# Systems Perspectives as Motor for New Frontier Research

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# The holism versus reductionism debate

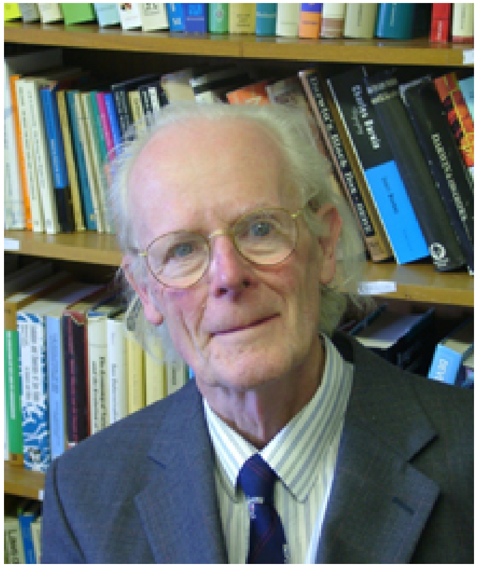
**The holistic approach**

Macroscopic biologists aim at a top-down approach to describe the phenomena observed in biology.

↔

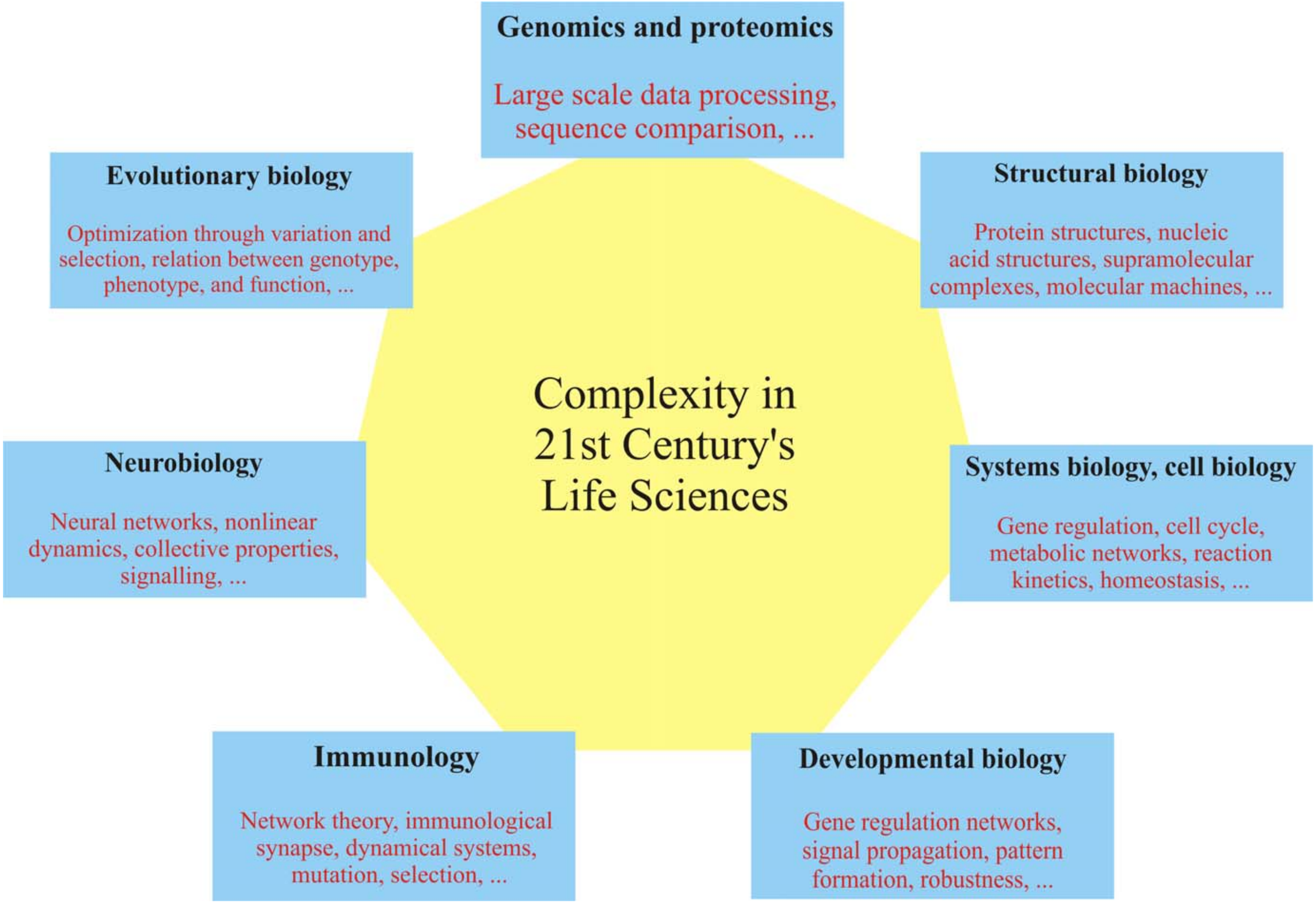
**The reductionists' program**

Molecular biologist perform a bottom-up approach to interpret biological phenomena by the methods of chemistry and physics.



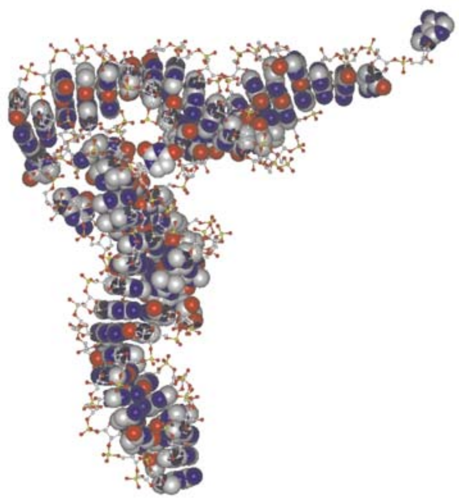
What should be the attitude of a biologist working on whole organisms to molecular biology? It is, I think, foolish to argue that we (the macroscopic biologists) are discovering things that disprove molecular biology. It would be more sensible to say to molecular biologists that **there are phenomena that they will one day have to interpret in their terms**.

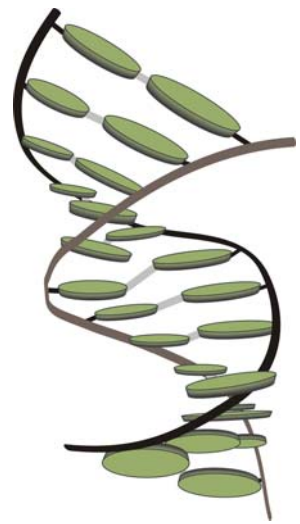
John Maynard Smith, The problems of biology. Oxford University Press, 1986.

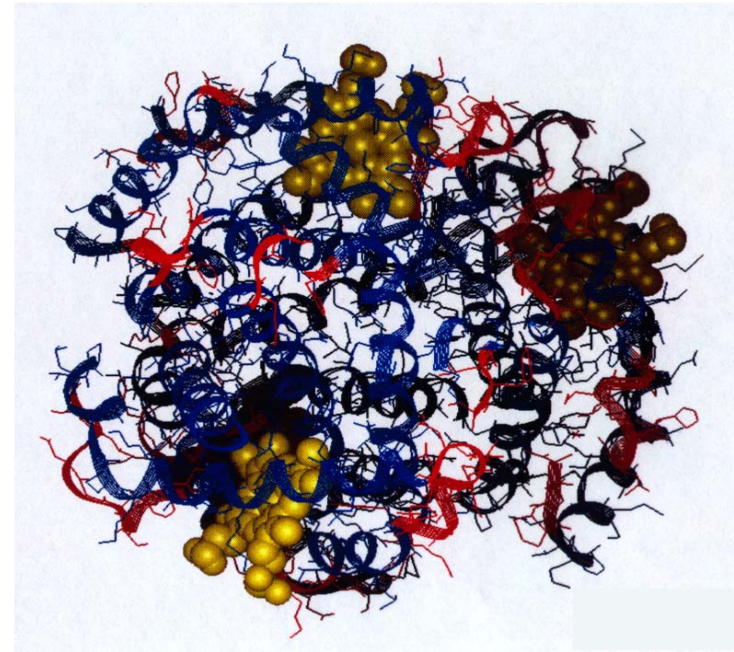

Genomics and proteomics
Large scale data processing, sequence comparison, ...
Evolutionary biology
Optimization through variation and selection, relation between genotype, phenotype, and function, ...
Structural biology
Protein structures, nucleic acid structures, supramolecular complexes, molecular machines, ...
Complexity in 21st Century's Life Sciences
Neurobiology
Neural networks, nonlinear dynamics, collective properties, signalling, ...
Systems biology, cell biology
Gene regulation, cell cycle, metabolic networks, reaction kinetics, homeostasis, ...
Immunology
Network theory, immunological synapse, dynamical systems, mutation, selection, ...
Developmental biology
Gene regulation networks, signal propagation, pattern formation, robustness, ...

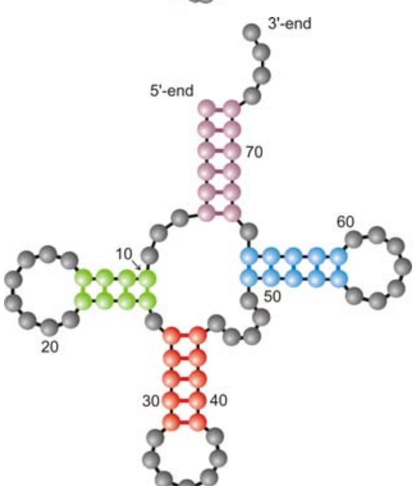
# Structural biology

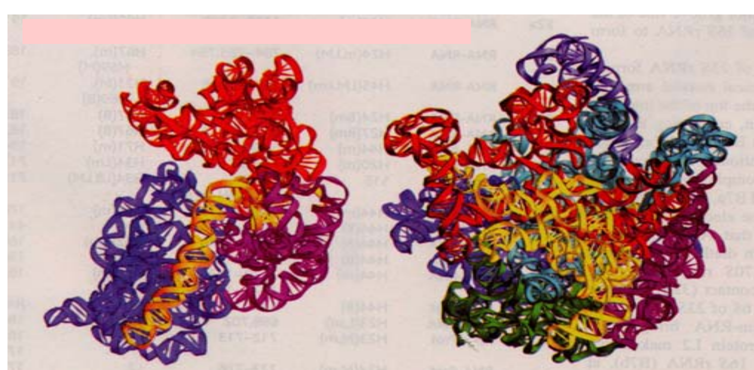
Protein structures, nucleic acid structures, supramolecular complexes, molecular machines, ...

