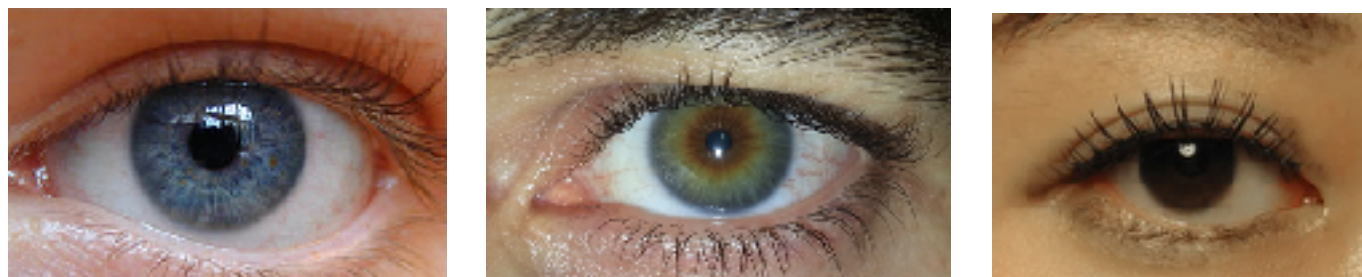
Gene regulatory networks

Gene facts

- gene = basic physical and functional unit of heredity
- 20,000-25,000 human genes, length from a few 100 bp to 2 Mbp
- <1% different between humans
- alleles = alternate forms of the same gene

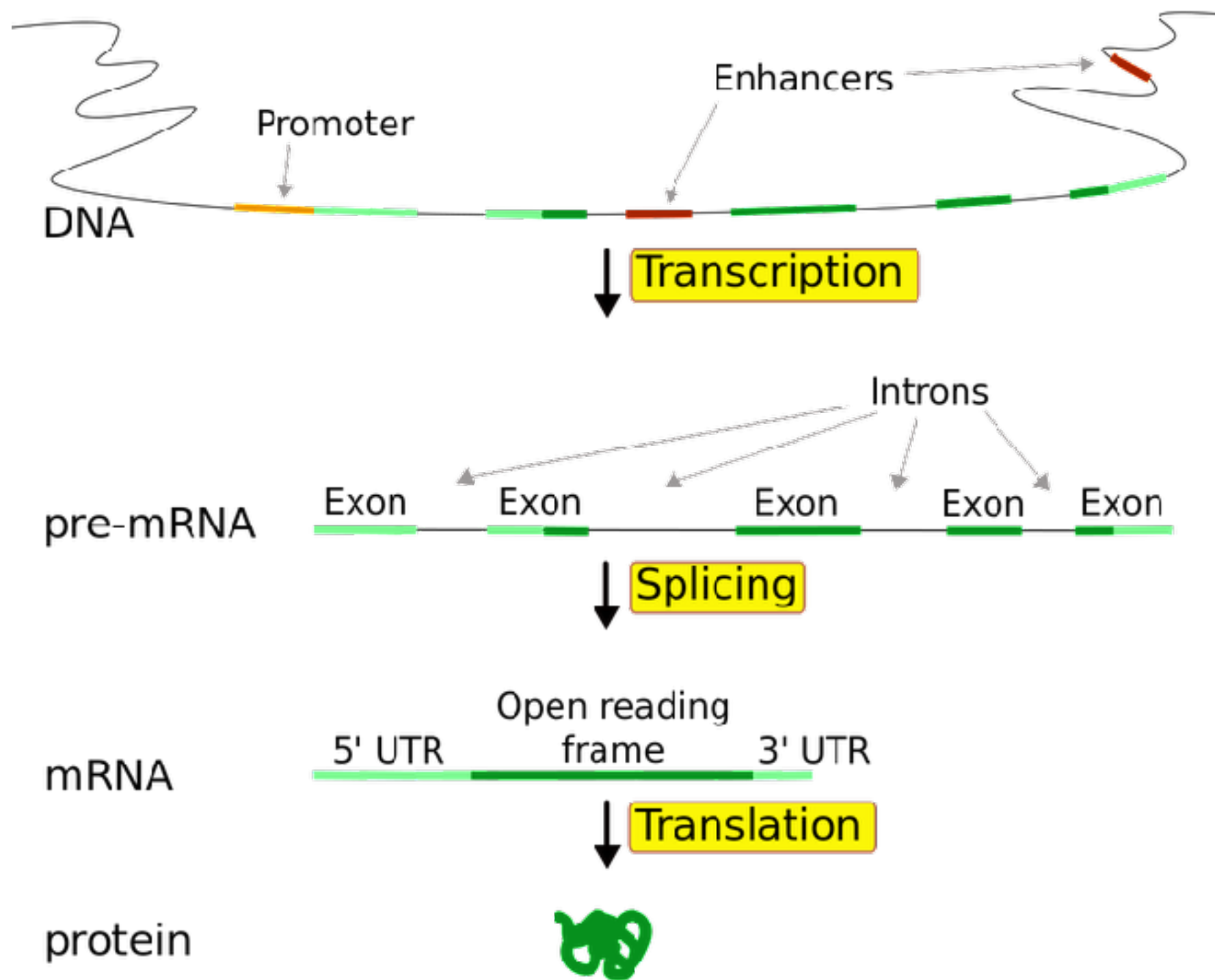


Courtesy: National Human Genome Research Institute



www.genome.gov

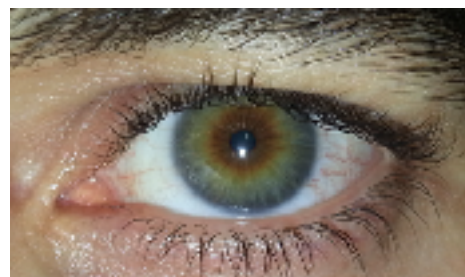
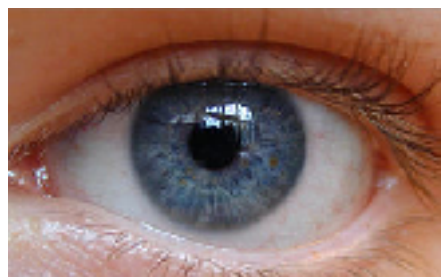
dunkel@math.mit.edu



Gene facts

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- 20,000-25,000 human genes, length from a few 100 bp to 2 Mbp
- <1% different between humans
- alleles = alternate forms of the same gene

Organism	Estimated Size Million bases	Estimated gene number	Average gene density	Chromosome Number
Human	3000	~30000	1 gene per 10000 bases	46
Rat	2750	~30000	-- do --	42
Mouse	2500	~30000	-- do --	40
Fruit Fly	180	~13600	1 gene per 5000 bases	8
A type of Plant	125	25500	1 gene per 4000 bases	5
Round worm	97	19100	1 gene per 6000 bases	6
Yeast	12	6300	1 gene per 2000 bases	16
E-Coli (Bacteria)	4.7	5200	1 gene per 1400 bases	1
H-influenzae (bacteria)	1.0	1700	1 gene per 1000 bases	1



Human Genome Project

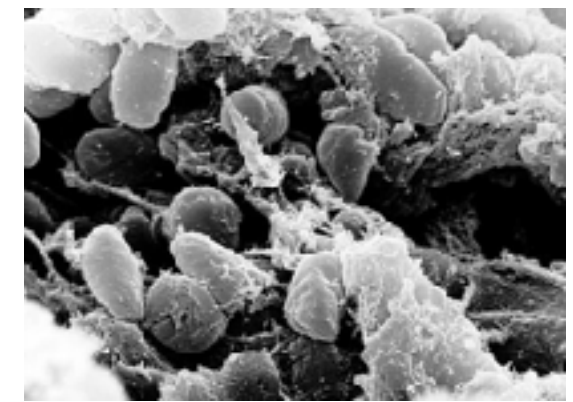
Completed in 2003, the Human Genome Project (HGP) was a 13-year project coordinated by the U.S. Department of Energy (DOE) and the National Institutes of Health. During the early years of the HGP, the Wellcome Trust (U.K.) became a major partner; additional contributions came from Japan, France, Germany, China, and others. Project goals were to

- *identify* all the approximately 20,500 genes in human DNA,
- *determine* the sequences of the 3 billion chemical base pairs that make up human DNA,
- *store* this information in databases,
- *improve* tools for data analysis,
- *transfer* related technologies to the private sector, and
- *address* the ethical, legal, and social issues (ELSI) that may arise from the project.

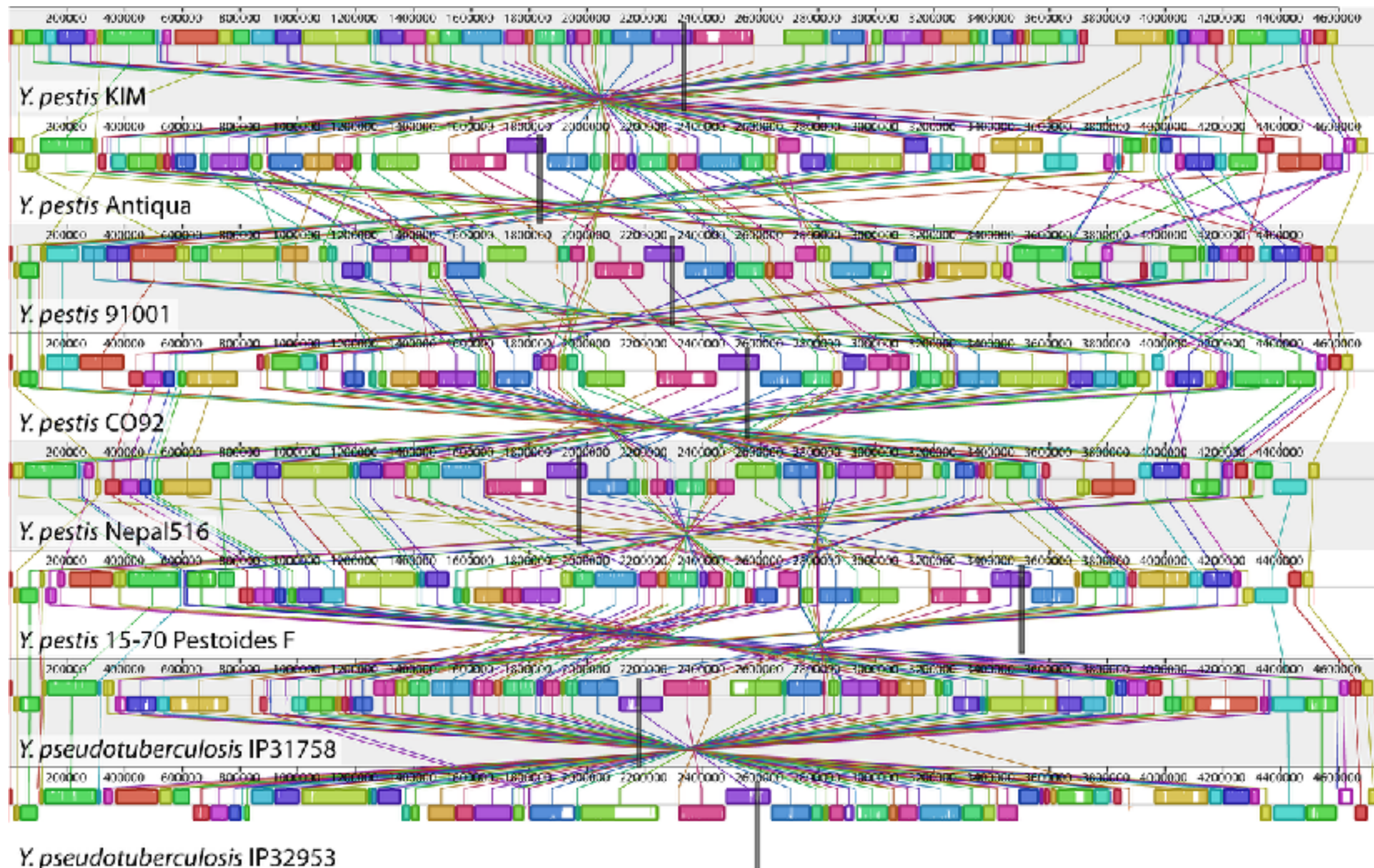
Though the HGP is finished, analyses of the data will continue for many years.

http://web.ornl.gov/sci/techresources/Human_Genome/index.shtml

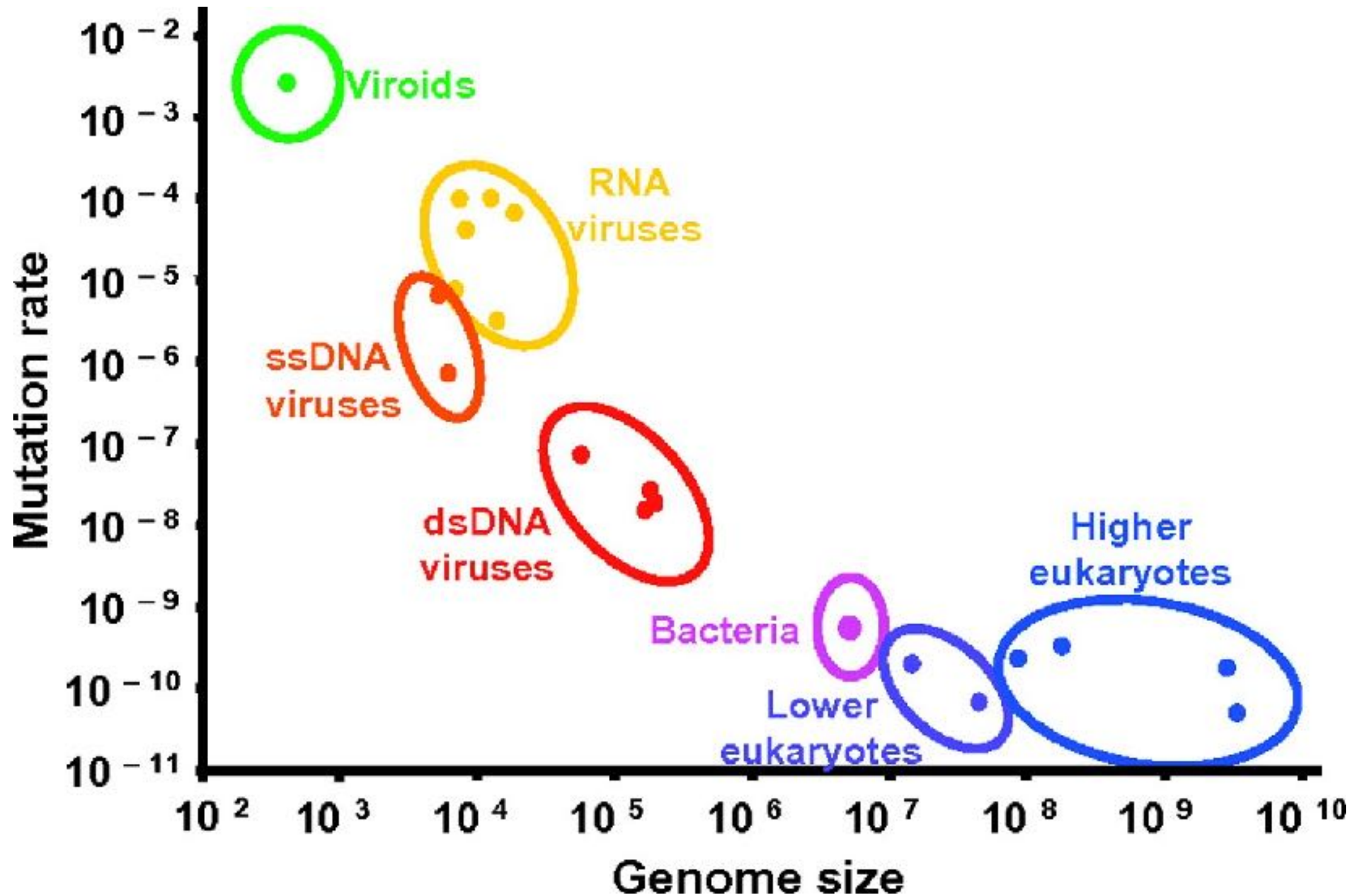
Comparative genomics



8 Yersinia bacteria

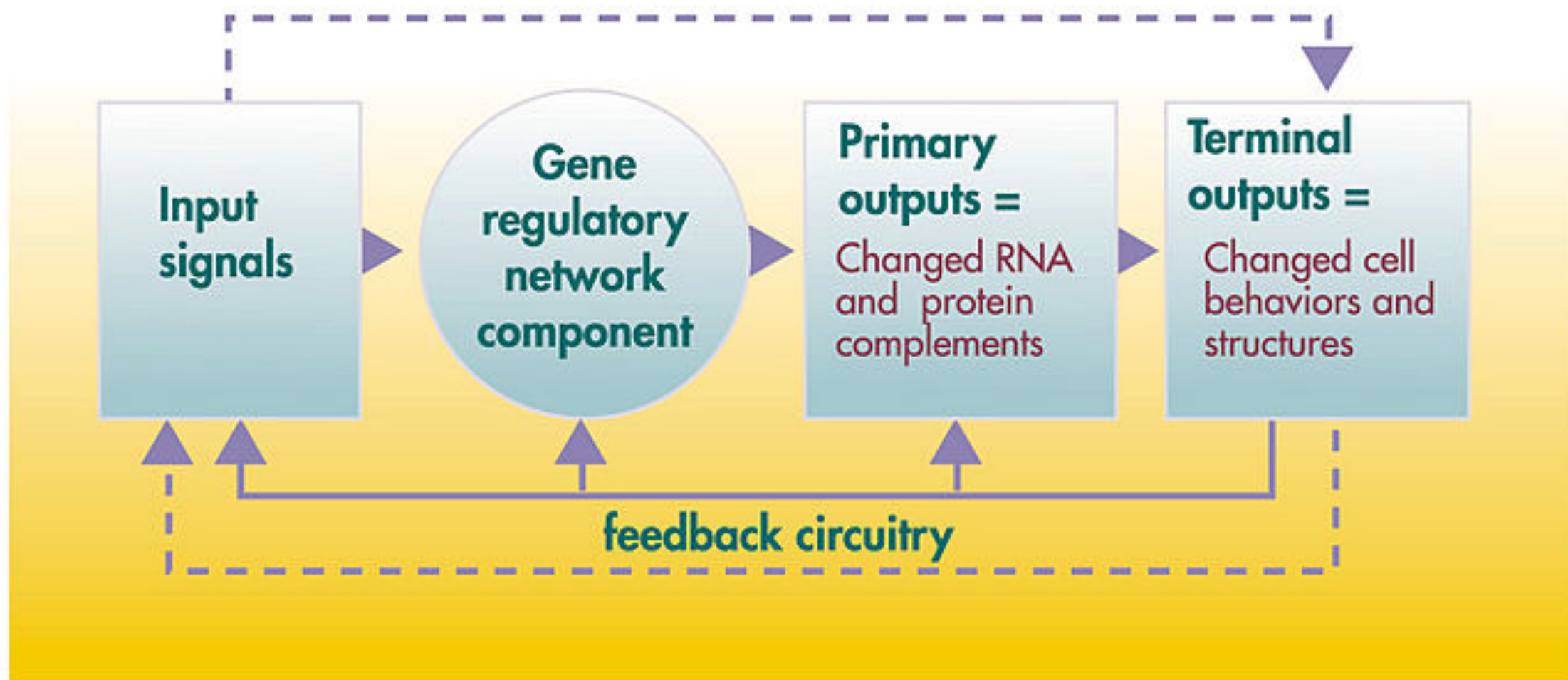


Relationship between mutation rate per nucleotide site and genome size for different genomic systems including viruses. [Reproduced with permission from ref. 19 (Copyright 2009, AAAS).].



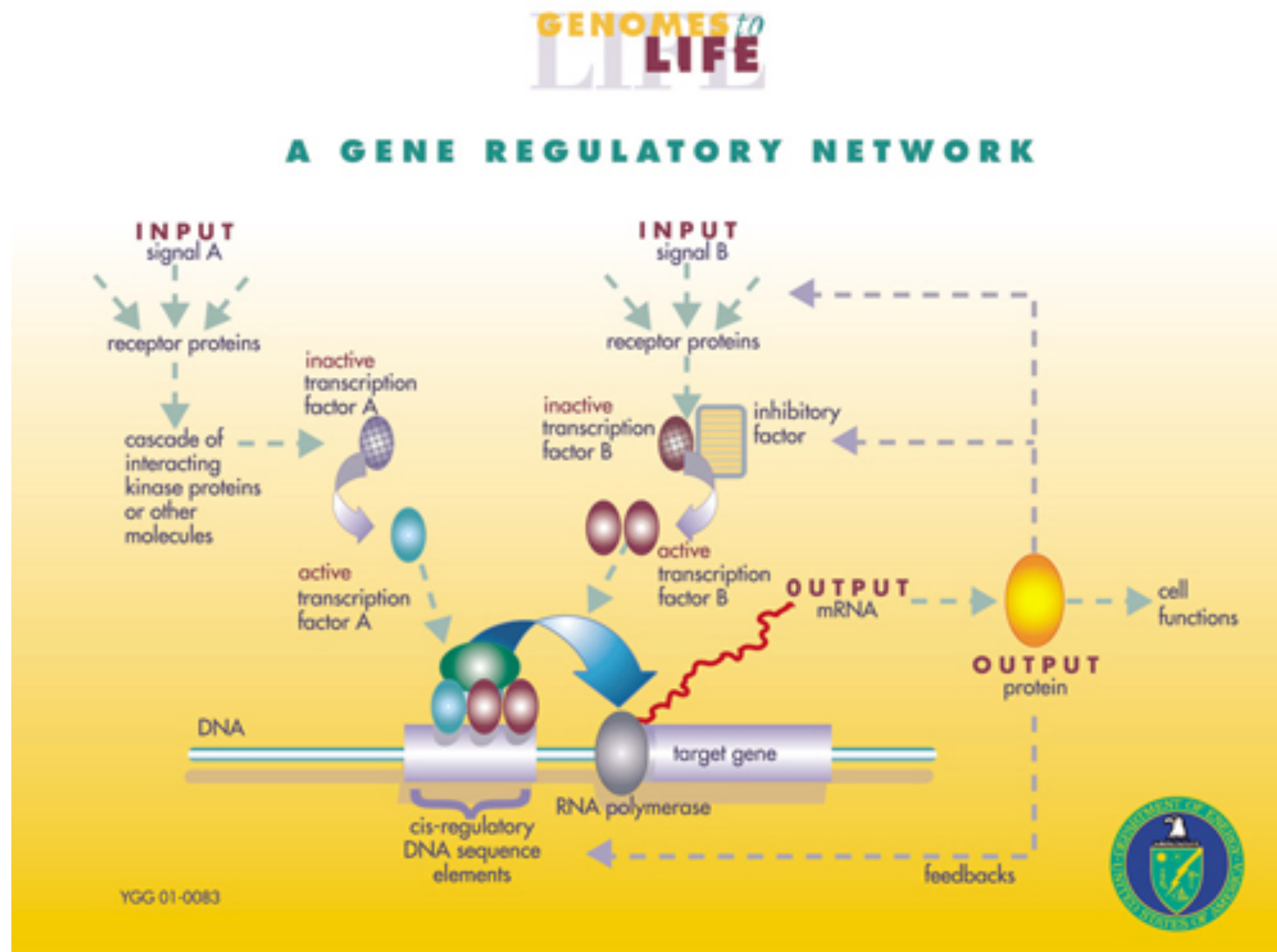
Holmes PNAS (2010) 107:1742-1746

Gene regulatory networks

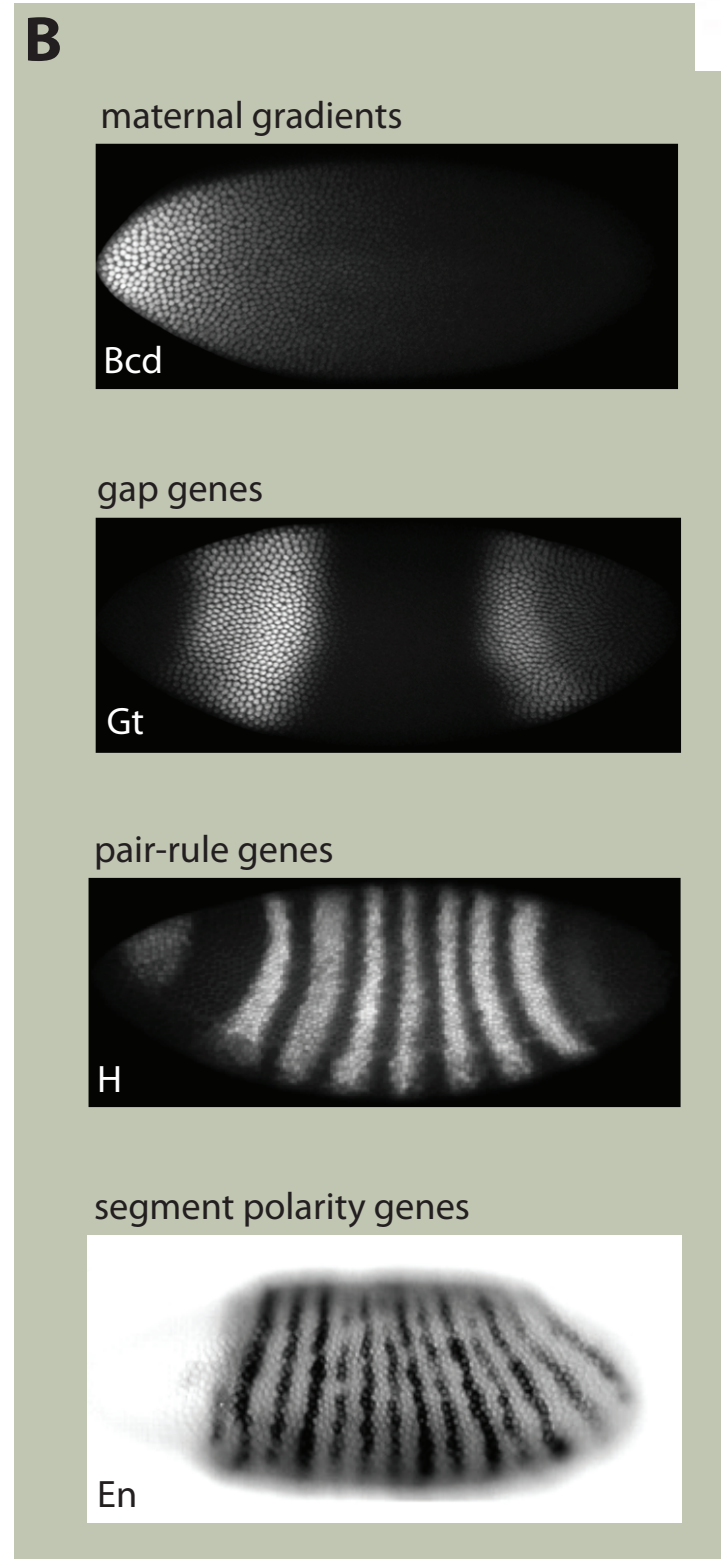
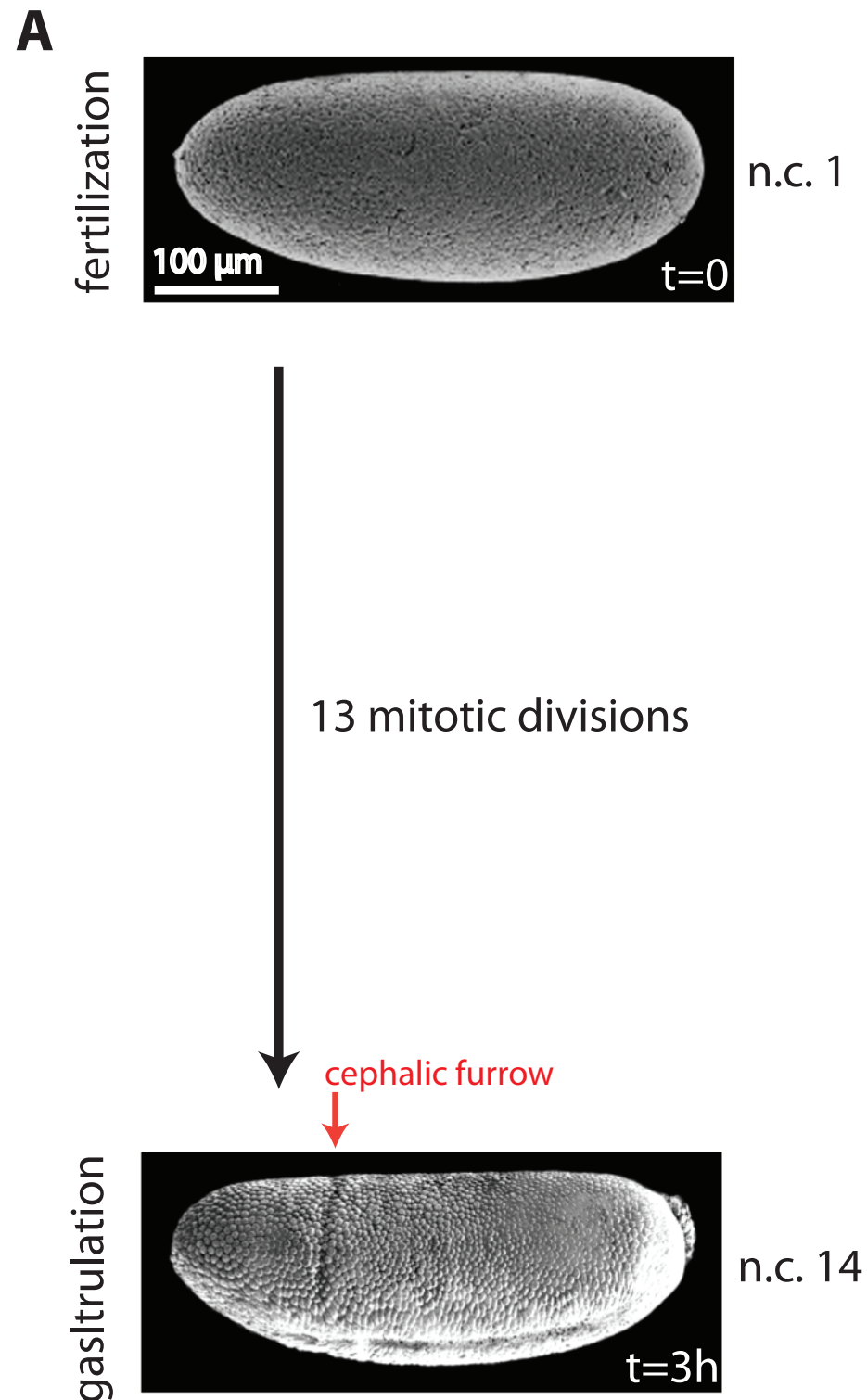


