Introduction to Biophysics

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Outline

- Introduction: What is biophysics and why is it important for Africa?
- Biophysics at different scales: macroscopic → microscopic
  - The biological cell
  - Protein functions
  - Membranes
- Quantum biology
- Experimental examples

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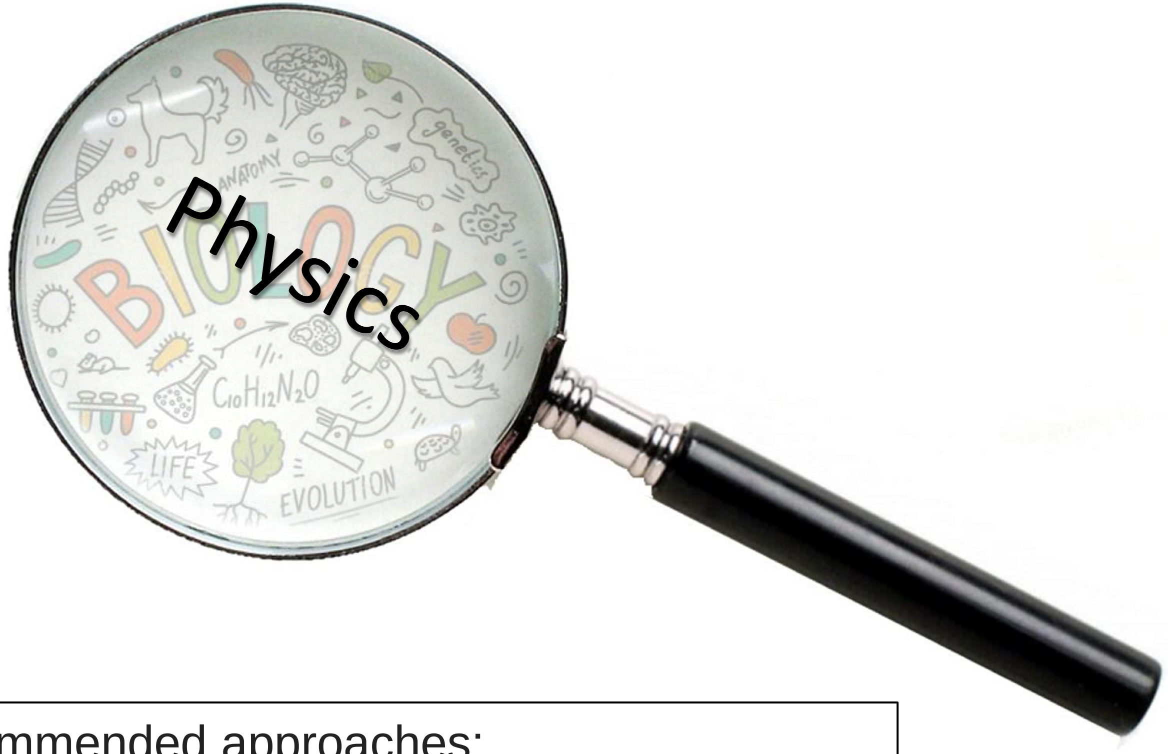
What is Biophysics?

What is Biophysics?



Two recommended approaches:

1. Physics in a biological context
2. Problem-oriented: use the best available tools

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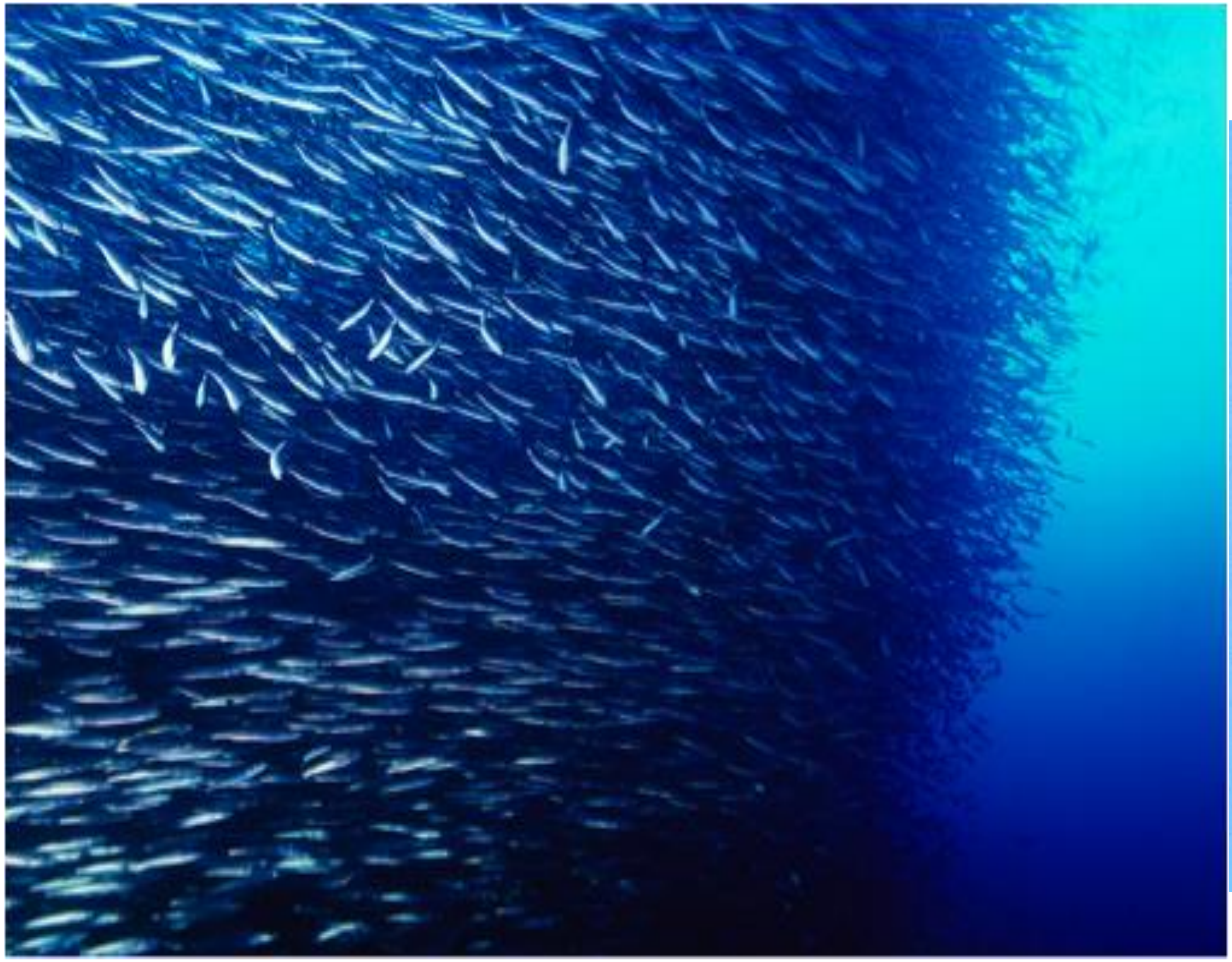
Biophysics is all around us