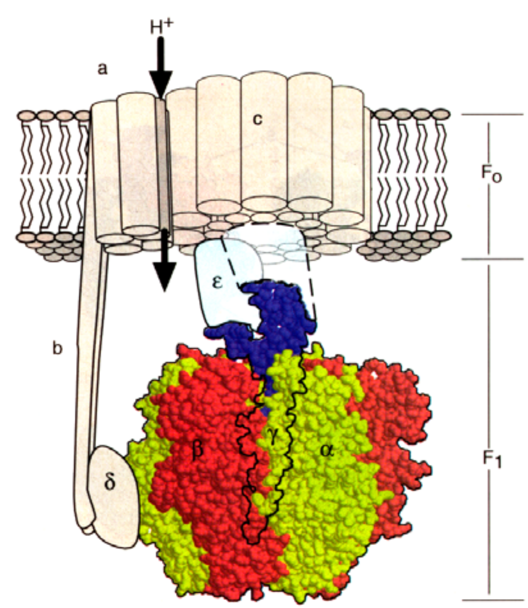






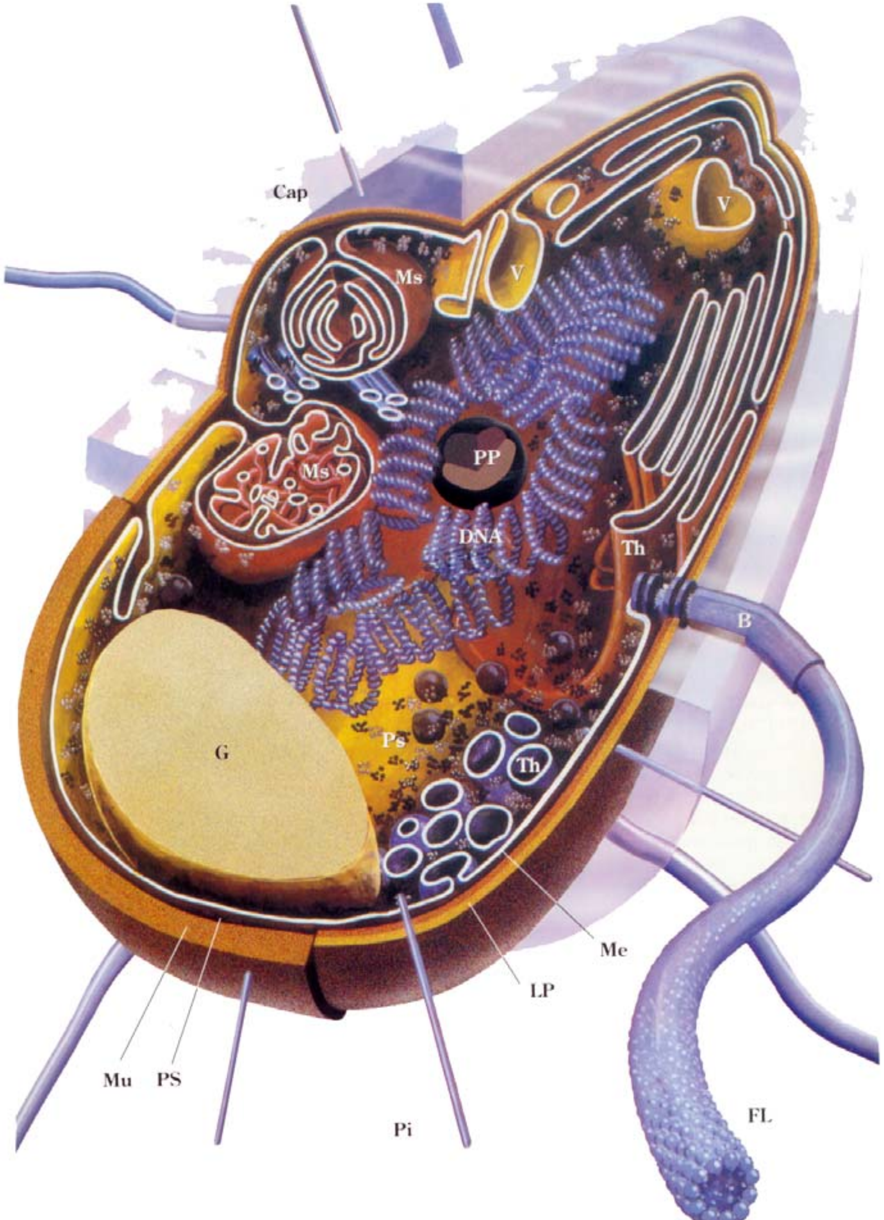


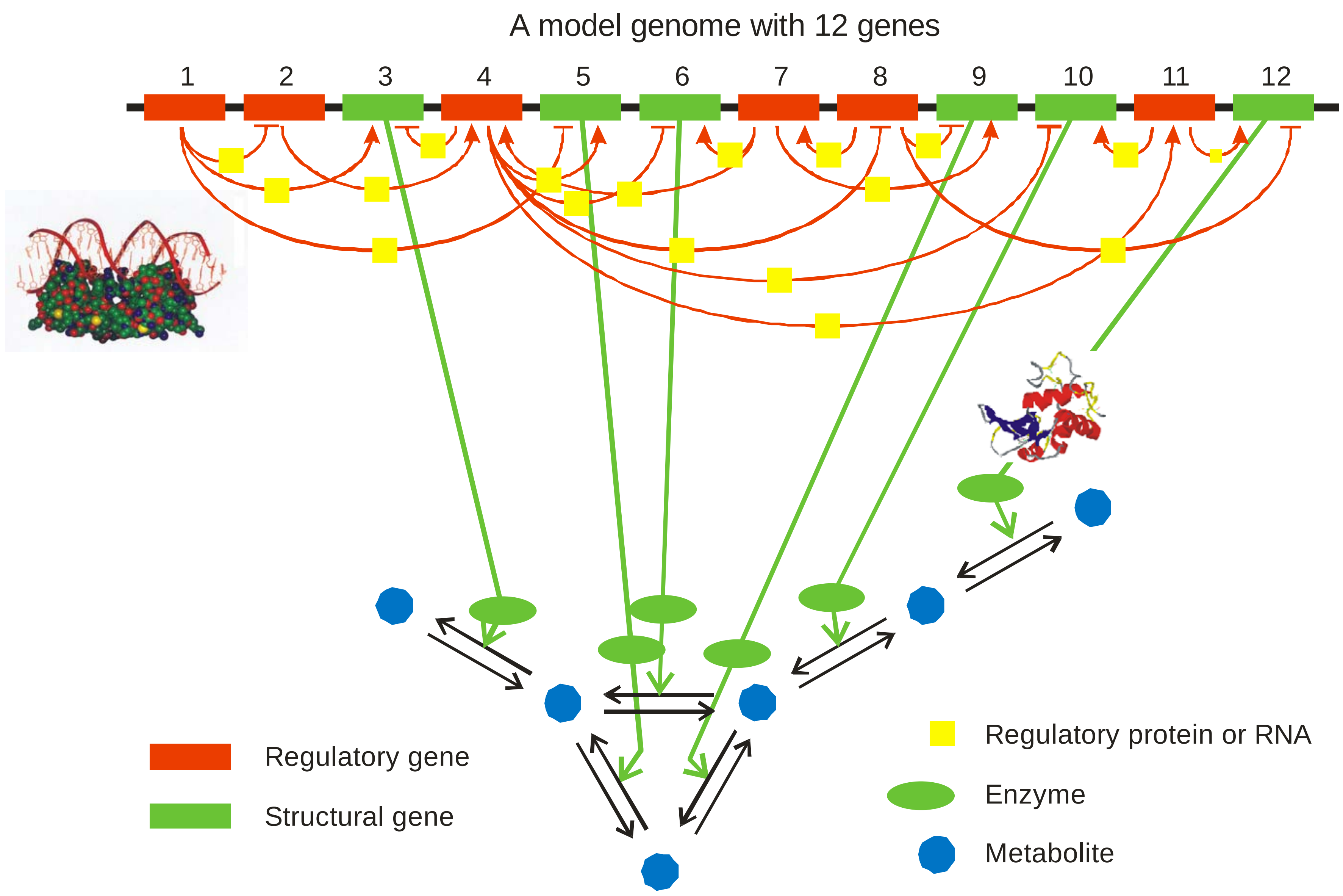


## Systems biology, cell biology

Regulation of the cell cycle, genetic and metabolic networks, reaction kinetics, homeostasis, ...

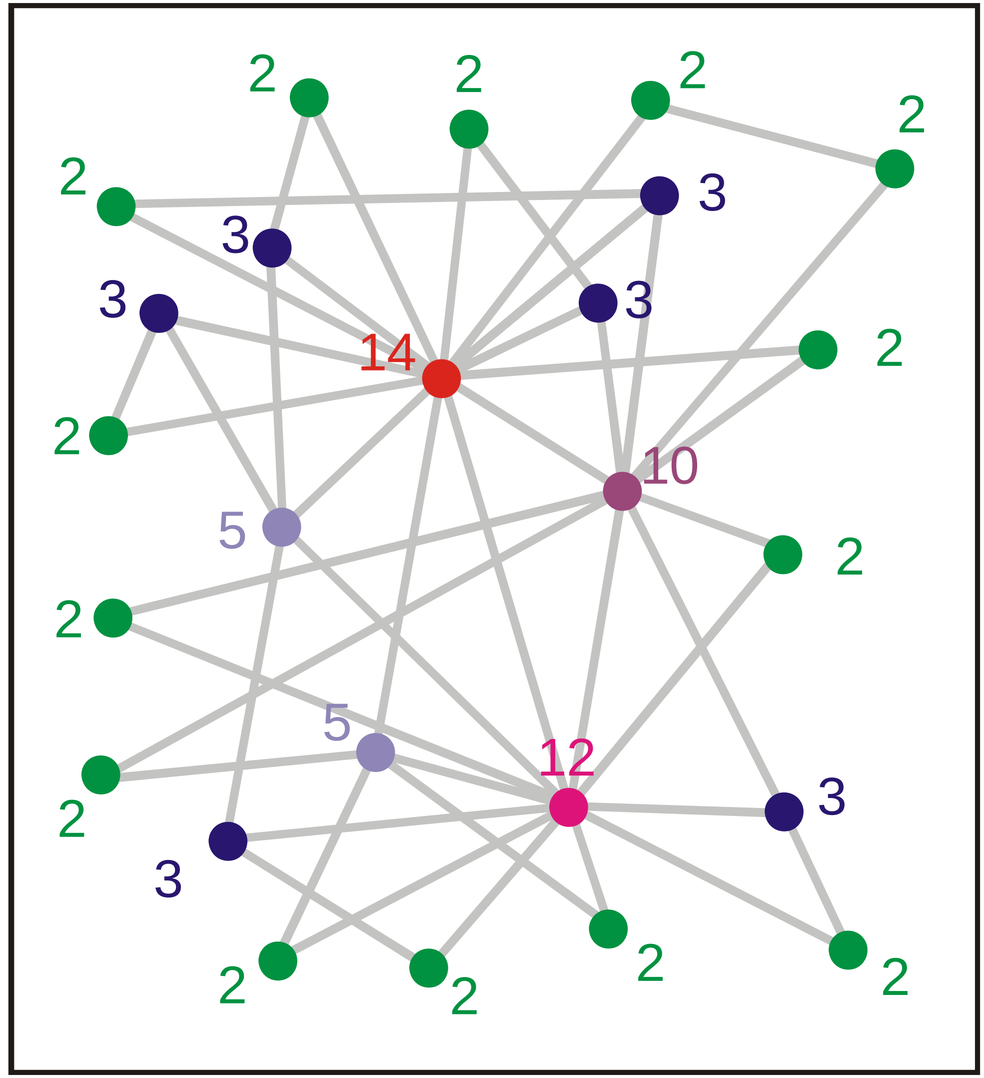



The bacterial cell as an example for the simplest form of autonomous life




Sketch of a genetic and metabolic network

| links | # nodes |
|---|---|
| 2 | 14 |
| 3 | 6 |
| 5 | 2 |
| 10 | 1 |
| 12 | 1 |
| 14 | 1 |



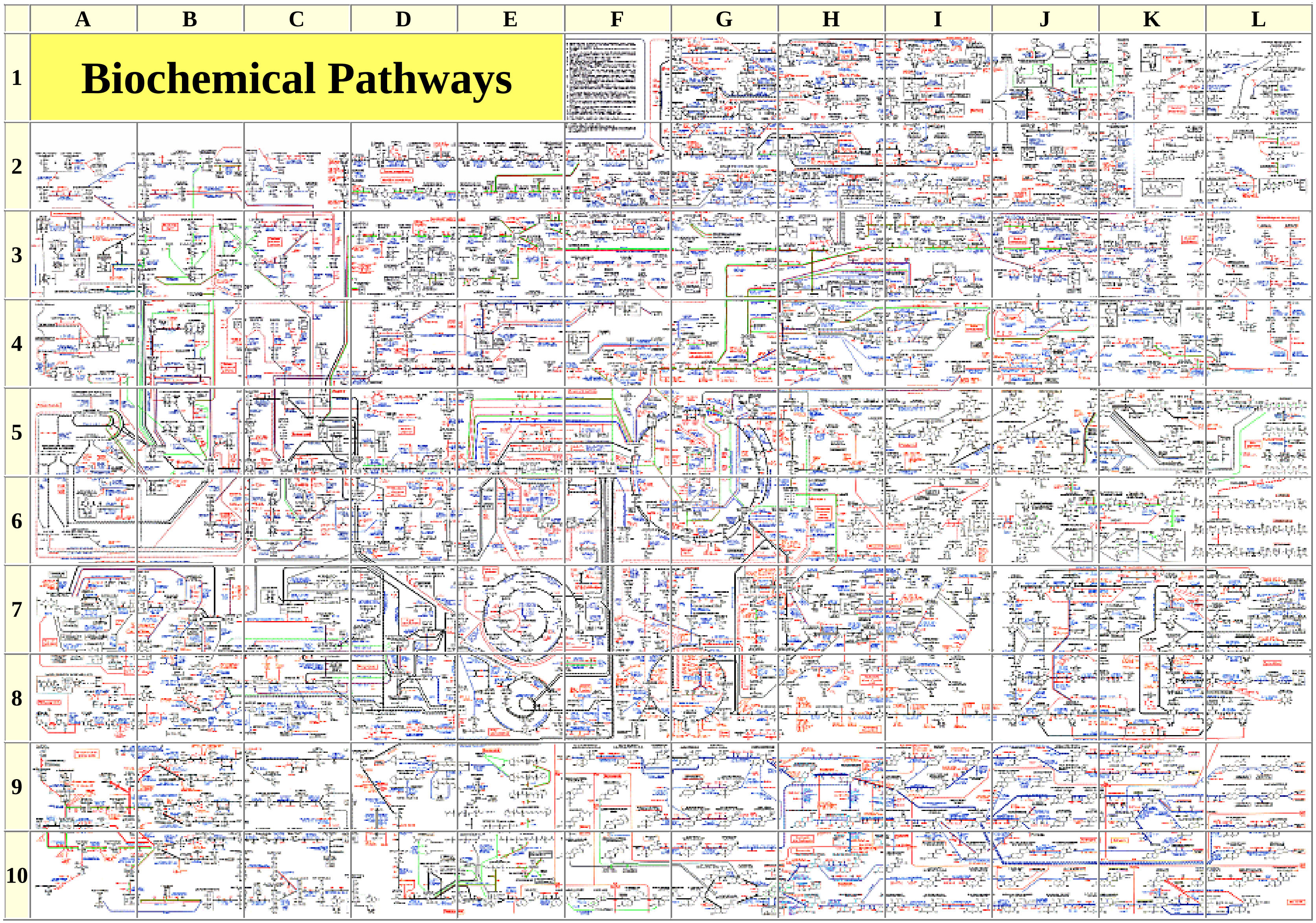

Analysis of nodes and links in a step by step evolved network

| | | |
|---|---|---|
| **E. coli**: | Length of the Genome | $4\times10^6$ Nucleotides |
| | Number of Cell Types | 1 |
| | Number of Genes | 4 000 |
| **Man**: | Length of the Genome | $3\times10^9$ Nucleotides |
| | Number of Cell Types | 200 |
| | Number of Genes | 30 000 - 60 000 |