YGG 01-0086

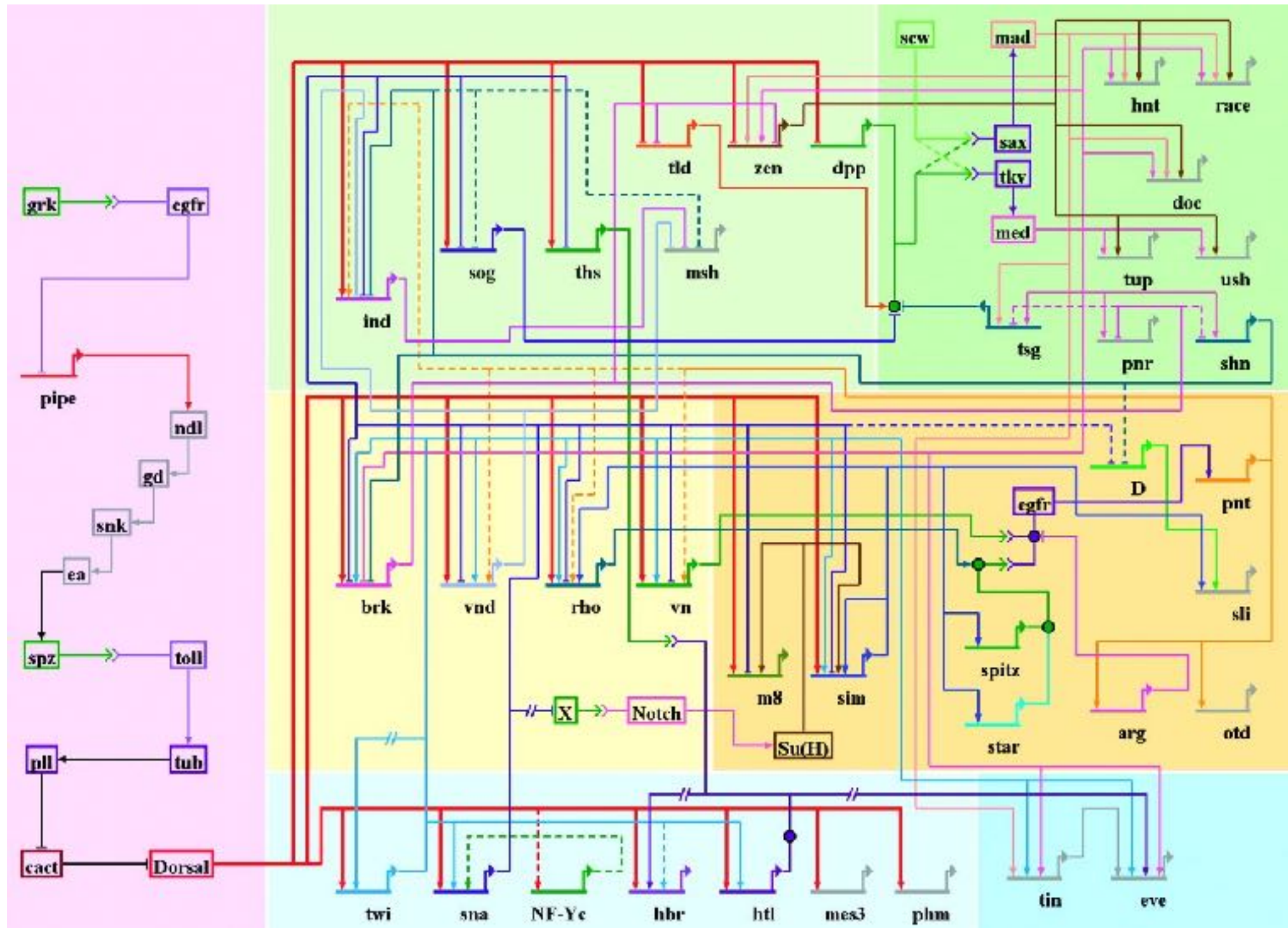
Gene regulatory networks



Example: *Drosophila* embryo



The dorsal-ventral GRN in *Drosophila*



Levine and Davidson PNAS (2005) 102, 4936

Gap gene network

Molecular Systems Biology 9; Article number 639; doi:10.1038/msb.2012.72
Citation: *Molecular Systems Biology* 9:639
www.molecularsystemsbiology.com



Accurate measurements of dynamics and reproducibility in small genetic networks

Julien O Dubuis^{1,2}, Reba Samanta³ and Thomas Gregor^{1,2,*}

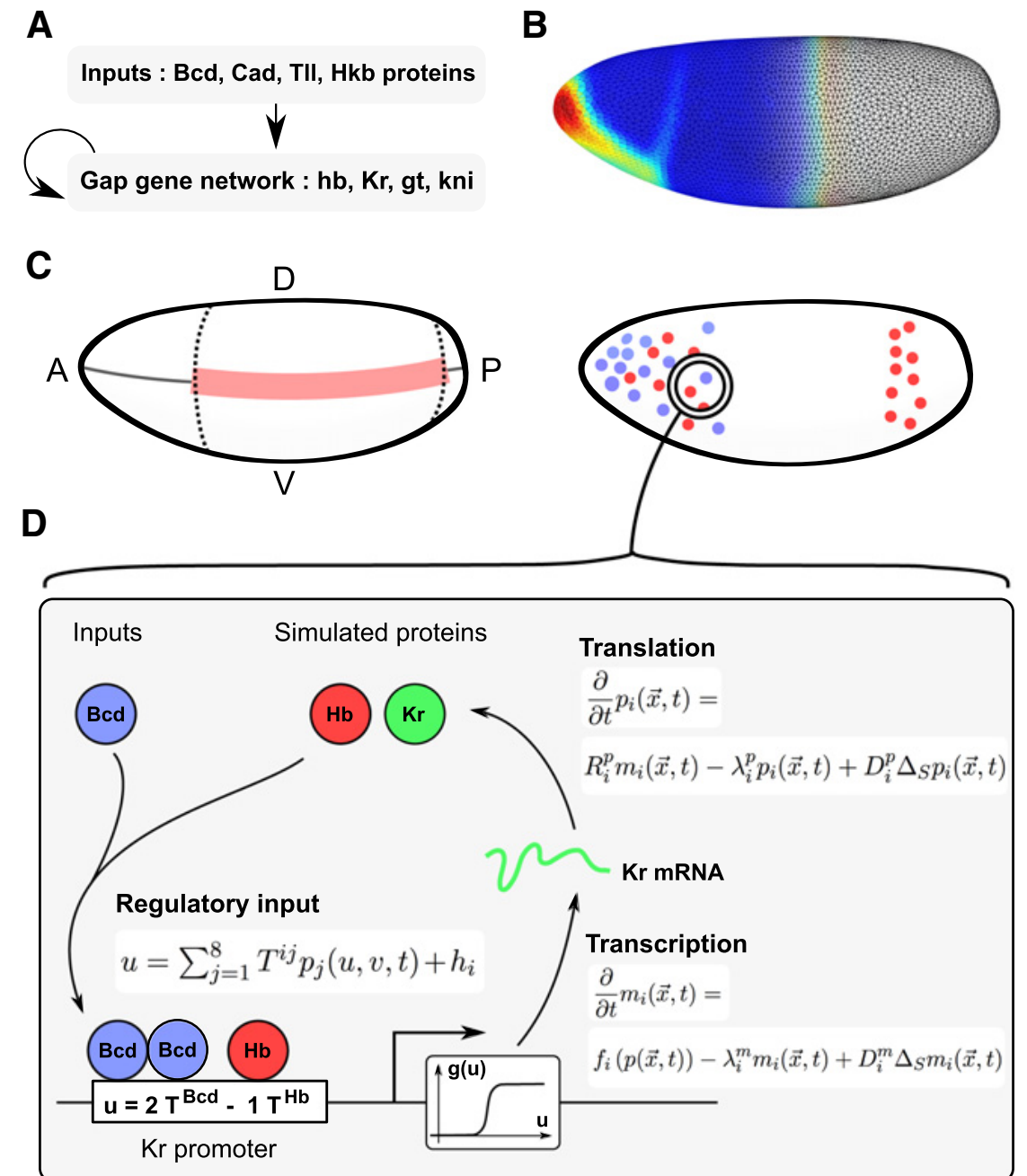
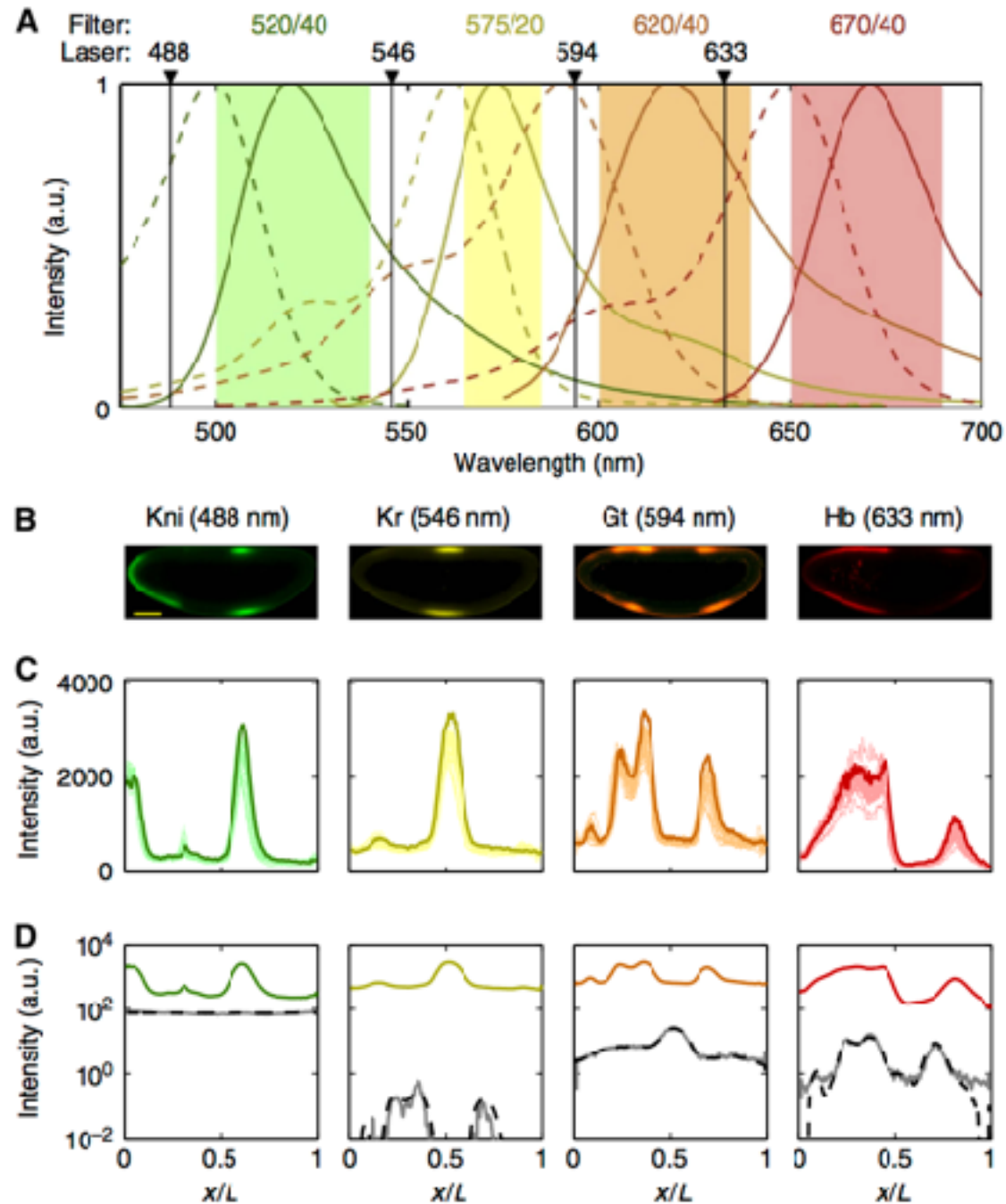
Biophysical Journal Volume 101 July 2011 287–296

287

Whole-Embryo Modeling of Early Segmentation in *Drosophila* Identifies Robust and Fragile Expression Domains

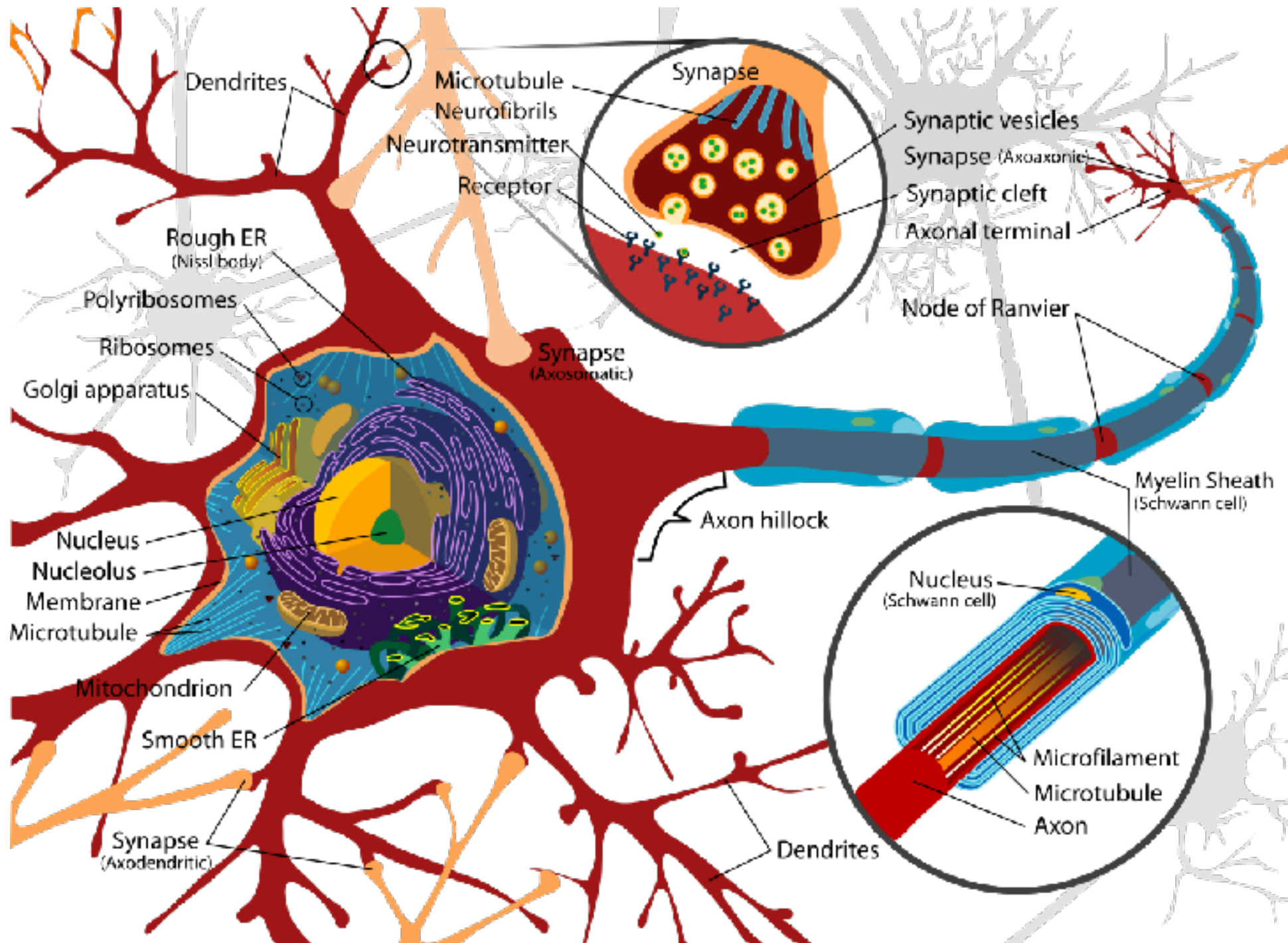
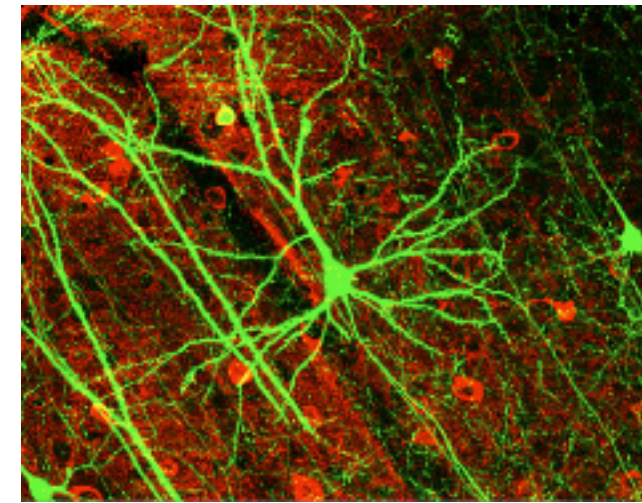
Jonathan Bieler, Christian Pozzorini, and Felix Naef*

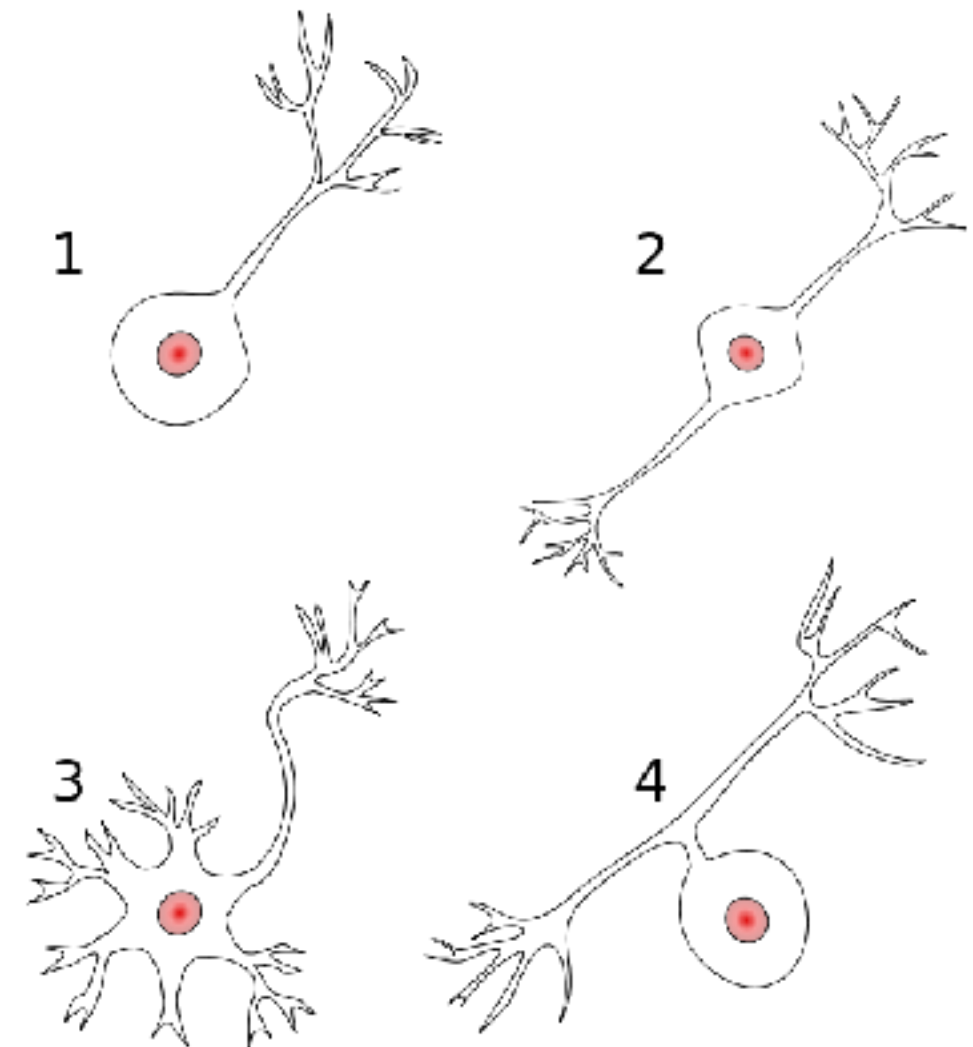
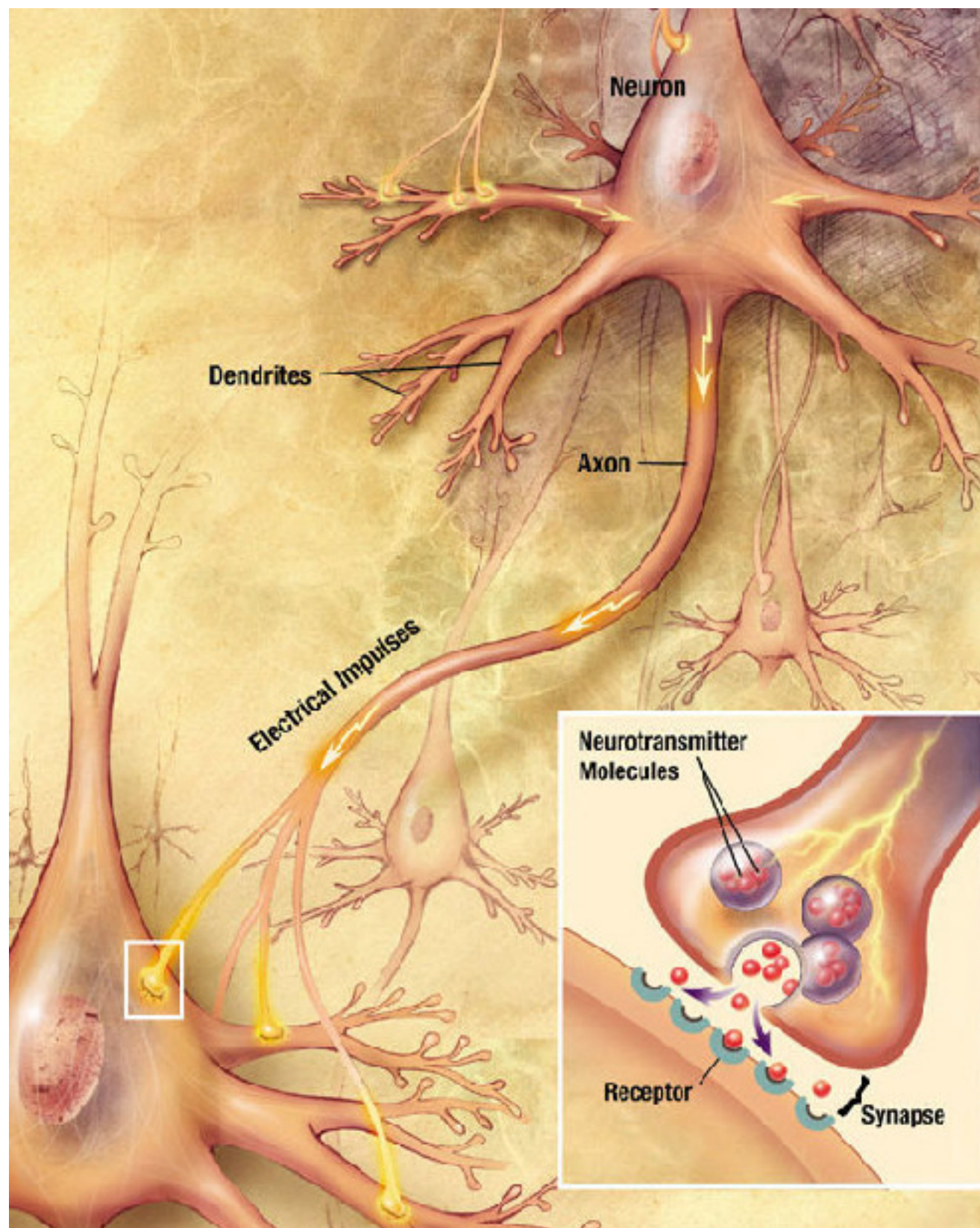
The Institute of Bioengineering, School of Life Sciences, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland



Neur(on)al networks

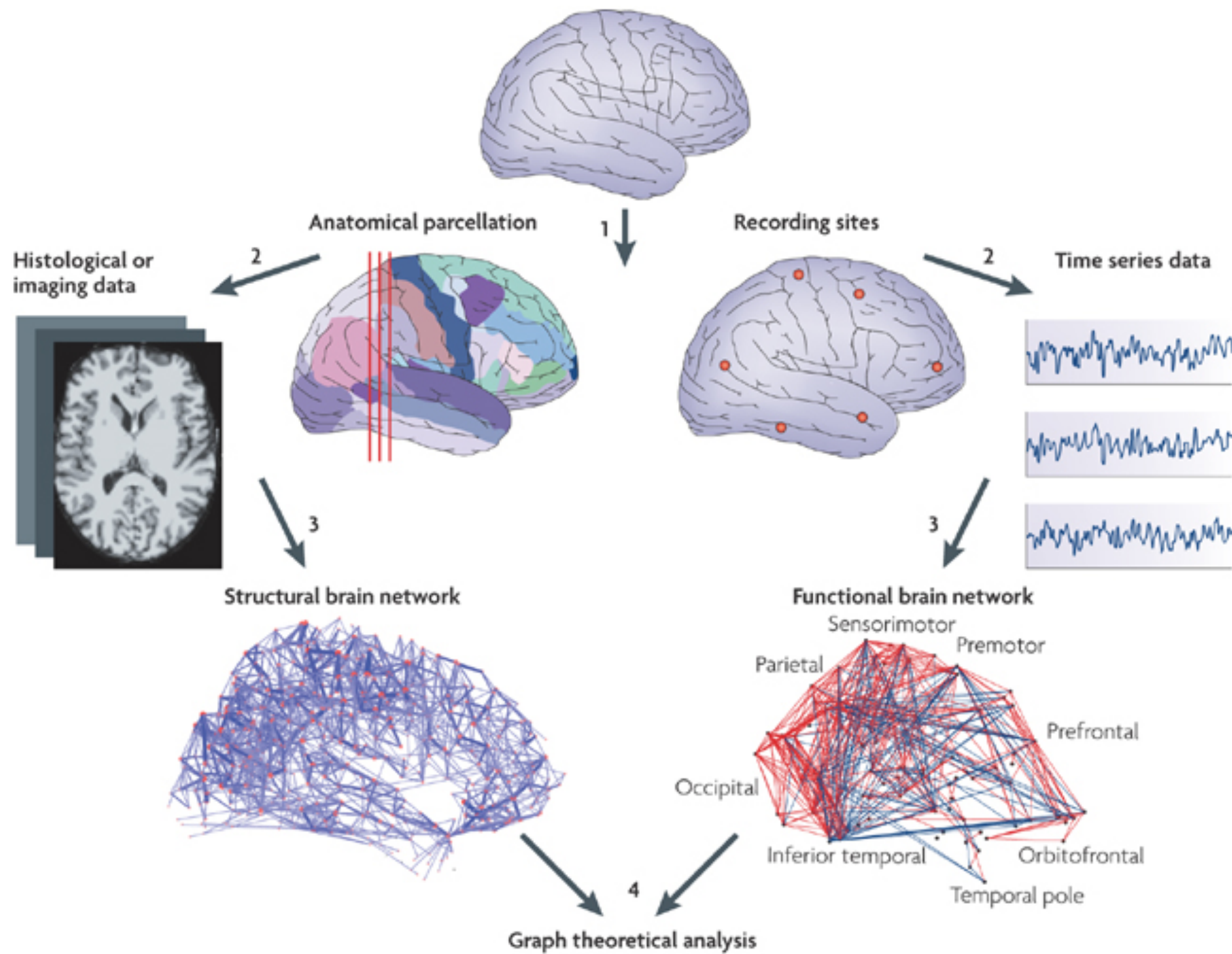
Image of pyramidal neurons in mouse [cerebral cortex](#) expressing [green fluorescent protein](#). The red staining indicates [GABAergic interneurons](#)

