Modelling biological systems: a computational challenge

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Acknowledgments --- Apologies

- I wish to thank Enrico for the opportunity he gave me to present this material

- and all the people of the Biophysics group of ToV (especially Silvia) for ∞-ly many discussions which are at the origin of these lectures

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- Choice of arguments was made on the basis on my tastes, preferences and incompetence

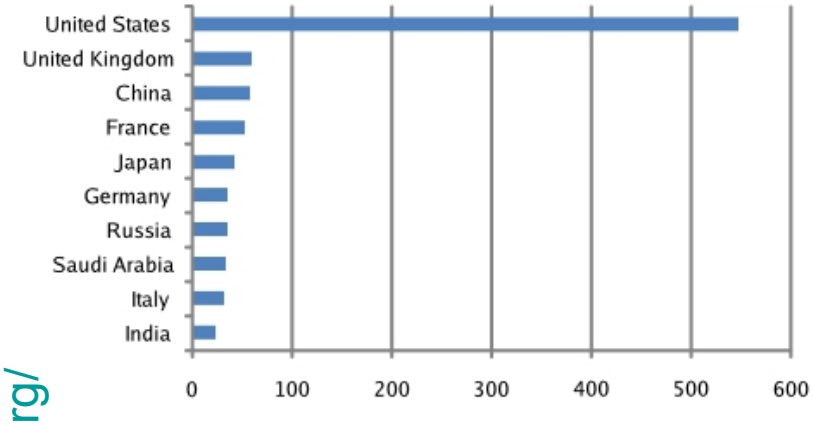
- The amount of underlying biological knowledge behind most of the arguments I will touch is essentially unlimited and well beyond my competence

- Thus, I will try to convey you rather than a fully detailed biological information, some general description of certain broad classes of systems and problems on which one can probably say something interesting and useful

- I hope you'll find some of these problems intellectually appealing and exciting, not less than High Energy Physics (**HEP**) or Astrophysics, if not for their dramatic impact on our everyday life

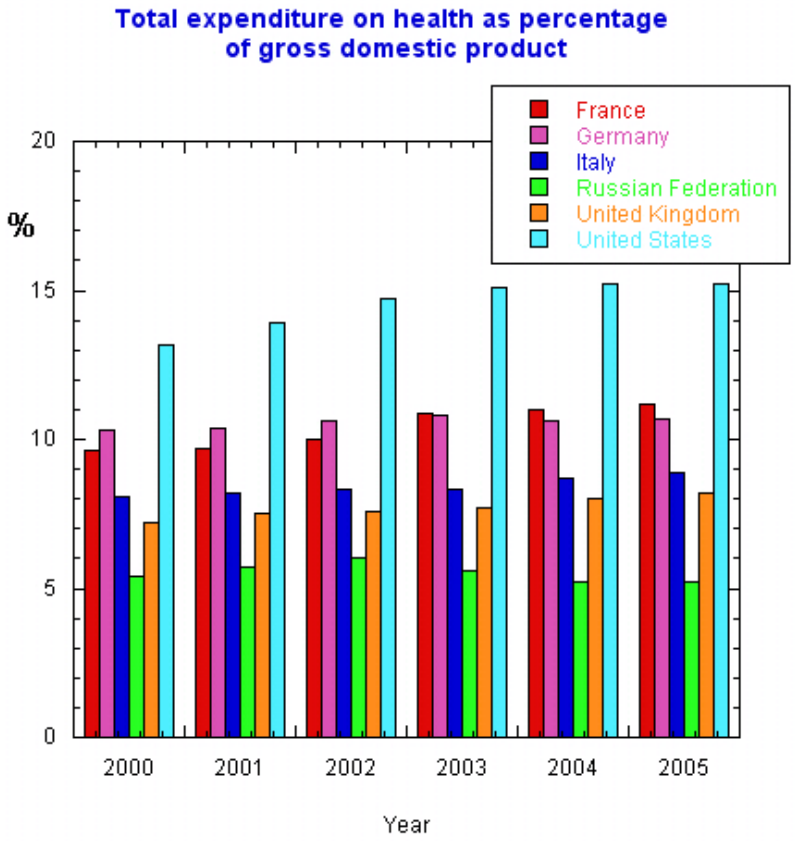
Outline?

The field of health care and biomedical sciences is where the **action** is (in developed countries)



Billions US $ in 2007

http://www.who.int/en/



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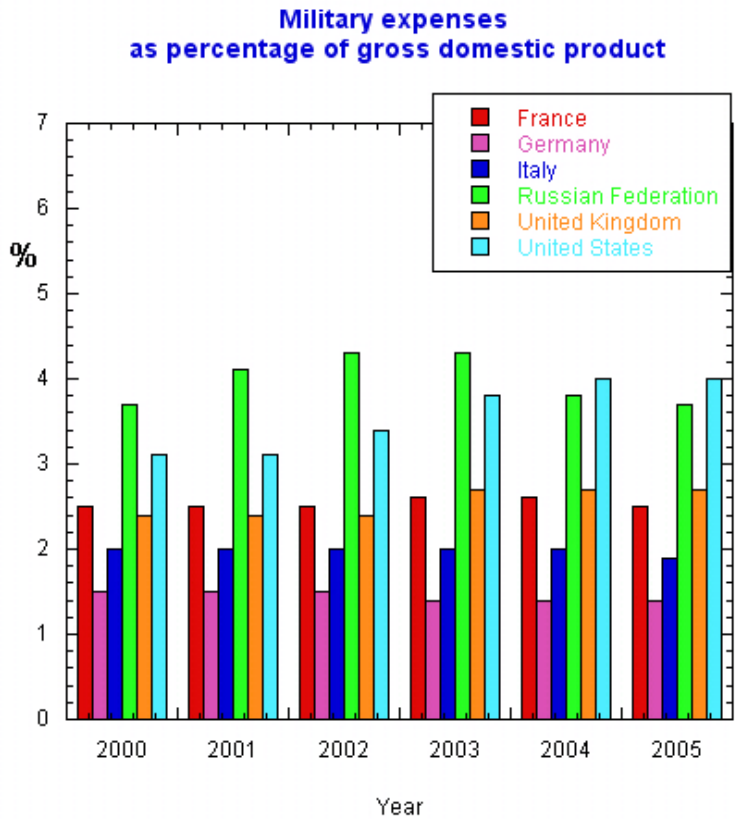


Outline

I. Reductionism *vs* complexity

II. Data, (physical) models and (mathematical) tools

III. What we would like to know and/or to do

IV. What we can actually do and/or are really doing

V. Conclusions and outlook

From concepts to action

I. Reductionism *vs* complexity

- A bit of philosophy
- A bit of phenomenology

A bit of “philosophy”

Biology *vs* Physics

(the viewpoint of a theoretical physicist)

- Compare and contrast the situation in the study of Biological systems
  - “Complex” structures governed by (as yet) unknown macro-laws
  - Powerful and cheap experimental techniques
  - Huge amount of data
  - Inadequate models: poor understanding of “micro” to “macro” transition
- and, at the other extreme, of Elementary Particle Physics
  - Supposedly “simple” systems governed by “elegant” known micro-laws
  - Very complicated and expensive experiments
  - Very few new experimental data (LHC is coming!)
  - Rather good models (almost “theories”)

Physics (until very recently) has always found its way by progressively moving towards more and more elementary structures

matter → atoms → nucleons → quarks → ???

guided by the "radical reductionism" paradigm according to which

FUNDAMENTAL LAWS GOVERN ELEMENTARY OBJECTS

This attitude has been very fruitful in the "paradigmatic" case of **HEP**, but it is not obviously being employed in other emerging fields of investigation

- **Dynamical** systems
  - Weather forecasting
  - Catalytic reactions
  - Fluidodynamics (turbulence)

  key words: non-linearity, chaos

- **Disordered** systems — Glasses, Spin glasses

  key-words: frustration, disorder

- **Biological** systems

  key-words: complexity, and perhaps all of the above

1 - There are implications for the notion of modelling and the nature of physical laws

- Even in **Fundamental Physics** what we usually call

  Relativity
  Field
  String
  } Theories

  are actually Models, formulated in the language of Mathematics, from which they borrow the necessary internal logical consistency

- Complications of everyday life (like friction in Mechanics) are considered (conceptually) irrelevant (up to a certain point - airplanes, cars,...!)

- Theories become progressively simpler in the process of understanding

- For **Biosystems**, Models (nobody would call them theories) tend to become more and more complicated, as they develop (not simpler!), with a limit: the model shouldn't become as complicated as the system itself!

- The key questions about modelling in **Biology** are then

  ⇒ When do we decide that we have "understood"?
  protein folding
  functional behaviour of the cell
  ⇒ What kind of knowledge/predictions will we be happy with?

2 - There are implications for the notions of experiment and reproducibility

- The Central Dogma of Physics

  Theories (models) are validated through reproducible experiments

- In many biological instances the situation is somewhat more complicated. For instance, to put it in a provocative way

"The experiment of testing ***in vivo*** the effectiveness of a drug (working ***in vitro***), would certainly not be considered a failure if, say, only **30%** of ill people recover"

- Can we somehow understand this situation?

  1. Biological experiments may not give reproducible results because not all the relevant dof's are/can be kept under control $\Rightarrow$ # dof's >> 1
  2. On the other hand, in most cases (but, see later) it is not of any interest to be able to predict the properties of the final state of a biological system, or process, in its finest details $\Rightarrow$ disorder & redundancy
  3. Models are very crude (when they exist at all) and most often overwhelming complicated $\Rightarrow$ need for some intrinsically new concept?

The systems of interest

Reductionism

- Elementary is an object characterized by a small # of properties
- All elementary objects of a given kind are alike (electrons)
- Simple physical laws (theories) apply to elementary objects
- Strict determinism and experimental reproducibility follow

Complexity

- Complex systems have many dof's and many functionally relevant components
- One should talk of classes of systems, e.g.
  - the class of nervous cells, the class of liver cells
  - or, more generally, the class of nucleated cells

  Classes are defined by identifying the common properties of the constituent systems
- Models yield a mathematical description of common features of systems belonging to a given class in terms of probability distribution functions (PDF)
- Class averages are computed and compared to results coming from averages over sets of experiments

3 - There are implications for the amount and the nature of the possible information output

Key point

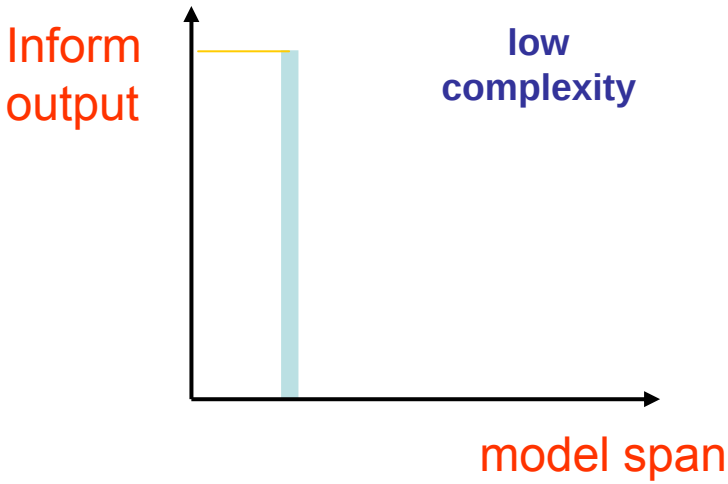
is the accuracy by which a class of homogeneous objects can be defined

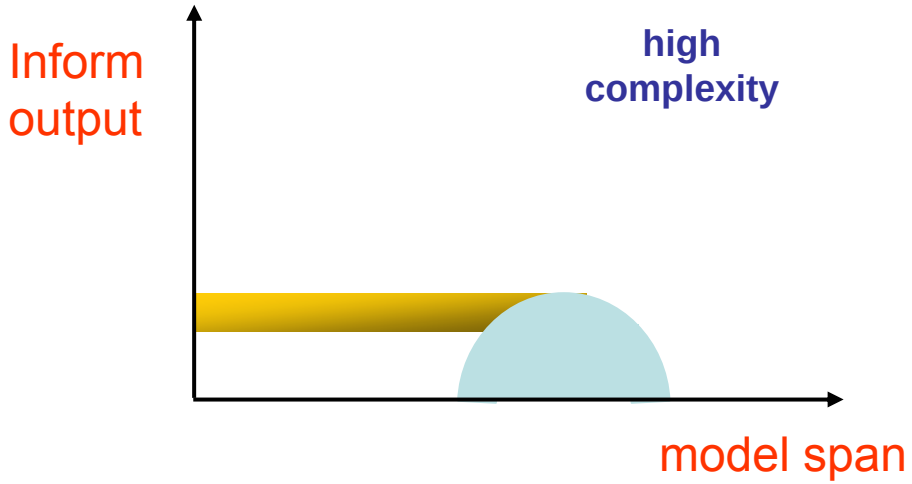
The more accurate (looser) the definition of the objects belonging to a certain class

the simpler (more complicated) the model

the sharper (more involved) its mathematical description

the more precise (fuzzier) the information output





Key questions at this point are

Q1: What is complexity?
A1: Its meaning is context dependent

Q2: Are biosystems complex objects?
A2: Looks like they are

1. Algorithmic Complexity of Kolmogorov and Chaitin

- Definition:

Given a string *S* of **N** symbols → **AC** = # of bits of a T.M. code that can produce *S* as an output

- Such a definition does not look interesting for us

AC (random string) >> AC (π)

AC (random string) ~ **N**

AC (π) ~ log **N** [actually the digits of π are totally random]

2. Logical depth of Bennett

- Definition:

Given a string *S* of **N** symbols → **LD** = time (# of operation) for a T.M. to run the shortest code that can produce *S* as an output

- A somewhat more interesting definition

LD (random string) $\propto$ time to read *S* ~ **N**

LD (π) $\propto$ time to generate π ~ **N**

Biological Complexity

- is not **randomness** → Box of molecules with random velocities

S=large

S=0

- is not **entropy** → Box of molecules with all parallel velocities
- is not **logical depth** → Life emerged from a very short (random) program, but it took 10^9 y to run the code: very high LD! What about running the code today?