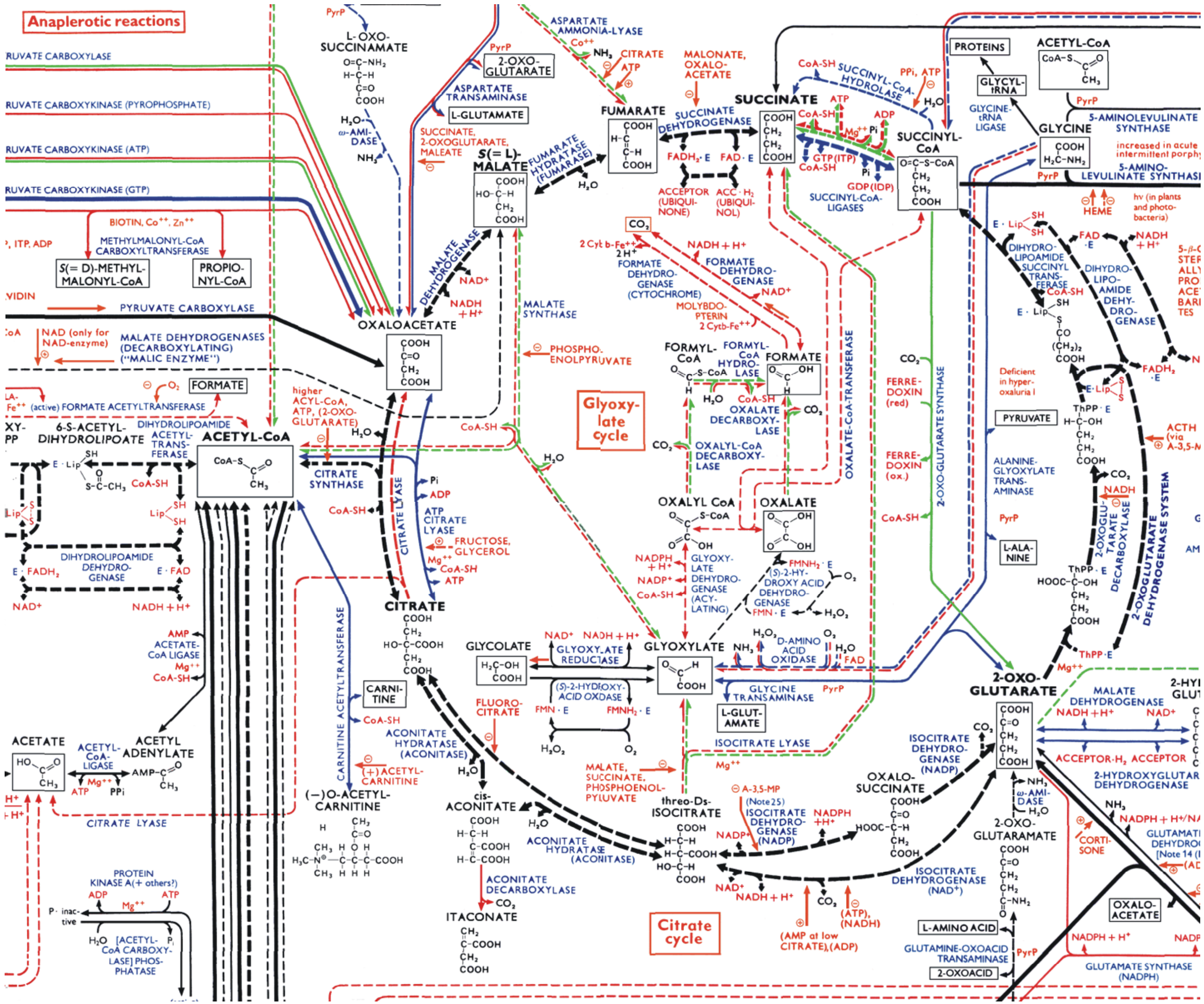
**The human body**

$10^{14}$ cells = $10^{13}$ eukaryotic cells + $9\times10^{13}$ bacterial (prokaryotic) cells

100 kg = 99.1 kg + 0.9 kg



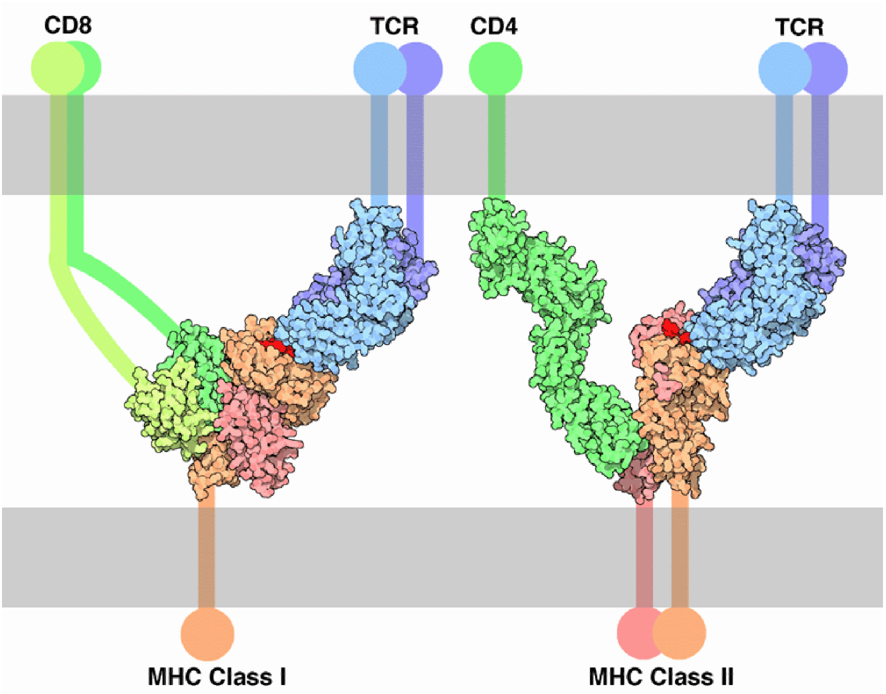

The reaction network of cellular metabolism published by Boehringer-Ingelheim.

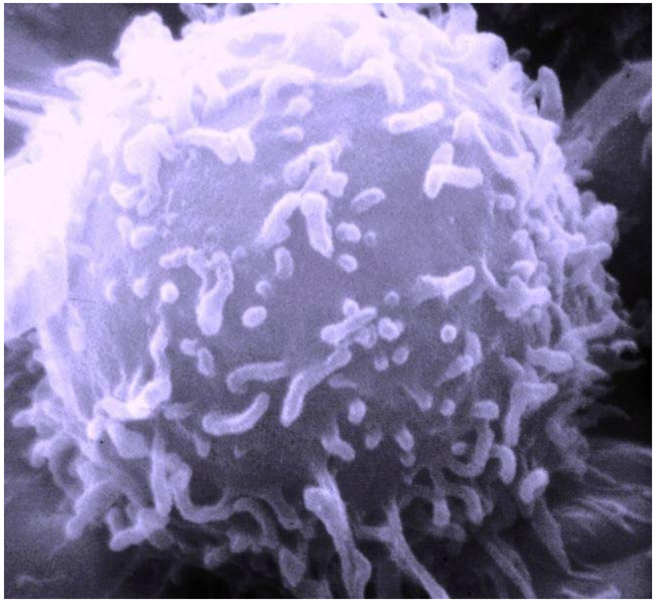


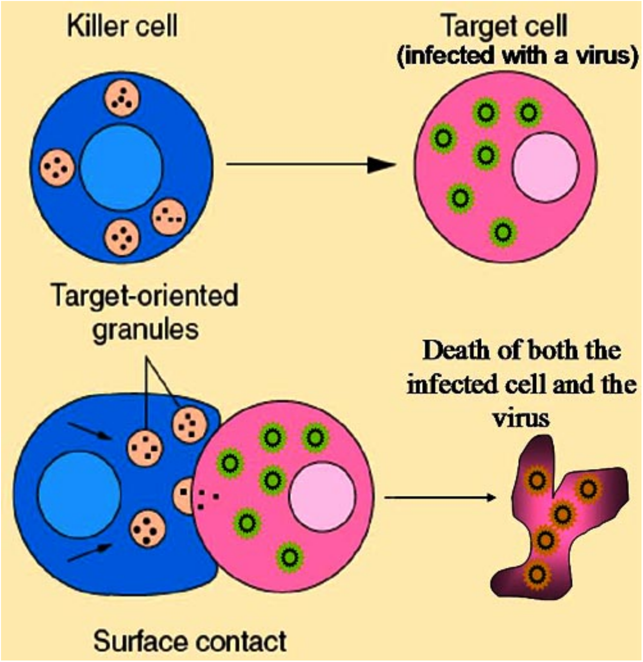

The citric acid or Krebs cycle (enlarged from previous slide).

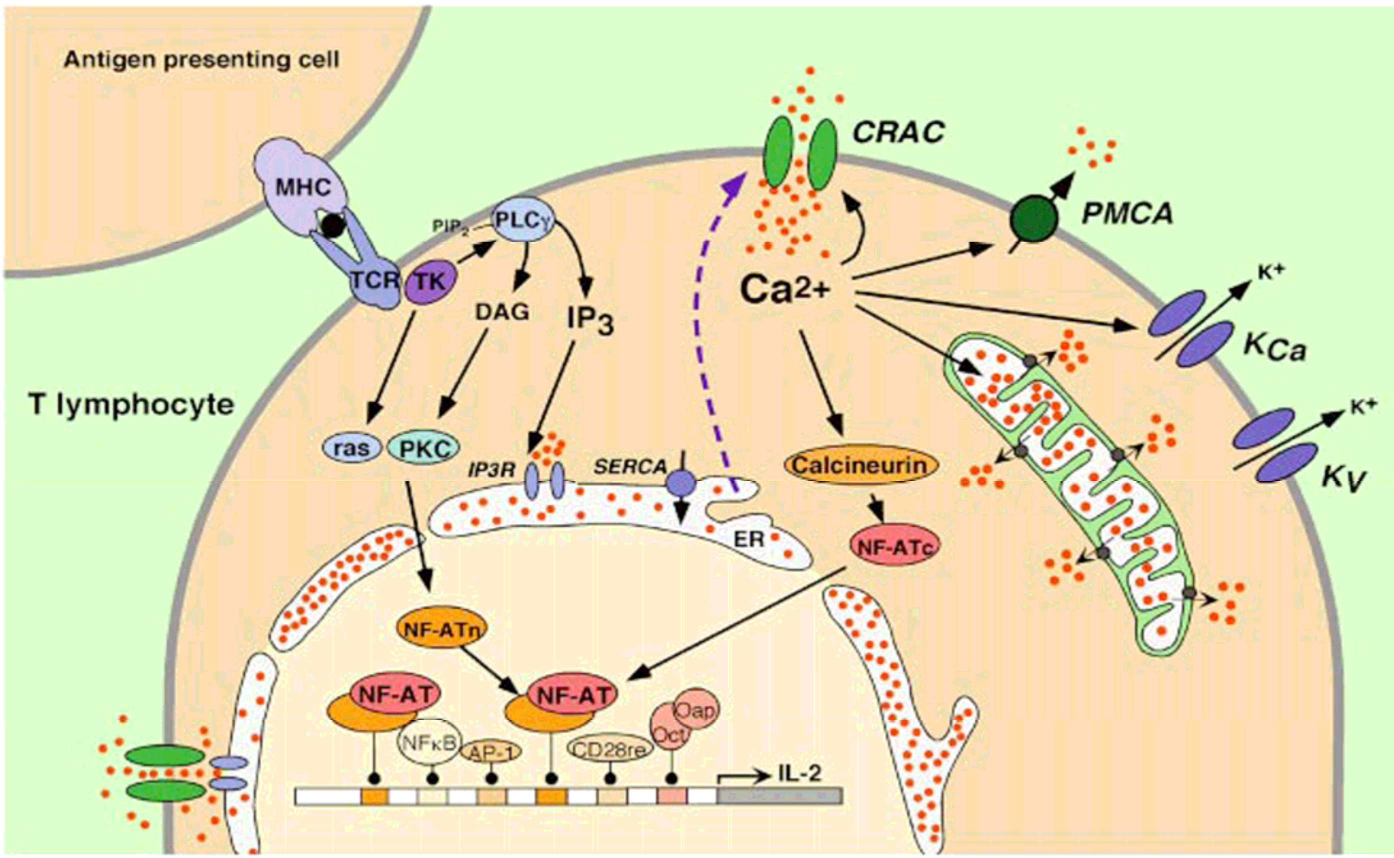
# Immunology

Network theory, immunological synapse, dynamical systems, mutation, selection, ...