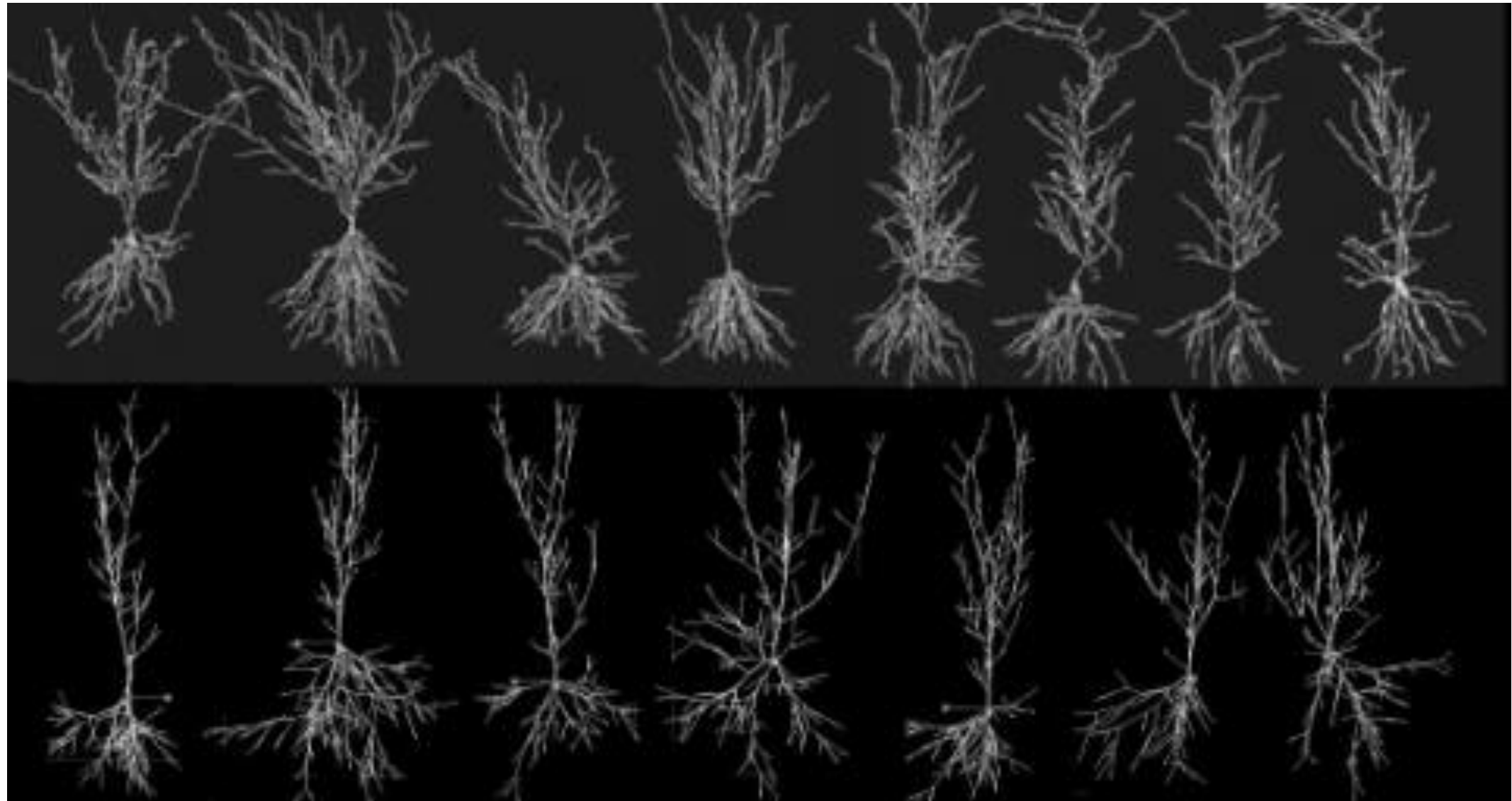




Different kinds of neurons:

- 1 Unipolar neuron
- 2 Bipolar neuron
- 3 Multipolar neuron
- 4 Pseudounipolar neuron






















Real hippocampal pyramidal cells (top) obtained from an experimental archive are used to extract fundamental parameters and generate virtual neurons (bottom), with Tamori's algorithm. No two virtual or real neurons are ever identical, though they belong to a recognizable morphological class.

<http://krasnowl.gmu.edu/cn3/L-Neuron/HTM/paper.htm>

Table 2 | Expected values for a generic rodent and primate brains of 1.5 kg, and values observed for the human brain (Azevedo et al., 2009).

	Generic rodent brain	Generic primate brain	Human brain
Brain mass	1500 g	1500 g	1508 g
Total number of neurons in brain	12 billion	93 billion	86 billion
Total number of non-neurons in brain	46 billion	112 billion	85 billion
Mass, cerebral cortex	1154 g	1412 g	1233 g
Neurons, cerebral cortex	2 billion	25 billion	16 billion
Relative size of the cerebral cortex	77% of brain mass	94% of brain mass	82% of brain mass
Relative number of neurons in cerebral cortex	17% of brain neurons	27% of brain neurons	19% of brain neurons
Mass, cerebellum	133 g	121 g	154 g
Neurons, cerebellum	10 billion	61 billion	69 billion
Relative size of the cerebellum	9% of brain mass	8% of brain mass	10% of brain mass

Notice that although the expected mass of the cerebral cortex and cerebellum are similar for these hypothetical brains, the numbers of neurons that they contain are remarkably different. The human brain thus exhibits seven times more neurons than expected for a rodent brain of its size, but 92% of what would be expected of a hypothetical primate brain of the same size. Expected values were calculated based on the power laws relating structure size and number of neurons (irrespective of body size) that apply to average species values for rodents (Herculano-Houzel et al., 2006) and primate brains (Herculano-Houzel et al., 2007), excluding the olfactory bulb.

Name	Neurons in the brain/whole nervous system	Details	Image	Source
Sponge	0			
<i>Trichoplax</i>	0			[1]
<i>Caenorhabditis elegans</i> (roundworm)	302	~ 7,500 synapses		[2]
Jellyfish	800			[3]
Medicinal leech	10,000			[4]
Pond snail	11,000			[5]
Sea slug	18,000			[6]
Fruit fly	100,000	~ 10 ⁷ synapses		[7]
Larval zebrafish	100,000			[8]
Lobster	100,000			[9]
Ant	250,000	Varies per species		[11]
Honey bee	960,000	~ 10 ⁹ synapses		[12]
Cockroach	1,000,000			[13]
Adult zebrafish	~10,000,000 cells (neurons + other)			[14]
Frog	16,000,000			[15]
Mouse	71,000,000	~ 10 ¹¹ synapses		[16]
Rat	200,000,000	4.48 × 10 ¹¹		[3]
Octopus	300,000,000			[17]
Human	86,000,000,000	For average adult; 10 ¹⁴ –10 ¹⁵ synapses		[18][19][20]



2012
nature
Channelrhodopsin
Crystal Structure →

Method of the Year: 2010 →
nature **methods**
Optogenetics

2010
**SCIENTIFIC
AMERICAN**
Optogenetics Article →

2011 Primer
Cell
Opsin Genomics and
Structure-Function →

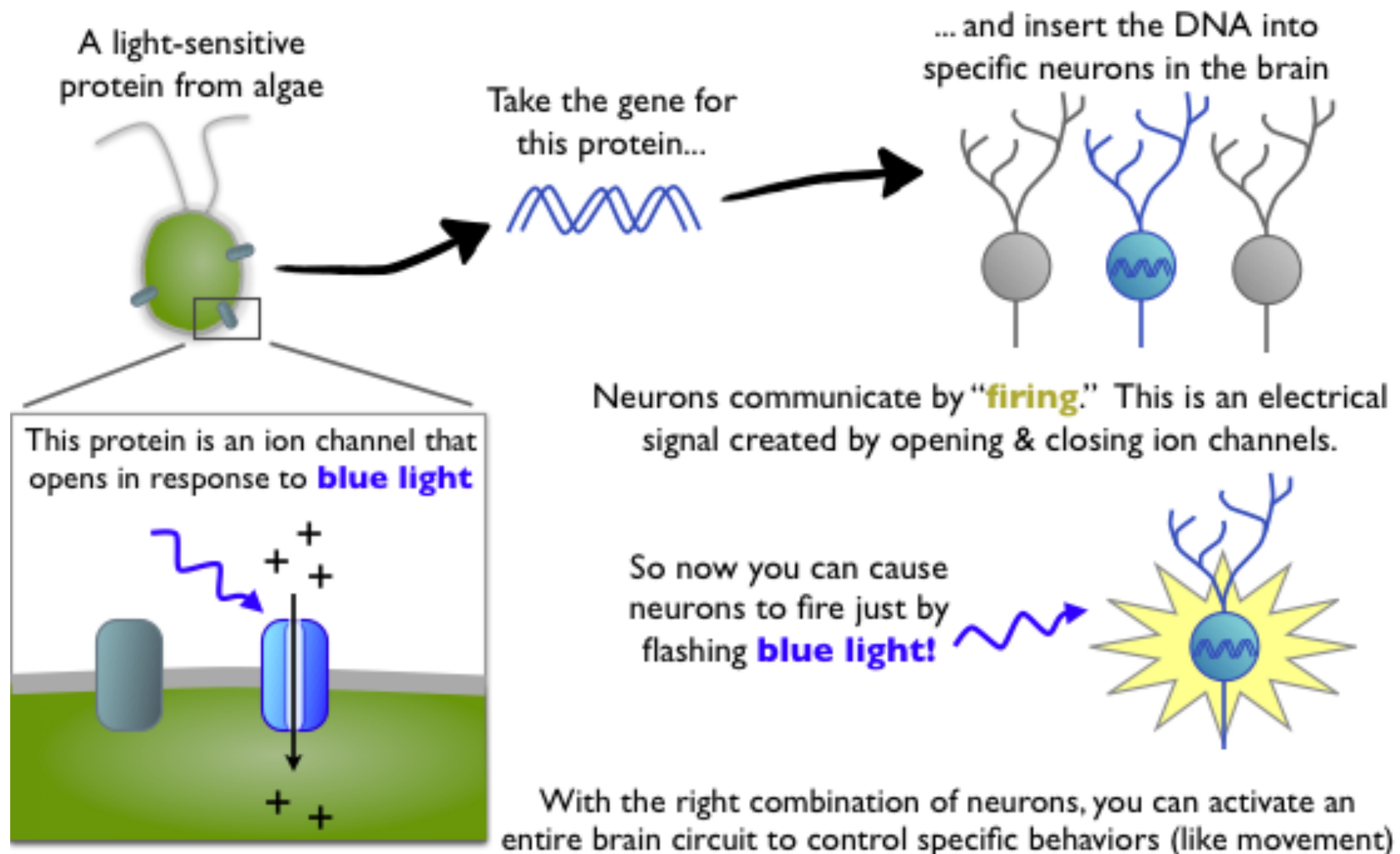
2011 Primer
Neuron
Optogenetics in
Neural Systems →

nature
protocols
optogenetics
protocols →

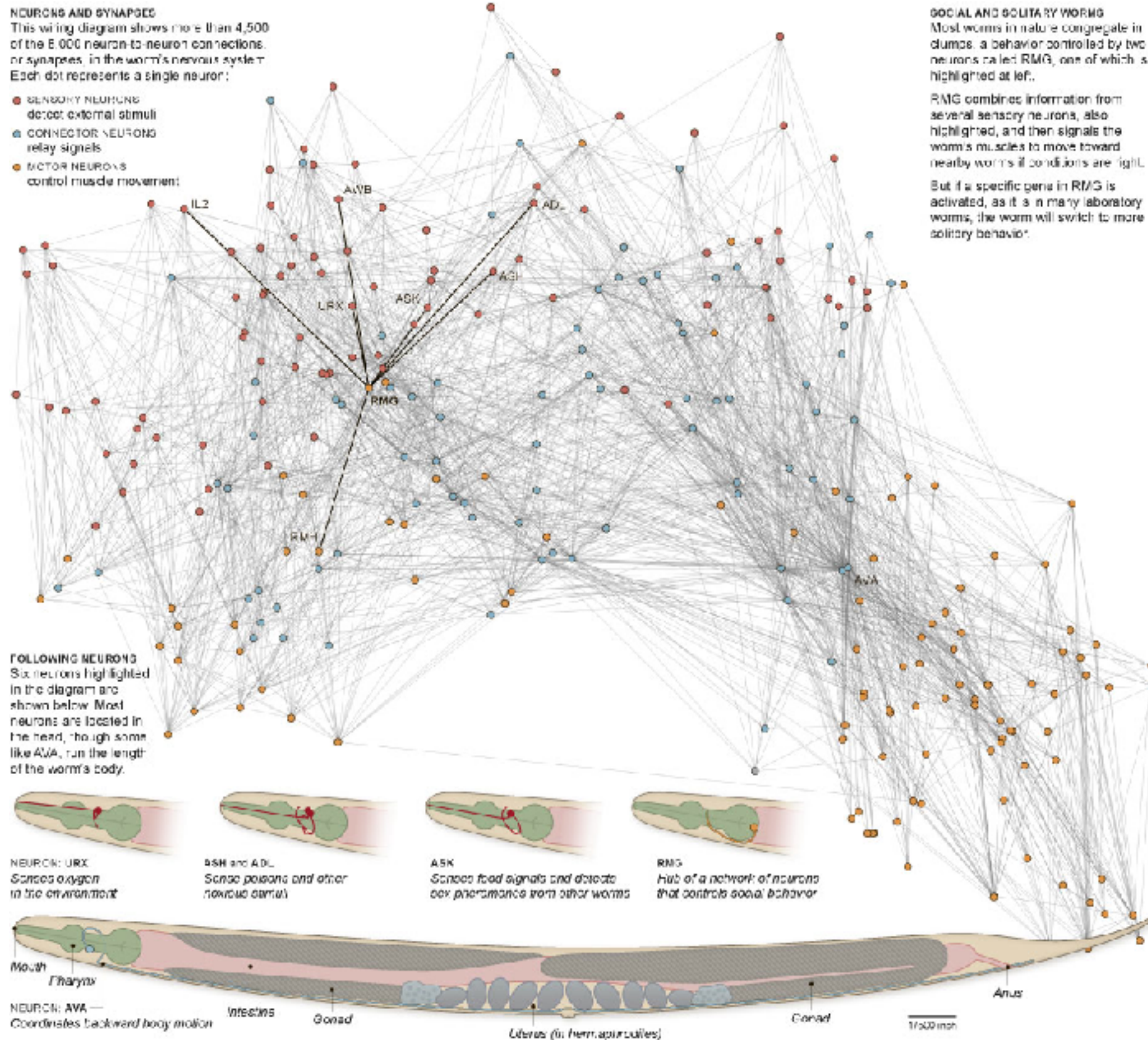
2012 Analysis
nature **methods**
Quantitative Opsin
Properties →

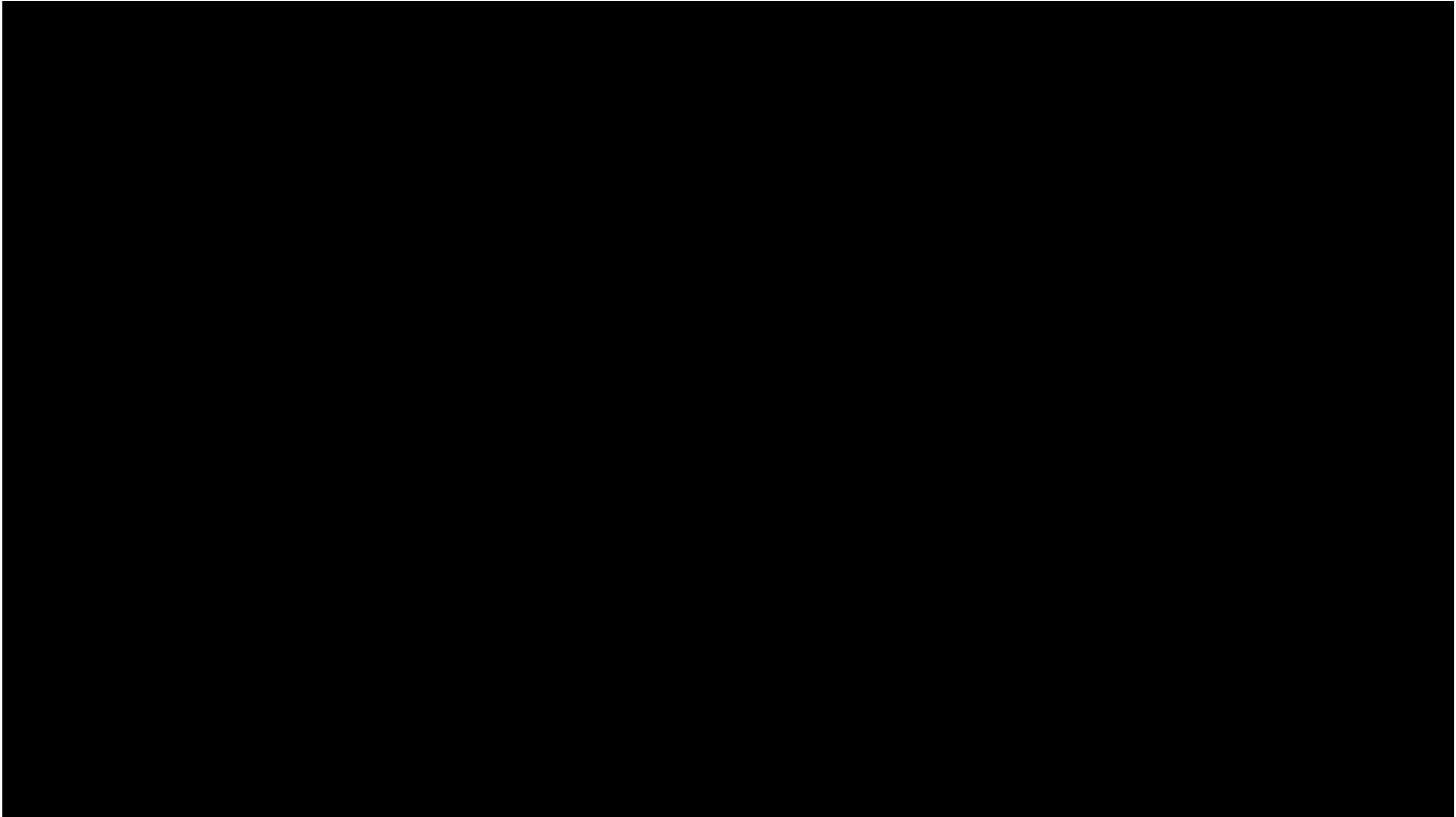


How optogenetics works



C elegans (302 neurons)



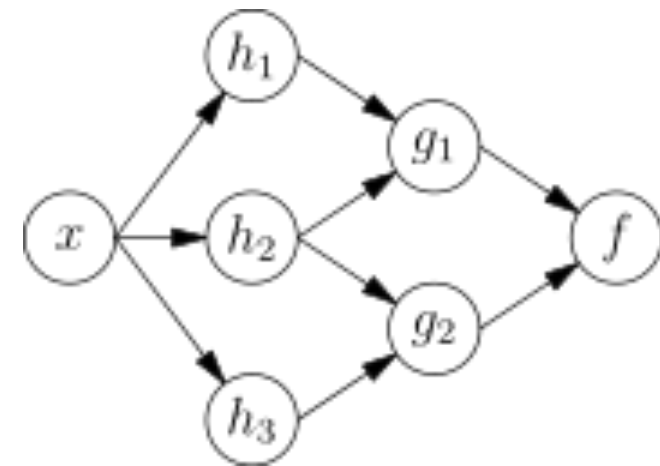
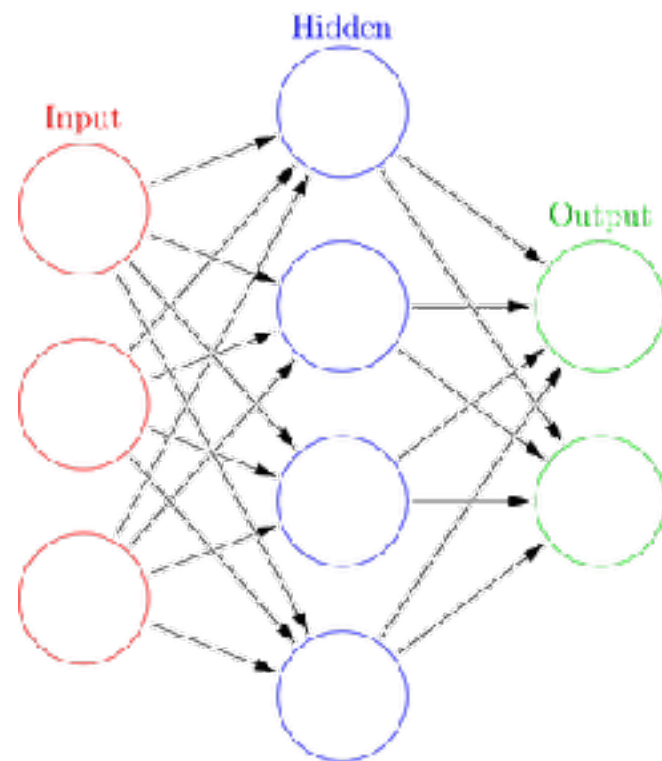


<https://www.youtube.com/watch?v=I64X7vHSHOE>

Artificial neural networks (ANNs)

An ANN is typically defined by three types of parameters:

1. The interconnection pattern between the different layers of neurons
2. The learning process for updating the weights of the interconnections
3. The activation function that converts a neuron's weighted input to its output activation.

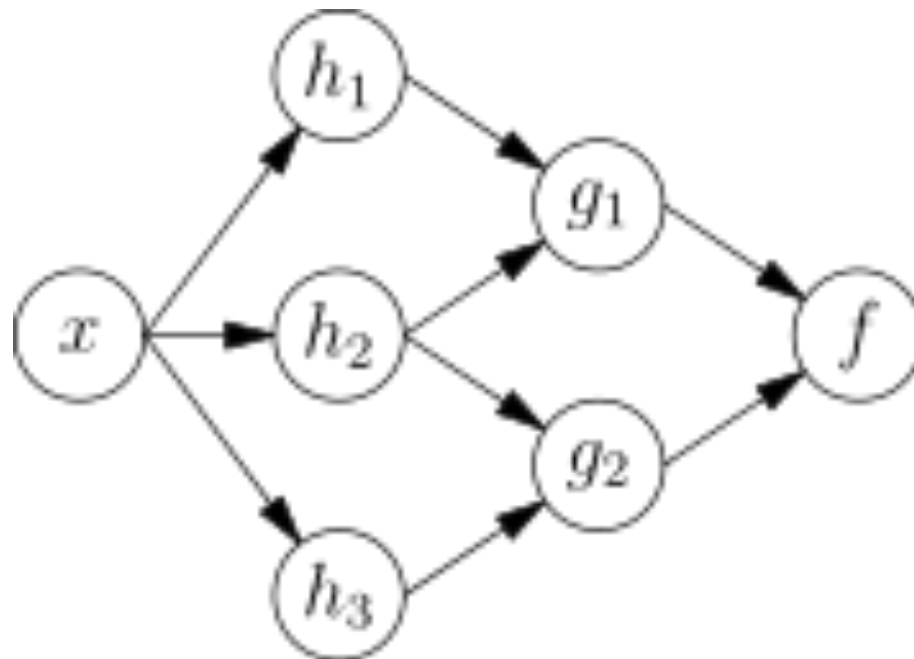


Mathematically, a neuron's network function f is defined as a composition of other functions h, g

Learning

Given a specific *task* to solve, and a *class* of functions $\mathbf{F}=\{f\}$, learning means using a set of *observations* to find f^* in \mathbf{F} which solves the task in some *optimal* sense.

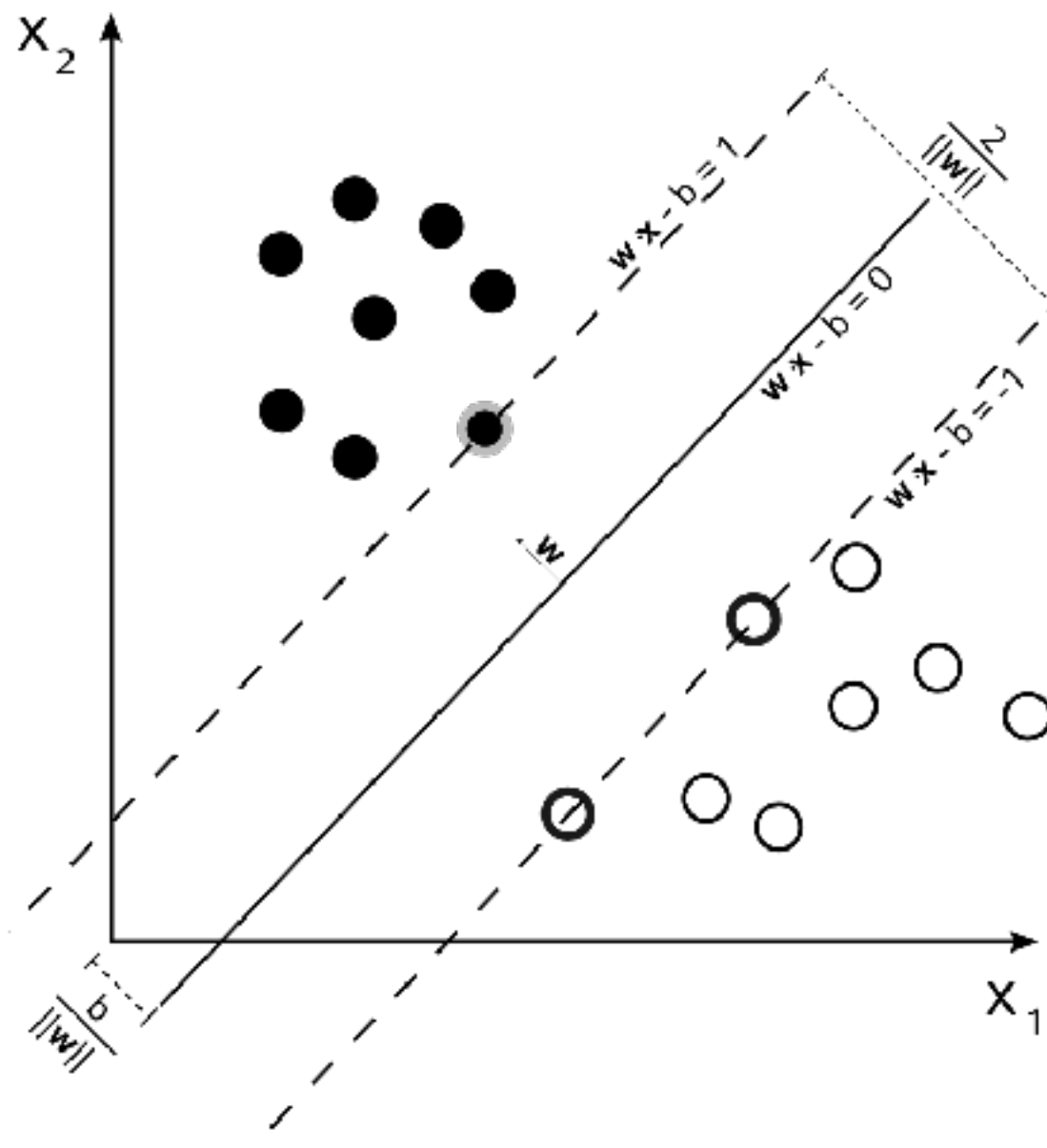
Needs real-valued typically convex cost function $\mathbf{C}(f)$ to determine what's optimal



Example: Support vector machines

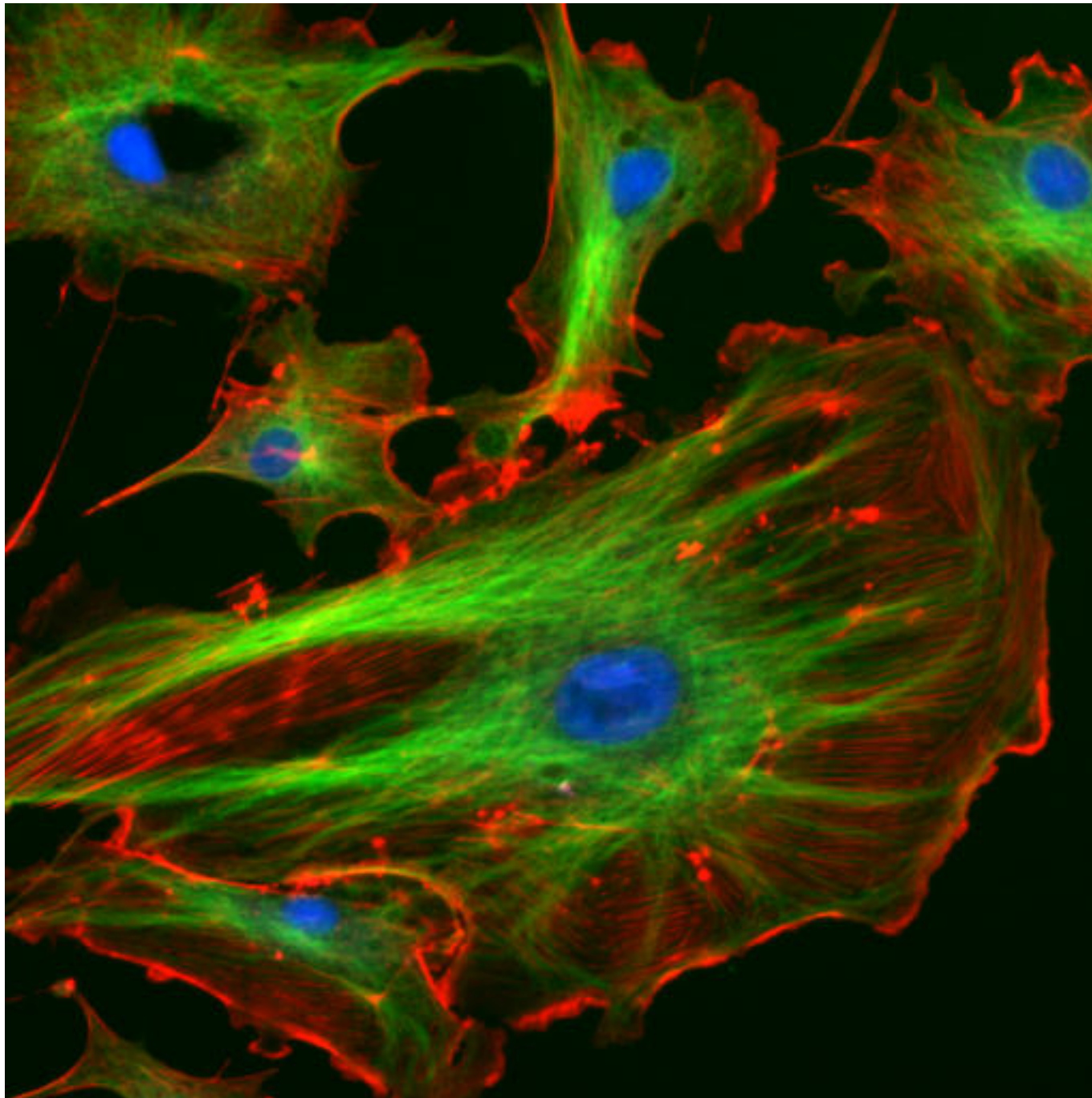
Choose the hyperplane so that the distance from it to the nearest data point on each side is maximized.