Then what is it?

Necessary conditions

- many variables
- many relevant dof's

Here a bit of “phenomenology” starts

Numerosity

	# of elementary constituents (atoms)
ATOM	1
AMINO ACID	10
PROTEIN	10^3-10^5
CELL	10^{10}
.	
.	
.	
HUMAN BODY	5×10^{28} (nucleons)

Numerosity and Heterogeneity

- Proteins
  - 10^2 -10^3 amino acids
  - 10^3 -10^5 atoms → (only ~10^7 expressed)
  - 20^{300} different possible sequences!
- Immune system
  - 10^6 actual repertoire of Ab's
  - 10^7 available repertoire
  - 10^8 lymphocytes
- Brain
  - 10^{10} neurons
  - x 10^3~10^4
  - 10^{13}-10^{14} synapses
- Genoma
  - $3x10^9$ bases (human DNA)
  - 4^n with $n = 3x10^9$ possible genomes
  - (only 10^{60} expressed @ 1 mut/sec) Eigen

2-3 nm helix x 2 m long
2x23 chromosomes V~(1.5 μm)^3

It is not so much the number of "elementary" objects that is important (gas), but rather the existence of a large number of "functionally" relevant distinct components

- There is a lot of disorder in Biosystems

They have (~ ∞-ly) many randomly distributed microscopic variables and few (still very many!) mesoscopic variables controlling the system

Not every detail can be encoded in DNA, nor every Genoma has been tried

No optimal evolution

- There is a lot of redundancy in Biosystems

They can exist in very many "equilibrium/metastable" states

Individuals
Organs
Immune system states
Proteins

Microscopically different organs (harts, brains,…) equally well accomplish their task

High degeneracy

Complexity: here is a sort of "phenomenological" definition

The more one can say about a class of systems,
the more the systems of that class are complex

Complexity is complexity of classification

1. Sequences of random numbers

Not much can be said

all instances belong to the same class

⇒ It is a very simple class of systems

2. Equilibrium states of a system of spins at H = 0, T ~ 0

Only two states: spin up, spin down

⇒ It is a simple system

3. Class of sequences of symbols giving rise to “books”

Many things can be said

Language	⇒	English, Italian, German, ...
Style	⇒	Poem, Tragedy, ...
Plot	⇒	Love story, Detective story, ...
...	⇒	...

Many “description levels” or tasks	⇒	Various possible “types of classification”

It is a complex class of systems

4. Set of painters

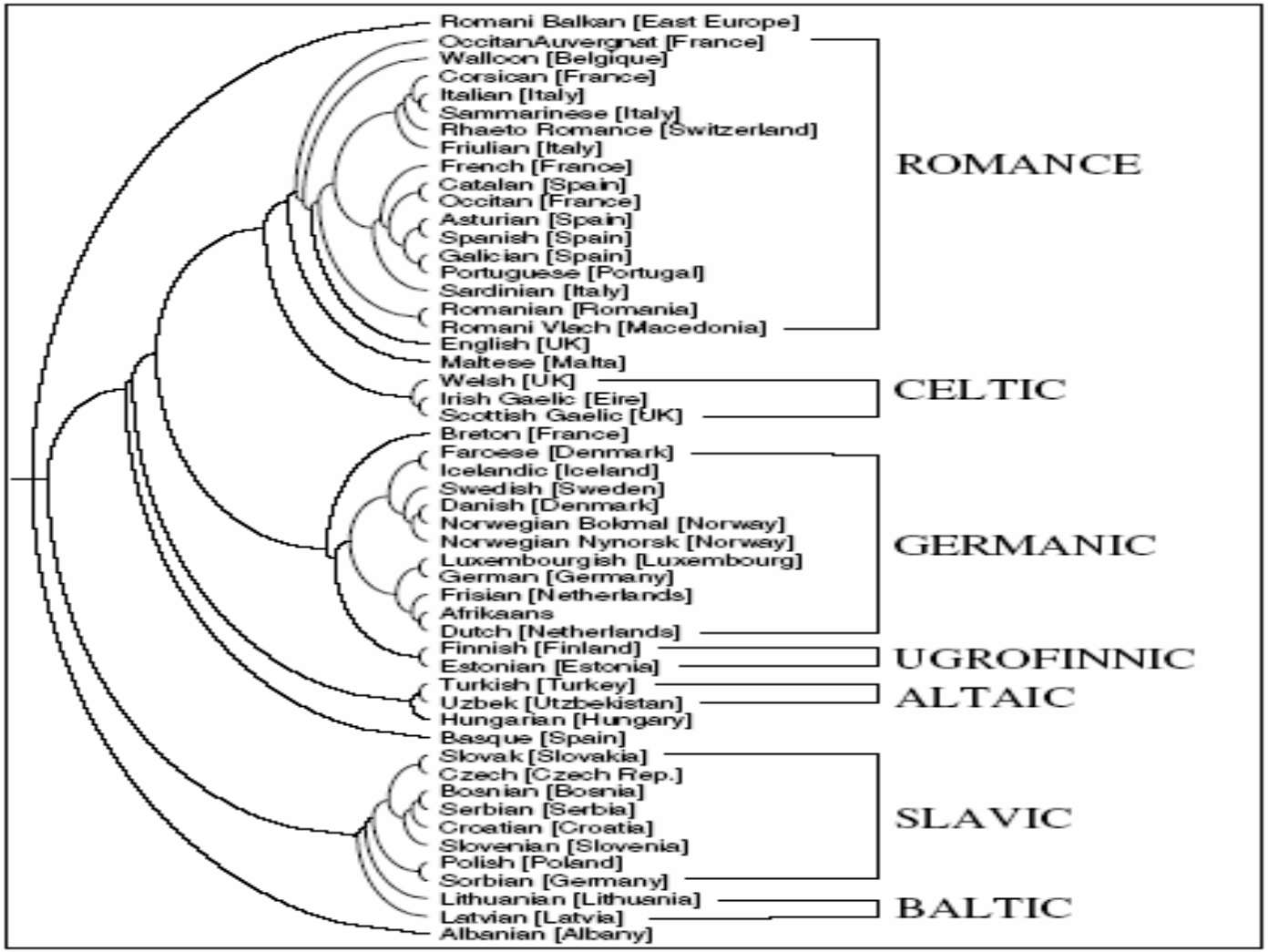
We could learn a lot, if we could establish

When they were active	⇒	Date of birth
Where they were active	⇒	Place of birth
Their style	⇒	Relative influence
...	⇒	...

Many “description levels” or tasks	⇒	Various possible “types of classification”