Ca$^{2+}$-signalling at the immune synapse

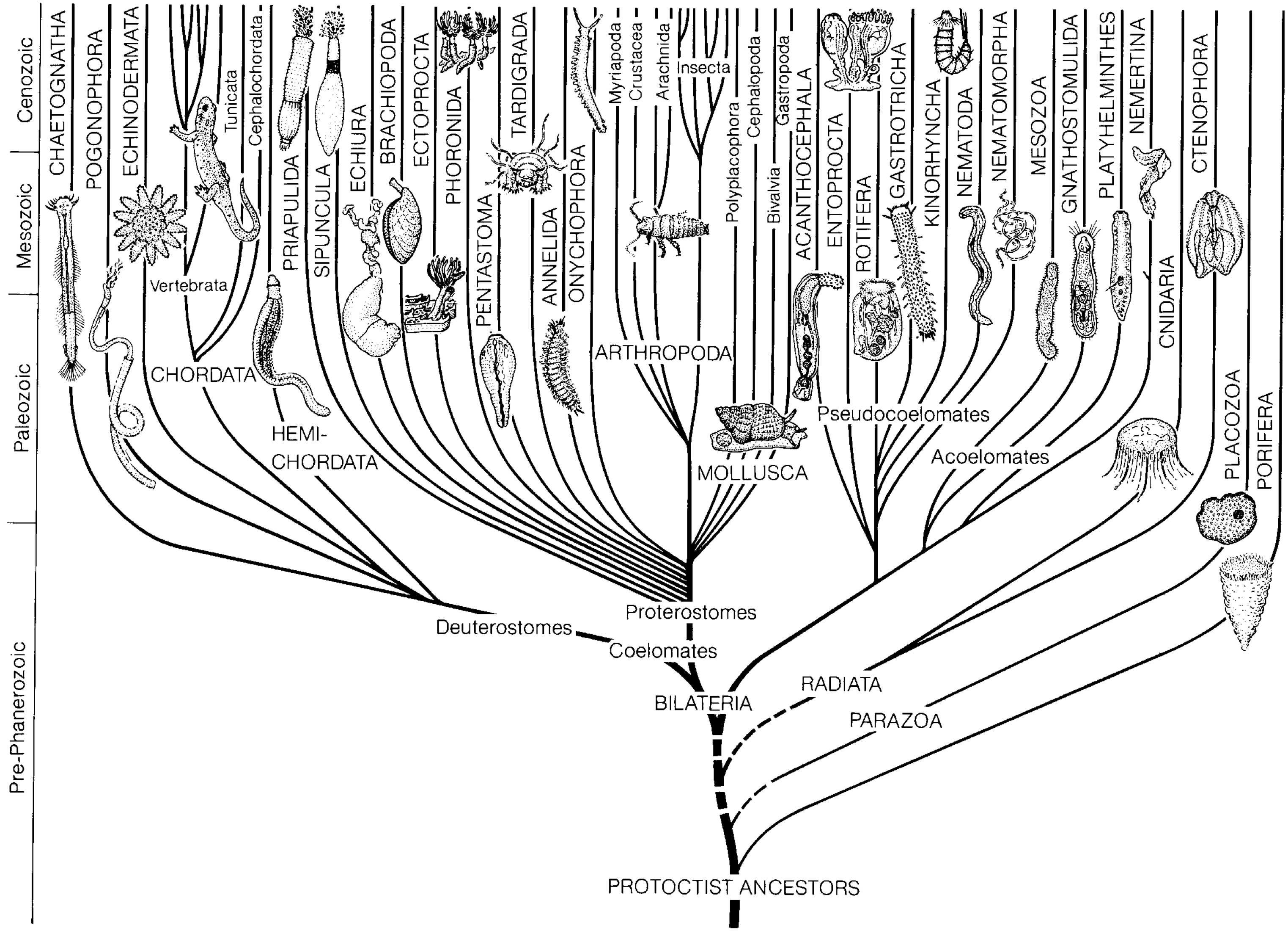
# Evolutionary biology

Optimization through variation and selection, relation between genotype, phenotype, and function, ...

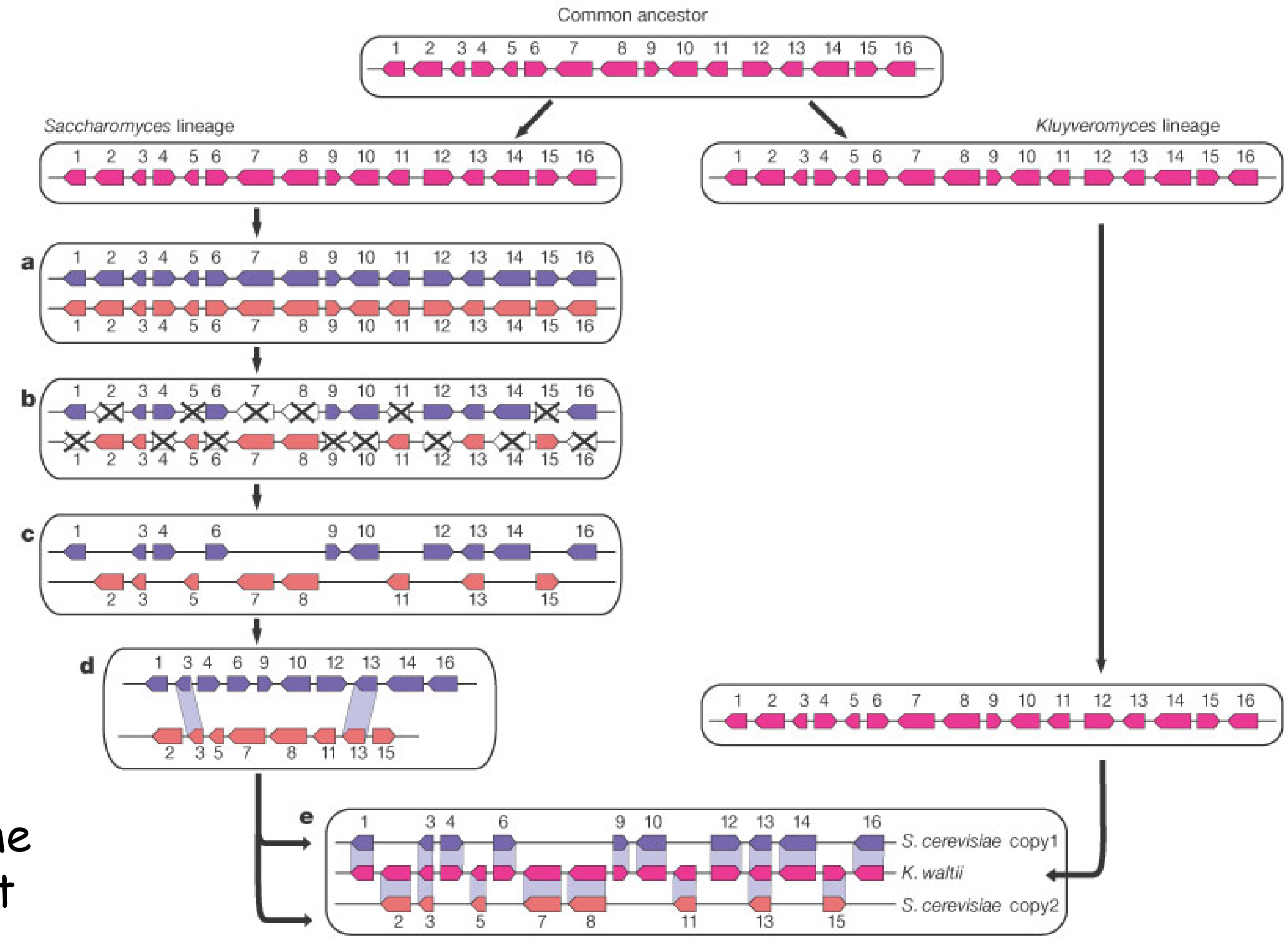
| | Generation time | Selection and adaptation 10 000 generations | Genetic drift in small populations $10^6$ generations | Genetic drift in large populations $10^7$ generations |
|---|---|---|---|---|
| RNA molecules | 10 sec<br>1 min | 27.8 h = 1.16 d<br>6.94 d | 115.7 d<br>1.90 a | 3.17 a<br>19.01 a |
| Bacteria | 20 min<br>10 h | 138.9 d<br>11.40 a | 38.03 a<br>1 140 a | 380 a<br>11 408 a |
| Multicelluar organisms | 10 d<br>20 a | 274 a<br>200 000 a | 27 380 a<br>$2 \times 10^7$ a | 273 800 a<br>$2 \times 10^8$ a |

Time scales of evolutionary change


Reconstruction of a phylogenetic tree from present day seqeunces

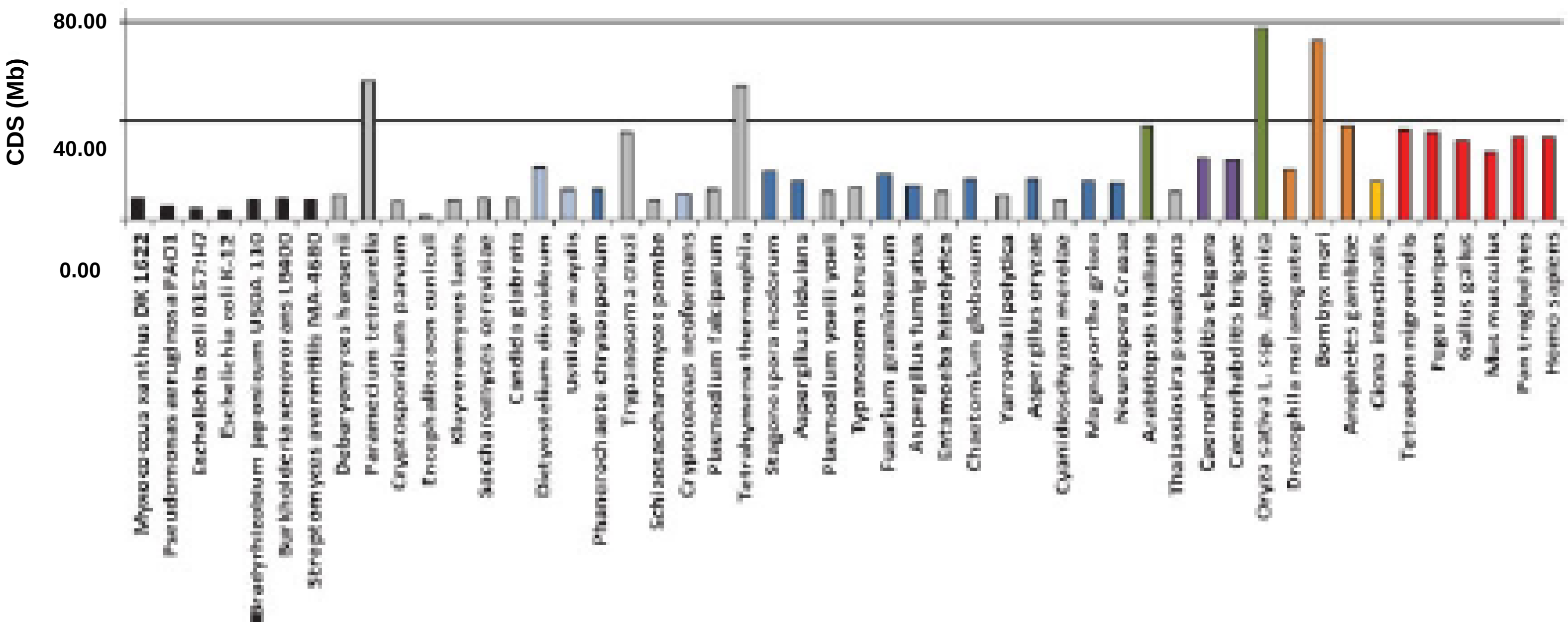


Cenozoic
Mesozoic
Paleozoic
Pre-Phanerozoic
CHAETOGNATHA
POGONOPHORA
ECHINODERMATA
Vertebrata
Tunicata
Cephalochordata
CHORDATA
HEMI-
CHORDATA
PRIAPULIDA
SIPUNCULA
ECHIURA
BRACHIOPODA
ECTOPROCTA
PHORONIDA
PENTASTOMA
TARDIGRADA
ANNELIDA
ONYCHOPHORA
Myriapoda
Crustacea
Arachnida
Insecta
ARTHROPODA
Polyplacophora
Cephalopoda
Bivalvia
Gastropoda
MOLLUSCA
ACANTHOCEPHALA
ENTOPROCTA
ROTIFERA
GASTROTRICHA
KINORHYNCHA
NEMATODA
NEMATOMORPHA
Pseudocoelomates
MESOZOA
GNATHOSTOMULIDA
PLATYHELMINTHES
NEMERTINA
Acoelomates
CNIDARIA
CTENOPHORA
PLACOZOA
PORIFERA
Deuterostomes
Proterostomes
Coelomates
BILATERIA
RADIATA
PARAZOA
PROTOCTIST ANCESTORS