If such a hyperplane exists, it is known as the *maximum-margin hyperplane* and the linear classifier it defines is known as a *maximum margin classifier*, or equivalently, the *perceptron of optimal stability*.



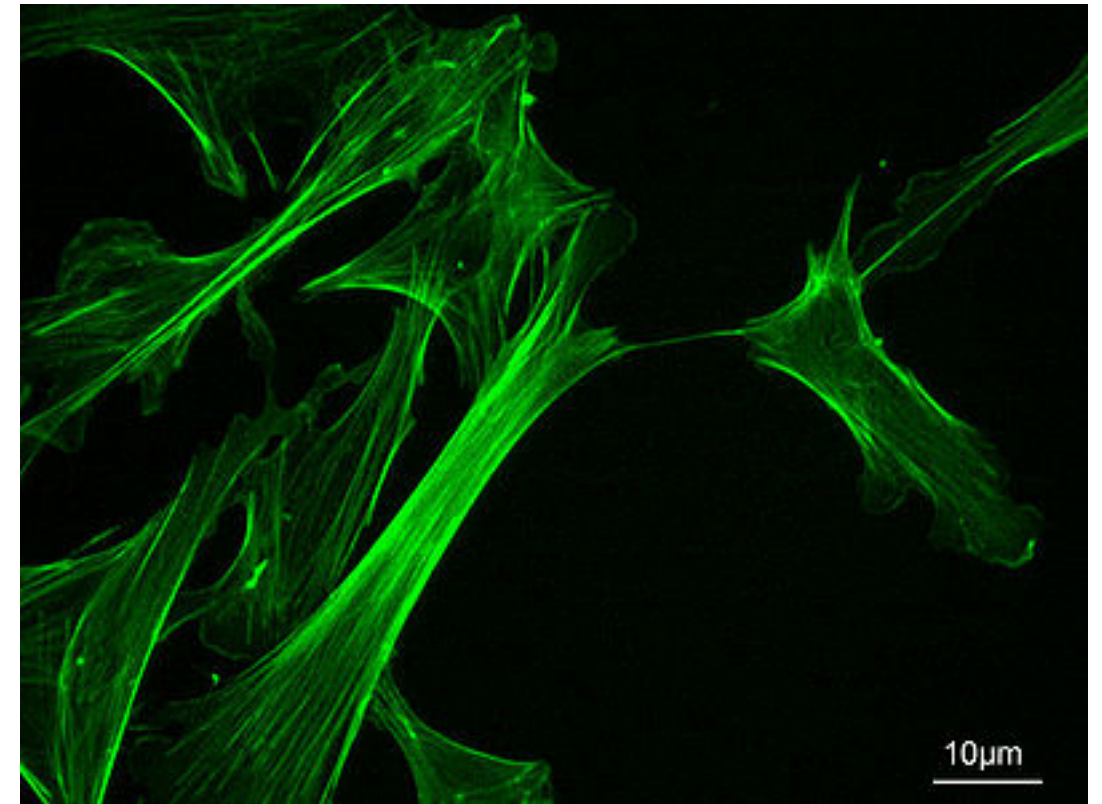
Structural networks

Cytoskeleton



The **eukaryotic** cytoskeleton. **Actin filaments** are shown in red, **microtubules** are in green, and the **nuclei** are in blue.

<http://rsb.info.nih.gov/ij/images/>



Actin cytoskeleton of **mouse embryo fibroblasts**, stained with **phalloidin**

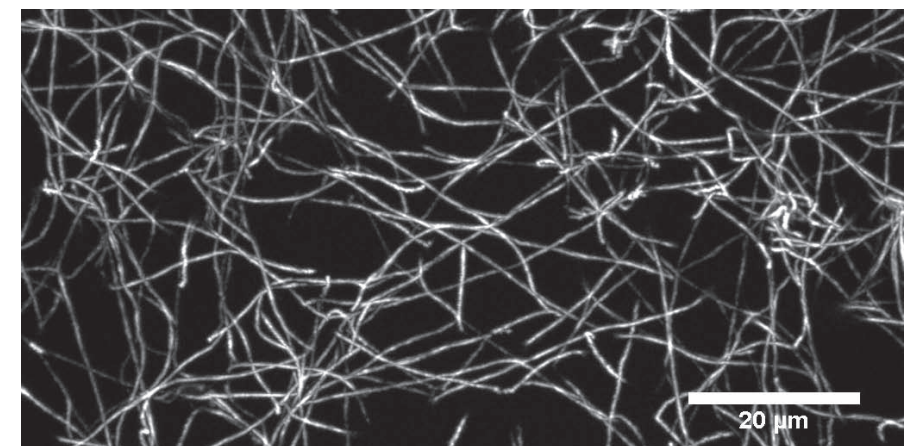
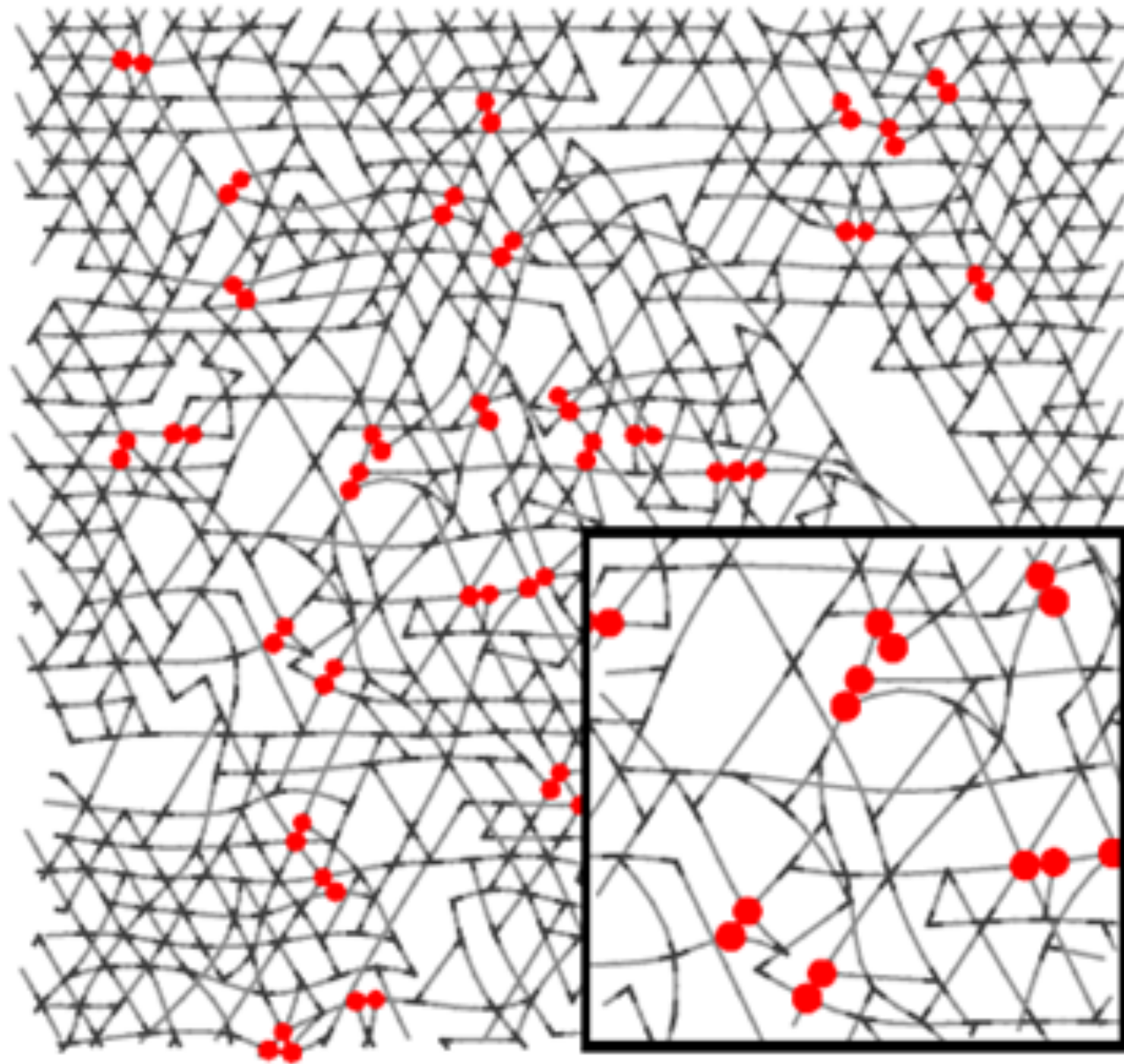


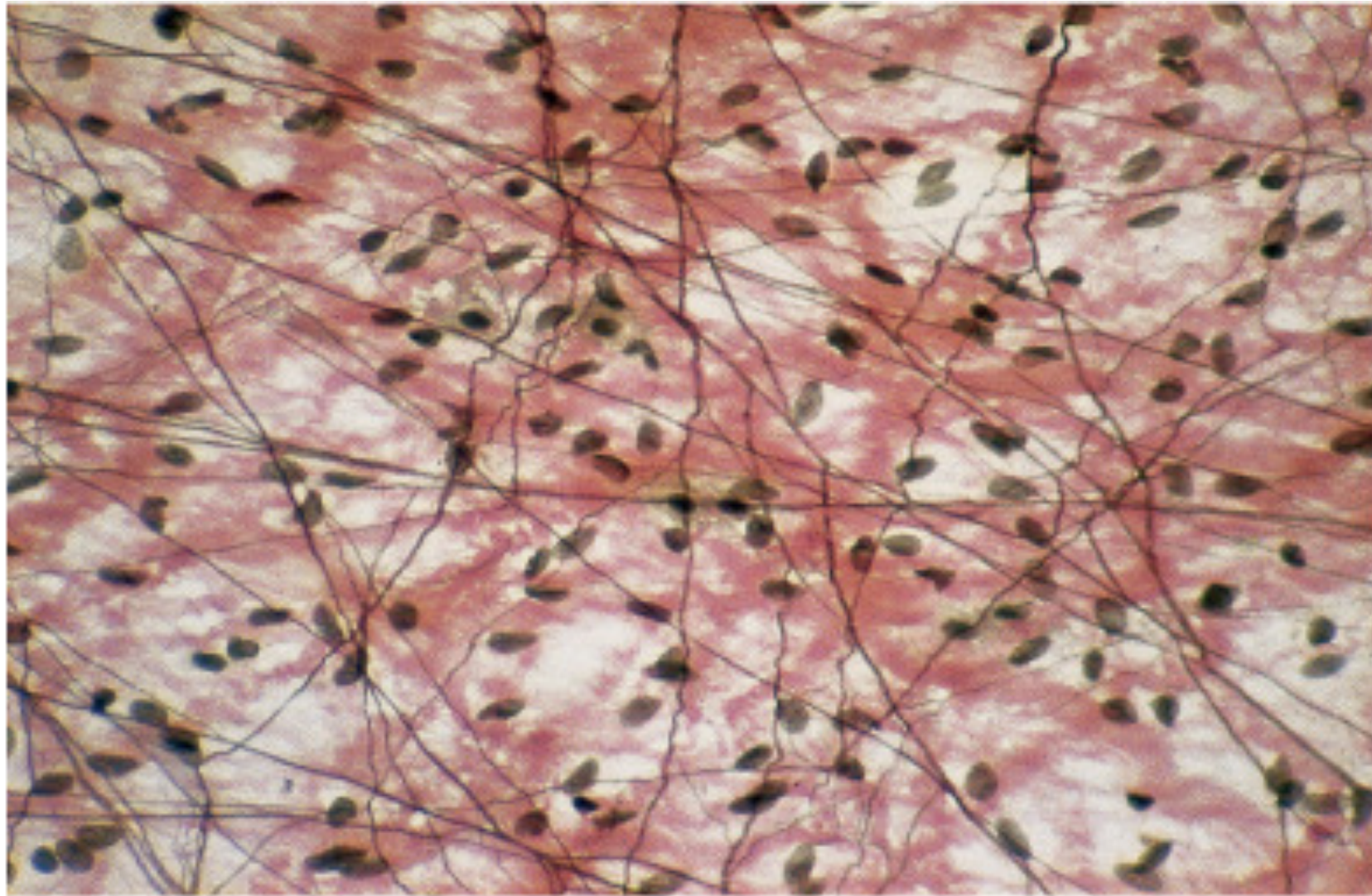
FIG. 2 Confocal microscopy image of a fluorescently labeled collagen network with a concentration of 0.4 mg/ml. Courtesy of Stefan Münster (Erlangen-Nurnberg).

Molecular motors stiffen non-affine semiflexible polymer networks



see also Brodersz & MacKintosh, Rev Mod Phys (2014)

Connective and supporting tissues



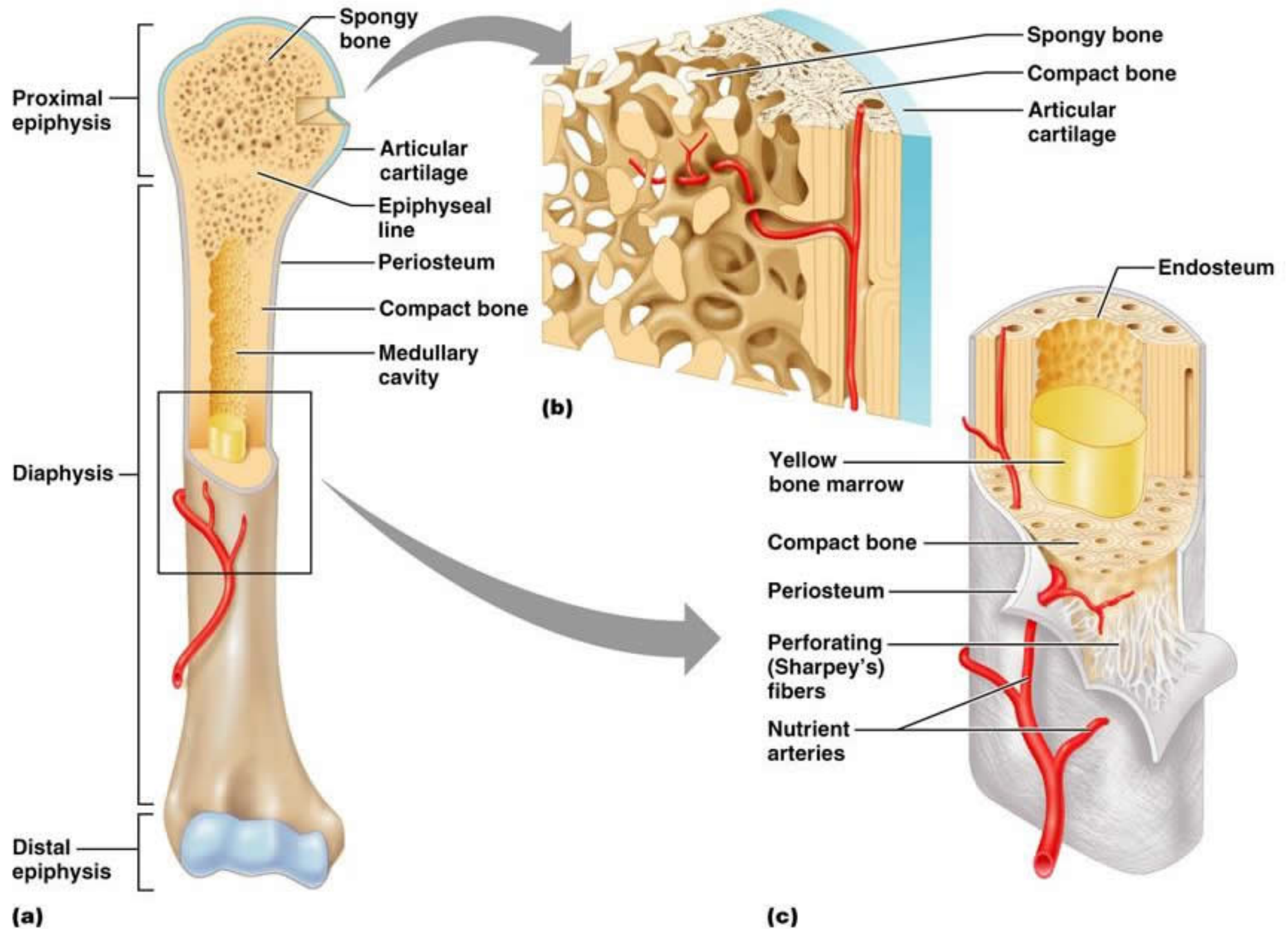
© Elsevier Ltd 2005. Standring: Gray's Anatomy 39e - www.graysanatomyonline.com

The connective tissues are defined as those composed predominantly of intercellular material, the extracellular matrix, which is secreted mainly by the connective tissue cells. The cells are therefore usually widely separated by their matrix, which is composed of fibrous proteins and a relatively amorphous ground substance.

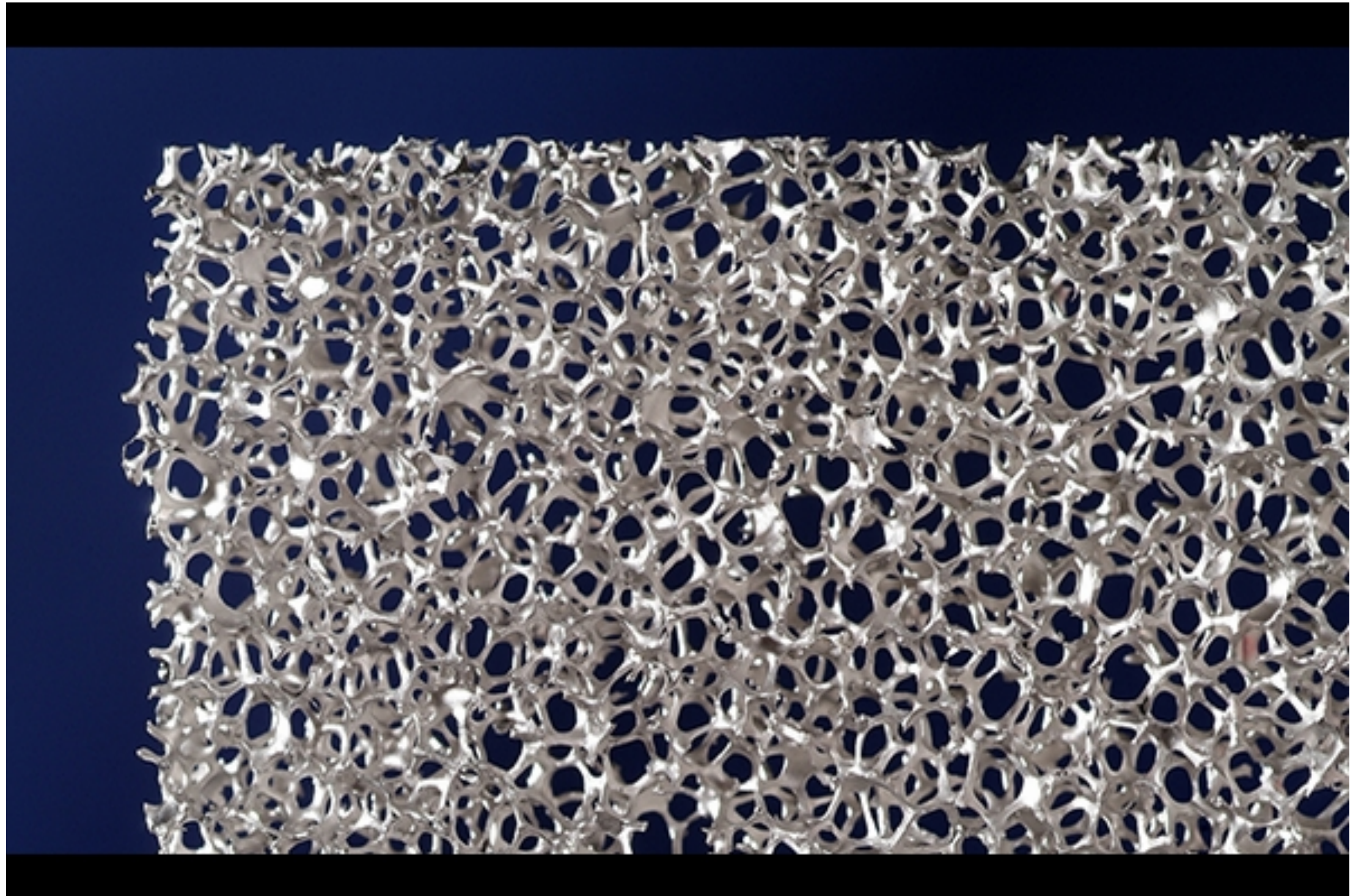
Bone structures



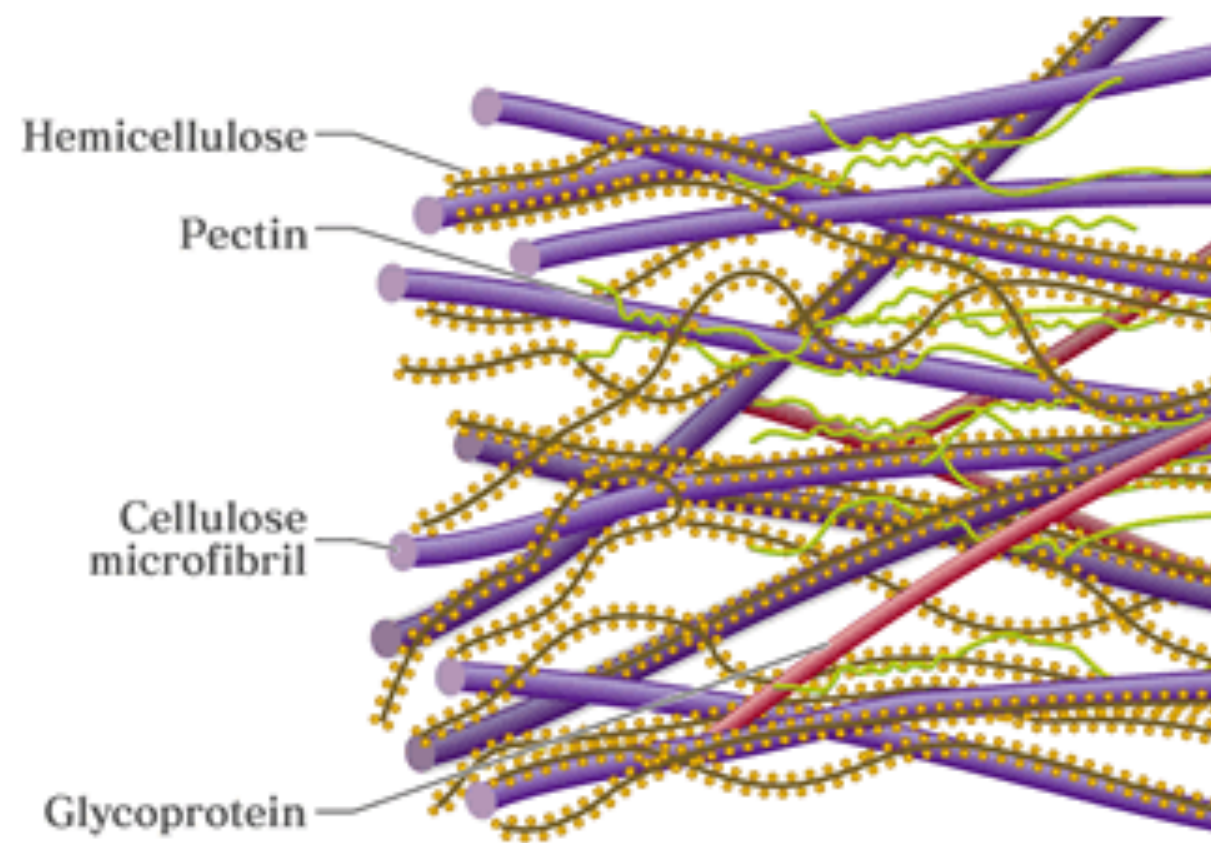
Coloured scanning electron micrograph (SEM) of cancellous (spongy) bone. This tissue, found in the interior of bones, is characterised by a honeycomb arrangement of trabeculae (columns) and spaces.