It is a complex class of systems

5. The class of human languages is a complex system



Evolutive tree

Cavalli Sforza
Piazza Menozzi
Mountain

Correlating Genetic Tree and Linguistic Phyla

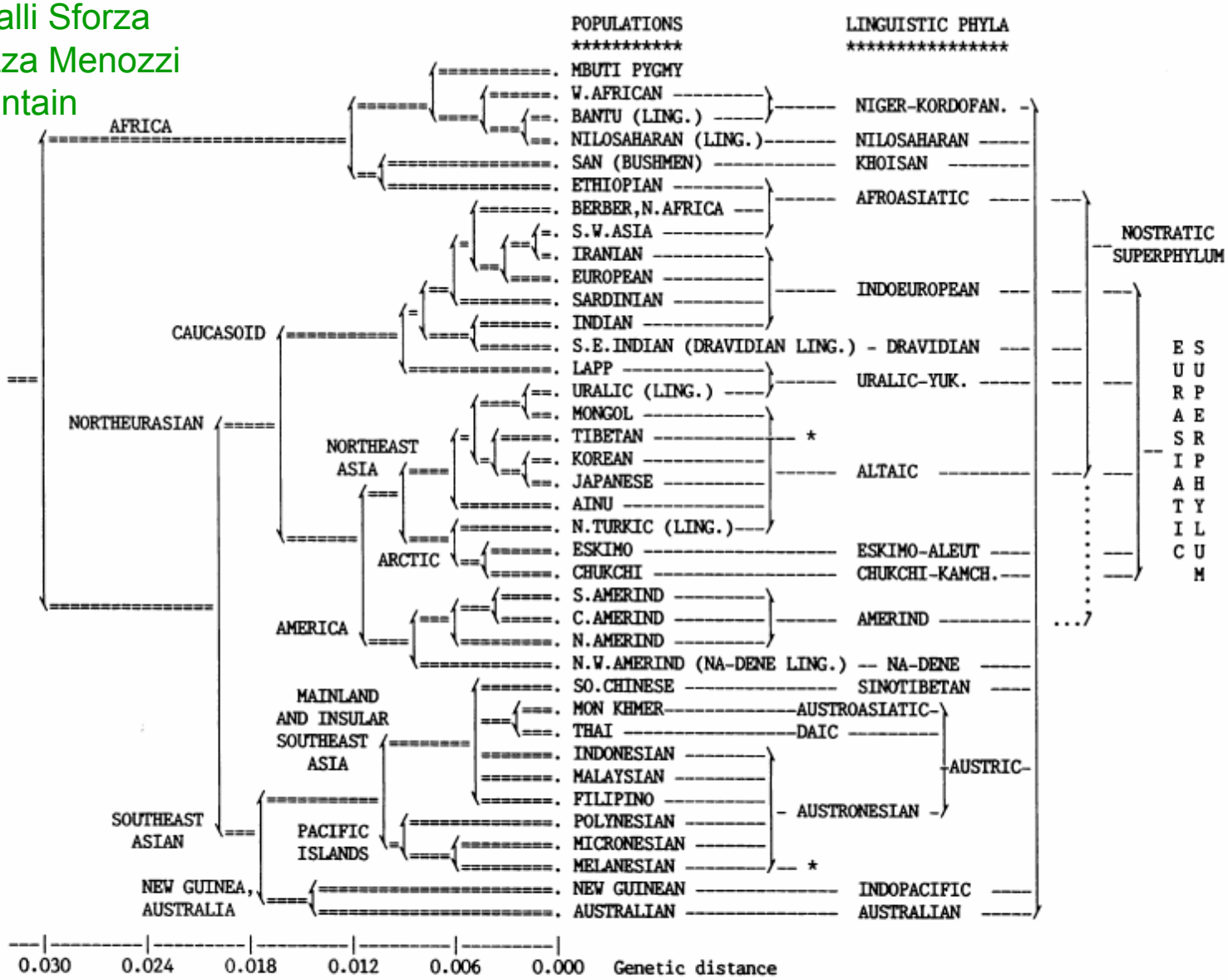
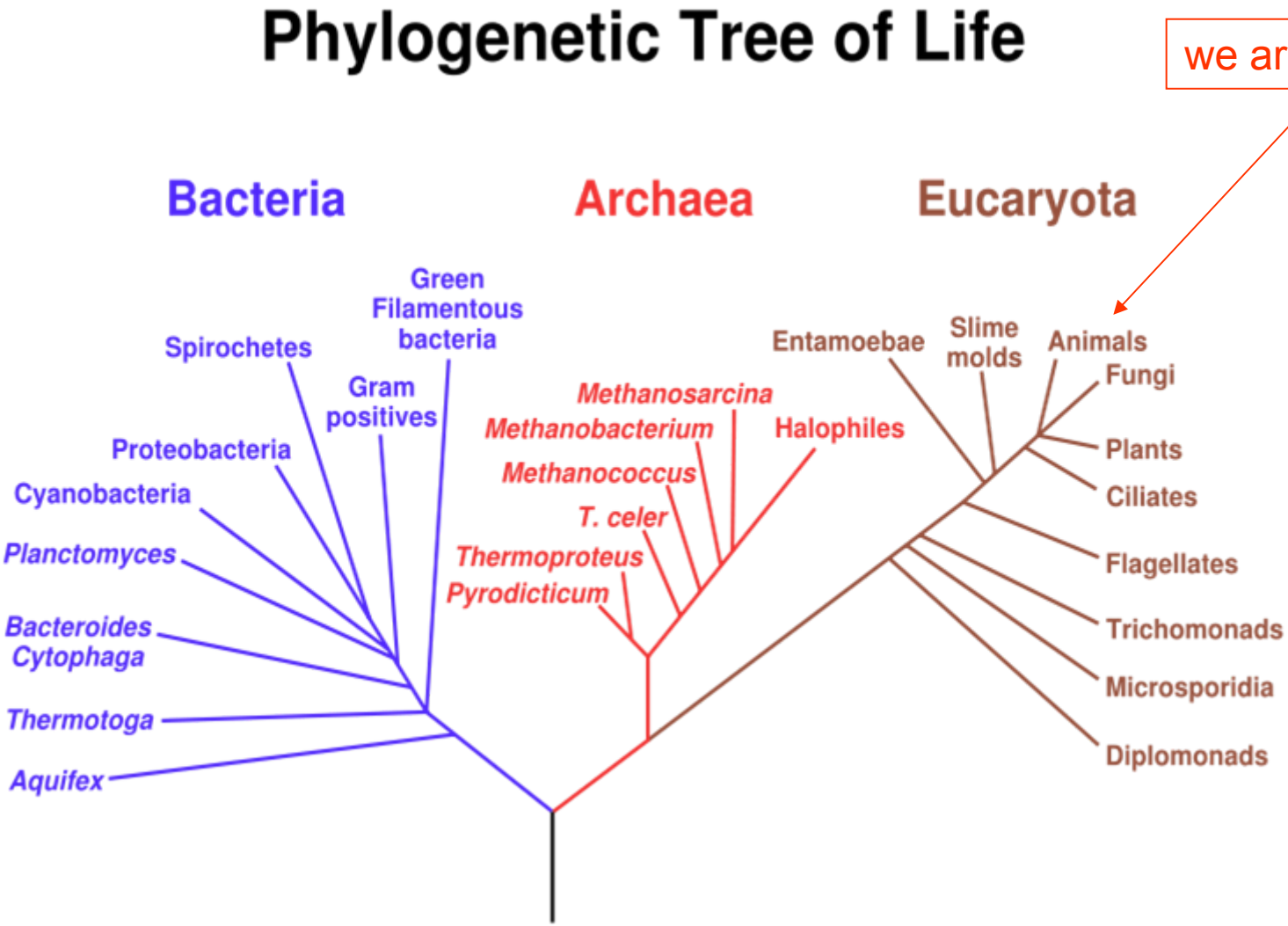
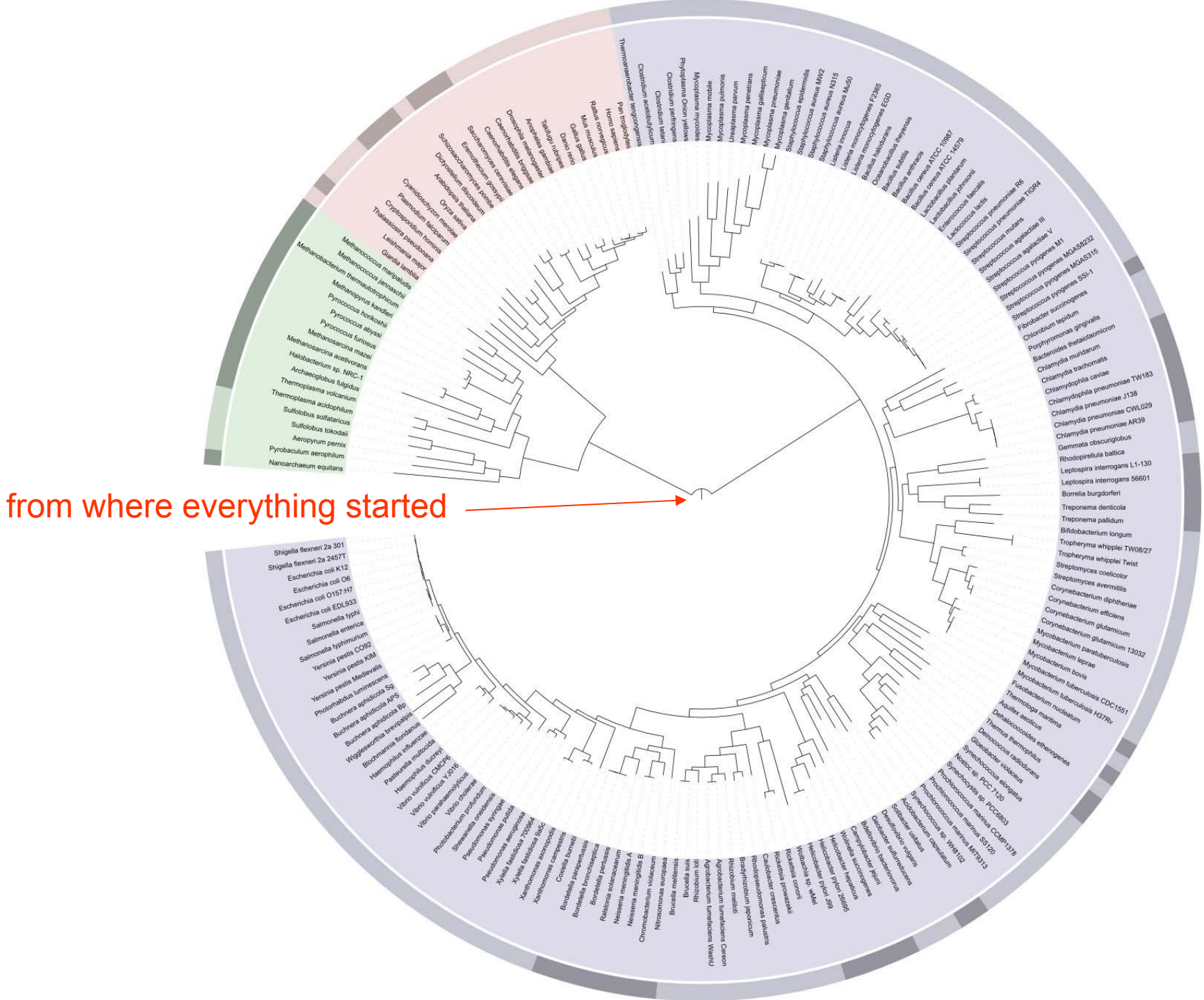


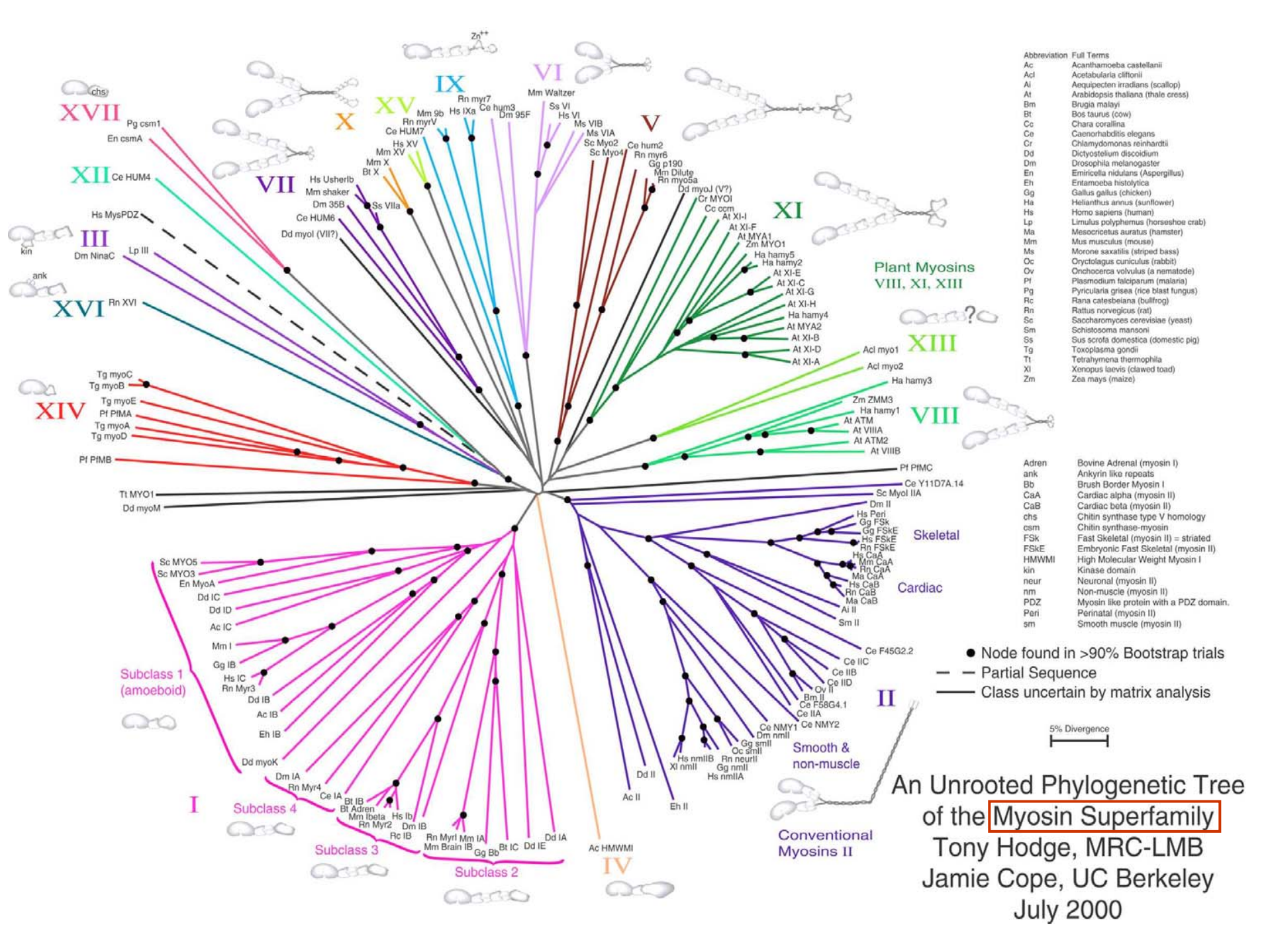
FIG. 1. Comparison of genetic tree and linguistic phyla. See text for details. (Ling.) indicates populations pooled on the basis of linguistic classification. The tree was constructed by average linkage analysis of Nei's genetic distances. Distances were calculated based on 120 allele frequencies from the following systems: *A1A2BO, MNS, RH, P, LU, K, FY, JK, DI, HP, TF, GC, LE, LP, PEPA, PEPB, PEPC, AG, HLAA* (12 alleles), *HLAB* (17 alleles), *PI, CP, ACP, PGD, PGM1, MDH, ADA, PTC, EI, SODA, GPT, PGK, C3, SE, ESD, GLO, KM, BF, LAD, E2, GM*, and *PG*.