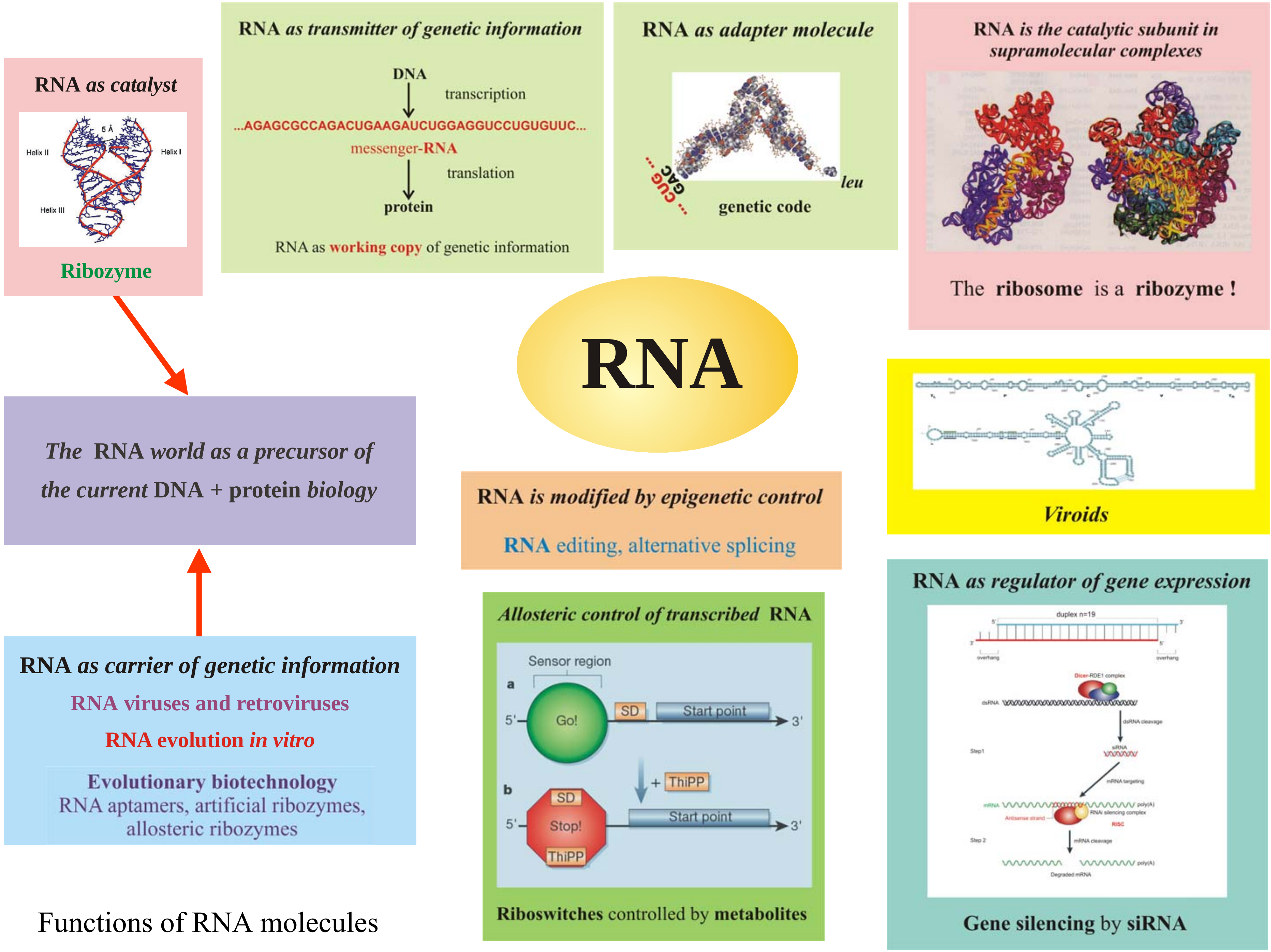



A model for genome duplication in yeast $\approx 1\times10^{8}$ years ago

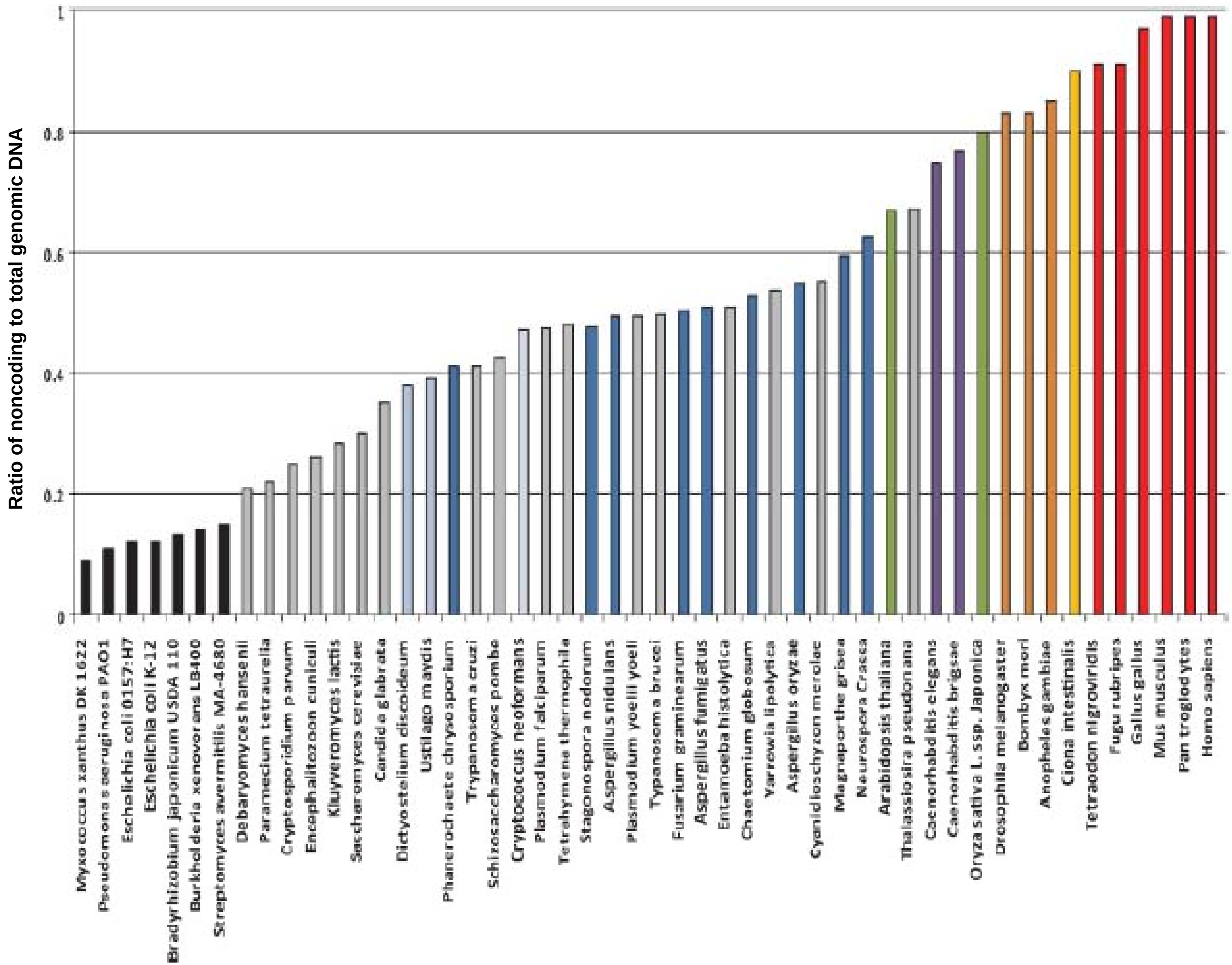
Manolis Kellis, Bruce W. Birren, and Eric S. Lander. Proof and evolutionary analysis of ancient genome duplication in the yeast *Saccharomyces cerevisiae*. *Nature* **428**: 617-624, 2004



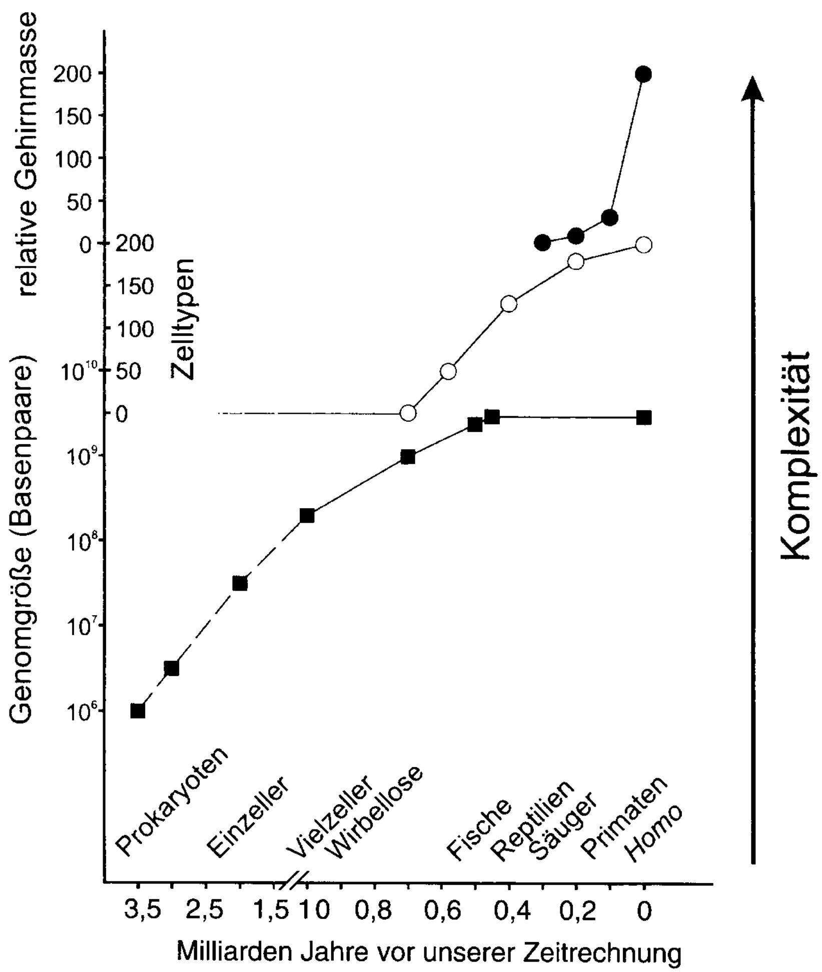

R.J.Taft, M.Pheasant, J.S.Mattick. The relationship between non-protein-coding DNA and eukayotic complexity. ***BioEssays* 29**:288-297, 2007.




Functions of RNA molecules




R.J.Taft, M.Pheasant, J.S.Mattick. The relationship between non-protein-coding DNA and eukayotic complexity. ***BioEssays*** **29**:288-297, 2007.



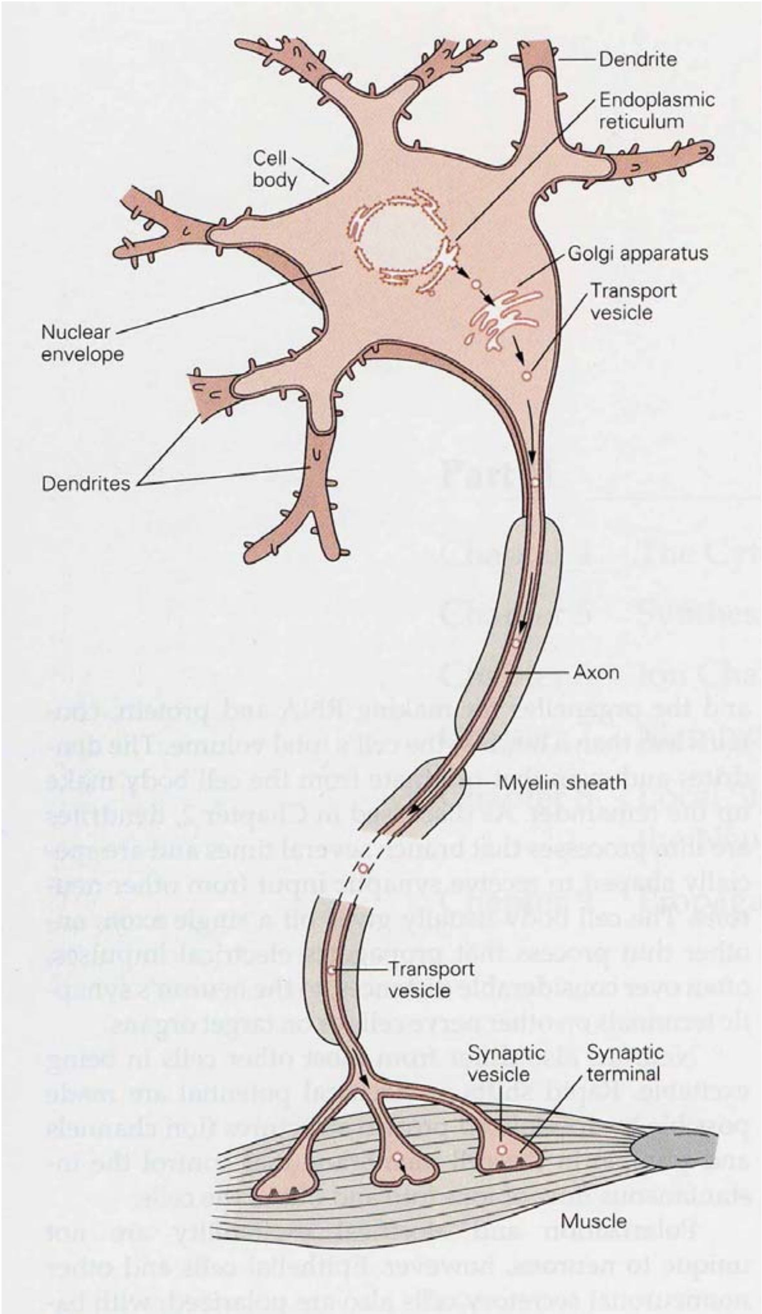

**4.10** Die Zunahme der Komplexität ist ein wesentlicher Aspekt der biologischen Evolution, wobei höhere Komplexität sowohl durch Vergrößerung der Zahl von miteinander in Wechselwirkung stehenden Elementen als auch durch Differenzierung der Funktionen dieser Elemente entstehen kann. In dieser Abbildung wird zwischen drei Phasen oder Strategien der Evolution von Komplexität unterschieden. *Untere Kurve*: Zunahme der Genomgröße; logarithmische Auftragung der Zahl der Basenpaare im Genom von Zellen seit Beginn der biologischen Evolution (Daten aus Abbildung 2.3). *Mittlere Kurve*: Zunahme der Zahl der Zelltypen in der Evolution der Metazoa (Daten aus Abbildung 4.8). *Obere Kurve*: Zunahme des relativen Gehirngewichts (bezogen auf die Körperoberfläche) bei Säugetieren (Daten aus Wilson 1985). Für die Abszisse wurden zwei Skaleneinteilungen verwendet, eine für den Zeitraum $>10^9$ Jahre, eine andere für den Zeitraum $<10^9$ Jahre vor der Gegenwart. Oberhalb der Abszisse sind die Namen einiger wichtiger taxonomischer Einheiten angeführt, deren Evolution in etwa beim jeweiligen Wortbeginn einsetzt.