Metallic foam structures as a bone substitute



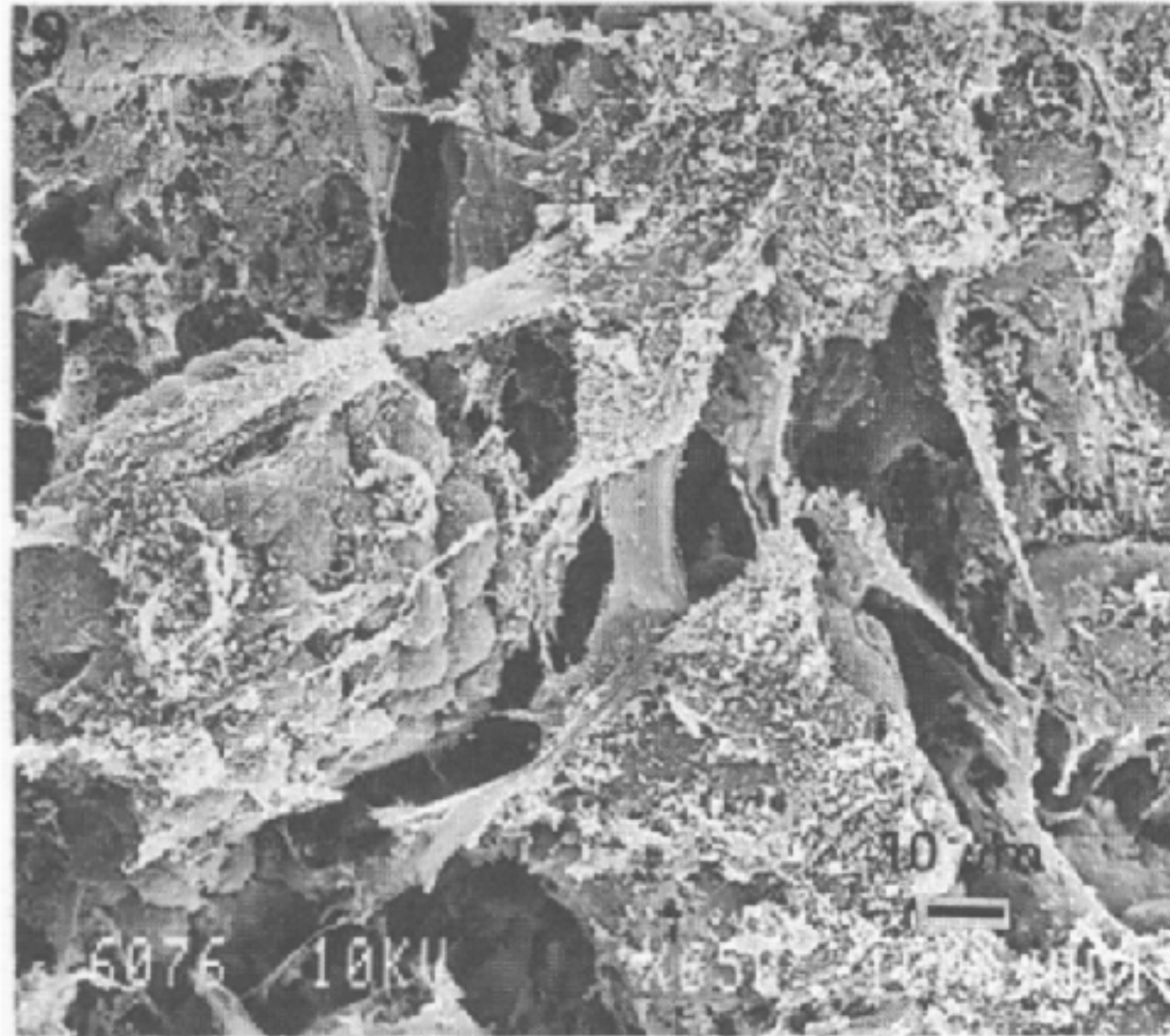
Inter-cellular matrix of plants



+ ZOOM

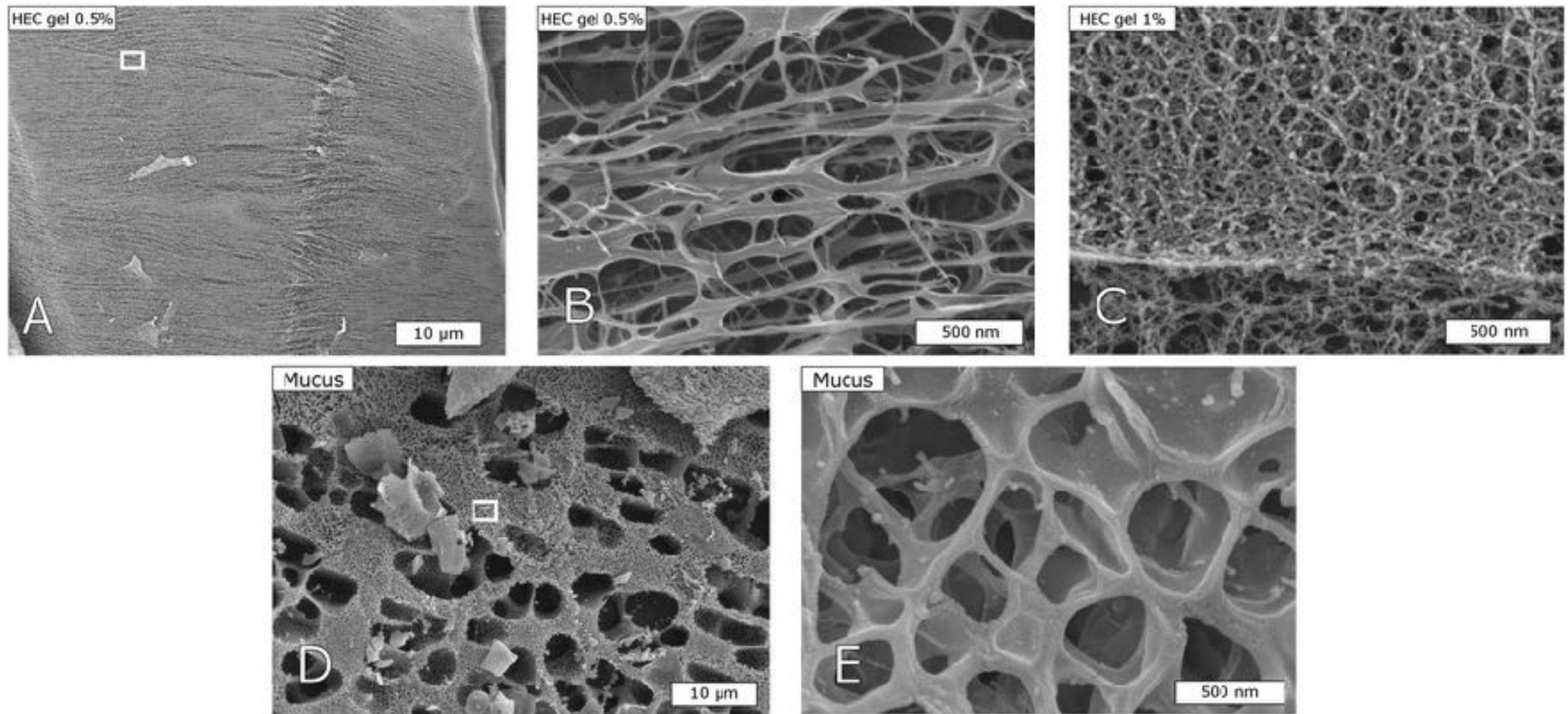
Mucus

Scanning electron microscopy image of rabbit stomach mucosa showing surface cells and numerous bundles of fiber-like mucus strands.
Scale bar 10 μm . Reproduced from Nunn et al. (51) with permission from Wiley.



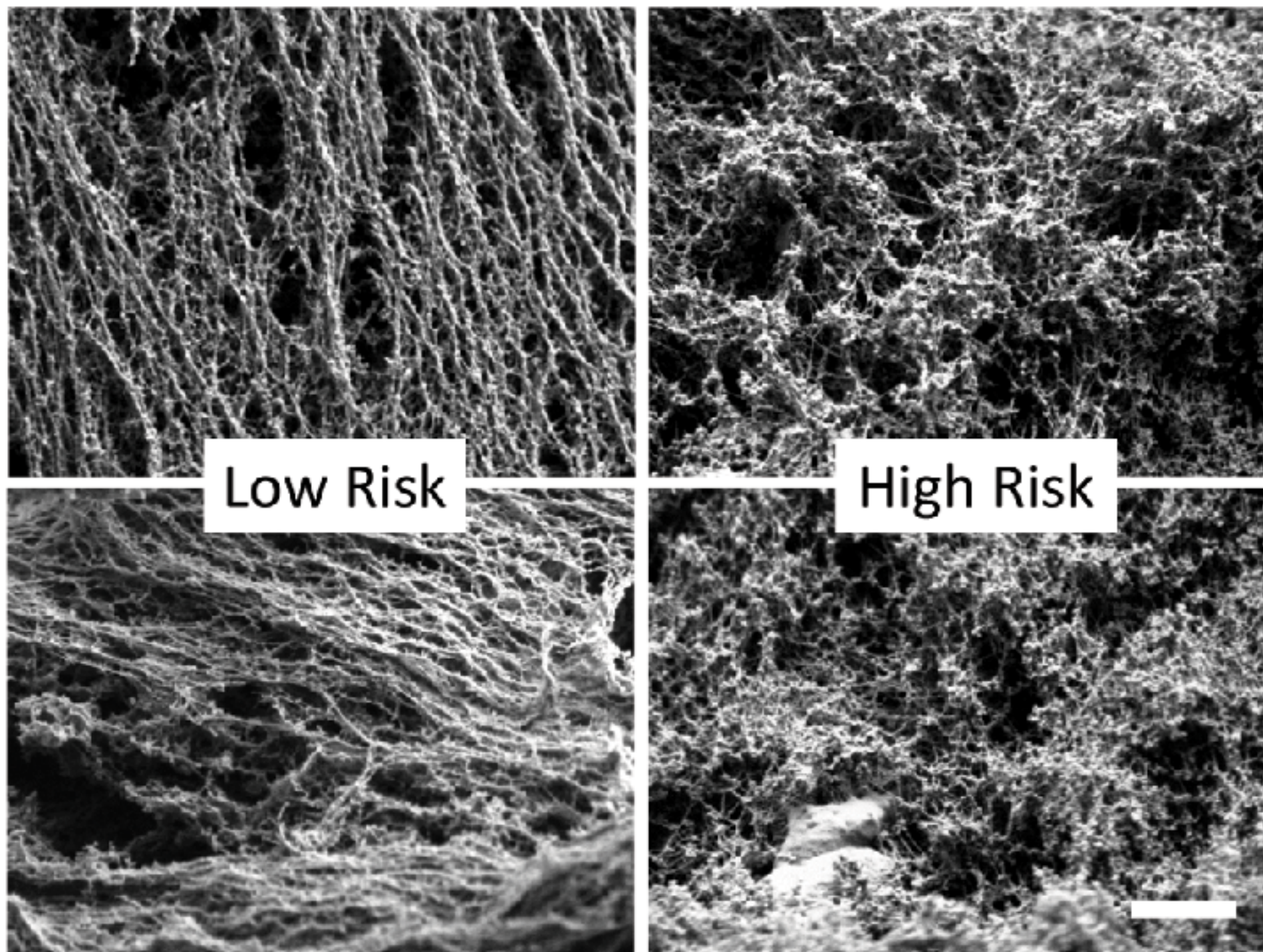
The influence of mucus microstructure and rheology in *Helicobacter pylori* infection

Representative cryo-SEM images of HEC hydrogels (A–C) and mucus (D and E).



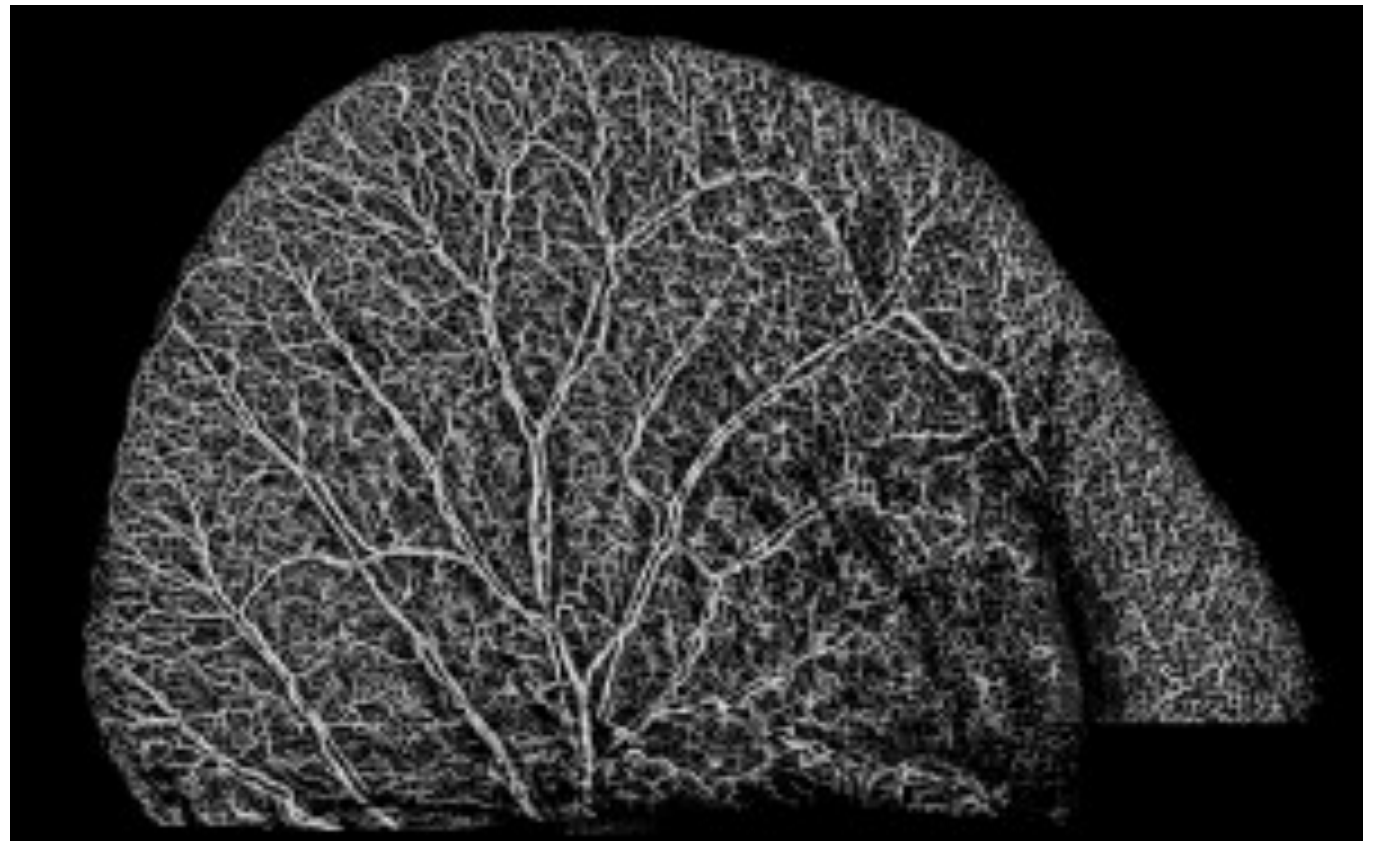
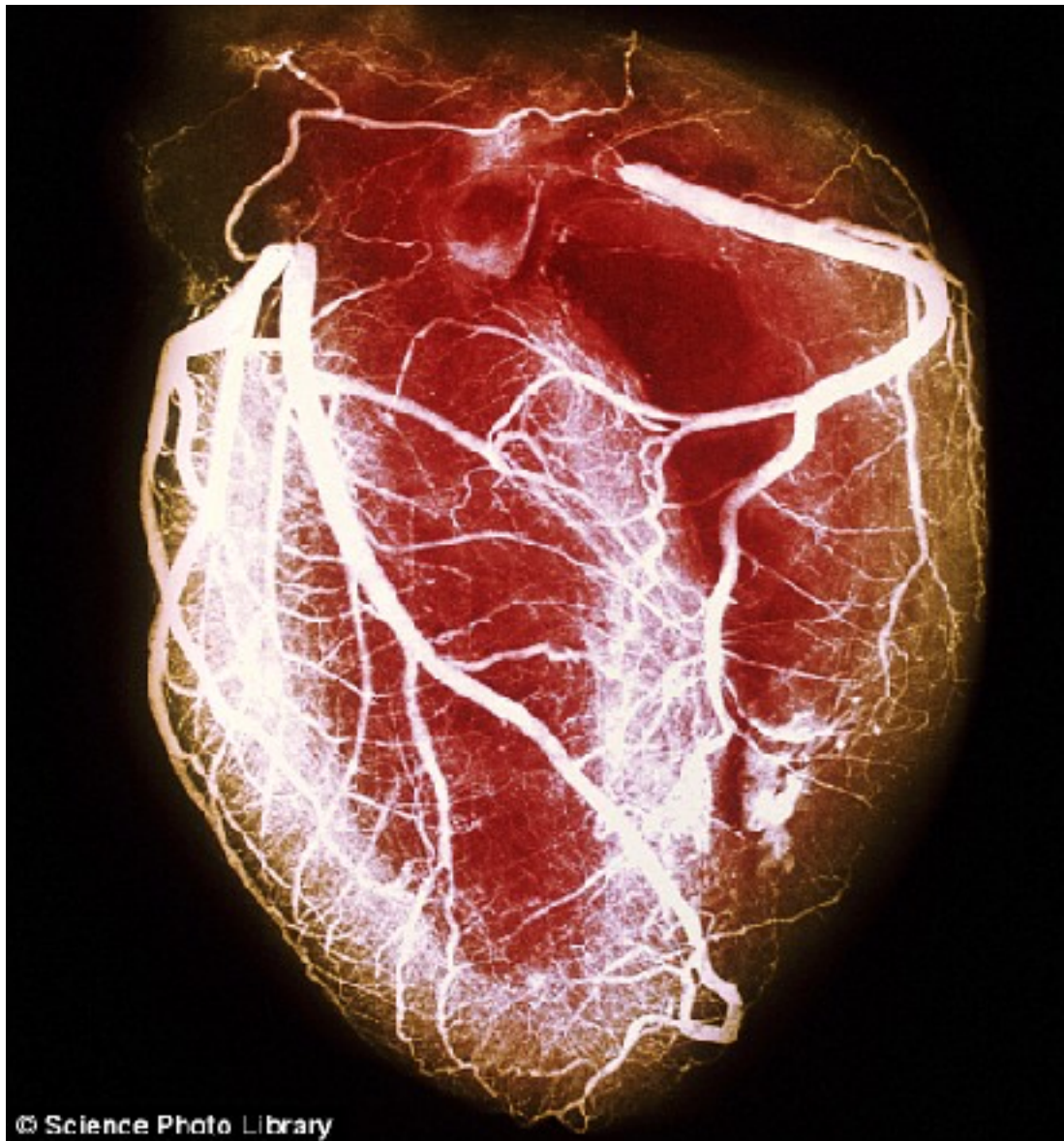
Optical tweezers reveal relationship between microstructure and nanoparticle penetration of pulmonary mucus
Kirch J et al. **PNAS** 2012;109:18355-18360

Cervical Mucus Properties Stratify Risk for Preterm Birth



Transport networks

Blood vessels

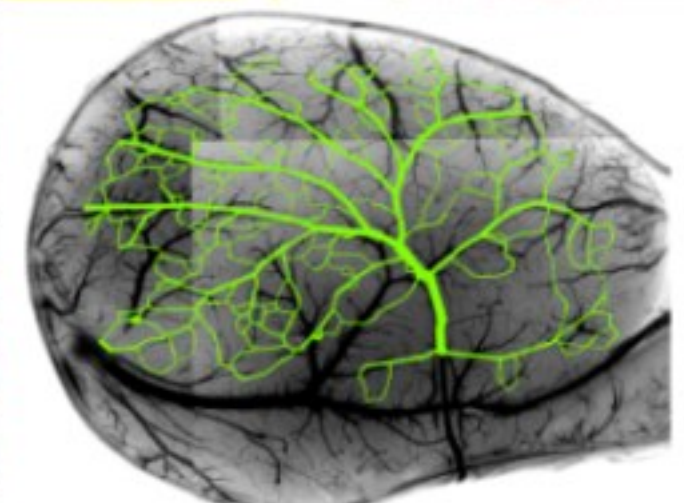
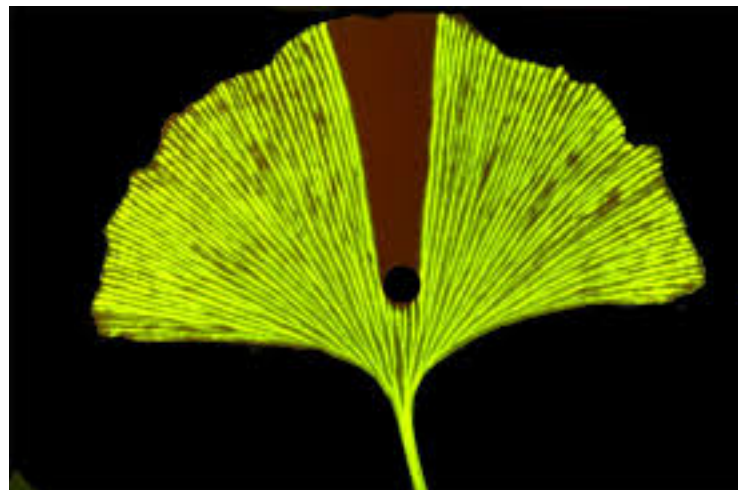
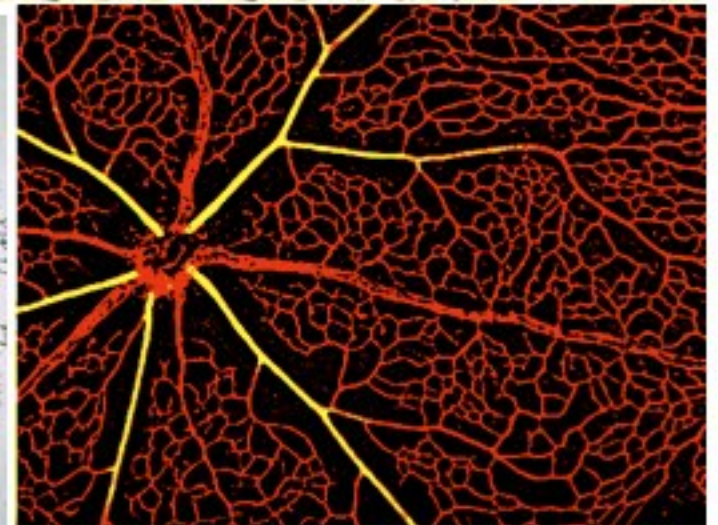
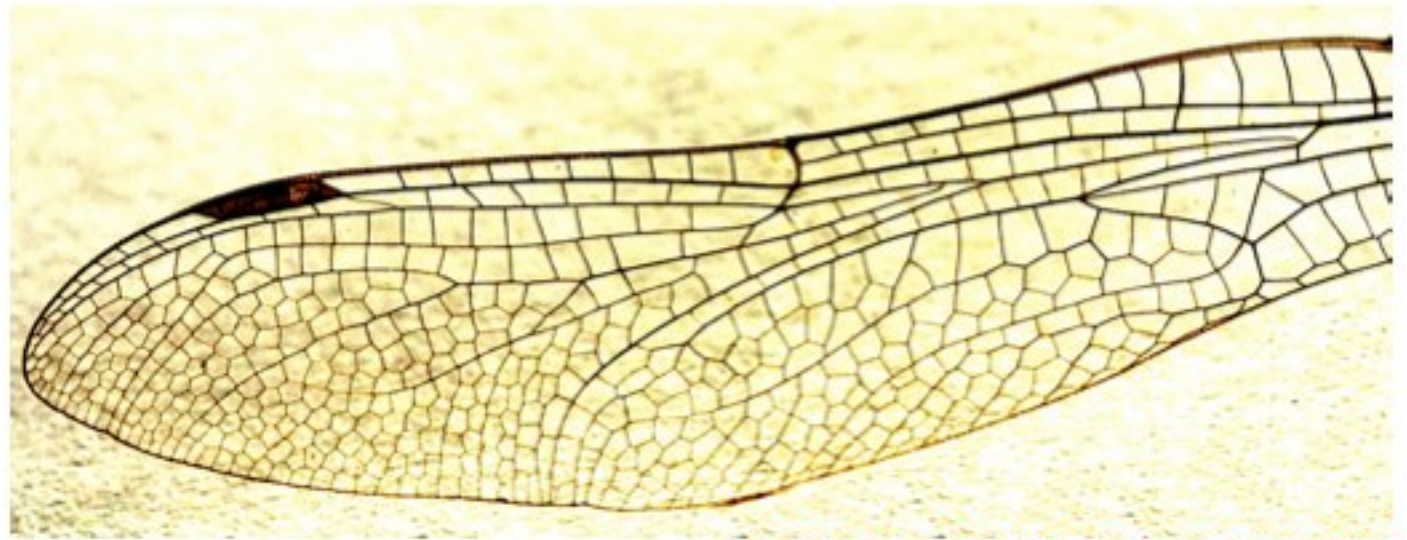
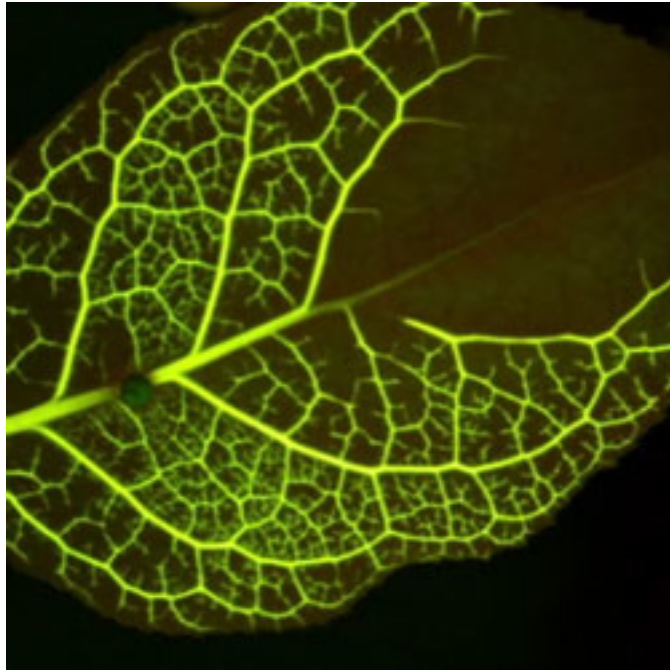


High-resolution microvasculature of a mouse ear from optical imaging microangiography. *Siavash Yousefi, U of Washington*

~25,000 miles of capillaries in an adult, each with an individual length of about 1 mm