6. The set of living organisms on the Earth is a complex system

temporal evolutive tree




from where everything started
Thermoanaerobacter tengcongensis
Pan troglodytes
Homo sapiens
Rattus norvegicus
Mus musculus
Gallus gallus
Danio rerio
Takifugu rubripes
Drosophila melanogaster
Anopheles gambiae
Caenorhabditis briggsae
Caenorhabditis elegans
Saccharomyces cerevisiae
Eremothecium gossypii
Schizosaccharomyces pombe
Dictyostelium discoideum
Arabidopsis thaliana
Oryza sativa
Cyanidioschyzon merolae
Plasmodium falciparum
Cryptosporidium hominis
Thalassiosira pseudonana
Leishmania major
Giardia lamblia
Methanococcus maripaludis
Methanococcus jannaschii
Methanobacterium thermautotrophicum
Methanopyrus kandleri
Pyrococcus horikoshii
Pyrococcus abyssi
Pyrococcus furiosus
Methanosarcina mazei
Methanosarcina acetivorans
Halobacterium sp. NRC-1
Archaeoglobus fulgidus
Thermoplasma volcanium
Thermoplasma acidophilum
Sulfolobus solfataricus
Sulfolobus tokodaii
Aeropyrum pernix
Pyrobaculum aerophilum
Nanoarchaeum equitans
Clostridium acetobutylicum
Clostridium tetani
Clostridium perfringens
Phytoplasma Onion yellows
Mycoplasma mycoides
Mycoplasma mobile
Mycoplasma pulmonis
Ureaplasma parvum
Mycoplasma penetrans
Mycoplasma gallisepticum
Mycoplasma pneumoniae
Mycoplasma genitalium
Staphylococcus epidermidis
Staphylococcus aureus MW2
Staphylococcus aureus N315
Staphylococcus aureus Mu50
Listeria innocua
Listeria monocytogenes F2365
Listeria monocytogenes EGD
Bacillus halodurans
Oceanobacillus iheyensis
Bacillus subtilis
Bacillus anthracis
Bacillus cereus ATCC 10987
Bacillus cereus ATCC 14579
Lactobacillus plantarum
Lactobacillus johnsonii
Enterococcus faecalis
Lactococcus lactis
Streptococcus pneumoniae R6
Streptococcus pneumoniae TIGR4
Streptococcus mutans
Streptococcus agalactiae III
Streptococcus agalactiae V
Streptococcus pyogenes M1
Streptococcus pyogenes MGAS8232
Streptococcus pyogenes MGAS315
Streptococcus pyogenes SSI-1
Streptococcus suis
Streptococcus succinogenes
Fibrobacter succinogenes
Chlorobium tepidum
Porphyromonas gingivalis
Bacteroides thetaiotaomicron
Chlamydia muridarum
Chlamydia trachomatis
Chlamydophila caviae
Chlamydophila pneumoniae TW183
Chlamydia pneumoniae J138
Chlamydia pneumoniae CWL029
Chlamydia pneumoniae AR39
Gemmata obscuriglobus
Rhodopirellula baltica
Leptospira interrogans L1-130
Leptospira interrogans 56601
Borrelia burgdorferi
Treponema denticola
Treponema pallidum
Bifidobacterium longum
Tropheryma whipplei TW08/27
Tropheryma whipplei Twist
Streptomyces coelicolor
Streptomyces avermitilis
Corynebacterium diphtheriae
Corynebacterium efficiens
Corynebacterium glutamicum
Corynebacterium glutamicum 13032
Mycobacterium paratuberculosis
Mycobacterium bovis
Mycobacterium leprae
Mycobacterium tuberculosis CDC1551
Mycobacterium tuberculosis H37Rv
Fusobacterium nucleatum
Thermotoga maritima
Aquifex aeolicus
Dehalococcoides ethenogenes
Thermus thermophilus
Deinococcus radiodurans
Gloeobacter violaceus
Synechococcus elongatus
Nostoc sp. PCC 7120
Synechocystis sp. PCC6803
Prochlorococcus marinus CCMP1378
Prochlorococcus marinus MIT9313
Prochlorococcus marinus SS120
Synechococcus sp. WH8102
Acidobacterium capsulatum
Silicibacter pomeroyi
Silicibacter sulfexigens
Desulfovibrio vulgaris
Geobacter sulfurreducens
Bdellovibrio bacteriovorus
Campylobacter jejuni
Wolinella succinogenes
Helicobacter hepaticus
Helicobacter pylori 26695
Helicobacter pylori J99
Wolbachia sp. wMel
Rickettsia conorii
Rickettsia prowazekii
Caulobacter crescentus
Rhodopseudomonas palustris
Bradyrhizobium japonicum
Rhizobium meliloti
Agrobacterium tumefaciens Cereon
Agrobacterium tumefaciens WashU
Brucella suis
Brucella melitensis
Ochrobactrum anthropi
Nitrosomonas europaea
Chromobacterium violaceum
Neisseria meningitidis A
Neisseria meningitidis B
Ralstonia solanacearum
Bordetella pertussis
Bordetella bronchiseptica
Bordetella parapertussis
Coxiella burnetii
Xanthomonas campestris
Xanthomonas axonopodis
Xylella fastidiosa 9a5c
Xylella fastidiosa 700964
Pseudomonas aeruginosa
Pseudomonas putida
Pseudomonas syringae
Shewanella oneidensis
Photobacterium profundum
Vibrio cholerae
Vibrio parahaemolyticus
Vibrio vulnificus YJ016
Vibrio vulnificus CMCP6
Pasteurella multocida
Haemophilus ducreyi
Haemophilus influenzae
Blochmannia floridanus
Wigglesworthia brevipalpis
Buchnera aphidicola Bp
Buchnera aphidicola APS
Buchnera aphidicola Sg
Photorhabdus luminescens
Yersinia pestis Medievalis
Yersinia pestis KIM
Yersinia pestis CO92
Salmonella typhimurium
Salmonella enterica
Salmonella typhi
Escherichia coli EDL933
Escherichia coli O157:H7
Escherichia coli O6
Escherichia coli K12
Shigella flexneri 2a 2457T
Shigella flexneri 2a 301


Zn++
chs
XVII
Pg csm1
En csmA
XII
Ce HUM4
Hs MysPDZ
III
kin
Dm NinaC
Lp III
ank
XVI
Rn XVI
XIV
Tg myoC
Tg myoB
Tg myoE
Pf PfMA
Tg myoA
Tg myoD
Pf PfMB
Tt MYO1
Dd myoM
Sc MYO5
Sc MYO3
En MyoA
Dd IC
Dd ID
Ac IC
Mm I
Gg IB
Hs IC
Rn Myr3
Dd IB
Ac IB
Eh IB
Dd myoK
Subclass 1
(amoeboid)
I
Dm IA
Rn Myr4
Ce IA
Bt IB
Bt Adren
Mm Ibeta
Hs Ib
Rn Myr2
Dm IB
Rc IB
Subclass 4
Subclass 3
Rn MyrI
Mm Brain IB
Mm IA
Gg Bb
Bt IC
Dd IE
Dd IA
Subclass 2
X
IX
XV
Rn myr7
Hs IXa
Ce hum3
Dm 95F
Mm 9b
Rn myrV
Ce HUM7
Hs XV
Mm XV
Mm X
Bt X
VII
Hs Usherlb
Mm shaker
Dm 35B
Ss VIIa
Ce HUM6
Dd myoI (VII?)
VI
Mm Waltzer
Ss VI
Hs VI
Ms VIB
Ms VIA
V
Sc Myo2
Sc Myo4
Ce hum2
Rn myr6
Gg p190
Mm Dilute
Rn myo5a
Dd myoJ (V?)
Cr MYOI
Cc ccm
XI
At XI-I
At XI-F
At MYA1
Zm MYO1
Ha hamy5
Ha hamy2
At XI-E
At XI-C
At XI-G
At XI-H
Ha hamy4
At MYA2
At XI-B
At XI-D
At XI-A
Plant Myosins
VIII, XI, XIII
?
XIII
Acl myo1
Acl myo2
Ha hamy3
Zm ZMM3
Ha hamy1
VIII
At ATM
At VIIIA
At ATM2
At VIIIB
Pf PfMC
Ce Y11D7A.14
Sc MyoI IIA
Dm II
Hs Peri
Gg FSk
Gg FSkE
Hs FSkE
Rn FSkE
Hs CaA
Mm CaA
Rn CaA
Ma CaA
Hs CaB
Rn CaB
Ma CaB
Al II
Sm II
Skeletal
Cardiac
Ce F45G2.2
Ce IIC
Ce IIB
Ce IID
Ov II
Bm II
Ce F58G4.1
Ce IIA
Ce NMY2
Ce NMY1
Dm nmII
Gg smII
Oc smII
Hs nmIIB
Xl nmII
Rn neurII
Gg nmII
Hs nmIIA
Smooth &
non-muscle
II
Dd II
Ac II
Eh II
Conventional
Myosins II
Ac HMWMI
IV
Abbreviation Full Terms
Ac Acanthamoeba castellanii
Acl Acetabularia cliftonii
Ai Aequipecten irradians (scallop)
At Arabidopsis thaliana (thale cress)
Bm Brugia malayi
Bt Bos taurus (cow)
Cc Chara corallina
Ce Caenorhabditis elegans
Cr Chlamydomonas reinhardtii
Dd Dictyostelium discoidium
Dm Drosophila melanogaster
En Emiricella nidulans (Aspergillus)
Eh Entamoeba histolytica
Gg Gallus gallus (chicken)
Ha Helianthus annus (sunflower)
Hs Homo sapiens (human)
Lp Limulus polyphemus (horseshoe crab)
Ma Mesocricetus auratus (hamster)
Mm Mus musculus (mouse)
Ms Morone saxatilis (striped bass)
Oc Oryctolagus cuniculus (rabbit)
Ov Onchocerca volvulus (a nematode)
Pf Plasmodium falciparum (malaria)
Pg Pyricularia grisea (rice blast fungus)
Rc Rana catesbeiana (bullfrog)
Rn Rattus norvegicus (rat)
Sc Saccharomyces cerevisiae (yeast)
Sm Schistosoma mansoni
Ss Sus scrofa domestica (domestic pig)
Tg Toxoplasma gondii
Tt Tetrahymena thermophila
Xl Xenopus laevis (clawed toad)
Zm Zea mays (maize)
Adren Bovine Adrenal (myosin I)
ank Ankyrin like repeats
Bb Brush Border Myosin I
CaA Cardiac alpha (myosin II)
CaB Cardiac beta (myosin II)
chs Chitin synthase type V homology
csm Chitin synthase-myosin
FSk Fast Skeletal (myosin II) = striated
FSkE Embryonic Fast Skeletal (myosin II)
HMWMI High Molecular Weight Myosin I
kin Kinase domain
neur Neuronal (myosin II)
nm Non-muscle (myosin II)
PDZ Myosin like protein with a PDZ domain.
Peri Perinatal (myosin II)
sm Smooth muscle (myosin II)
● Node found in >90% Bootstrap trials
– – Partial Sequence
—— Class uncertain by matrix analysis
5% Divergence
An Unrooted Phylogenetic Tree
of the Myosin Superfamily
Tony Hodge, MRC-LMB
Jamie Cope, UC Berkeley
July 2000

Biological systems and Spin glasses

Biosystems

Disorder

very many random variables,
few dynamical (relevant) dof's

Degeneracy

can exist in very many "equilibrium" states

Spin glasses

Disorder

random coupling among spins

Frustration

within triplets of spins

Complexity of classification

Spin glasses: a suggestive paradigm for biosystems

Protein folding (see below)	Iori Marinari Parisi
Associative memory	Hopfield
Scaling laws in taxonomy	Mezard Parisi Virasoro
Immune system memory and stability	Parisi
…	

A Spin glass Primer

- N individuals interacts pairwise with couplings

  $J_{AB}=+1$ if A likes B
  $J_{AB}=-1$ if A dislikes B

- Given 3 individuals, there is frustration if

  $J_{AB}\, J_{BC}\, J_{CA} = -1$

- The N individuals are asked to separate in 2 fields so as to minimize in each field the number of pairs of "enemies"

- Given a J-PDF and an initial subdivision, "equilibrium" is reached by asking each individual to decide to change field if the move lowers the frustration

- If many pairs are frustrated { system is highly unstable ↓ many possible equally good subdivisions

A locally optimal state is reached in polynomial time

A globally optimal state (if it can be reached at all) generically requires an exponential time (NP-problem)

An illuminating example

- M likes M W likes W
  M dislikes W W dislikes M

For any triplet $J^3=+1$
No frustration

⇒ Optimal state: 2 separate groups, [M] and [W]

- M dislikes M W dislikes W
  M likes W W likes M

For any triplet $J^3=-1$
Maximal frustration

⇒ Optimal state: any subdivision with equal number of M and W

Further examples of interesting physical systems

- Alloys, like $Fe_x\ Au_{100-x}$, with small x % → $H = \Sigma_{ik}\ \sigma_i\ J(|x_i-x_k|)\ \sigma_k$
  $J(|x_i-x_k|)$ very rapidly oscillating with $|x_i-x_k|$, almost a random function

- Electrons moving in a metallic glass, containing various types of atoms, located at fixed but random positions

⇒ We expect the electron conducibility not to depend on the detailed positions of the impurities (for not too small samples)

$H_{SG} = \Sigma_{ik}\ \sigma_i\ J_{ik}\ \sigma_k$, with some PDF for the J_{ik}

Basic Mathematics

Sherrington
Kirkpatrick
Parisi

- Hamiltonian

$$H_J[\sigma] = \Sigma_{ik}\, \sigma_i\, J_{ik}\, \sigma_k \qquad J_{ik} = J_{ki}\,,\; J_{ii} = 0$$