Wolfgang Wieser. *Die Erfindung der Individualität oder die zwei Gesichter der Evolution*. Spektrum Akademischer Verlag, Heidelberg 1998.

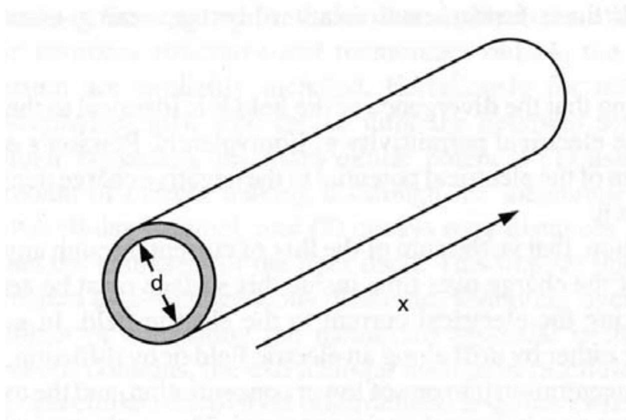
A.C.Wilson. *The Molecular Basis of Evolution*. Scientific American, Oct.1985, 164-173.

# Neurobiology

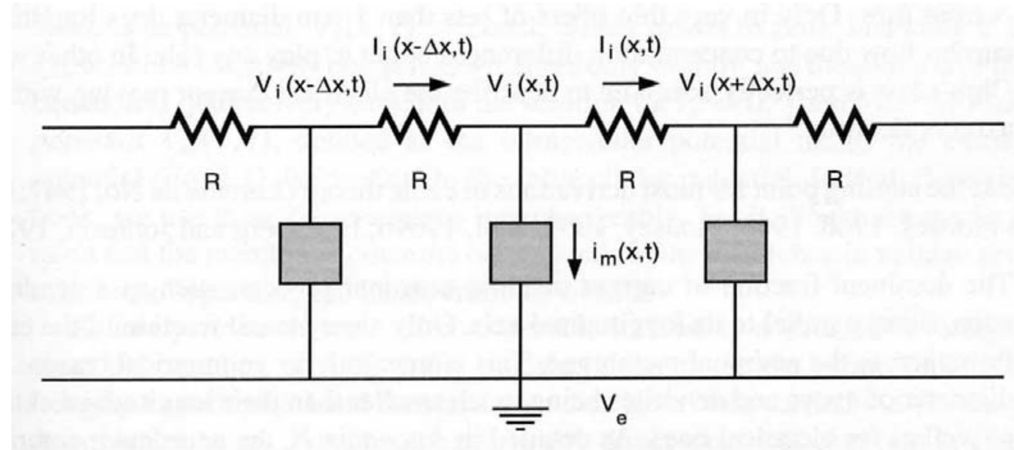
Neural networks, collective properties, nonlinear dynamics, signalling, ...




A single neuron signaling to a muscle fiber




**A**




**B**

**Fig. 2.2 Electrical Structure of a Cable** **(A)** Idealized cylindrical axon or dendrite at the heart of one-dimensional cable theory. Almost all of the current inside the cylinder is longitudional due to geometrical (the radius is much smaller than the length of the cable) and electrical factors (the membrane covering the axon or dendrite possesses a very high resistivity compared to the intracellular cytoplasm). As a consequence, the radial and angular components of the current can be neglected, and the problem of determining the potential in these structures can be reduced from three spatial dimensions to a single one. On the basis of the bidomain approximation, gradients in the extracellular potentials are neglected and the cable problem is expressed in terms of the transmembrane potential $V_m(x,t) = V_i(x,t) - V_e$. **(B)** Equivalent electrical structure of an arbitrary neuronal process. The intracellular cytoplasm is modeled by the purely ohmic resistance $R$. This tacitly assumes that movement of carriers is exclusively due to drift along the voltage gradient and not to diffusion. Here and in the following the extracellular resistance is assumed to be negligible and $V_e$ is set to zero. The current per unit length across the membrane, whether it is passive or contains voltage-dependent elements, is described by $i_m$ and the system is characterized by the second-order differential equation, Eq. 2.5.

Christof Koch, Biophysics of Computation. Information Processing in single neurons.
Oxford University Press, New York 1999.

$$\frac{1}{R}\frac{\partial^2 V}{\partial \xi^2} = C_M\,\theta\frac{\partial V}{\partial \xi} + [g_{Na}\, m^3\, h\,(V - V_{Na}) + g_K\, n^4\,(V - V_K) + g_l\,(V - V_l)]\,2\pi\, r\, L$$

$$\theta\frac{\partial m}{\partial \xi} = \alpha_m(1-m) - \beta_m m$$

$$\theta\frac{\partial h}{\partial \xi} = \alpha_h(1-h) - \beta_h h$$

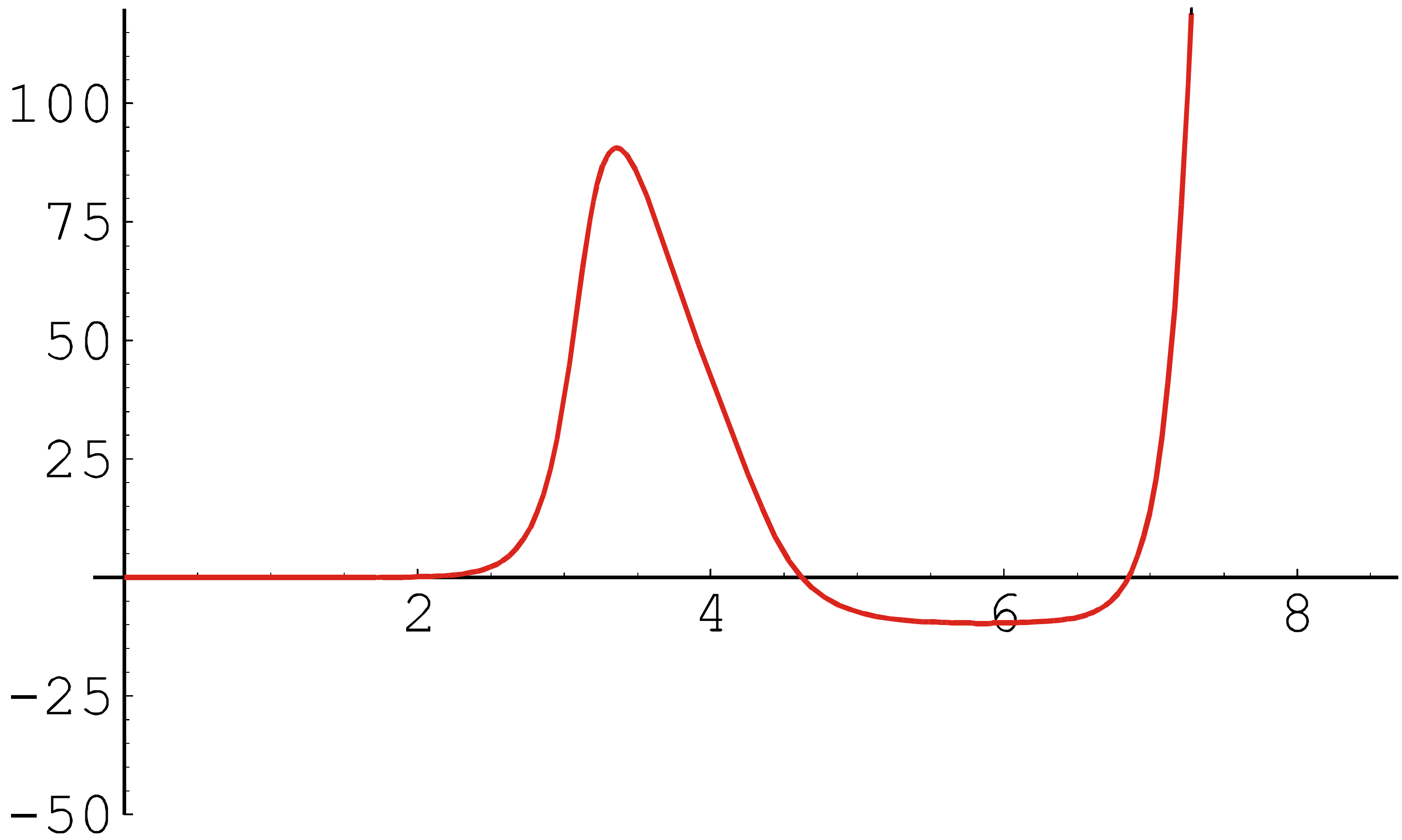
$$\theta\frac{\partial n}{\partial \xi} = \alpha_n(1-n) - \beta_n n$$

Hodgkin-Huxley ordinary differential equations (ODE)

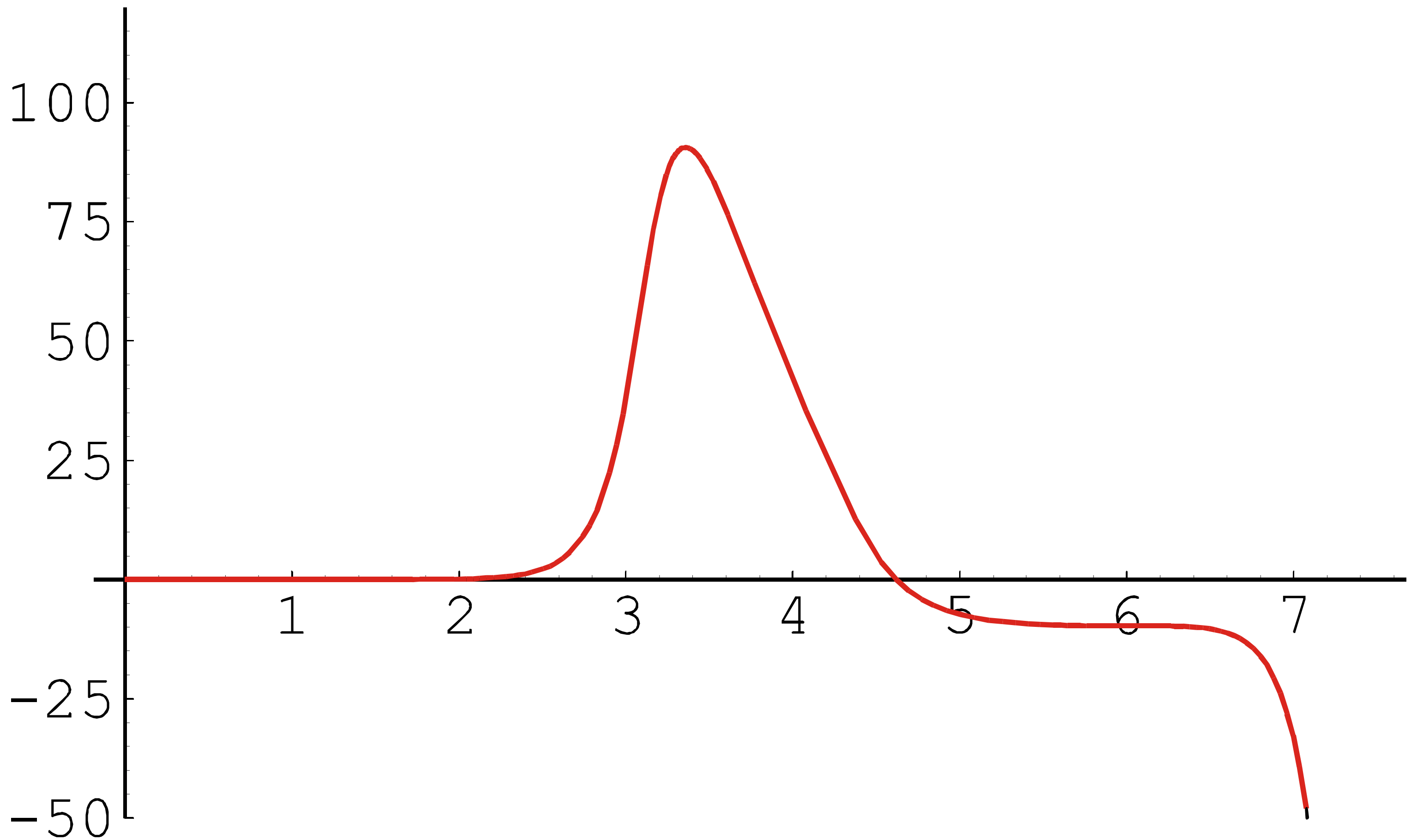
Travelling pulse solution: $V(x,t) = V(\xi)$ with