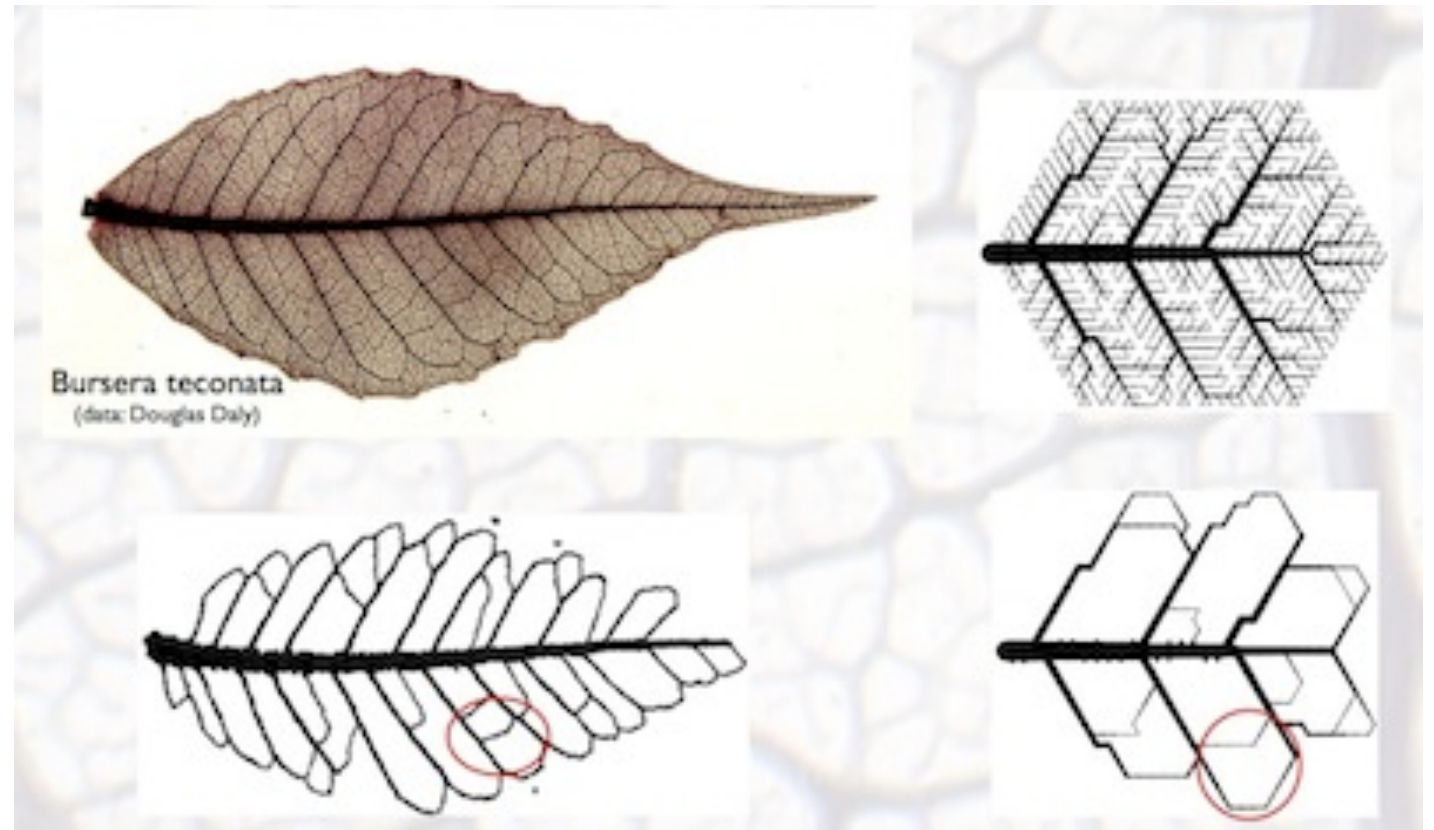
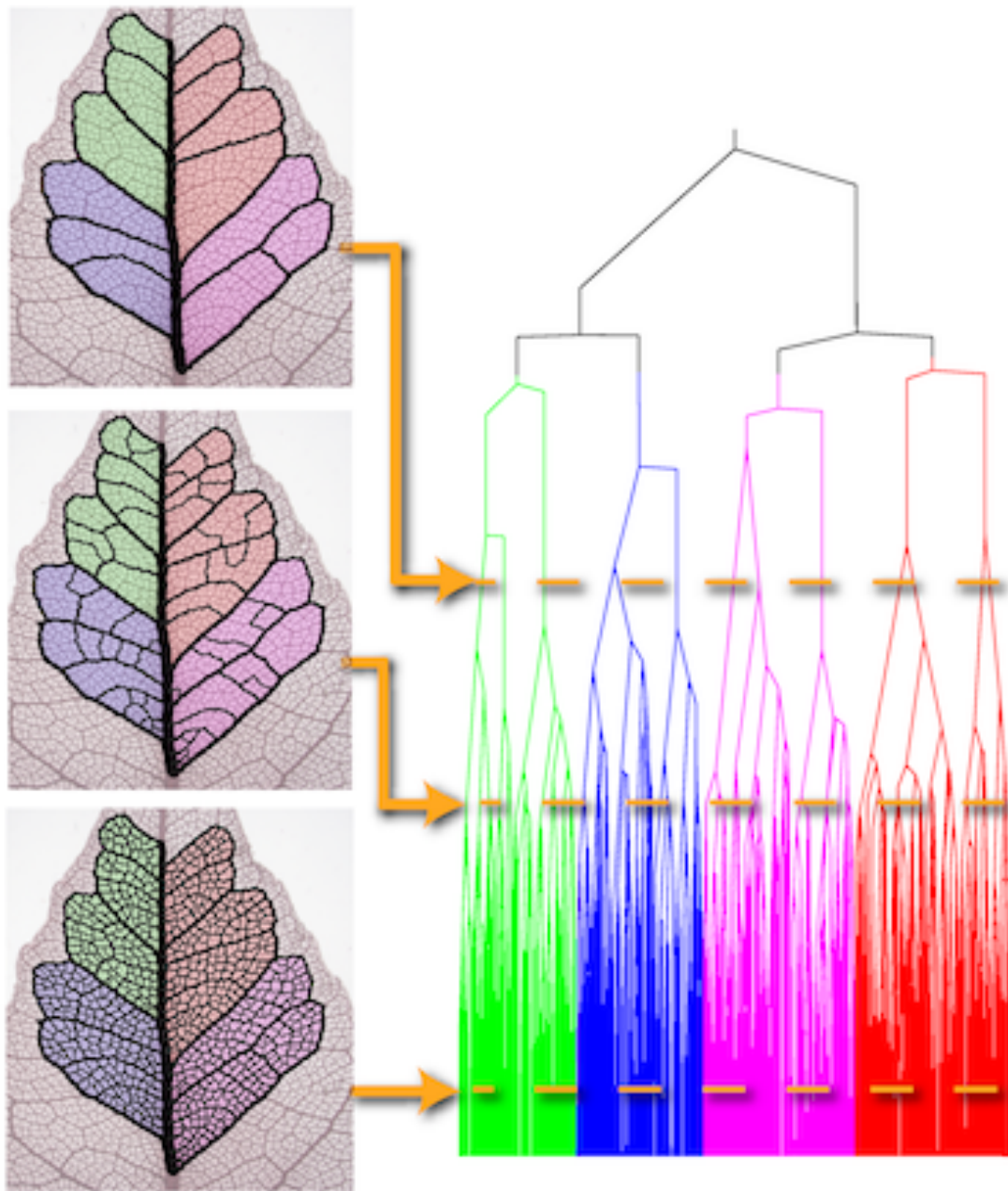
Liver vessels





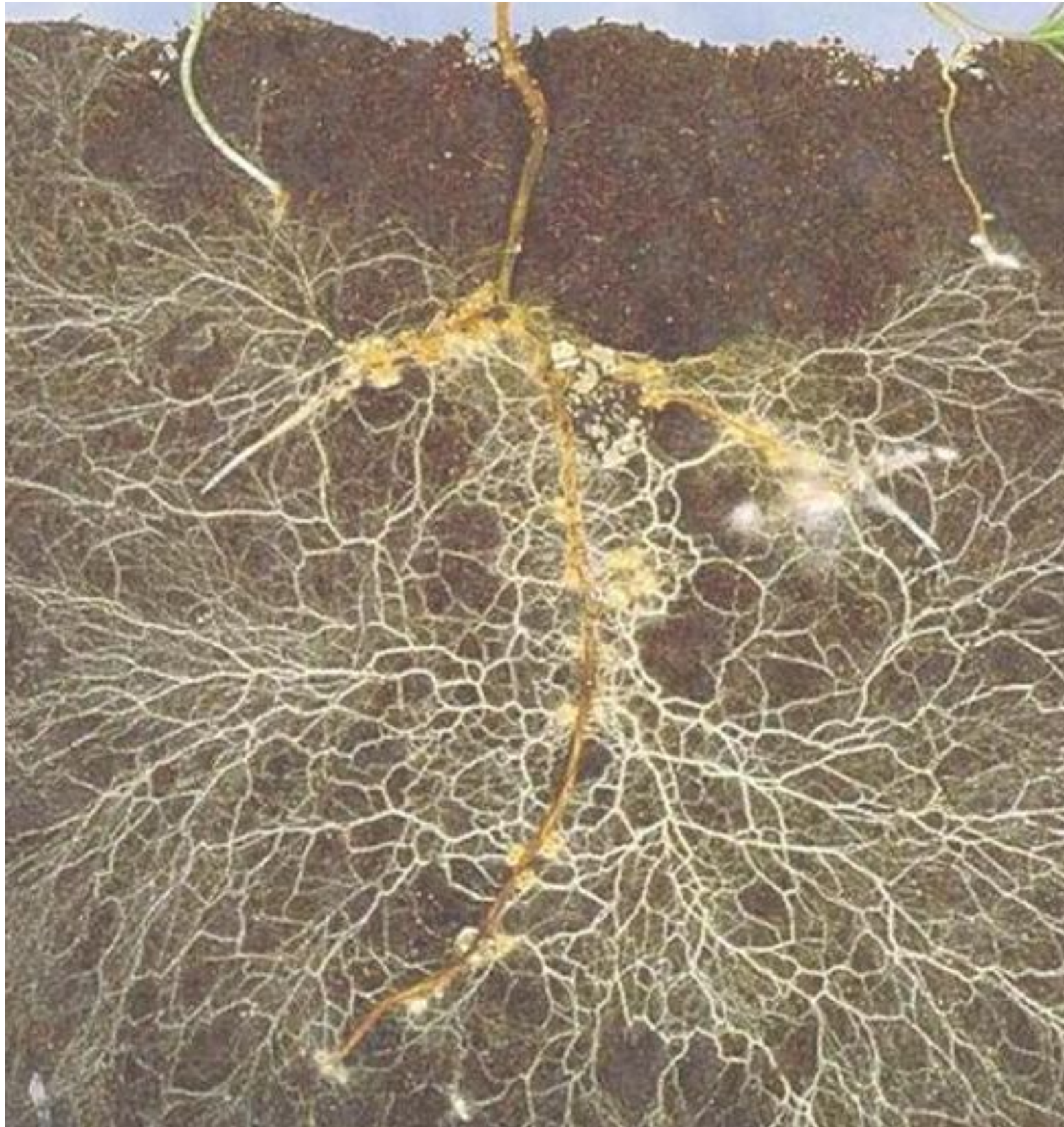
Katifori lab, MPI Goettingen

Network topology & optimization



Katifori lab, UPenn

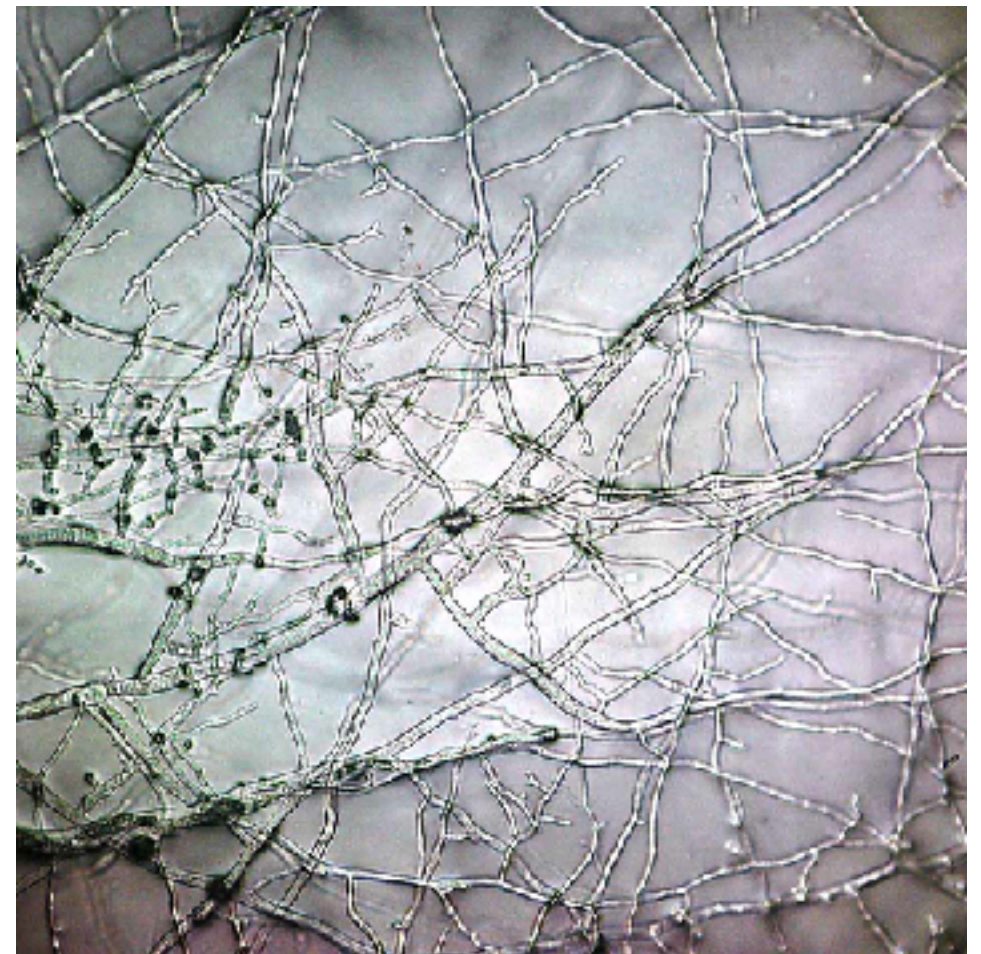
Root systems



Funghi

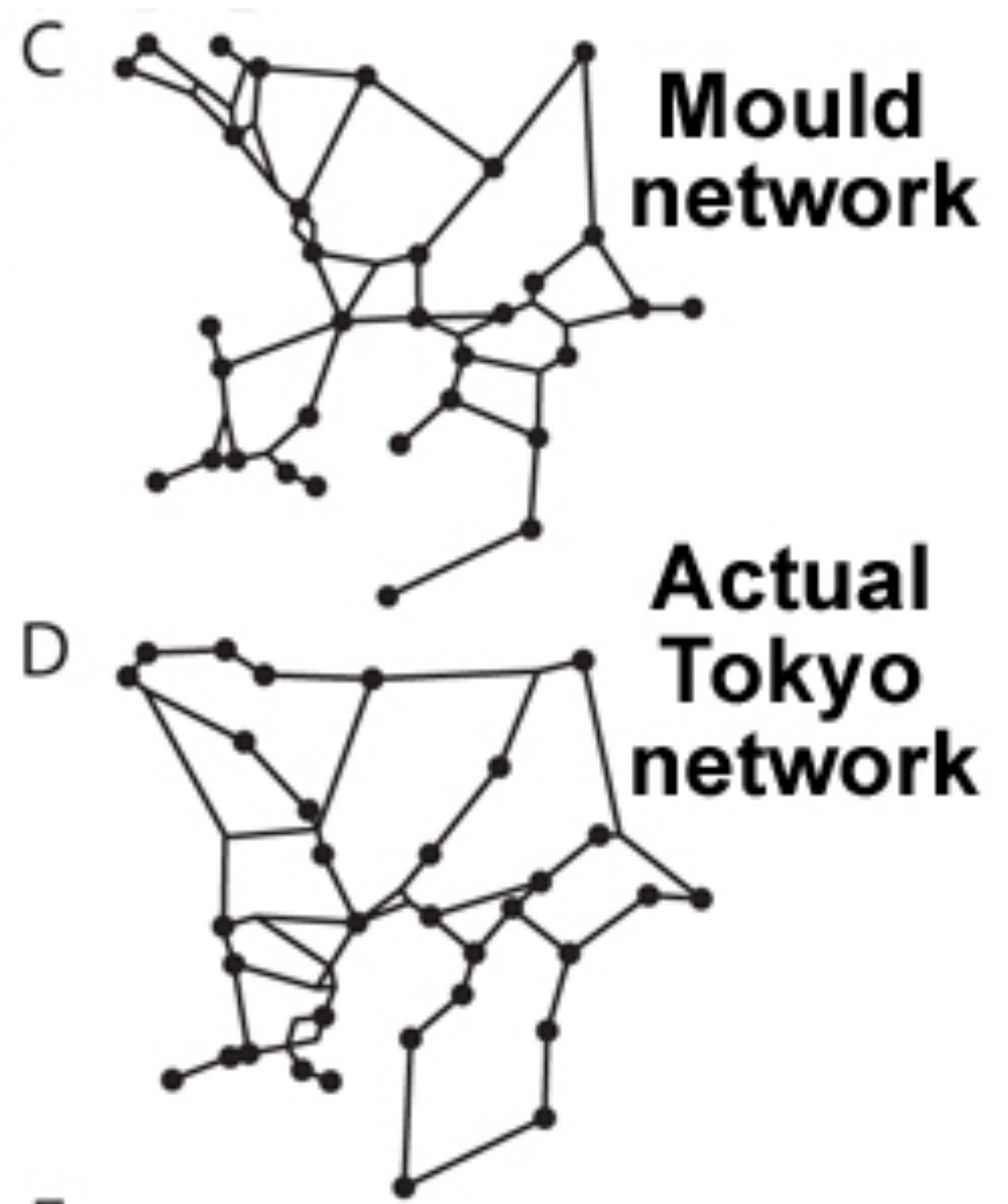
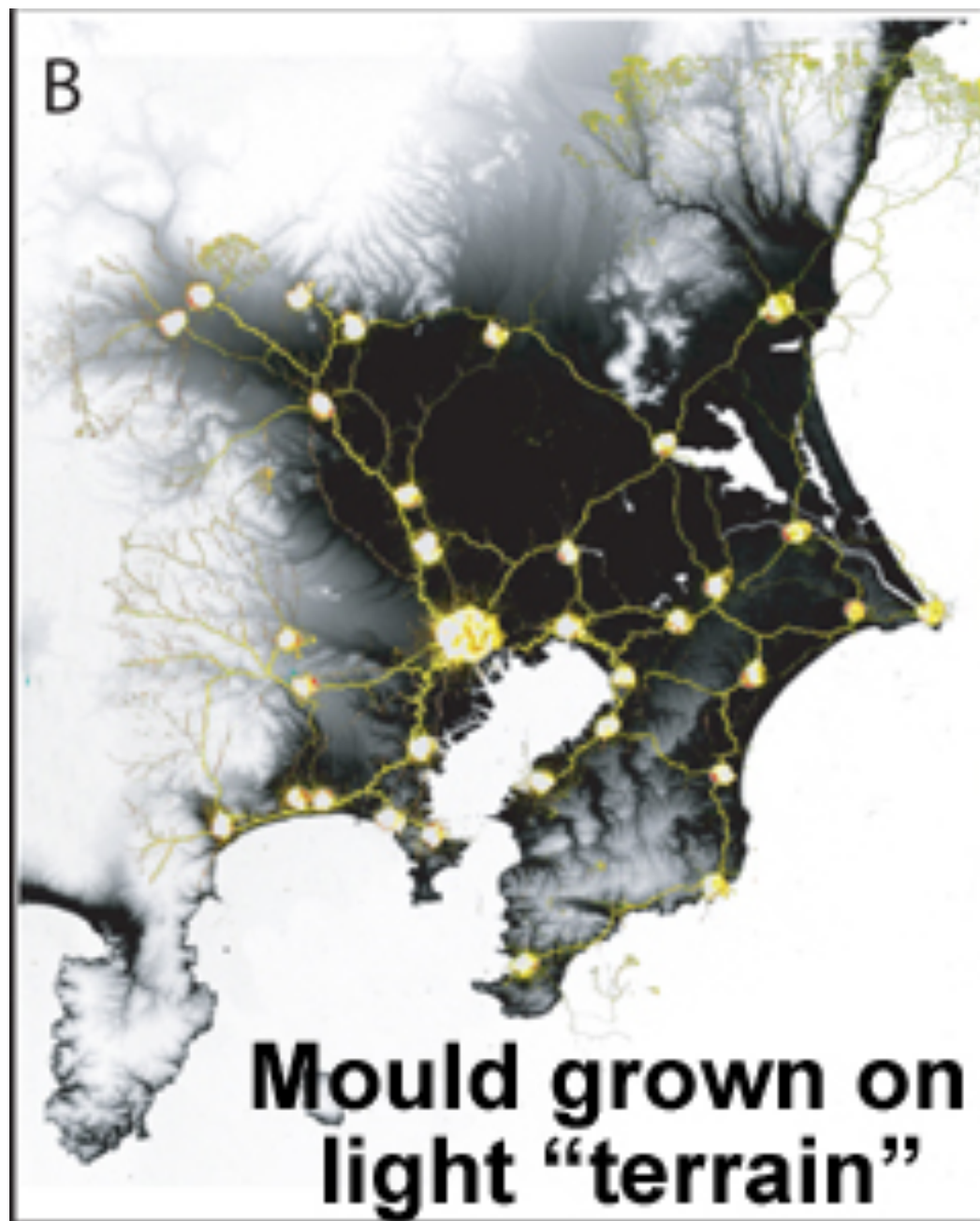


Mycorrhizae are mutualistic - they both need and are needed by the plants whose roots they inhabit