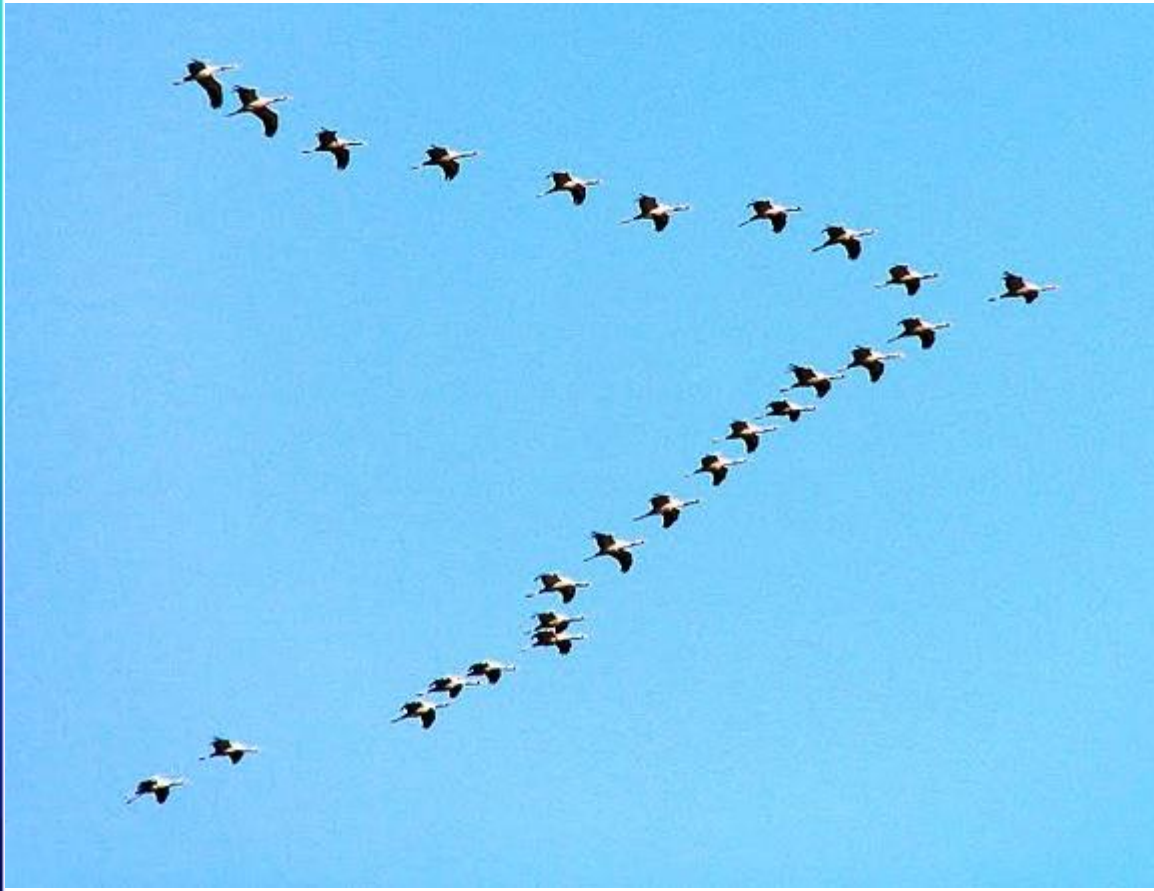


Image credit: Creative Commons

Biophysics is all around us

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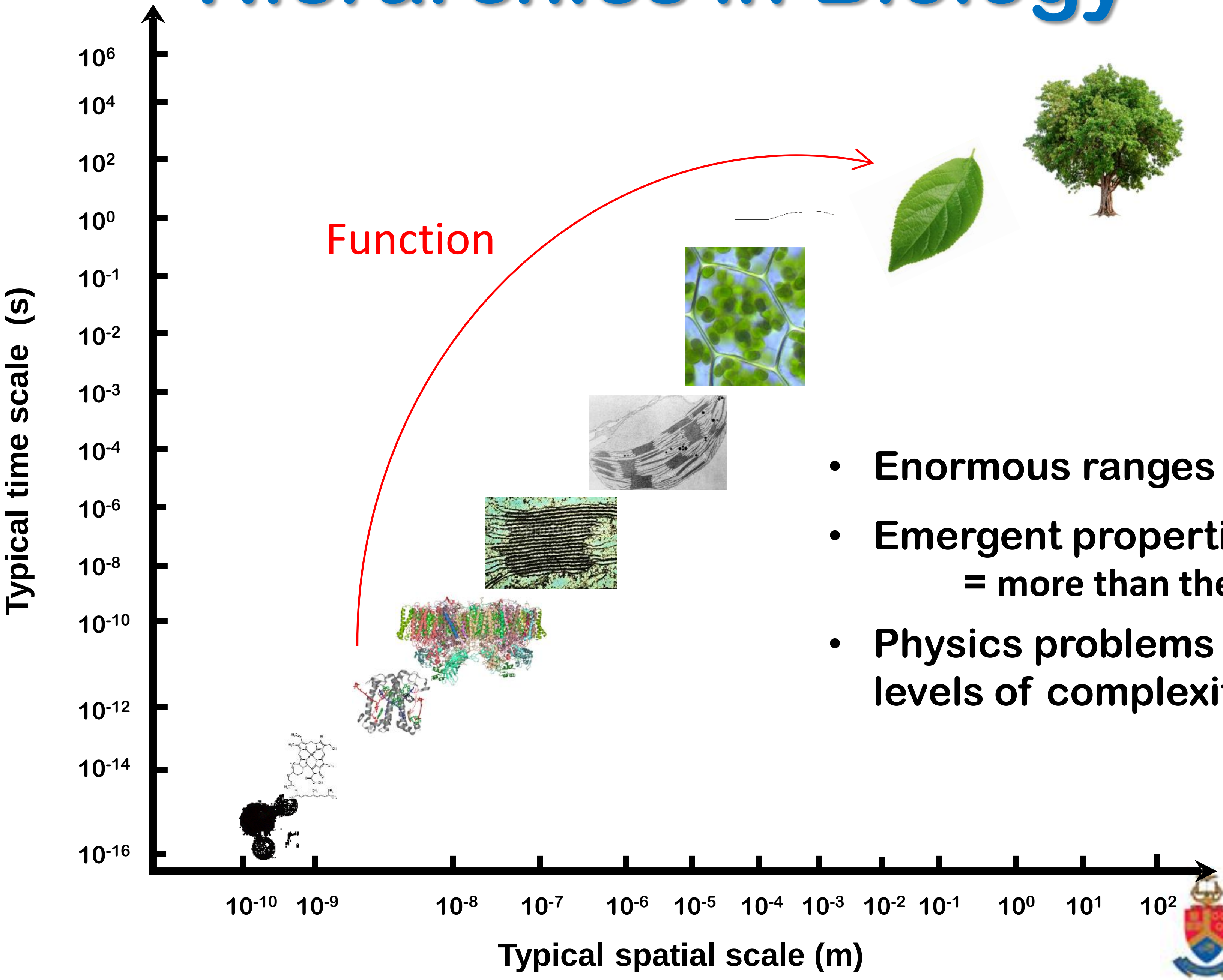
Hierarchies in Biology



- Enormous ranges in time & space
- Emergent properties
  = more than the sum of their parts
- Physics problems are solved at all levels of complexity