$$\xi = x + \theta\, t$$

Hodgkin-Huxley equations describing pulse propagation along nerve fibers




T = 18.5 C; θ = 1873.3324514717698 cm / sec

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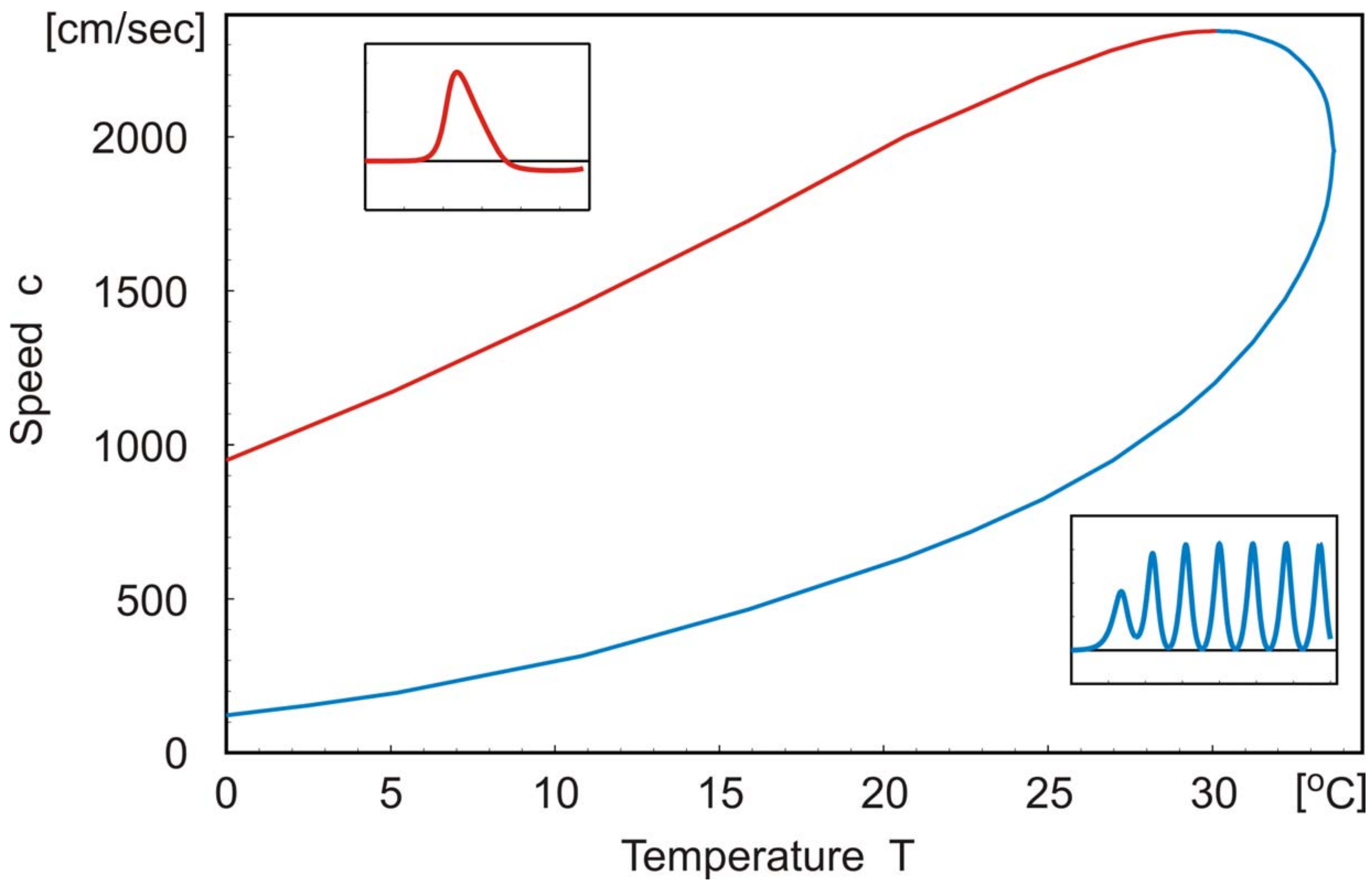
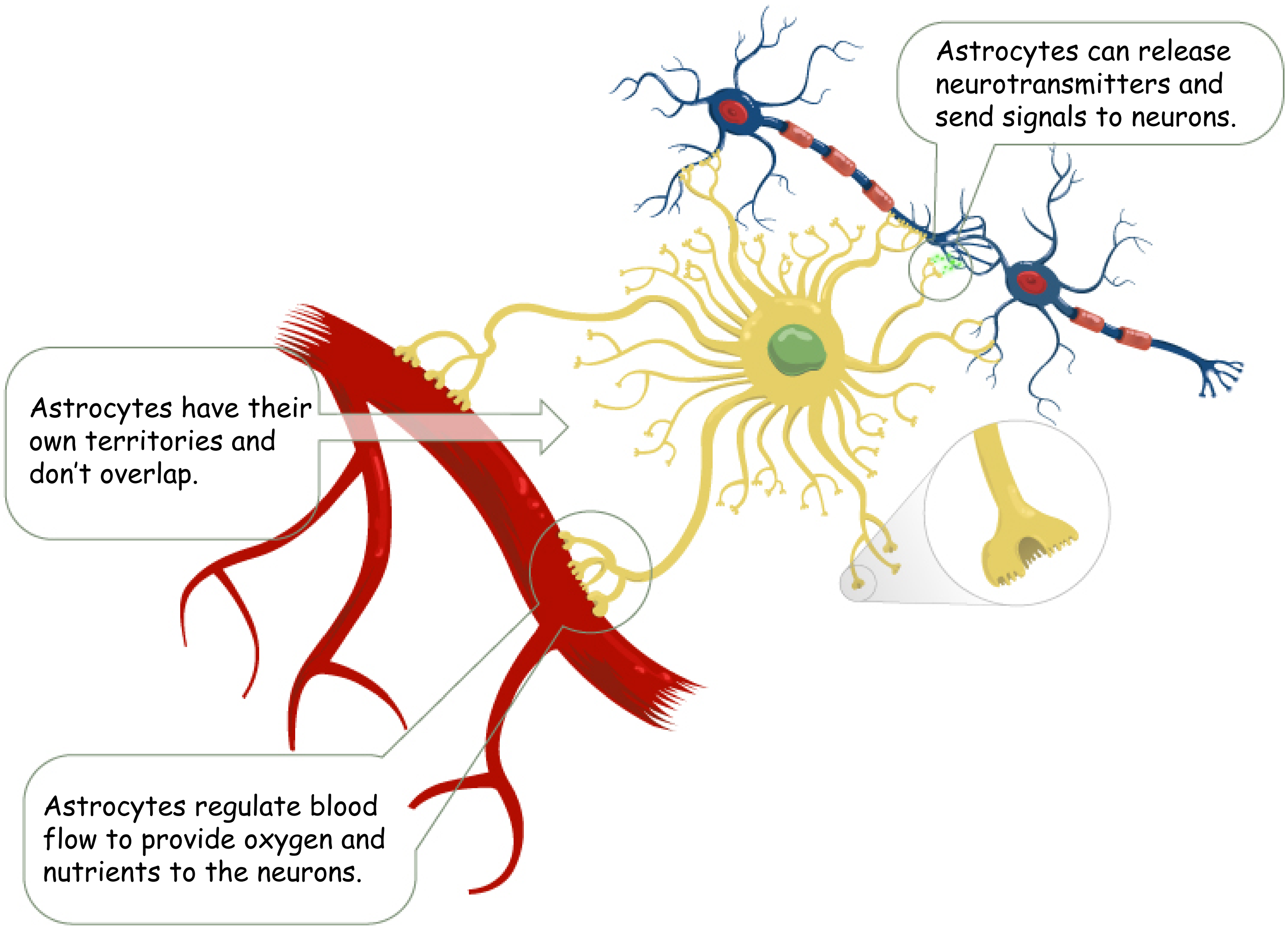
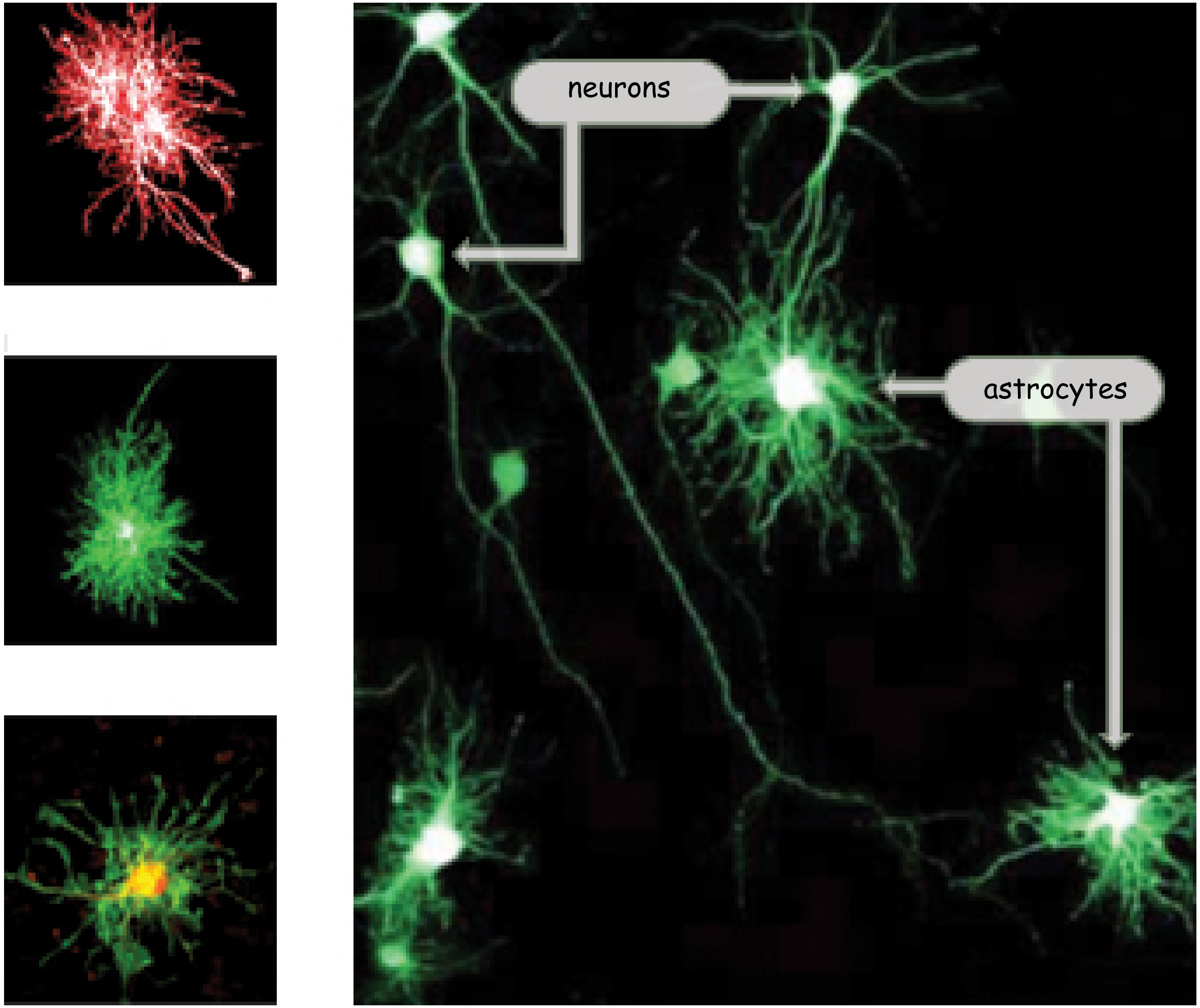