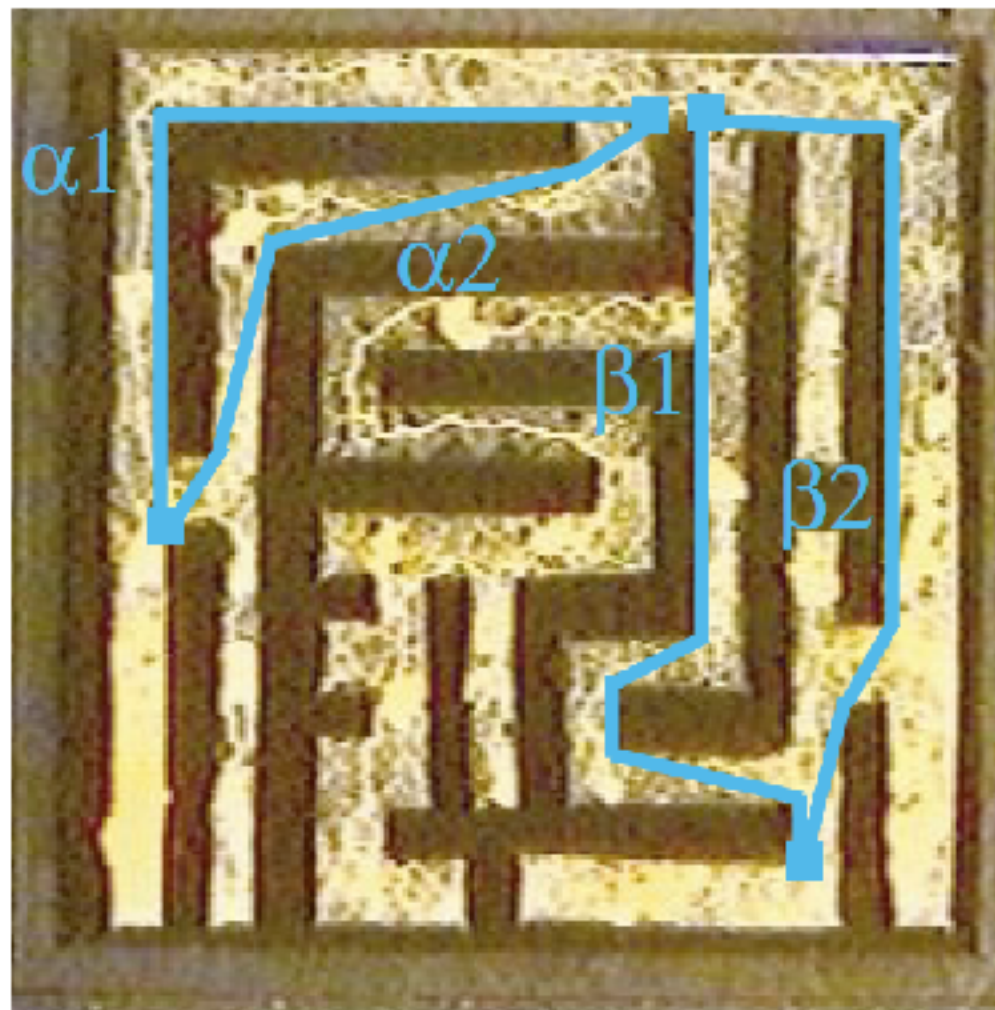


Tokyo rail network by *Physarum plasmodium*

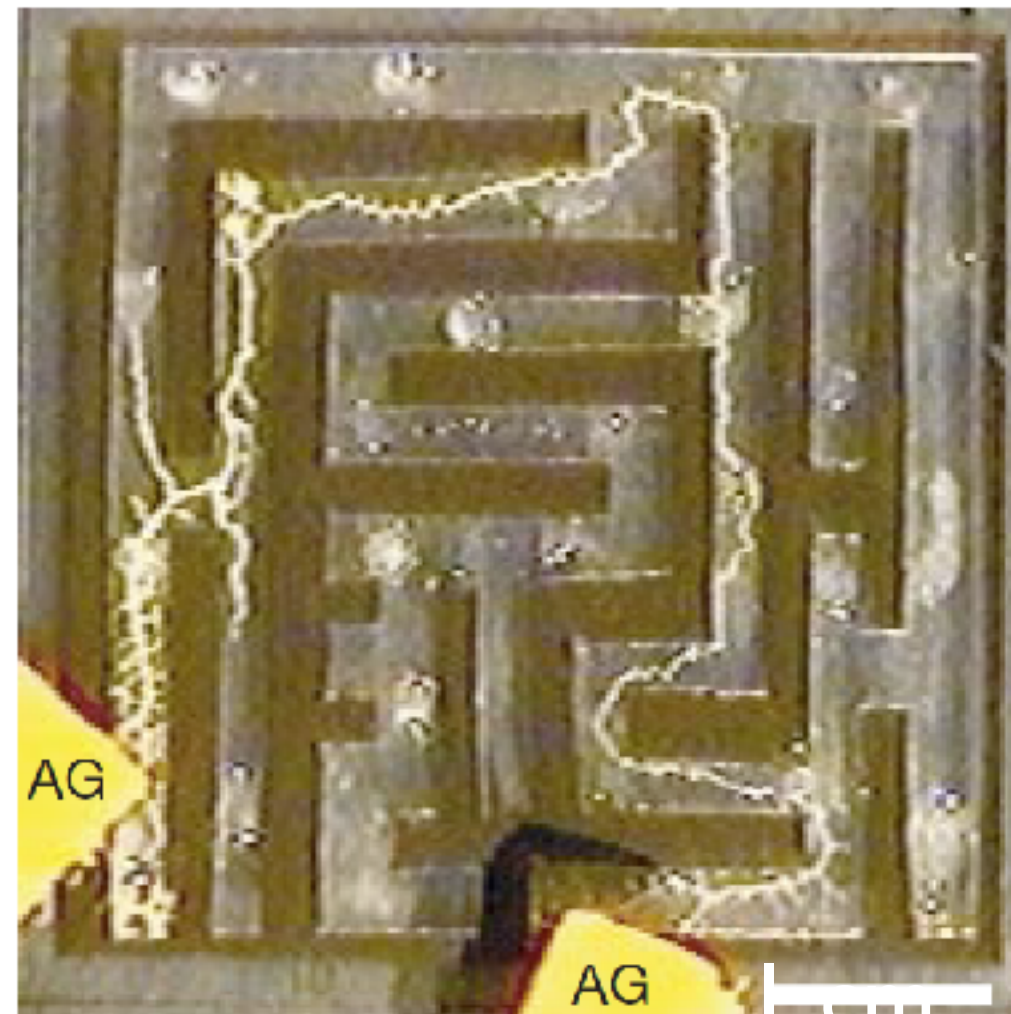




Maze solving

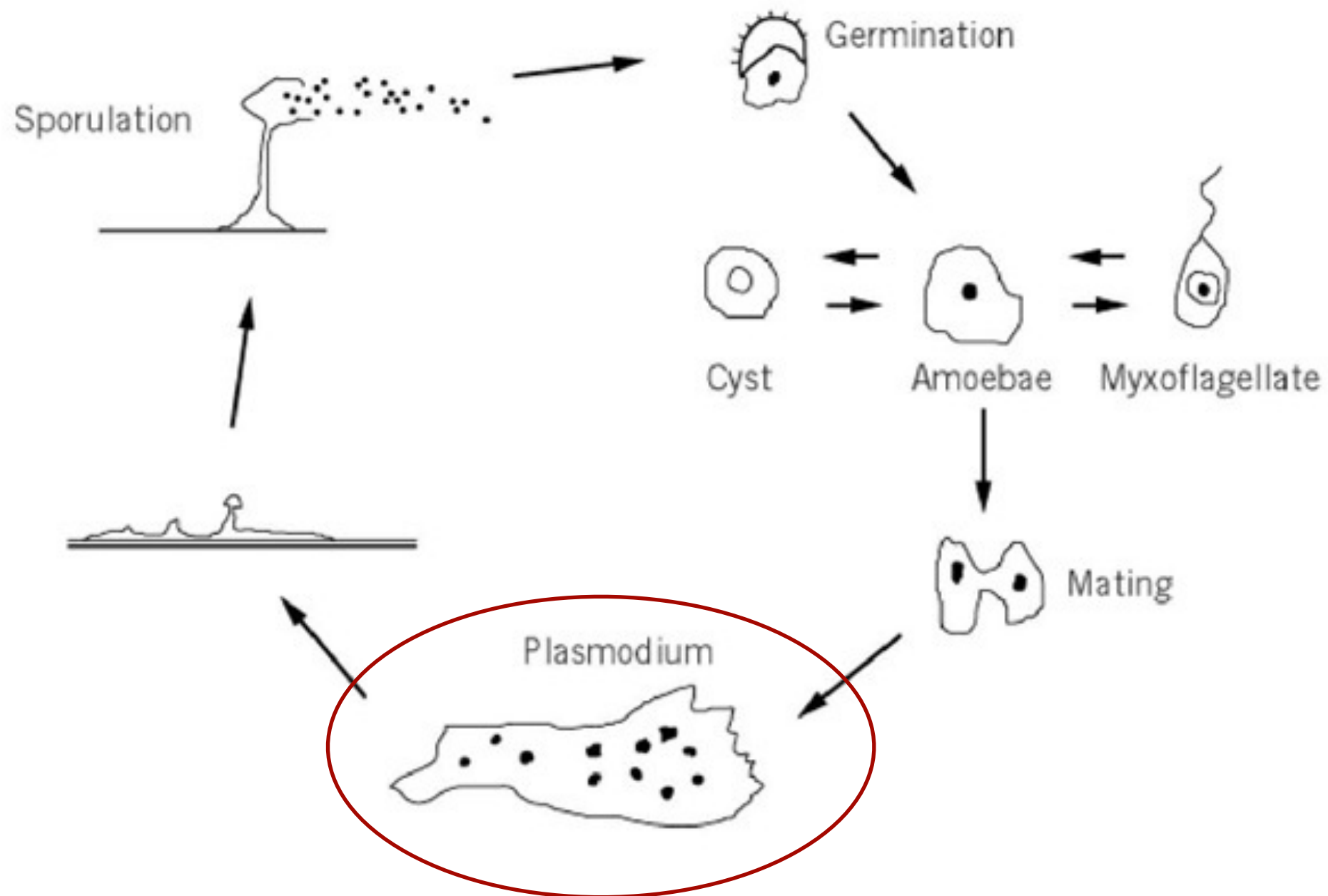


time = 0



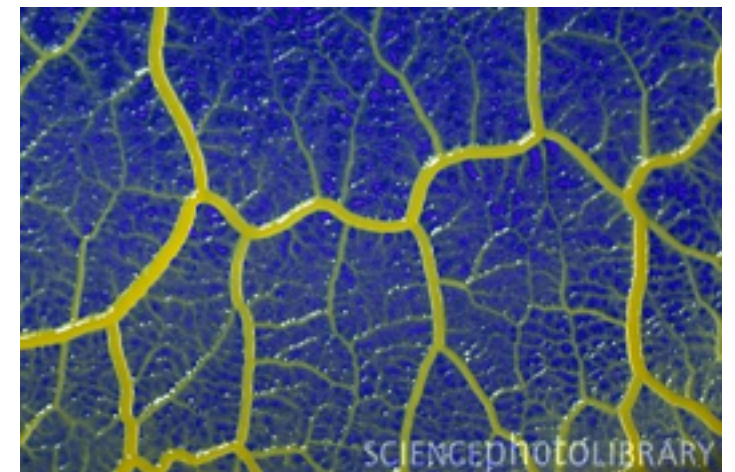
after 8 hours

Physarum developmental cycle

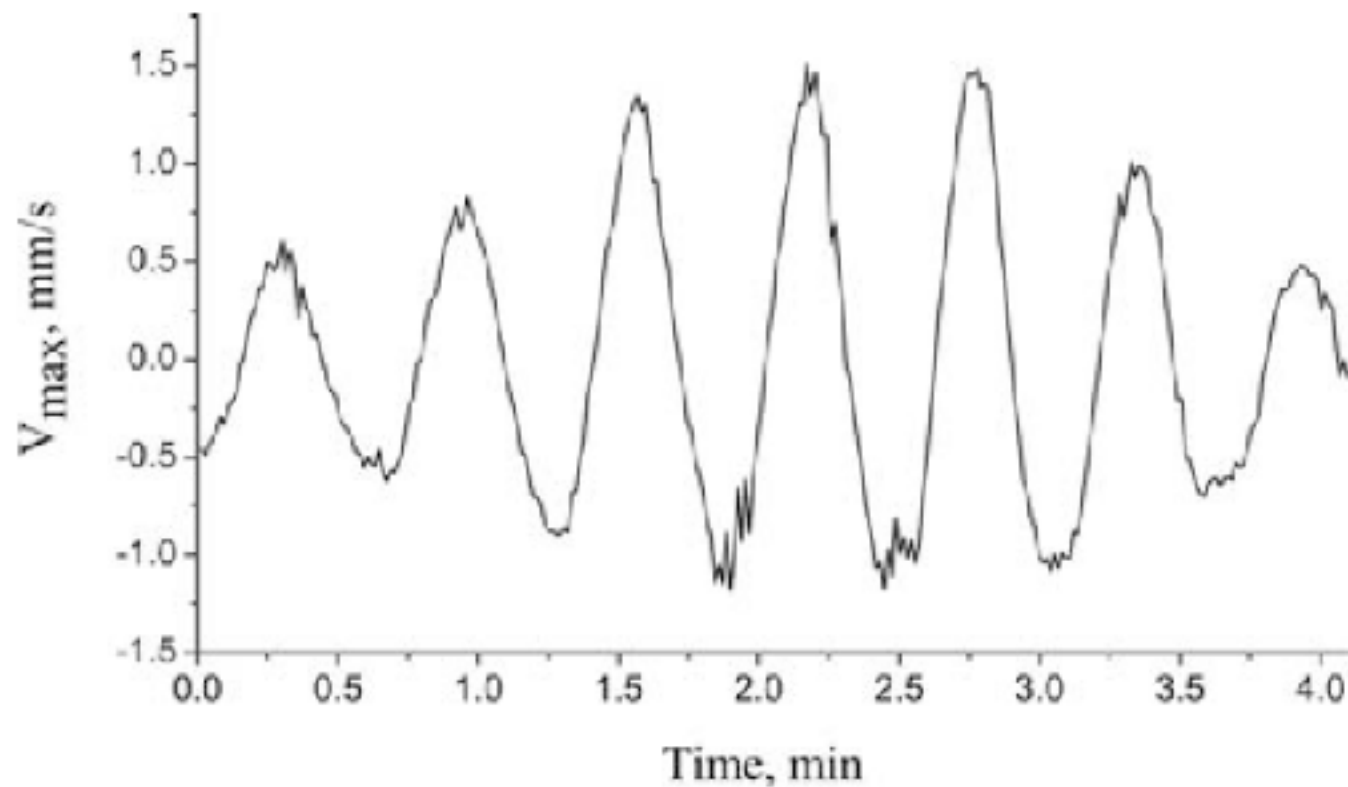
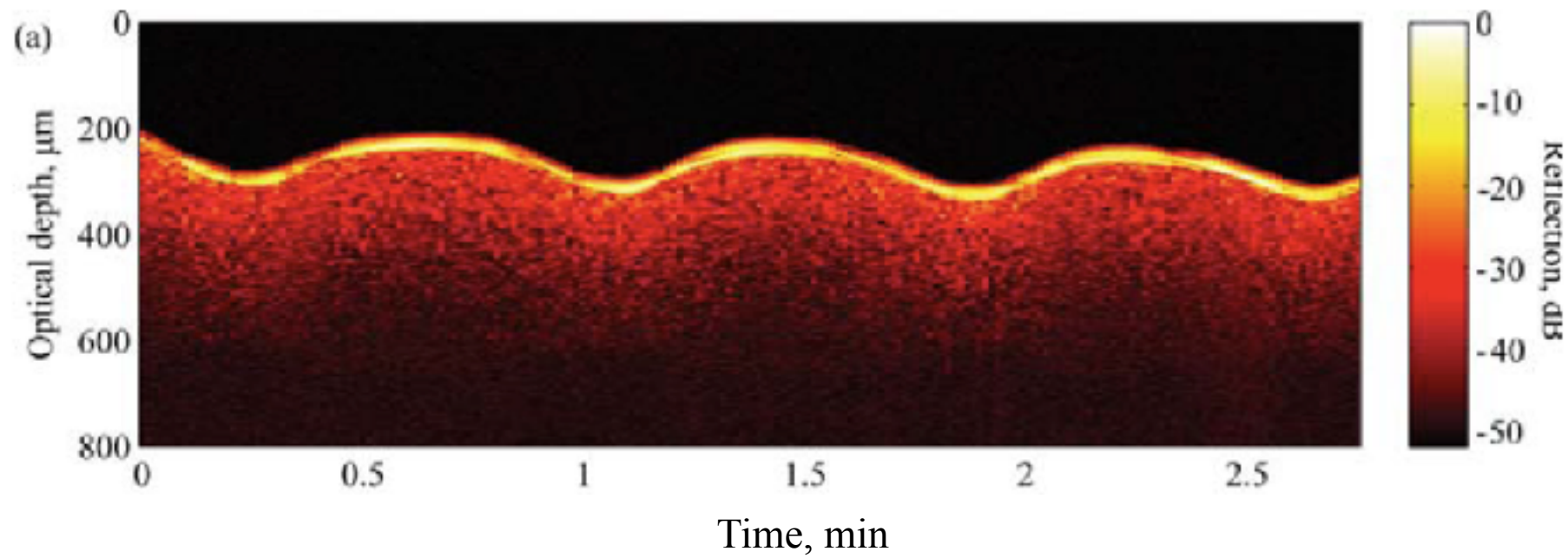
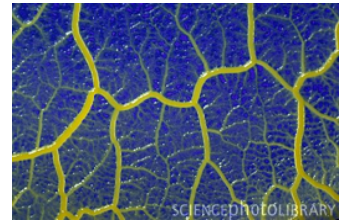


How does it work ?

- acto-myosin contractions
- hydrodynamics
- noise (?)
- feedback (?)



'Shuttle streaming'



Bykov *et al* (2009)
J Biophoton

‘Standard’ network model

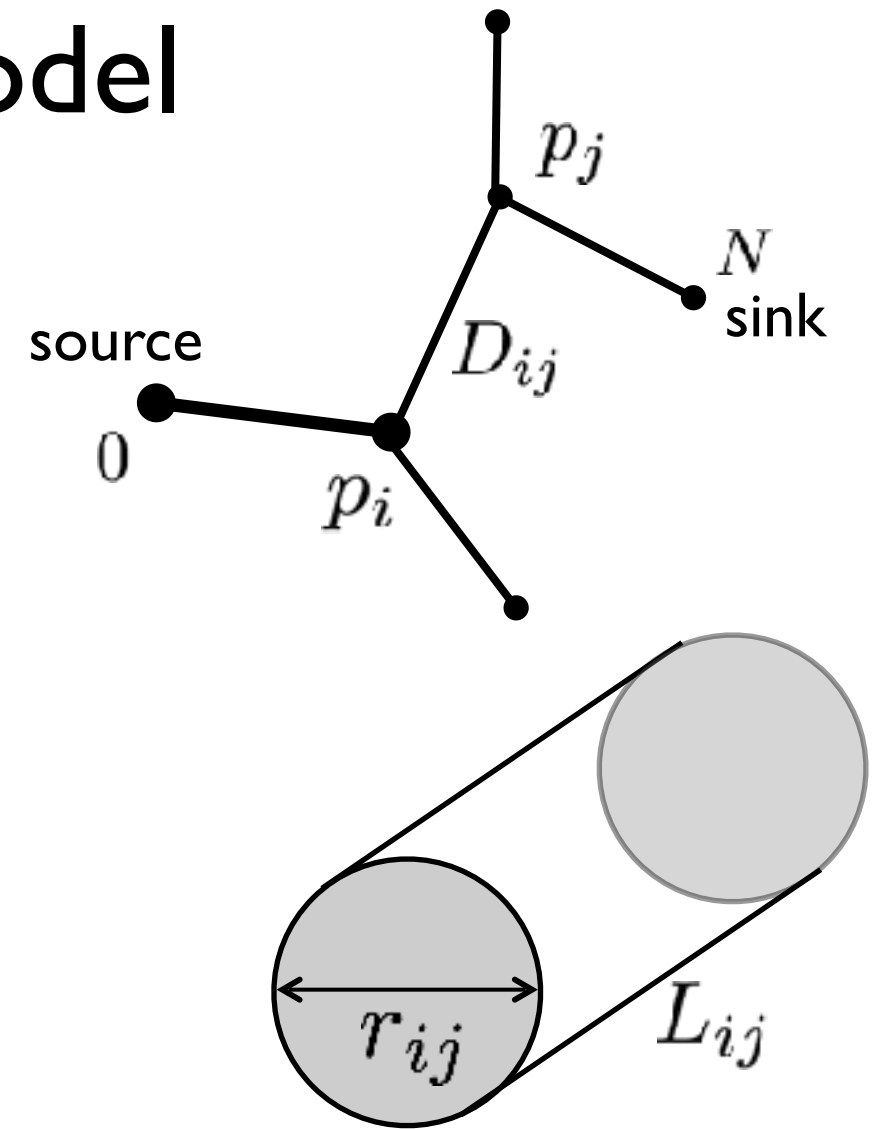
flux $Q_{ij} = \frac{D_{ij}}{L_{ij}}(p_i - p_j)$

conductivity $D_{ij} = \frac{\pi r_{ij}^4}{8\eta}$

Kirchhoff’s law

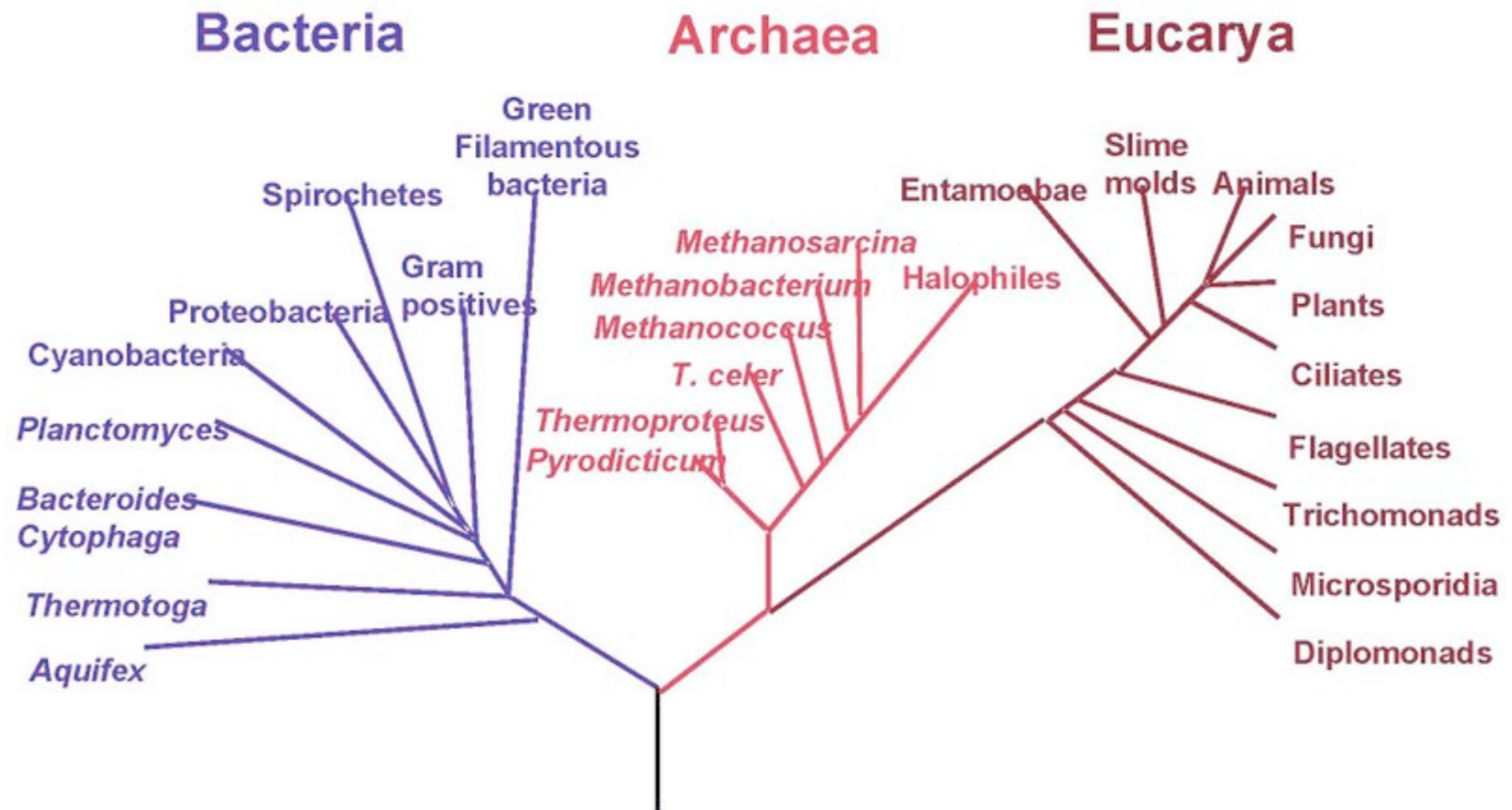
$$\sum_{i \in \mathcal{N}(j)} Q_{ij} = \begin{cases} -I_0, & j = 1 \\ 0 & j = 2, \dots, N-1 \\ I_0, & j = N \end{cases}$$

dynamics $\frac{d}{dt}D_{ij} = |Q_{ij}| - rD_{ij}$

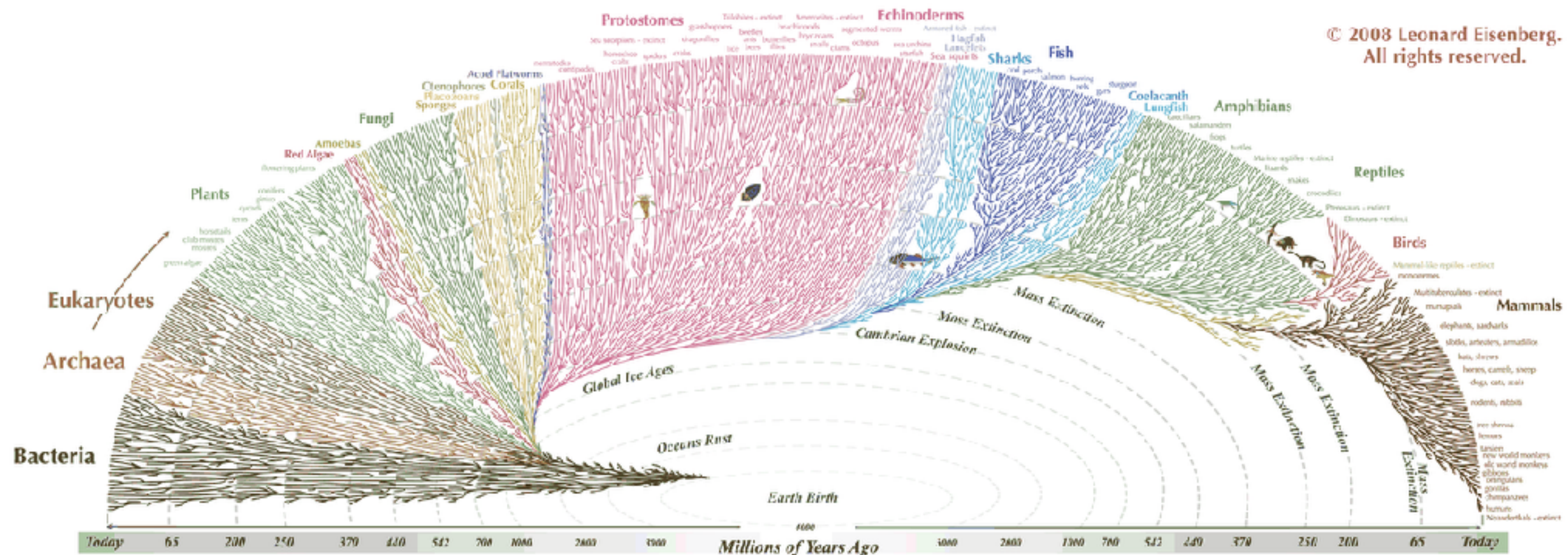


Tree structures

Phylogenetic Tree of Life

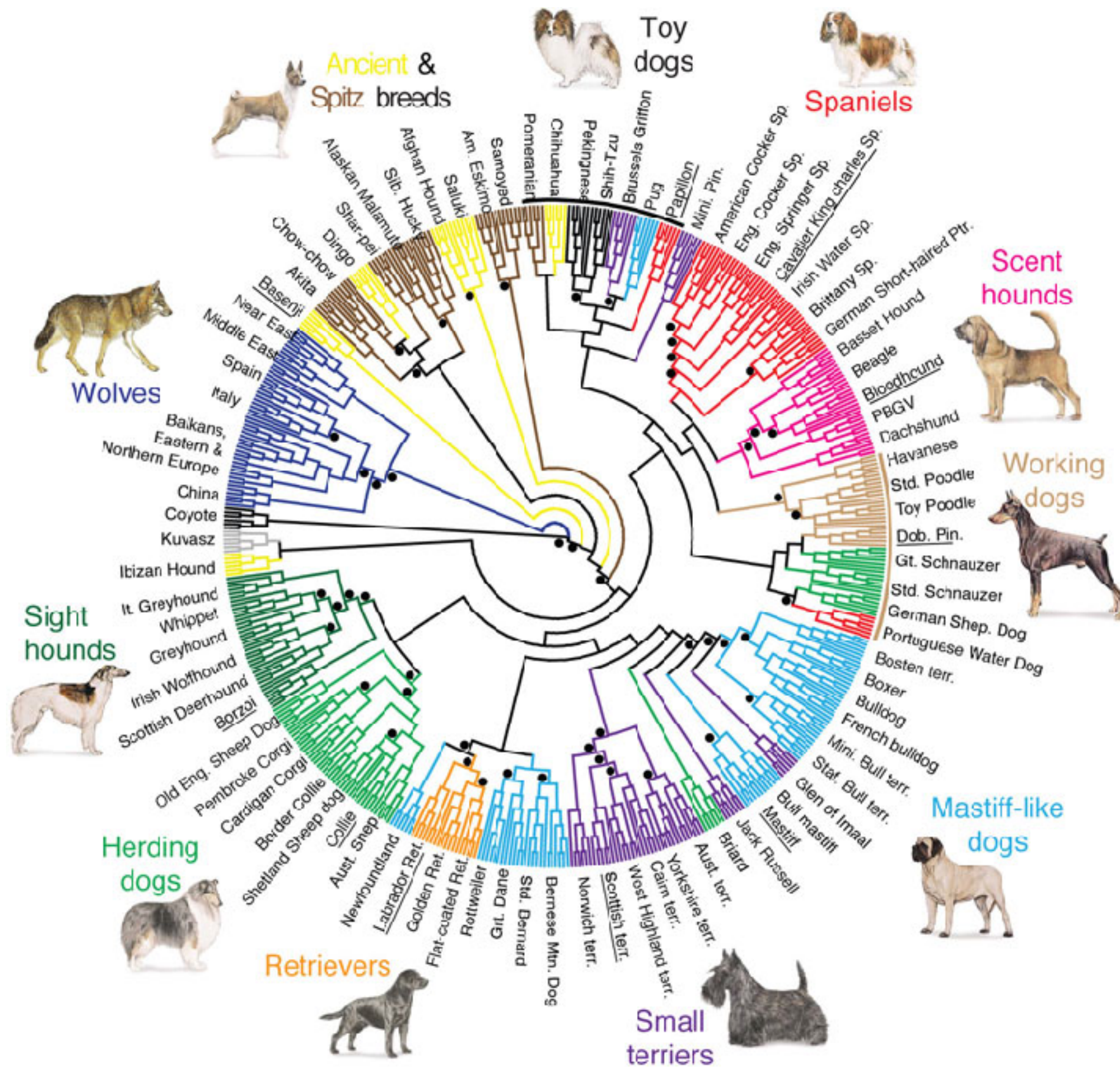


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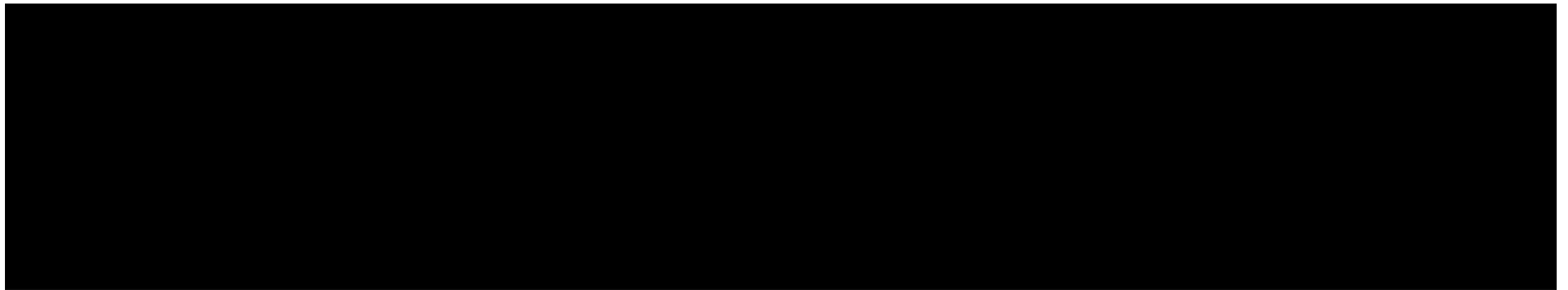
All the major and many of the minor living branches of life are shown on this diagram, but only a few of those that have gone extinct are shown. Example: Dinosaurs - extinct

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eisenberg.com



Phylogenetic genome mapping of dog breeds and their ancestors. Elaine A. Ostrander and Robert K. Wayne

Single cell studies



Cherry Tree Seasons



Springtime



Summertime



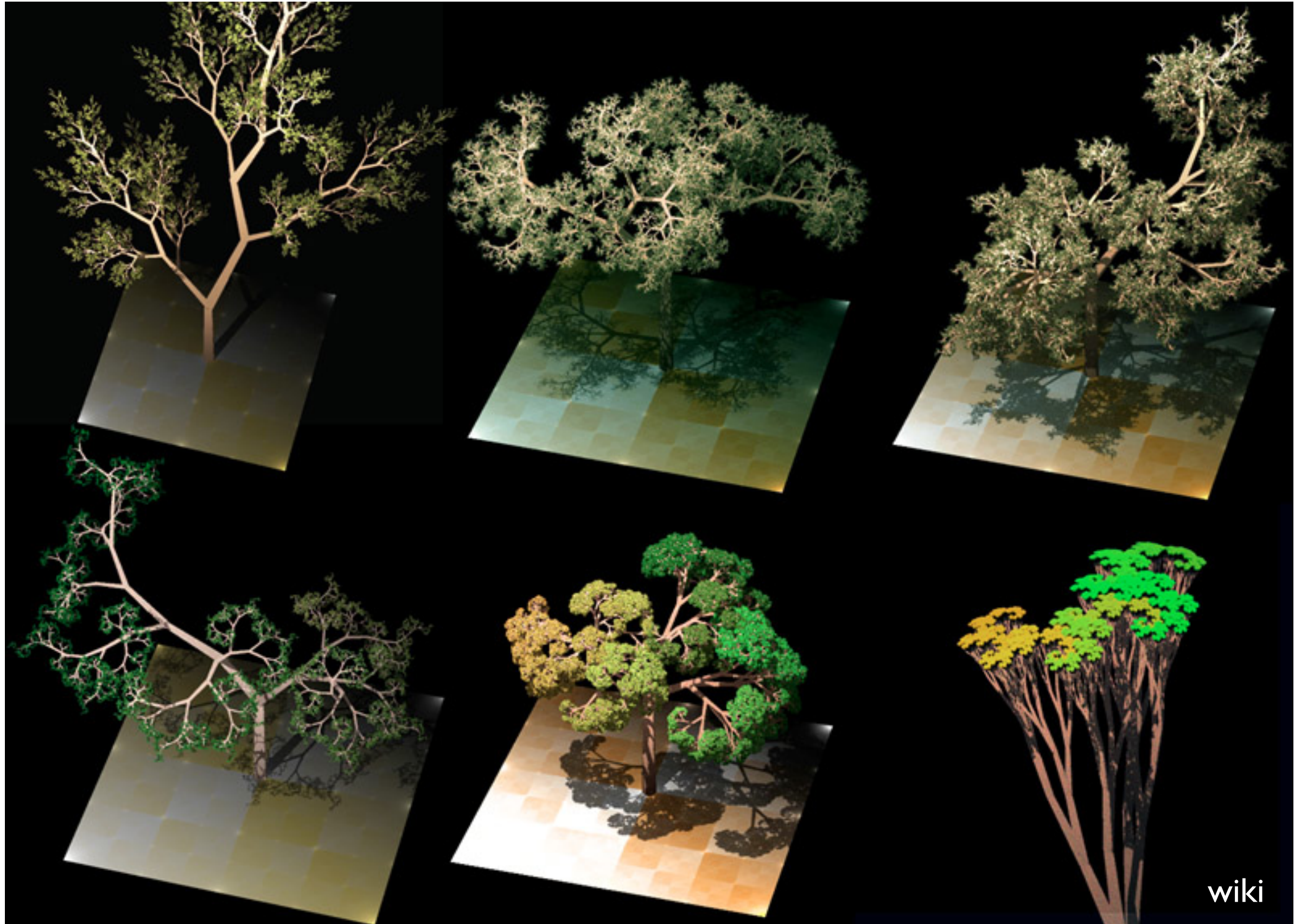
Autumntime



Wintertime

L-Systems

<http://algorithmicbotany.org/>



wiki

L-Systems

Example 3: Cantor dust

variables : A B

constants : none

start : A {starting character string}

rules : (A \rightarrow ABA), (B \rightarrow BBB)

Let *A* mean "draw forward" and *B* mean "move forward".

This produces the famous [Cantor's fractal set](#) on a real straight line **R**.