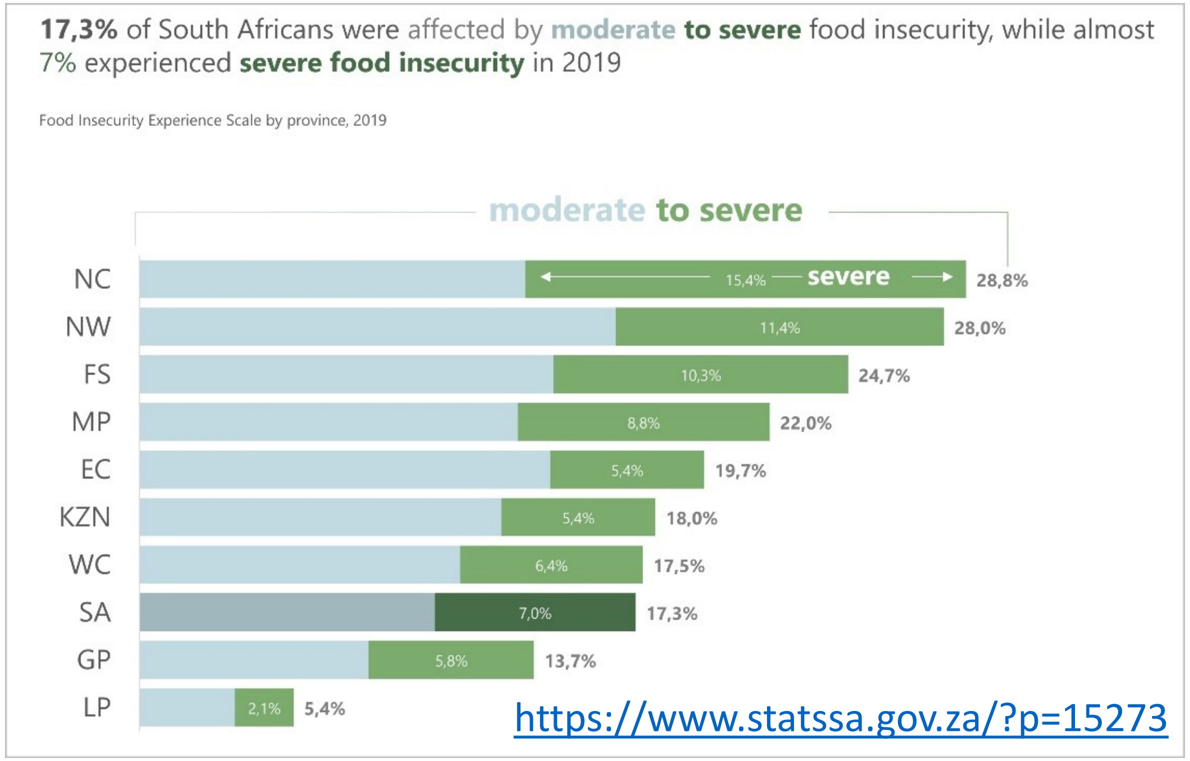
Why is biophysics important for Africa?

1. Africa's alarming food insecurity

Africa

- 20% of Africans are hungry
- ~40% in Sub-Saharan Africa live below the poverty line ($1.9/day)
- 40% of African children are stunted
- Every few minutes a child dies of hunger

South Africa



https://www.statssa.gov.za/?p=15273

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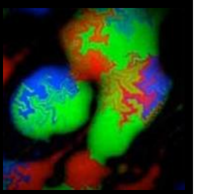
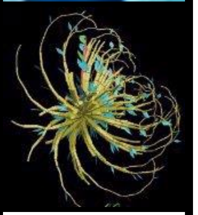
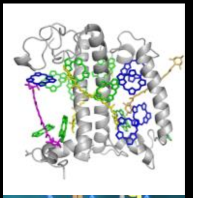
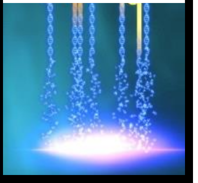
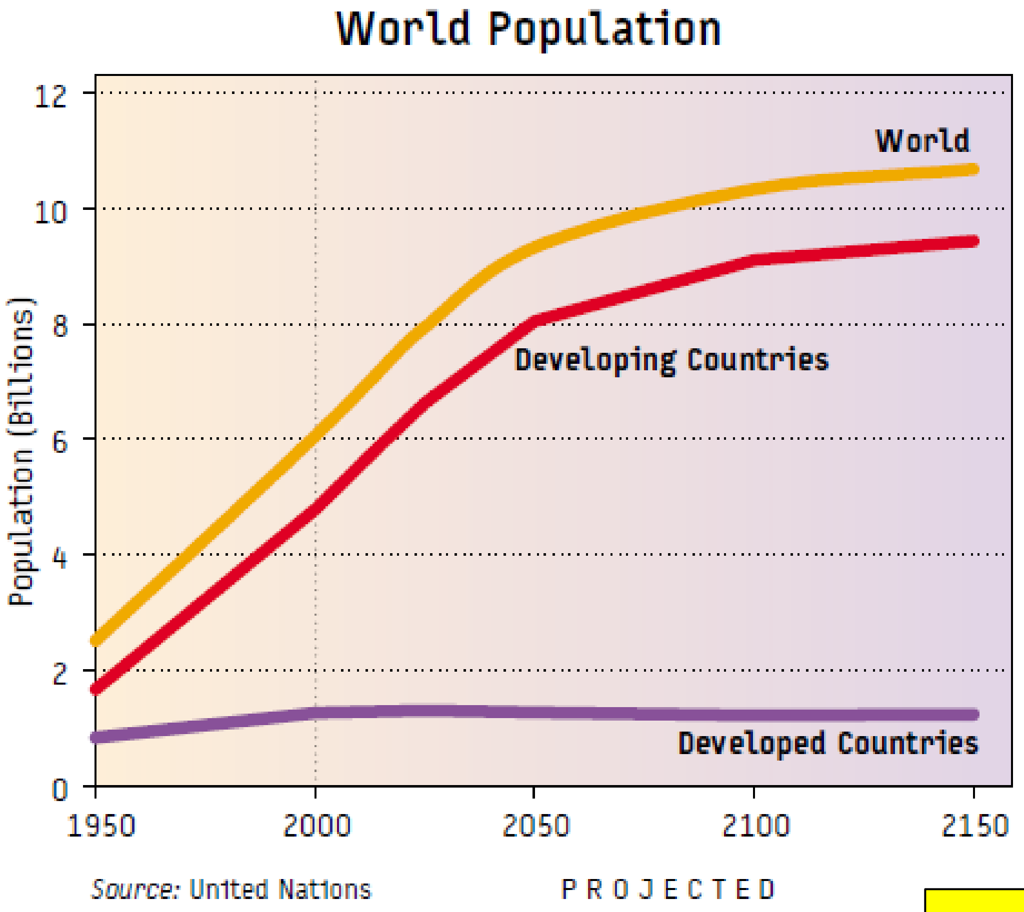
Projected food demands