  - J_{ik} are random variables with PDF $\Rightarrow P(J)$

- Partition Function and Free Energy at fixed $P(J)$

$$Z_J = \Sigma_{[\sigma]} \exp -\beta\, H_J[\sigma] \qquad \beta = 1/KT$$

$$F_J = -\frac{1}{\beta N} \log Z_J$$

  - N is the number of spins

- We want to compute the quenched average

$$F = \Sigma_J\, P(J)\, F_J = -\frac{1}{\beta N} \Sigma_J\, P(J) \log Z_J$$

and not the annealed average

$$F_{An} = -\frac{1}{\beta N} \log Z_{An} \qquad Z_{An} = \Sigma_J\, P(J)\, \Sigma_{[\sigma]} \exp -\beta\, H_J[\sigma]$$

  - time scale of J-dynamics >> time scale of σ-dynamics

The Replica Method

$$Z_n \equiv \Sigma_J P(J)\,(Z_J)^n$$

$$\Rightarrow \qquad \lim_{n\to 0} F_n = F$$

$$F_n = -\frac{1}{\beta N}\frac{1}{n}\log Z_n$$

the replica index

A simple proof

$$\lim_{n\to 0} -\frac{1}{\beta N}\frac{1}{n}\log Z_n = \lim_{n\to 0} \boxed{-\frac{1}{\beta N}\frac{1}{n}\log\left[\Sigma_J P(J)\,(Z_J)^n\right]} =$$

$$= \lim_{n\to 0} -\frac{1}{\beta N}\frac{1}{n}\log\left[\Sigma_J P(J)\,(1+n\log Z_J + \ldots)\right] =$$

$$= \lim_{n\to 0} -\frac{1}{\beta N}\frac{1}{n}\log\left[1+n\,\Sigma_J P(J)\log Z_J + \ldots)\right] =$$

$$= -\frac{1}{\beta N}\Sigma_J P(J)\log Z_J = F$$

looks OK, except that n is an integer…

Typical P(J)'s

Gaussian: $P(J) \propto \exp[-(J-J_0)^2/2\sigma_J^2]$

Uniform: $P(J=+1) = P(J=-1) = 1/2$

Phase structure

Edwards
Anderson

$$m_i(J) = \langle \sigma_i \rangle = \Sigma_{[\sigma]}\, \sigma_i \exp -\beta H_J[\sigma]$$

$$q(J) = \frac{1}{N} \Sigma_i [m_i(J)]^2 = \Sigma_J P(J) [m_i(J)]^2 = q$$

self-averaging

High temperature $m_i(J) = 0 \Rightarrow q = 0$

Low temperature

$m_i(J) \neq 0$ for some i

with $\Sigma_i [m_i(J)] = 0$, but

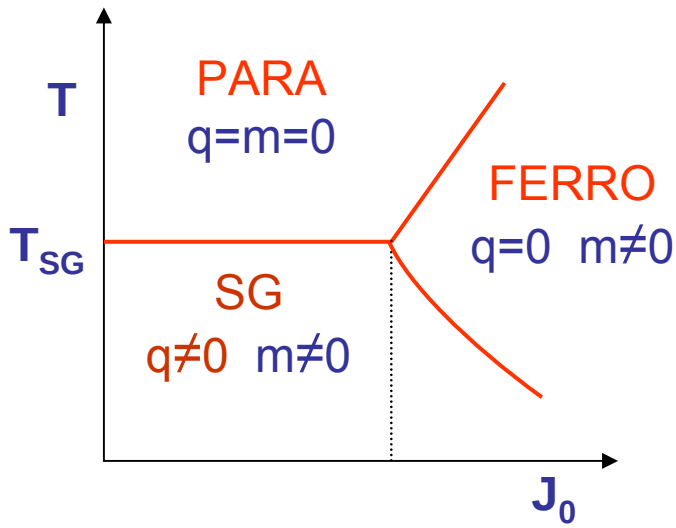
$q(J) = \frac{1}{N} \Sigma_i [m_i(J)]^2 \neq 0$

self-averaging

Order parameters

$$q = \frac{1}{N} \Sigma_i [m_i(J)]^2$$

$$m = \frac{1}{N} \Sigma_i [m_i(J)]$$



The whole game is to compute P(q)

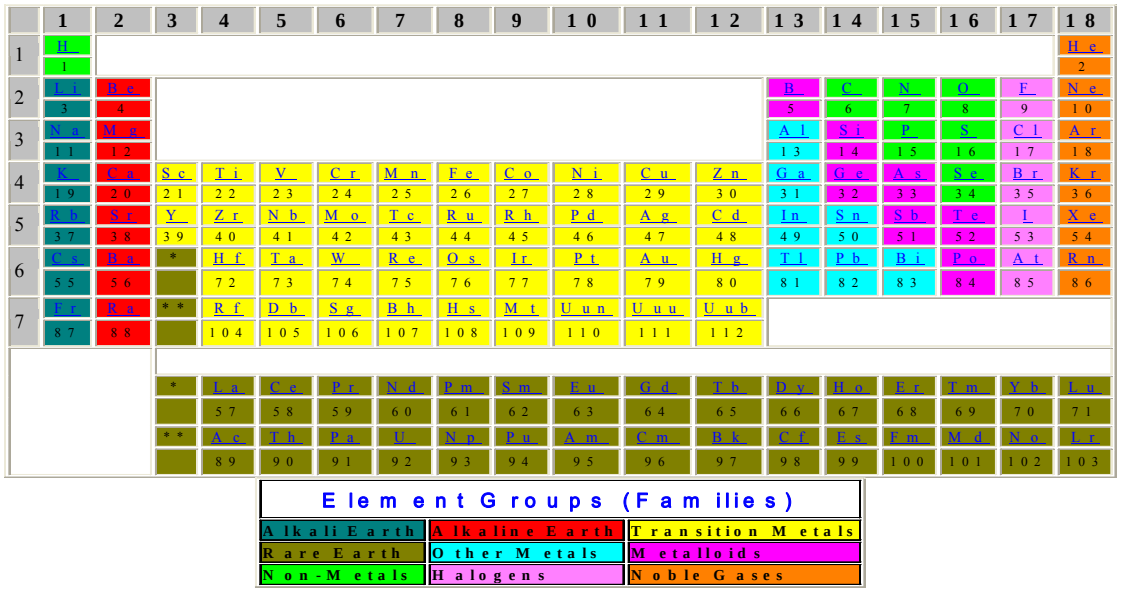
Few further numbers

dimensions
times
weights
chemical events

Human body: ~7 x 10^{27} atoms:
99% C, H, O and N; 87% are either H or O;
but 41 different elements

Estimated Atomic Composition of a lean 70 kg Male Human Body

Element	Sym		# Atoms	Element	Sym		# Atoms	Element	Sym		# Atoms
Hydrogen	H	1	4.22×10^{27}	Rubidium	Rb	37	2.2×10^{21}	Zirconium	Zr	40	2×10^{19}
Oxygen	O	8	1.61×10^{27}	Strontium	Sr	38	2.2×10^{21}	Cobalt	Co	27	2×10^{19}
Carbon	C	6	8.03×10^{26}	Bromine	Br	35	2×10^{21}	Cesium	Cs	55	7×10^{18}
Nitrogen	N	7	3.9×10^{25}	Aluminum	Al	13	1×10^{21}	Mercury	Hg	80	6×10^{18}
Calcium	Ca	20	1.6×10^{25}	Copper	Cu	29	7×10^{20}	Arsenic	As	33	6×10^{18}
Phosphorus	P	15	9.6×10^{24}	Lead	Pb	82	3×10^{20}	Chromium	Cr	24	6×10^{18}
Sulfur	S	16	2.6×10^{24}	Cadmium	Cd	48	3×10^{20}	Molybdenum	Mo	42	3×10^{18}
Sodium	Na	11	2.5×10^{24}	Boron	B	5	2×10^{20}	Selenium	Se	34	3×10^{18}
Potassium	K	19	2.2×10^{24}	Manganese	Mn	25	1×10^{20}	Beryllium	Be	4	3×10^{18}
Chlorine	Cl	17	1.6×10^{24}	Nickel	Ni	28	1×10^{20}	Vanadium	V	23	8×10^{17}
Magnesium	Mg	12	4.7×10^{23}	Lithium	Li	3	1×10^{20}	Uranium	U	92	2×10^{17}
Silicium	Si	14	3.9×10^{23}	Barium	Ba	56	8×10^{19}	Radium	Ra	88	8×10^{10}
Fluorine	F	9	8.3×10^{22}	Iodine	I	53	5×10^{19}				
Iron	Fe	26	4.5×10^{22}	Tin	Sn	50	4×10^{19}				
Zinc	Zn	30	2.1×10^{22}	Gold	Au	79	2×10^{19}	**TOTAL**			**6.71×10^{27}**



Estimated Molecular Content of a Typical 20-micron Human Cell

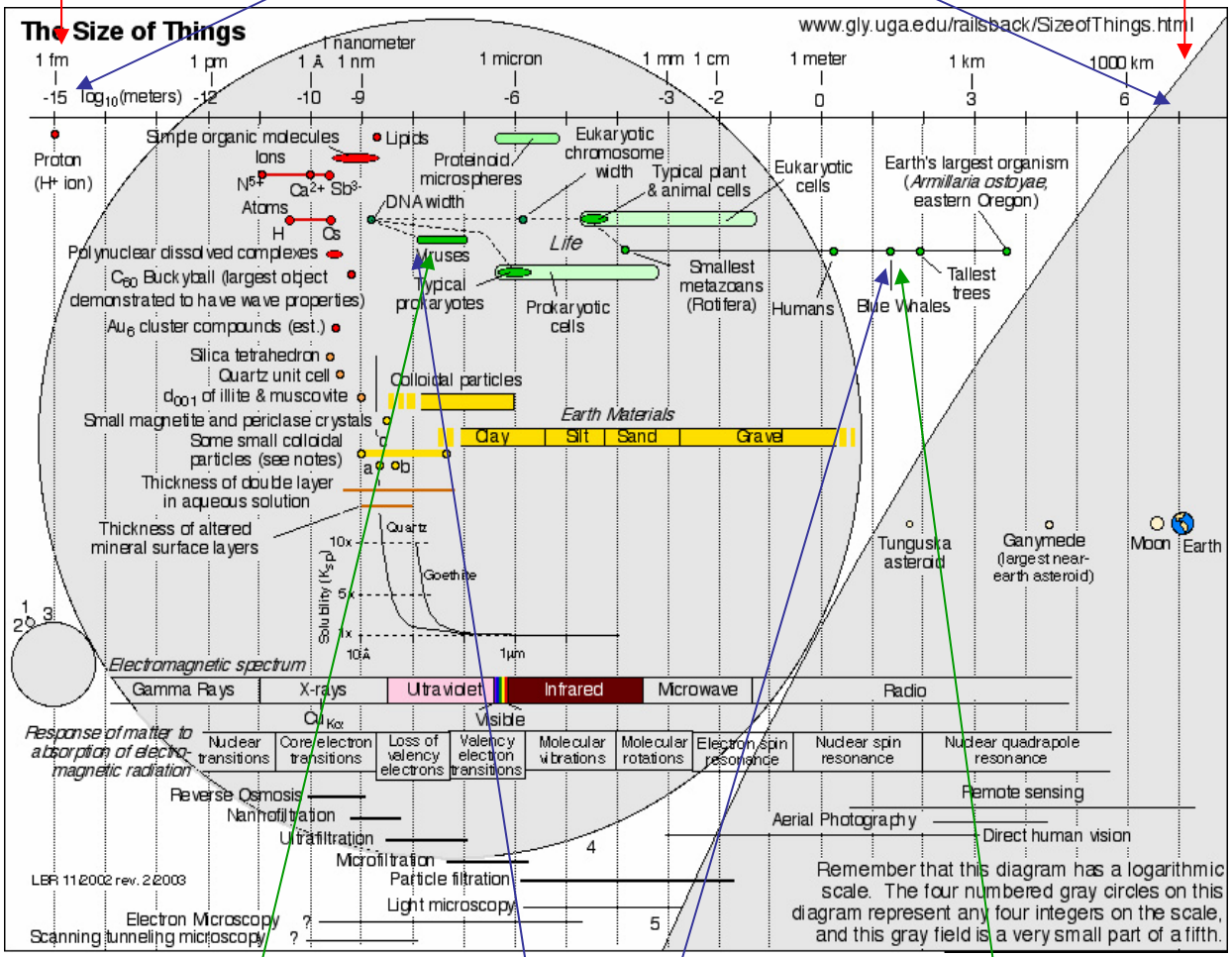
Molecule	Mass %	<MW> (Daltons)	# Molecules	Molecule %	# of Types
Water	65%	18	1.74×10^{14}	98.73 %	1
Other Inorganic	1.5%	55	1.31×10^{12}	0.74 %	20
Lipid	12%	700	8.4×10^{11}	0.475 %	50
Other Organic	0.4%	250	7.7×10^{10}	0.044 %	~200
Protein	20%	50,000	1.9×10^{10}	0.011 %	~5,000
RNA	1.0%	1×10^{6}	5×10^{7}	3×10^{-5} %	----
DNA	0.1%	1×10^{11}	46	3×10^{-11} %	----
TOTALS	100%	----	1.76×10^{14}	100%	----