Propagating wave solutions of the Hodgkin-Huxley equations

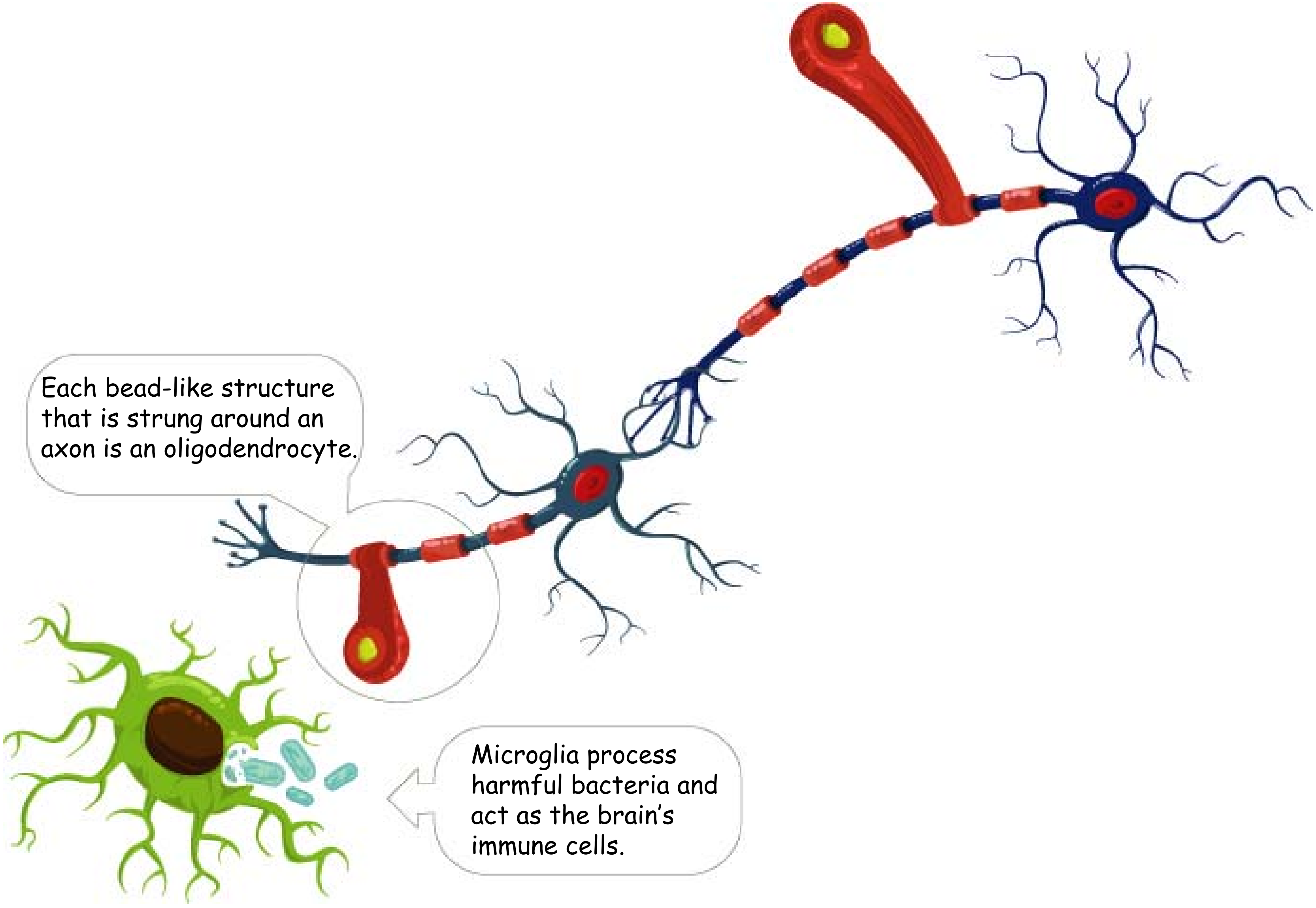


Astrocytes can release neurotransmitters and send signals to neurons.
Astrocytes have their own territories and don't overlap.
Astrocytes regulate blood flow to provide oxygen and nutrients to the neurons.

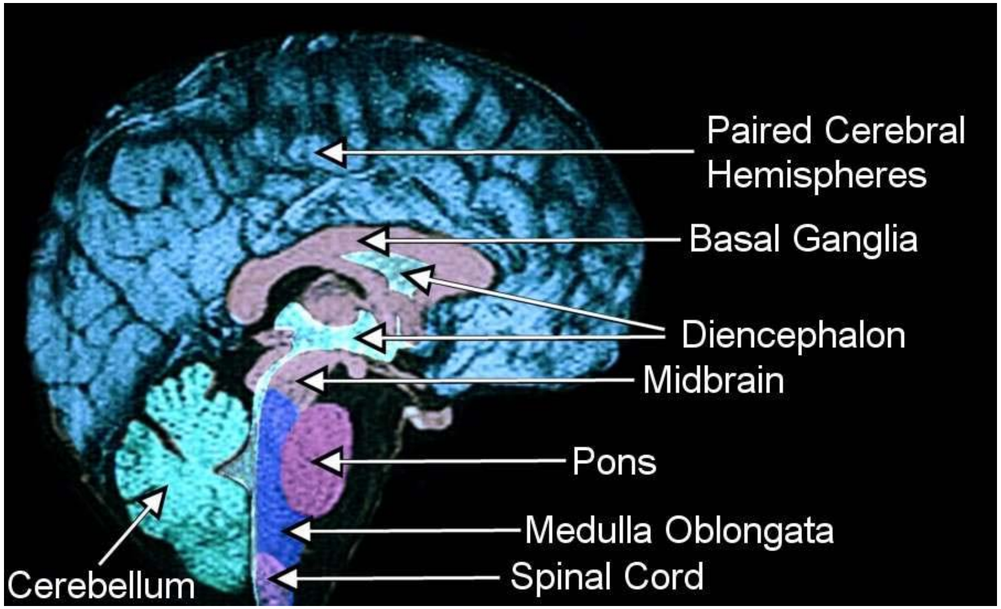

Astrocytes

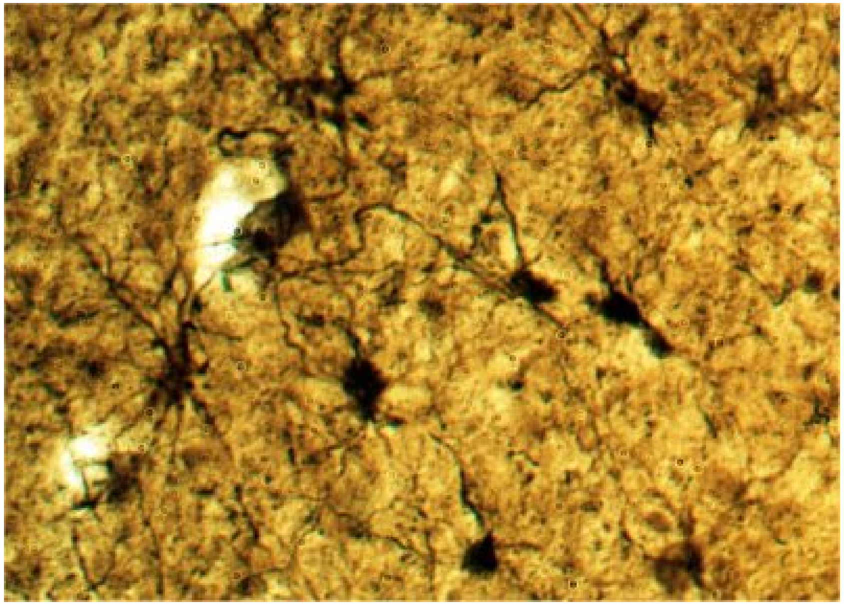



Photos of neurons and astrocytes




Oligodendrocyte



The human brain

$10^{11}$ neurons connected by ≈ $10^{13}$ to $10^{14}$ synapses

Computer axial tomography – CAT

Magnetic resonance imaging – MRI

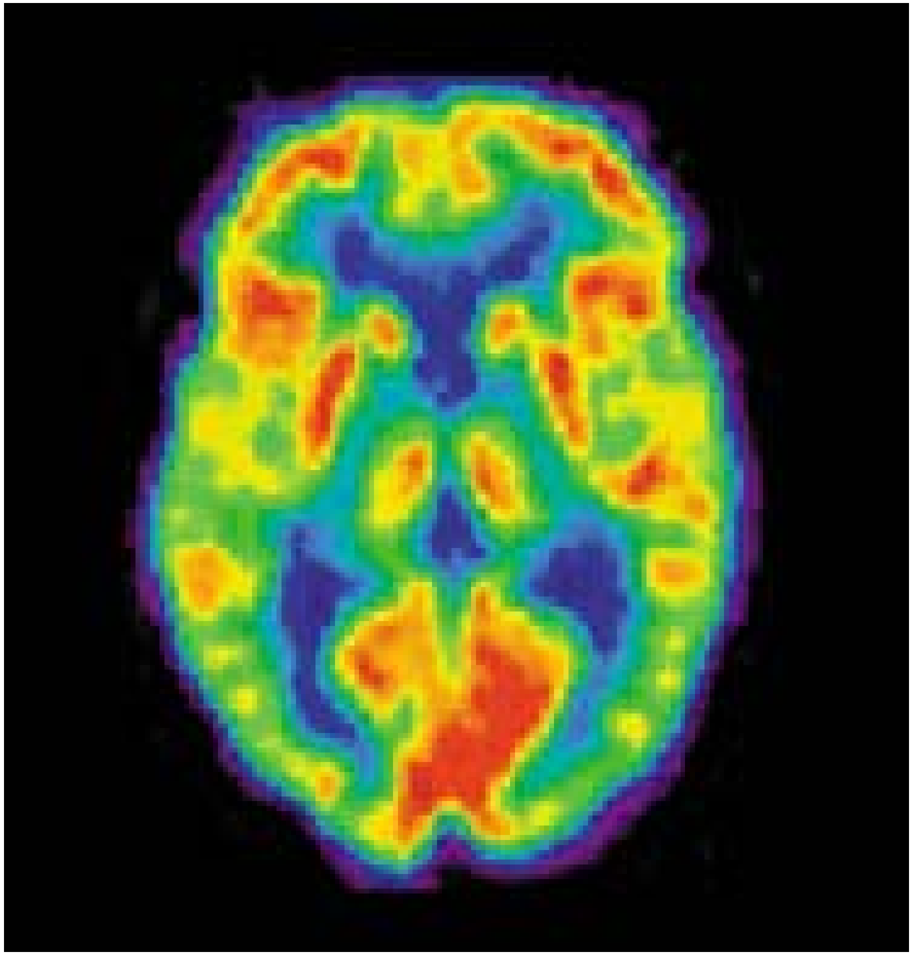
**Functional magnetic resonance imaging - fMRI**

Positron emission tomography – PET

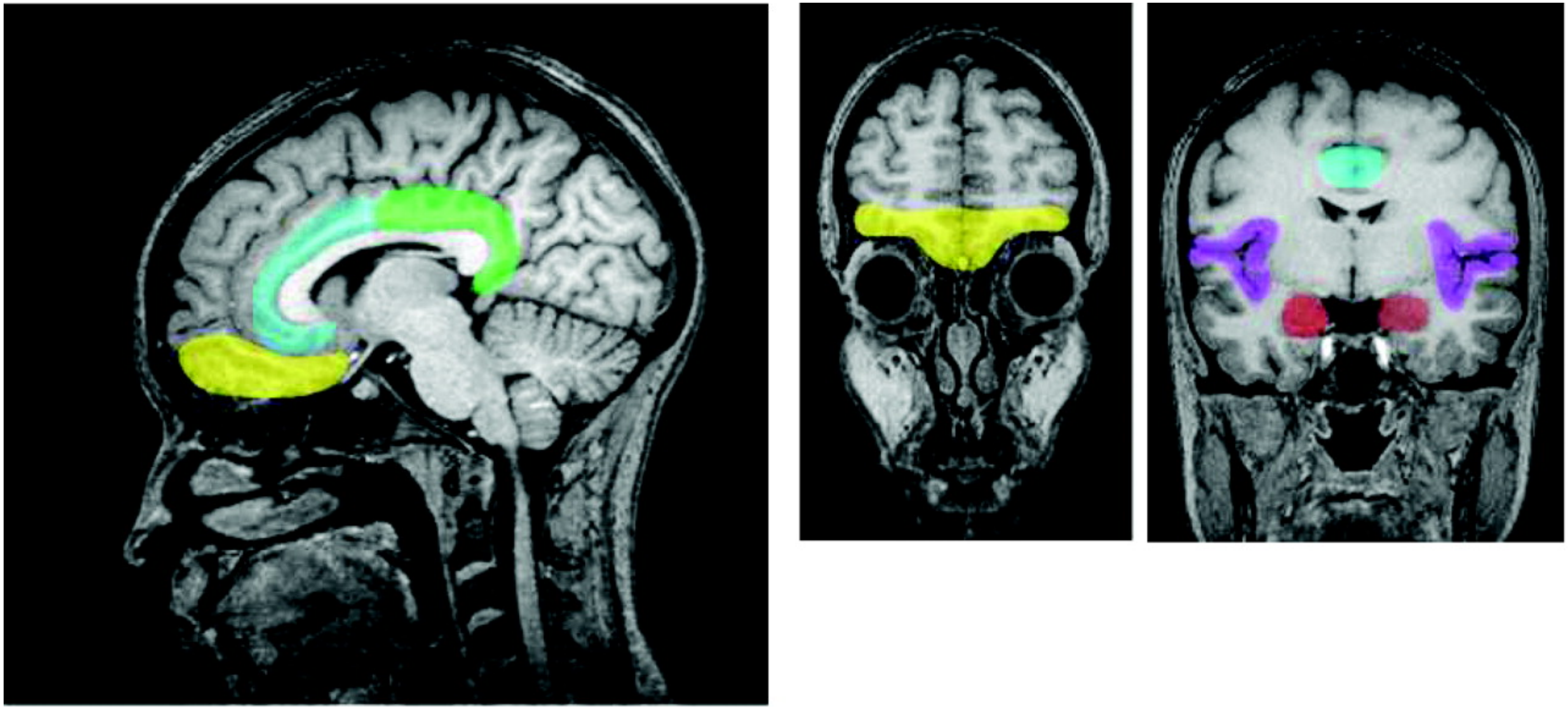
Single photon emission computed tomography - SPECT

Diffuse Optical Tomography - DOT


Neuroimaging techniques



Positron emission tomography - PET



Brain regions involved in emotional experience: Amygdala (linking perception, automatic emotional response and memory), orbitofrontal cortex, insular cortex, anterior and posterior cingulate cortices.

Picture taken from *Science* **298**, 1191-1194 (2002)

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