L-Systems

Example 5: Sierpinski triangle

The [Sierpinski triangle](#) drawn using an L-system.

variables : A B

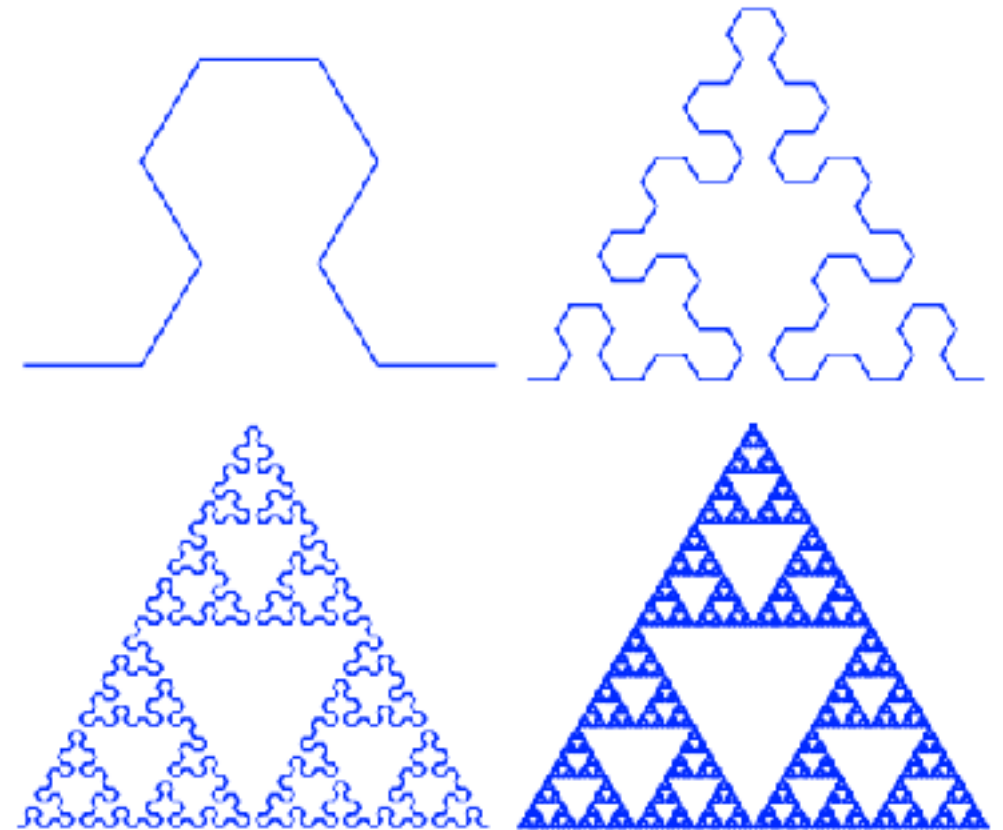
constants : + −

start : A

rules : $(A \rightarrow B-A-B)$, $(B \rightarrow A+B+A)$

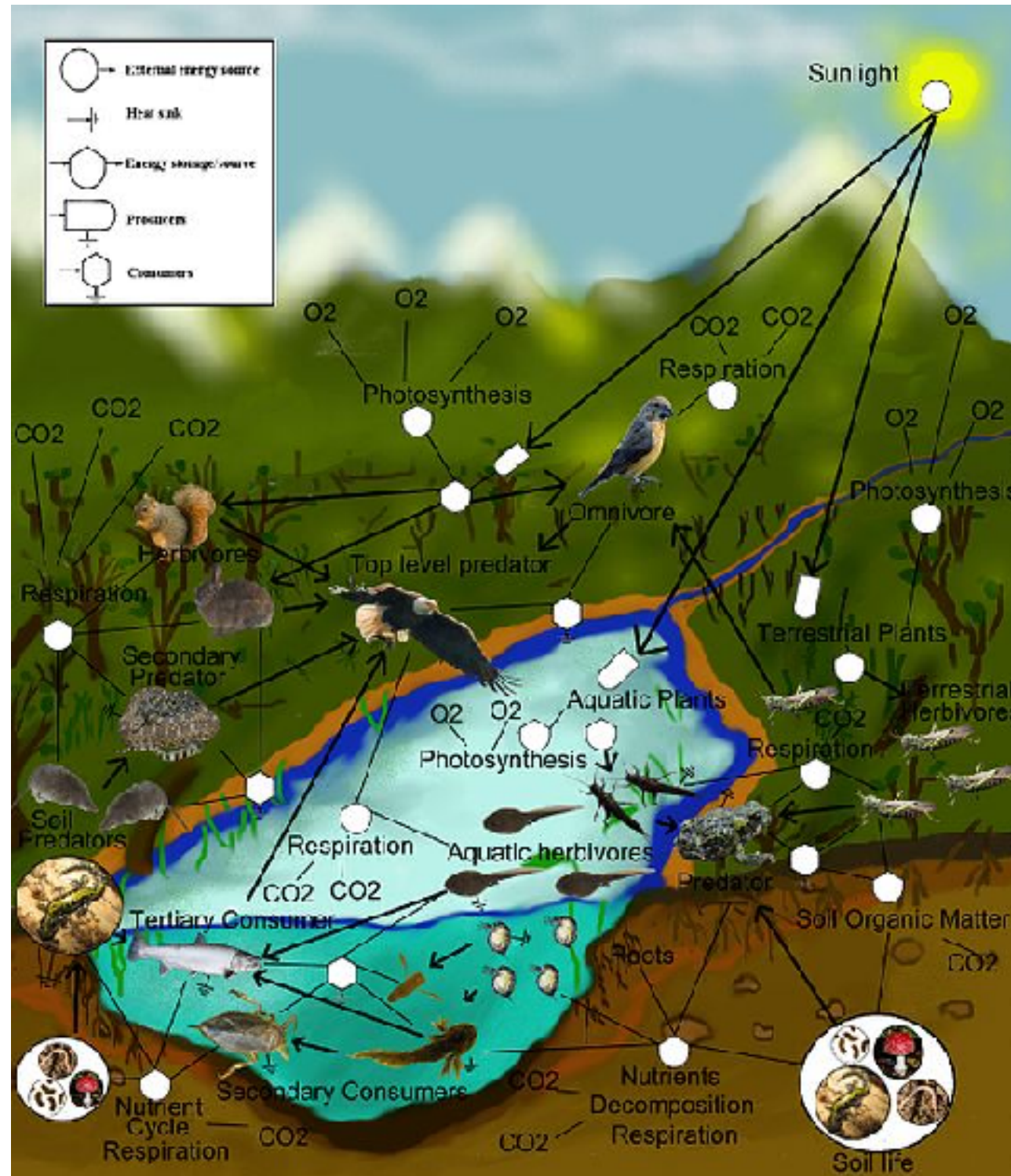
angle : 60°

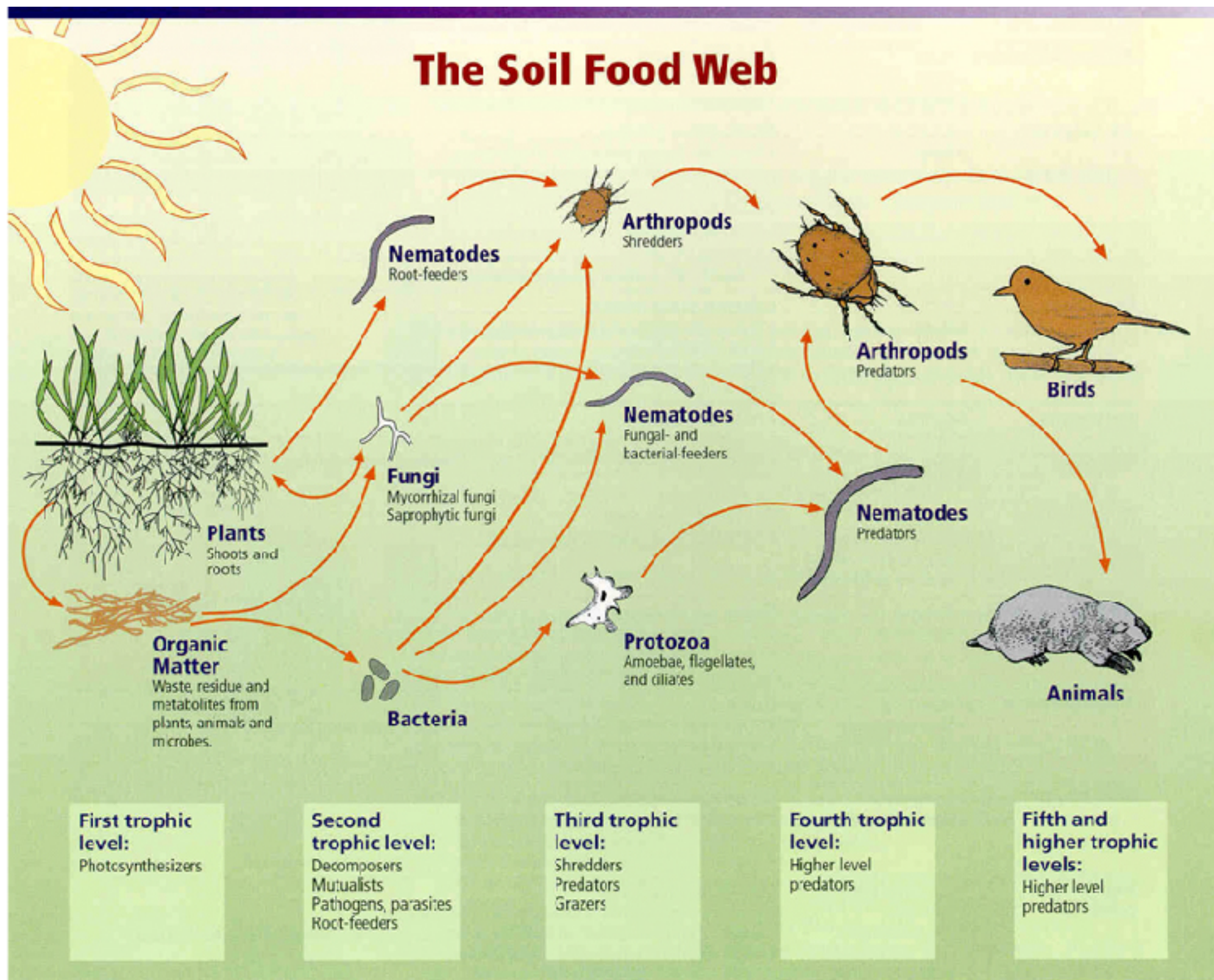
Here, A and B both mean "draw forward", + means "turn left by angle", and − means "turn right by angle". The angle changes sign at each iteration so that the base of the triangular shapes are always in the bottom (otherwise the bases would alternate between top and bottom).



Ecological networks

Food web

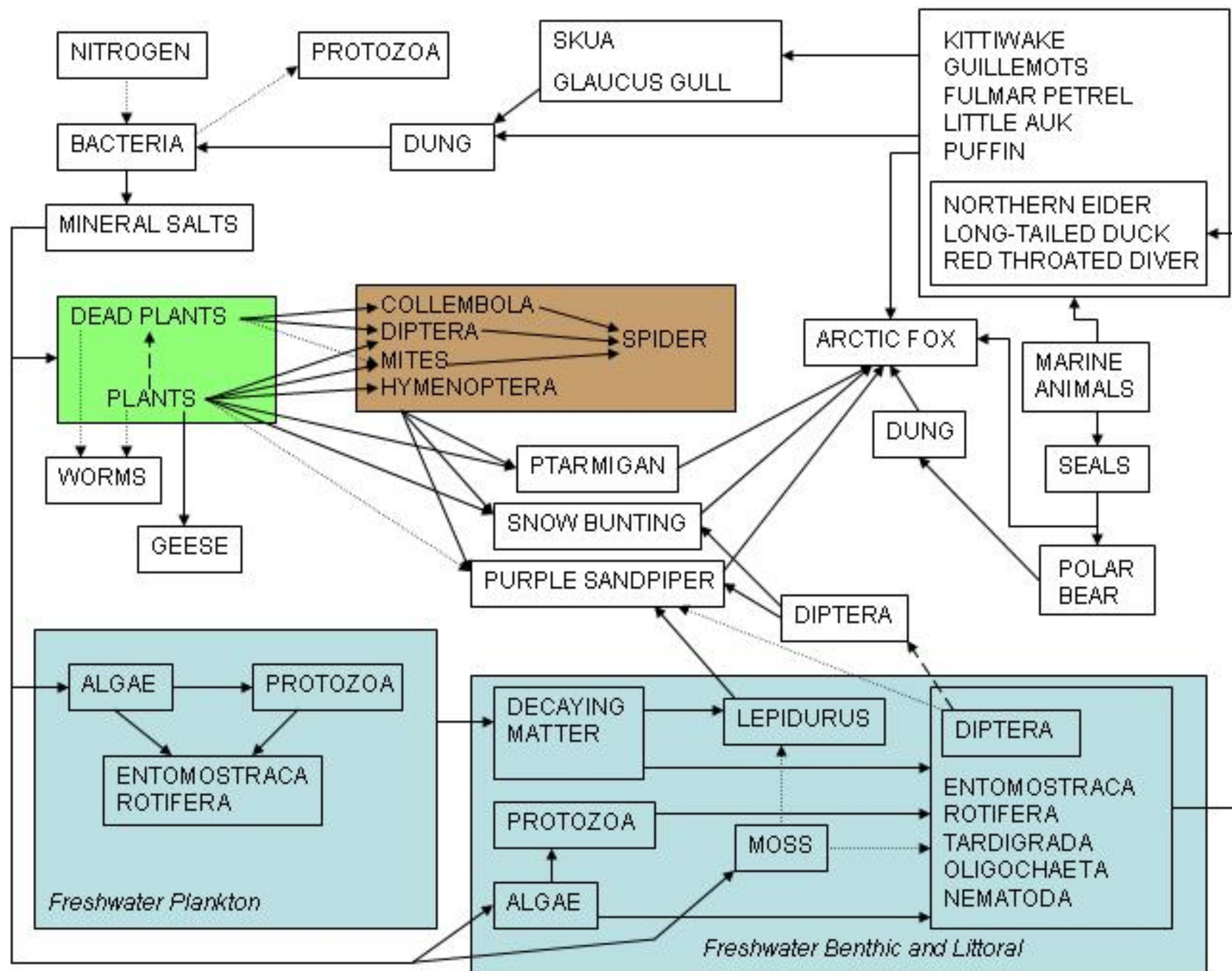




Relationships between soil food web, plants, organic matter, and birds and mammals

Image courtesy of USDA Natural Resources Conservation Service

http://soils.usda.gov/sqi/soil_quality/soil_biology/soil_food_web.html.



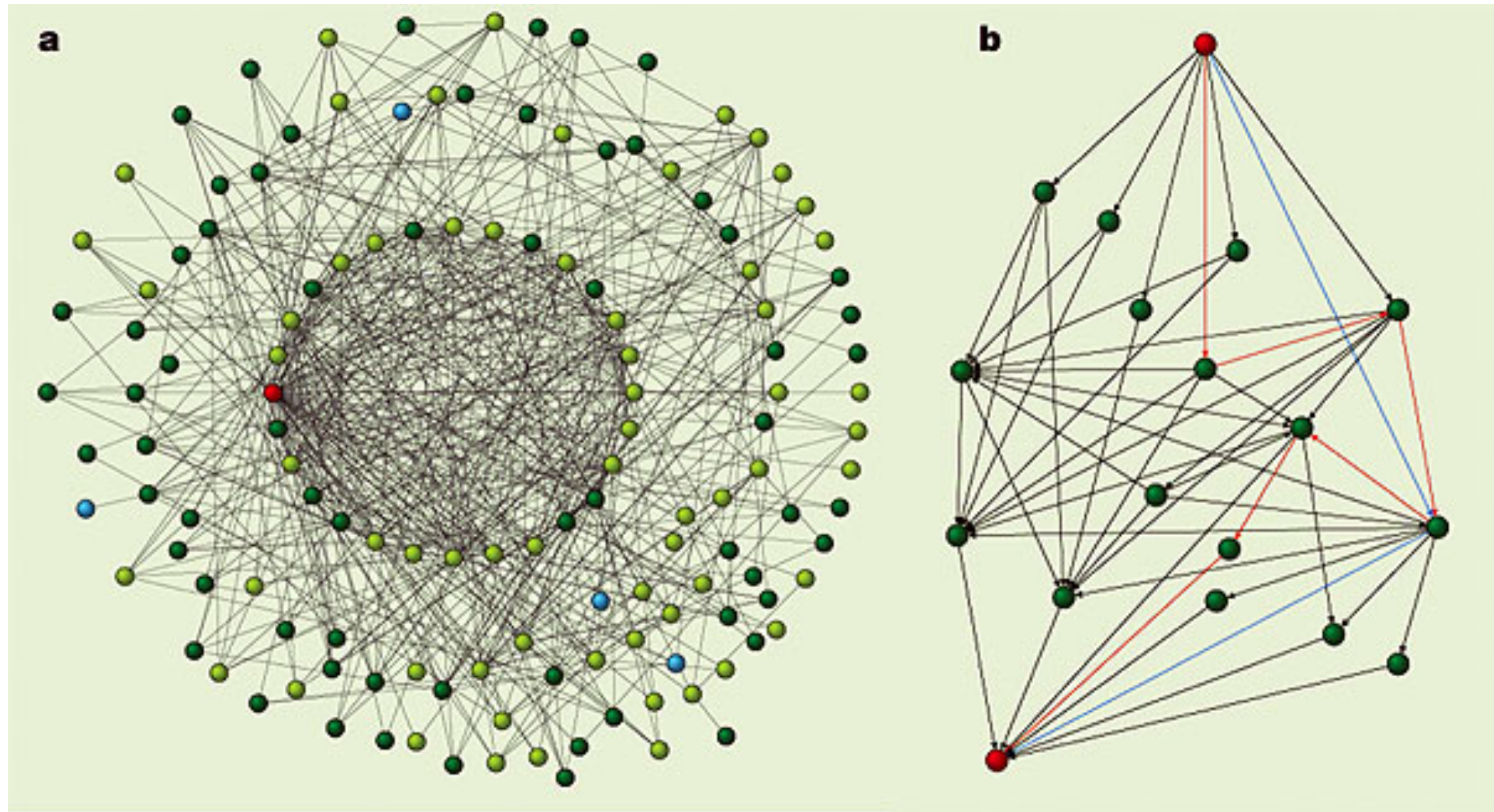
Shortest paths in a complex food web

Ecological networks and their fragility

José M. Montoya, Stuart L. Pimm and Ricard V. Solé

Nature **442**, 259–264 (20 July 2006)

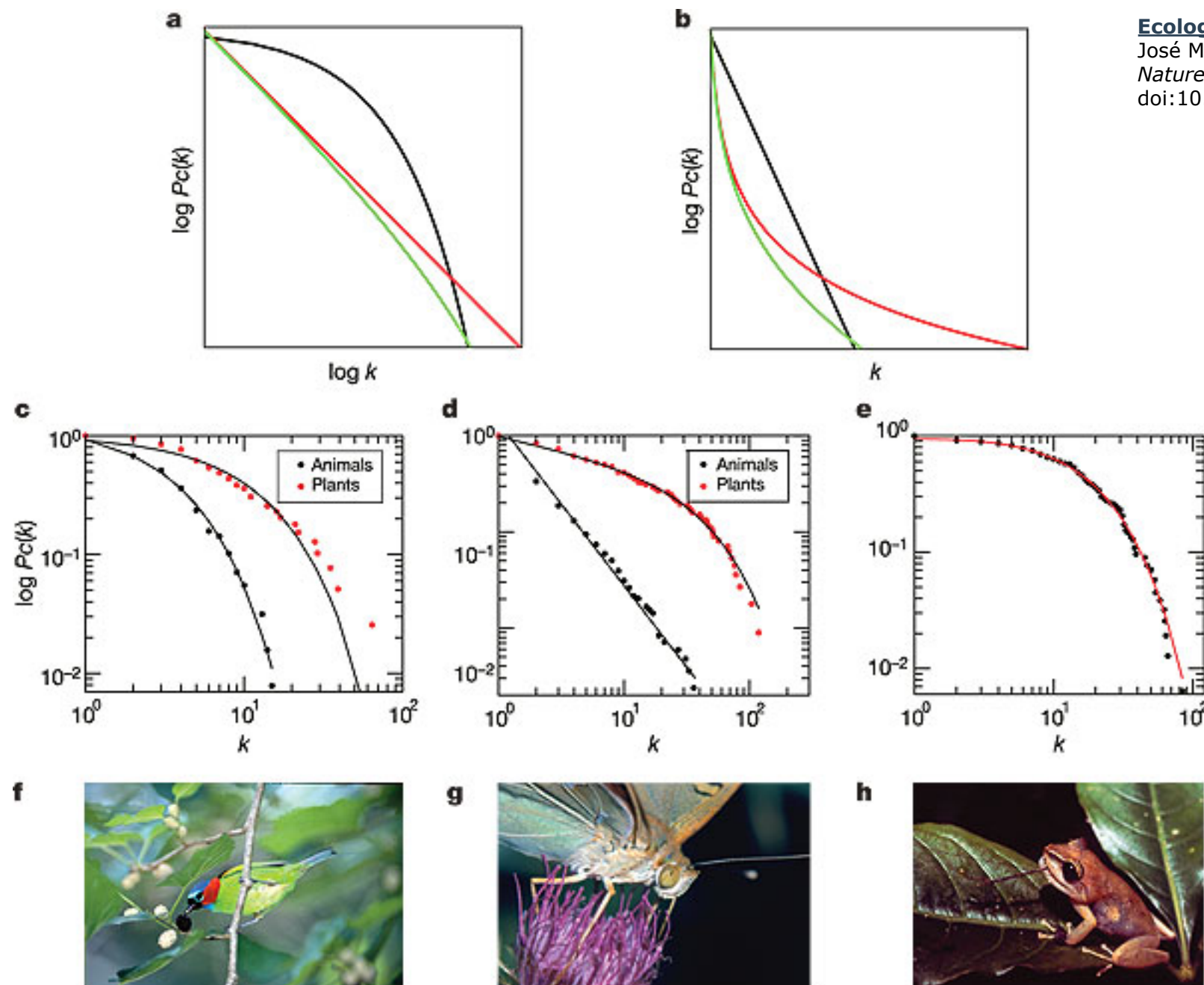
doi:10.1038/nature04927



The Ythan estuary food web^{66,73}. **a**, Node colour indicates the length of the shortest path linking the most connected species (the flounder *Platichthys flesus*, in red) and each other species from the network. (The trophic direction of the links—what eats what—is ignored). Dark green, species are one link apart; light green, two links; and blue, three links. The central circle represents the densest sub-web⁷⁵, which consists of 28 species with at least 7 links with the rest of the species from the sub-web. This sub-web contributes most to the observed clustering. **b**, Food chains between basal species of *Enteromorpha* (red node at the bottom) and the top predator, the cormorant *Phalacrocorax carbo* (red node at the top). Links corresponding to the shortest path connecting them are in blue (2-links), and those corresponding to the longest food chain between these two species are in red (6-links).

Ecological networks and their fragility

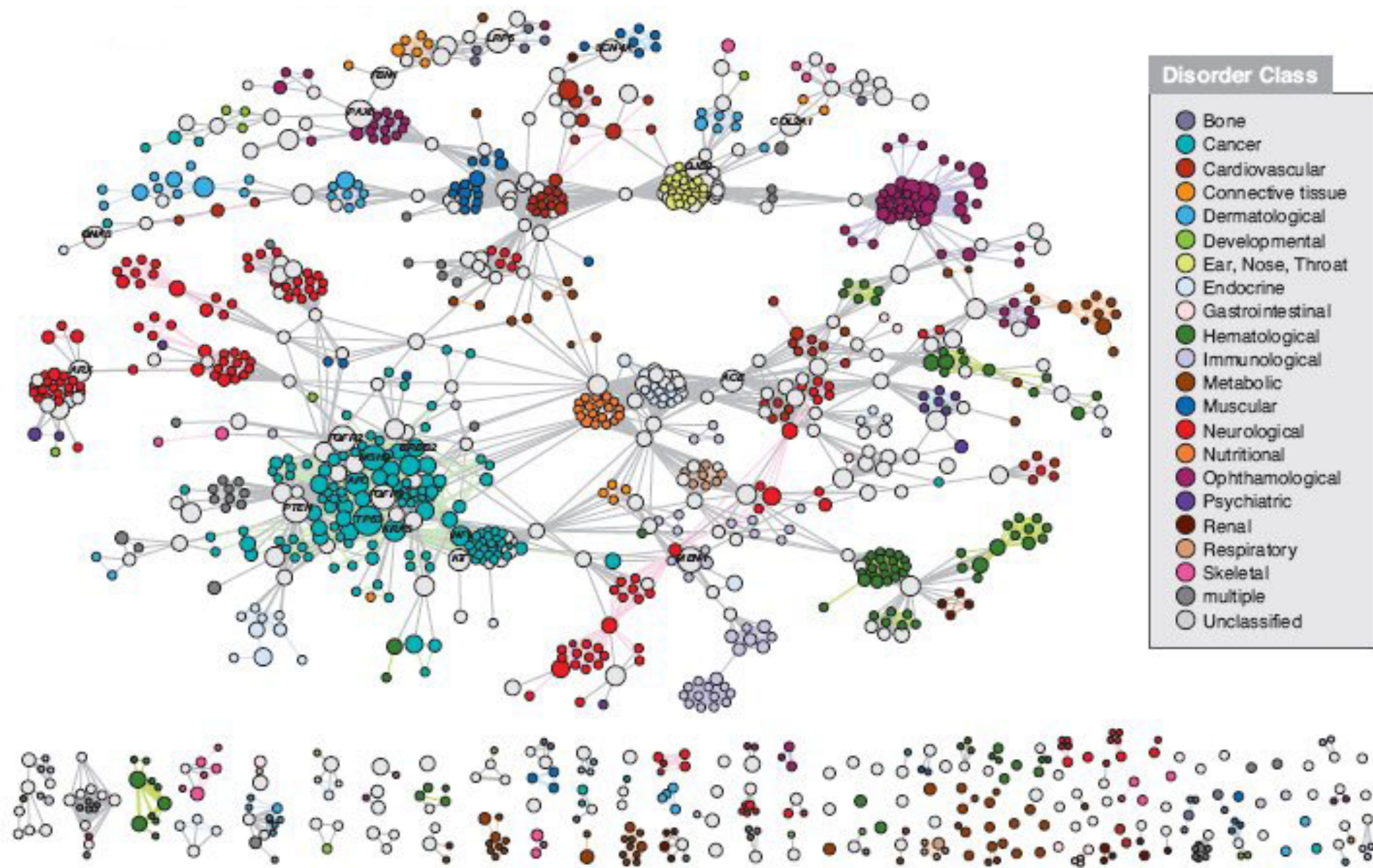
José M. Montoya, Stuart L. Pimm and Ricard V. Solé
Nature **442**, 259–264 (20 July 2006)
doi:10.1038/nature04927



a–e, The cumulative probabilities $P_c(k)$, for k , where $P(k)$ is the probability a species has k links to other species, and is given by $P(k)k^{-\gamma}e^{-k/\lambda}$ where $e^{-k/\lambda}$ introduces a cut-off at some characteristic scale. Panels **a** (log–log) and **b** (log–linear) show three different modelled networks. Black lines, single-scale networks; when λ is very small, the distribution has a fast decaying tail, typically exponential, $P(k)e^{-k/\lambda}$. Green lines, truncated scale-free networks; these correspond to intermediate values of λ where the distribution has a power law regime followed by a sharp cut-off, with an exponential decay of the tail. Red lines, scale-free networks; for large values of λ the number of connections per species decays as a power law, $P(k)k^{-\gamma}$, a function with a relatively 'fat tail'. **c–e**, Experimental data (filled circles) and best fits (lines); **c**, a frugivore–plant web⁷⁶; **d**, a pollinator–plant web⁷⁷; and **e**, the food web from El Verde rainforest⁷⁸. In **c** and **d**, for red circles, k is the number of plants species visited by an animal, and for black circles, k is the number of pollinator species visiting each plant species. In **e**, we sum prey–predator links and predator–prey links for each species. Best fits to the data in **c–e** are as follows: **c**, animals, exponential, $P(k) = e^{-k/3.998}$; plants, truncated power law, $P(k) = k^{-0.013}e^{-k/11.22}$; **d**, animals, power law, $P(k) = k^{-1.512}$; plants, truncated power law, $P(k) = k^{-0.2822}e^{-k/42.55}$; **e**, exponential, $P(k) = e^{-k/8.861}$. **f–h**, Photographs of a frugivore–plant (**f**), insect–flower (**g**) and predator–prey (**h**) interaction of webs depicted in **c–e**, respectively.

Genome-Wide Association Studies and Human Disease Networks

By: Leslie Pray, Ph.D. © 2008 Nature Education



Disease gene network (DGN).

In the DGN, each node is a gene, with two genes being connected if they are implicated in the same disorder. The size of each node is proportional to the number of disorders in which the gene is implicated. Nodes representing genes with links to multiple classes are colored dark grey, whereas unclassified genes are colored light grey. Genes associated with more than five disorders, and those mentioned in the text, are indicated with the gene symbol. Only nodes with at least one link are shown. © 2008 National Academy of Sciences, USA Goh, K.-I. et al. The human disease network. *Proceedings of the National Academy of Sciences* 104, 8685–8690 (2008). All rights reserved.