1 Da (Dalton) = 1 atomic unit = $m_a(^{12}C)/(12 \times 1{,}660540\ 10^{-27}$ kg ~ hydrogen mass)
dimensionless unit

Proton

10^{22}

Earth

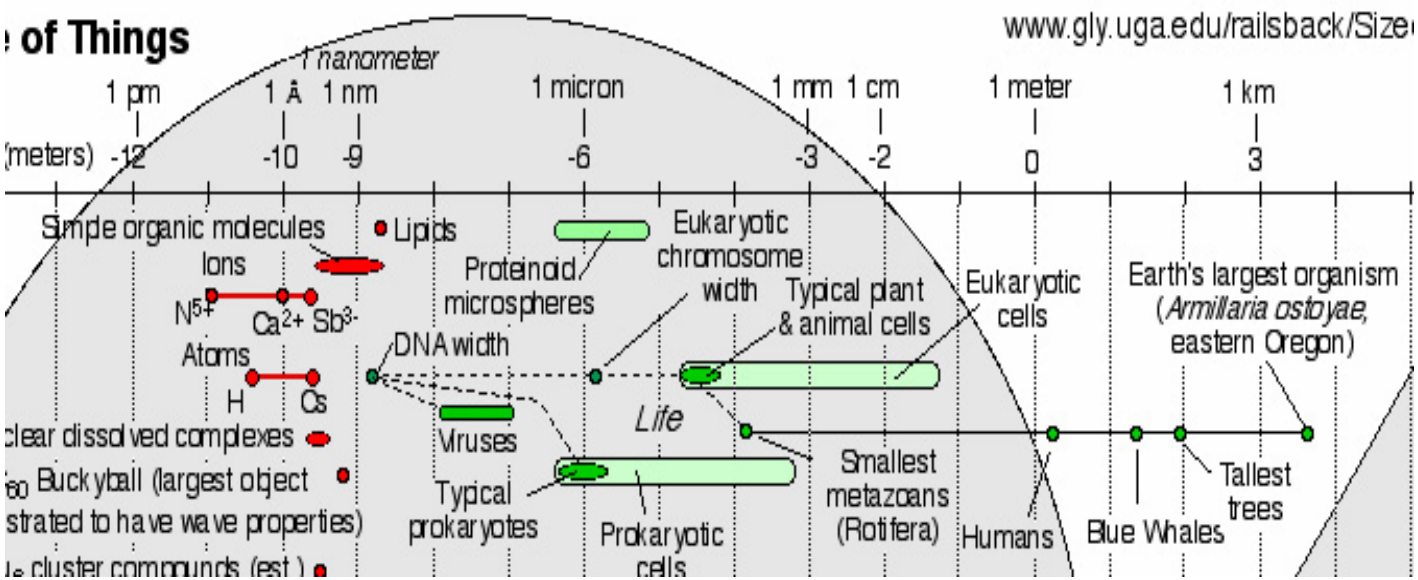


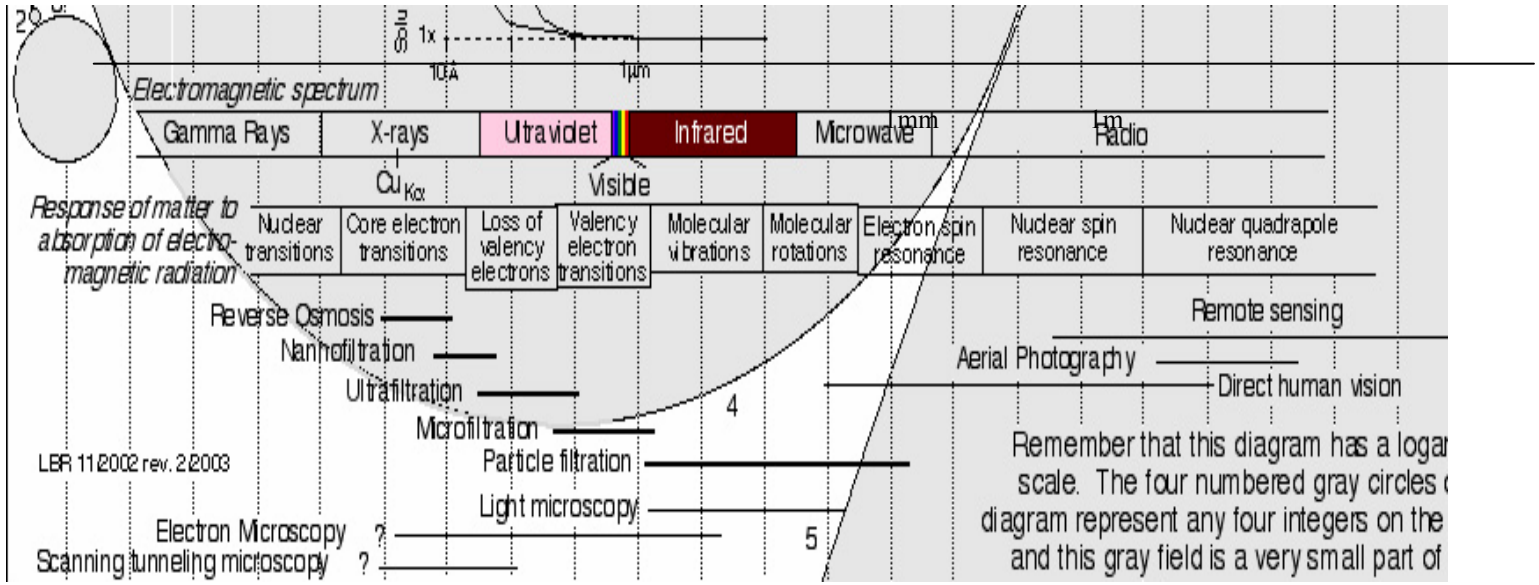
Virus

10^{9}

Blue whale

A blow up


of Things
www.gly.uga.edu/railsback/Size
1 nanometer
1 pm
1 Å
1 nm
1 micron
1 mm
1 cm
1 meter
1 km
(meters) -12
-10
-9
-6
-3
-2
0
3
Simple organic molecules
Lipids
Ions
Proteinoid microspheres
Eukaryotic chromosome width
Typical plant & animal cells
Eukaryotic cells
Earth's largest organism (Armillaria ostoyae, eastern Oregon)
Atoms
DNA width
Viruses
Life
Typical prokaryotes
Prokaryotic cells
Smallest metazoans (Rotifera)
Humans
Blue Whales
Tallest trees
Buckyball (largest object strated to have wave properties)


Electromagnetic spectrum
Gamma Rays
X-rays
Ultraviolet
Infrared
Microwave
Radio
Visible
Response of matter to absorption of electro-magnetic radiation
Nuclear transitions
Core electron transitions
Loss of valency electrons
Valency electron transitions
Molecular vibrations
Molecular rotations
Electron spin resonance
Nuclear spin resonance
Nuclear quadrapole resonance
Reverse Osmosis
Nanofiltration
Ultrafiltration
Microfiltration
Particle filtration
Light microscopy
Electron Microscopy
Scanning tunneling microscopy
Remote sensing
Aerial Photography
Direct human vision
LBR 11/2002 rev. 2/2003
Remember that this diagram has a logar
scale. The four numbered gray circles
diagram represent any four integers on the
and this gray field is a very small part of

The largest and smallest cells in the human body are the gametes or the sex cells

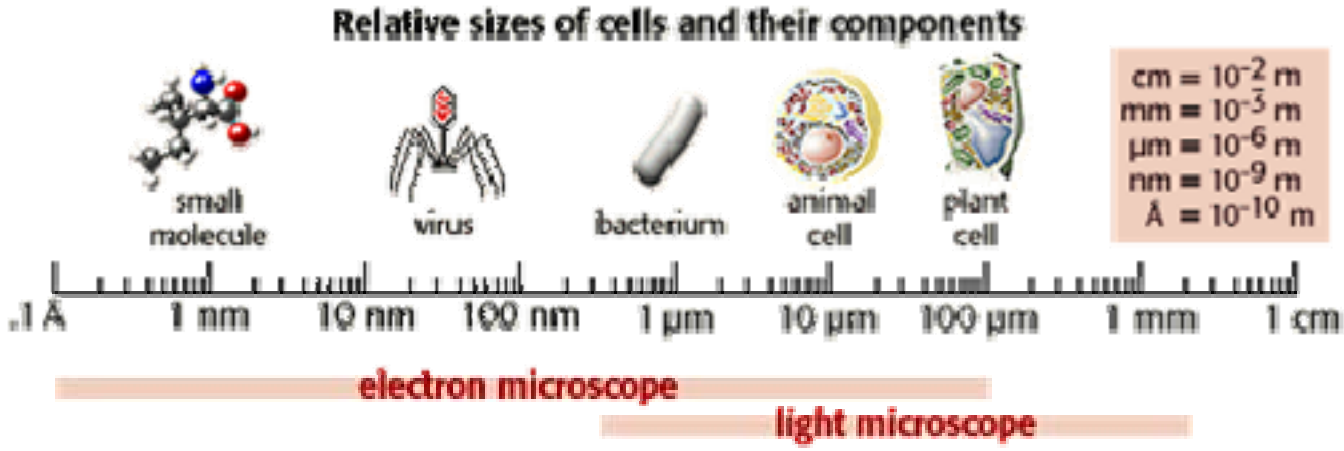
♀ **female = oocyte: Ø ≈ 35 μm (almost visible with the naked eye)**

♂ **male = spermatozoon: Ø ≈ 3 μm**

The smallest known organism capable of independent growth and reproduction

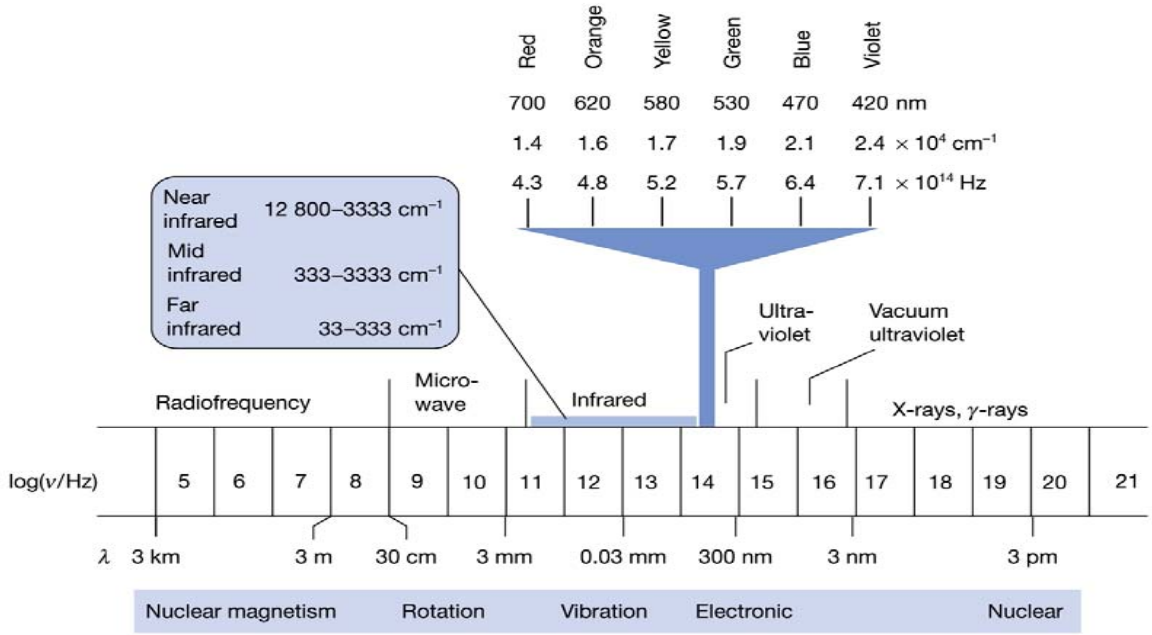
***Mycoplasma genitalium*: Ø ≈ 0.2 - 0.3 μm**

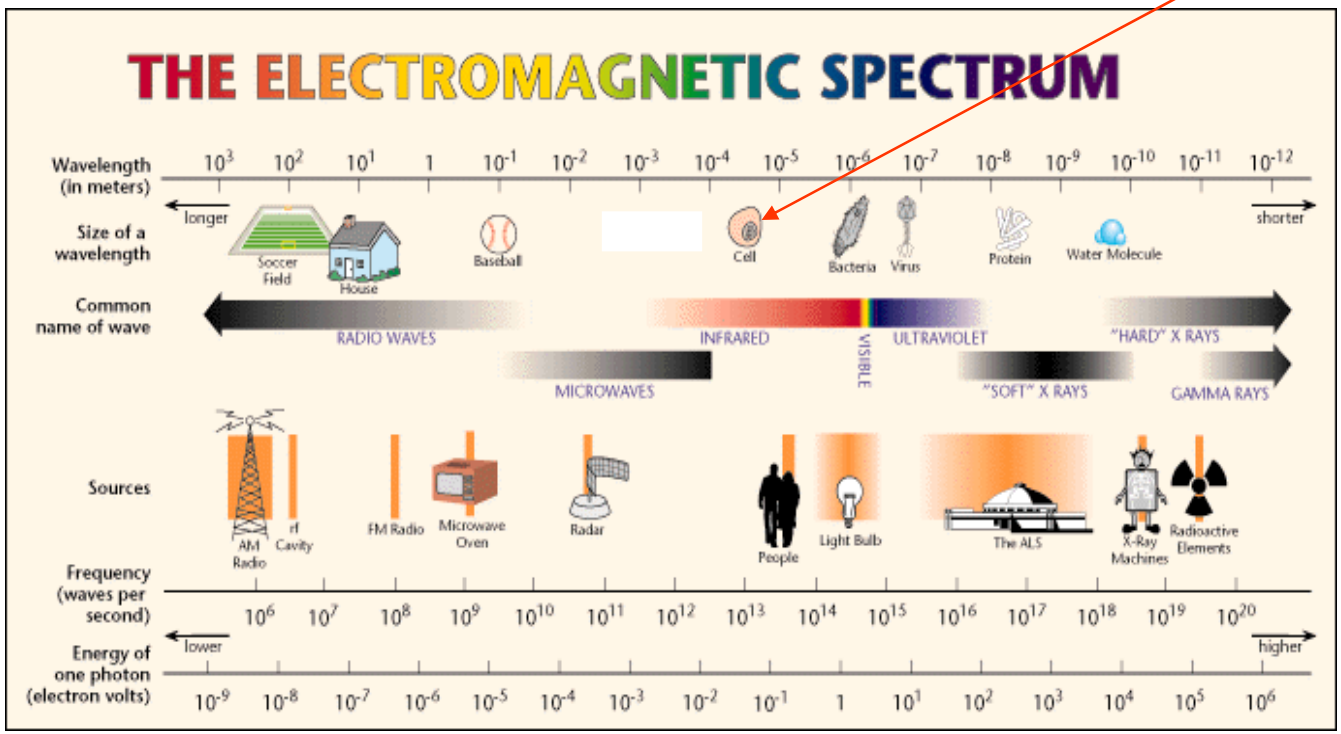
The smallest "theoretical" bacterium: Ø ≈ 0.17 μm



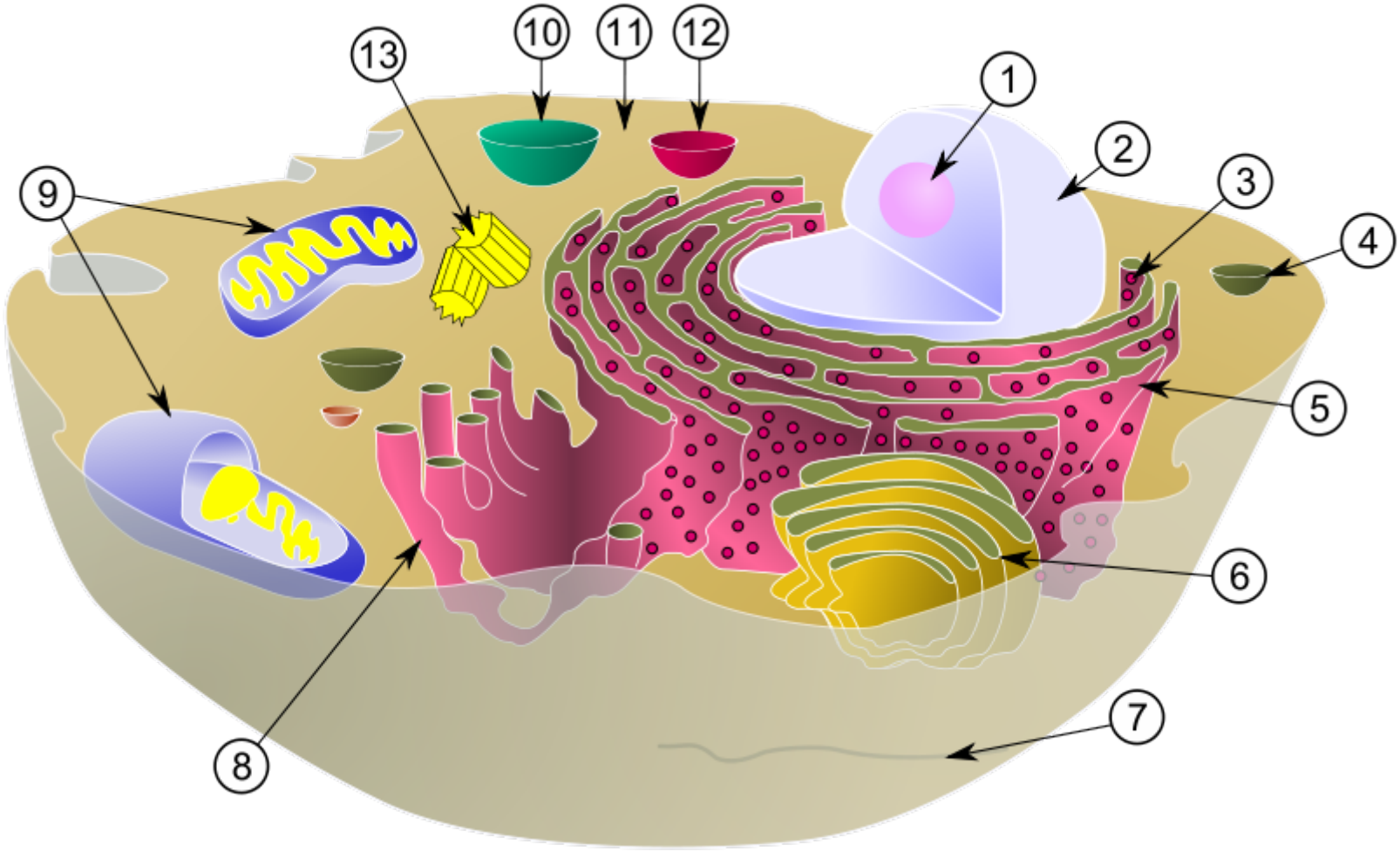
<Average bacterium>: rod shape V ≈ 1 μm² x 3 μm

<Average human cell>: spherical shape Ø ≈ 25 μm


Red
Orange
Yellow
Green
Blue
Violet
700 620 580 530 470 420 nm
1.4 1.6 1.7 1.9 2.1 2.4 × 10⁴ cm⁻¹
4.3 4.8 5.2 5.7 6.4 7.1 × 10¹⁴ Hz
Near infrared 12 800–3333 cm⁻¹
Mid infrared 333–3333 cm⁻¹
Far infrared 33–333 cm⁻¹
Ultra-violet
Vacuum ultraviolet
Radiofrequency
Micro-wave
Infrared
X-rays, γ-rays
log(ν/Hz)
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
λ 3 km 3 m 30 cm 3 mm 0.03 mm 300 nm 3 nm 3 pm
Nuclear magnetism
Rotation
Vibration
Electronic
Nuclear

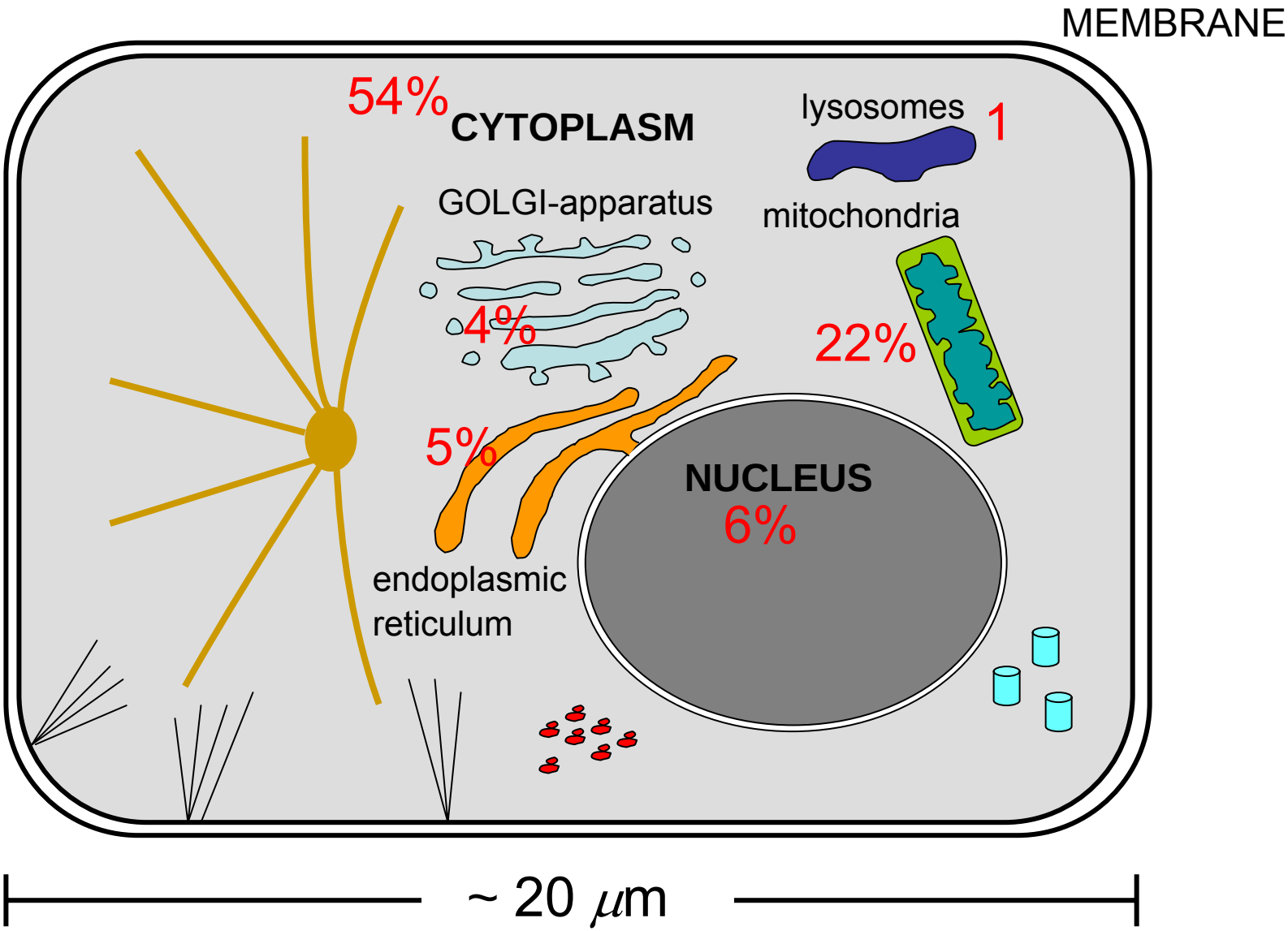

THE ELECTROMAGNETIC SPECTRUM
Wavelength (in meters)
longer
shorter
Size of a wavelength
Soccer Field
House
Baseball
Cell
Bacteria
Virus
Protein
Water Molecule
Common name of wave
RADIO WAVES
INFRARED
VISIBLE
ULTRAVIOLET
"HARD" X RAYS
MICROWAVES
"SOFT" X RAYS
GAMMA RAYS
Sources
AM Radio
rf Cavity
FM Radio
Microwave Oven
Radar
People
Light Bulb
The ALS
X-Ray Machines
Radioactive Elements
Frequency (waves per second)
lower
higher
Energy of one photon (electron volts)

A eukaryotic cell artistic view

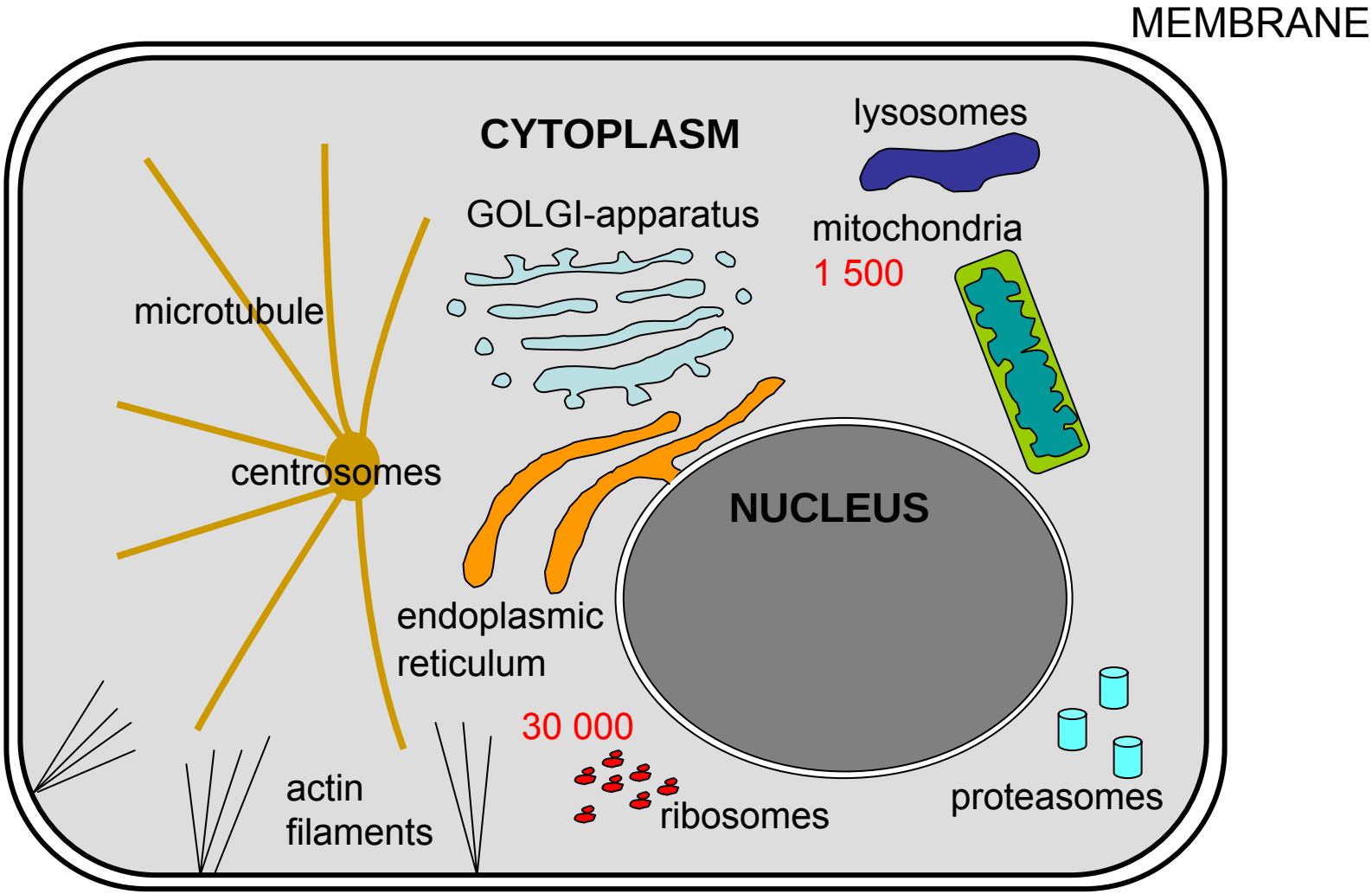


1. Nucleolus
2. Nucleus
3. Ribosome
4. Vesicle
5. Rough endoplasmic reticulum
6. Golgi apparatus
7. Cytoskeleton
8. Smooth endoplasmic reticulum
9. Mitochondrion
10. Vacuole
11. Cytosol
12. Lysosome
13. Centriole

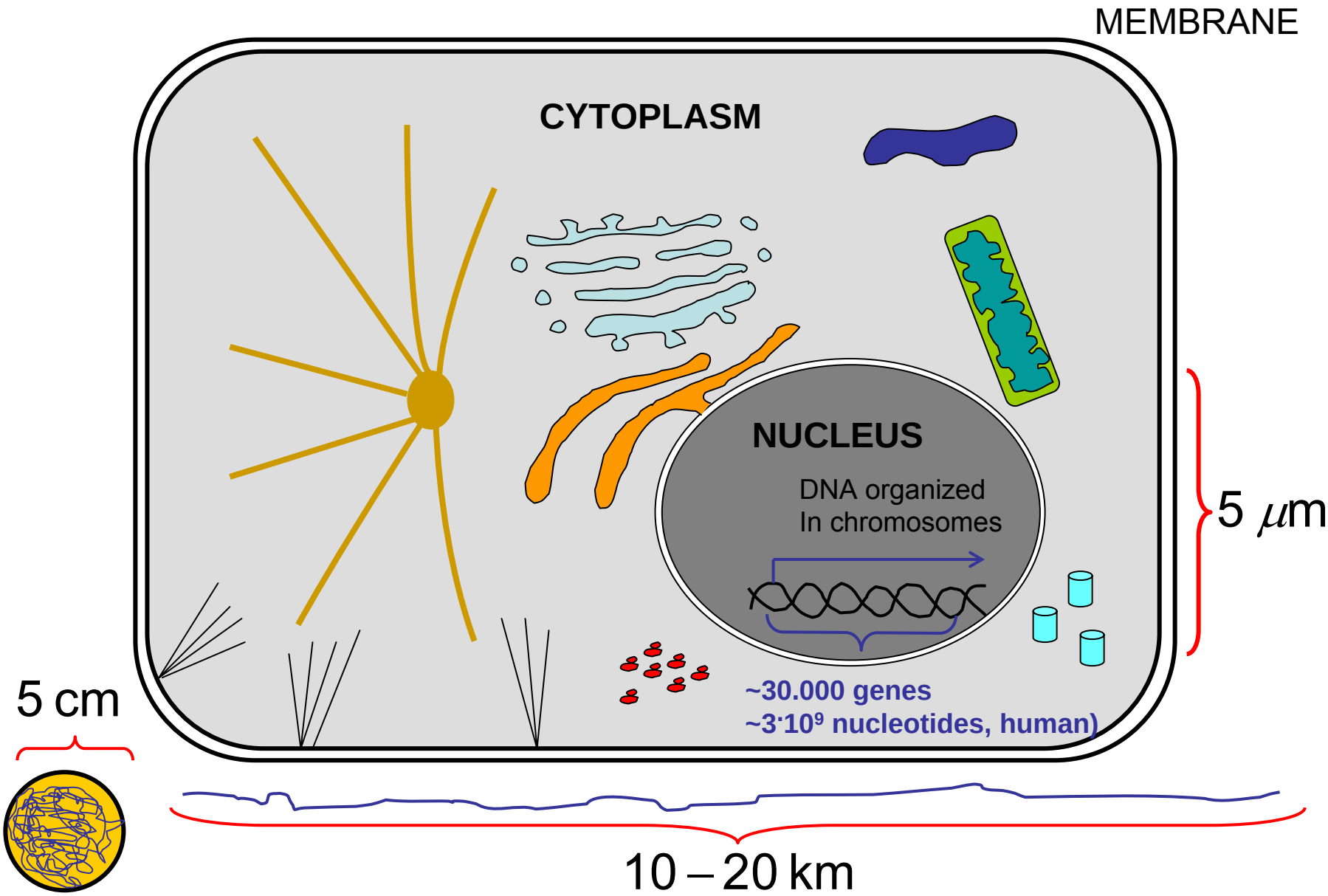
SCHEMATIC STRUCTURE OF LIVING EUCARYOTIC CELLS



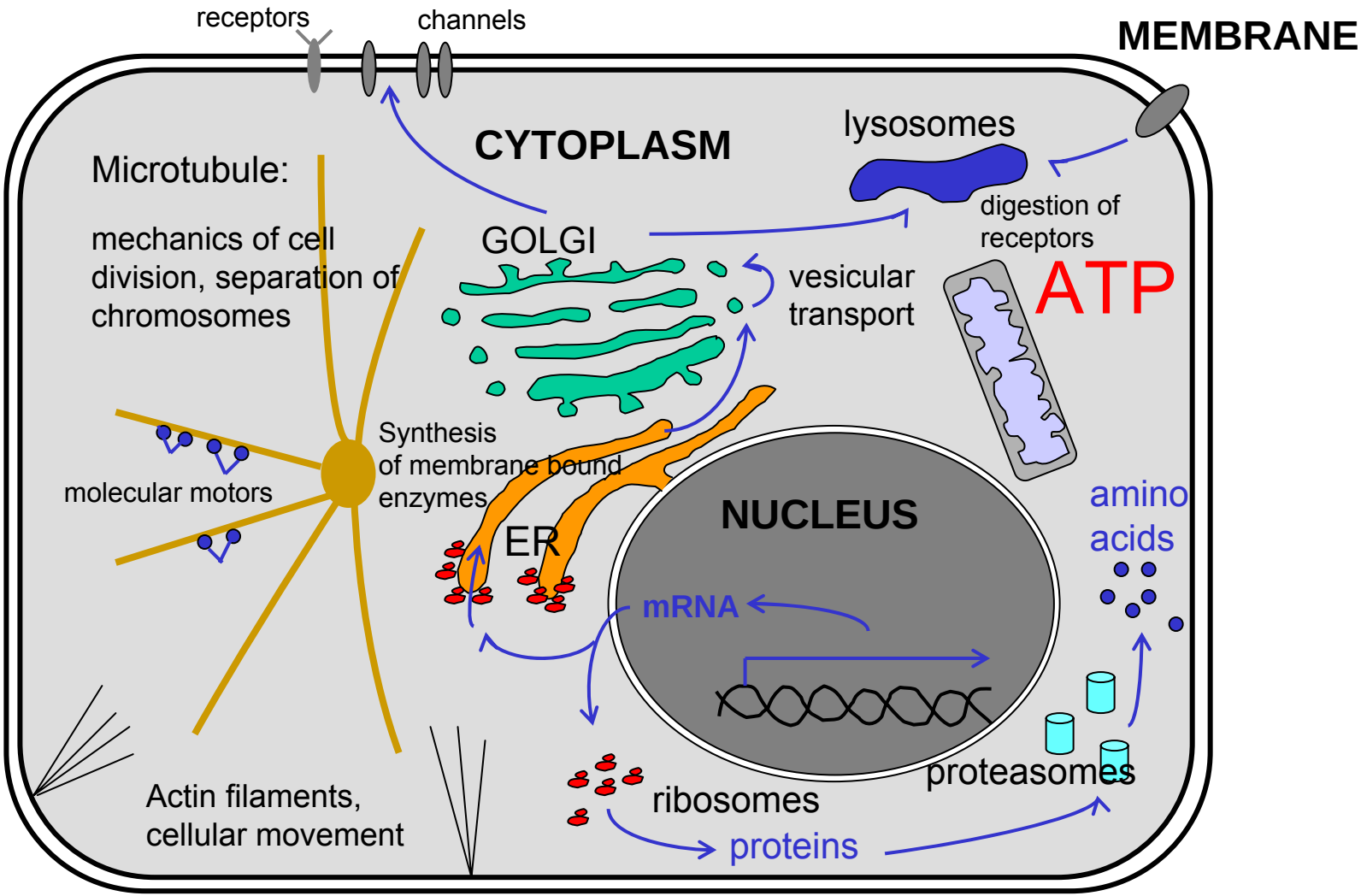
SCHEMATIC STRUCTURE OF LIVING EUCARYOTIC CELLS



SCHEMATIC STRUCTURE OF LIVING EUCARYOTIC CELLS



SCHEMATIC STRUCTURE OF LIVING EUCARYOTIC CELLS



Comparison of features of prokaryotic and eukaryotic cells

	Prokaryotes	Eukaryotes
Typical organisms	bacteria, archaea	protists, fungi, plants, animals
Typical size	~ 1-10 µm	~ 10-100 µm (sperm cells, apart from the tail, are smaller)
Type of nucleus	nucleoid region; no real nucleus	real nucleus with double membrane
DNA	circular (usually)	linear molecules (chromosomes) with histone proteins
RNA-/protein-synthesis	coupled in cytoplasm	RNA-synthesis inside the nucleus protein synthesis in cytoplasm
Ribosomes	50S+30S	60S+40S
Cytoplasmatic structure	very few structures	highly structured by endomembranes and a cytoskeleton
Cell movement	flagella made of flagellin	flagella and cilia containing microtubules; lamellipodia and filopodia containing actin
Mitochondria	none	one to several thousand (though some lack mitochondria)
Chloroplasts	none	in algae and plants
Organization	usually single cells	single cells, colonies, higher multicellular organisms with specialized cells
Cell division	Binary fission (simple division)	Mitosis (fission or budding) Meiosis

II. Data, (physical) models and (mathematical) tools