- Rapidly growing global food demand
- But shrinking fertile farmland

We need drastic agricultural intensification!

Biophysicists can help to improve plant health:

(1) 20–40% of agricultural loss due to **biotic stress** (pathogens, insects, fungi, parasites, worms, weeds)

(2) 50–70% of agricultural loss due to **abiotic stress** (e.g. soil salinity, nutrient deficiency, drought, extreme temperature, excess light)

Solution: timely, pre-symptomatic diagnosis of stress

How? By developing cost-effective equipment such as hyperspectral imaging / multidimensional spectroscopic devices

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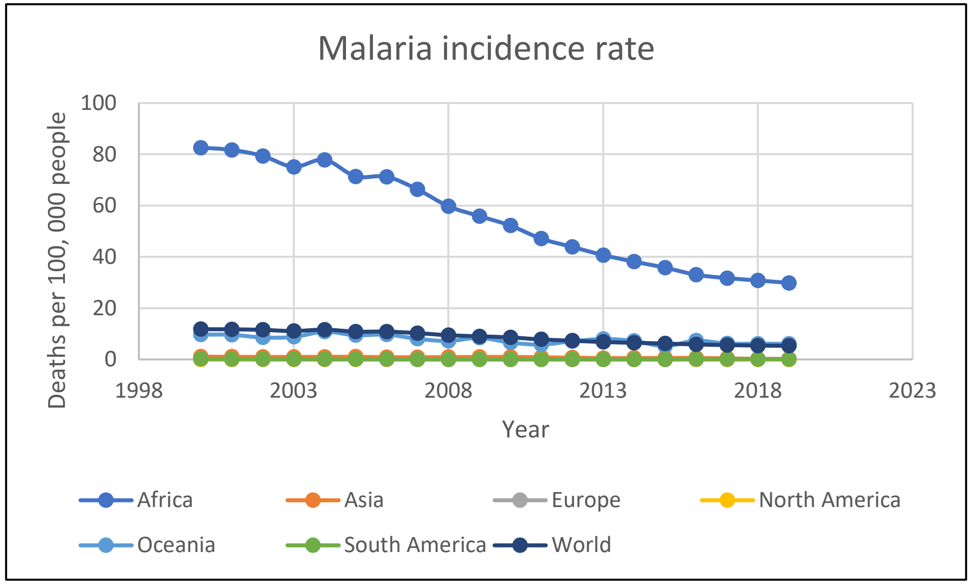
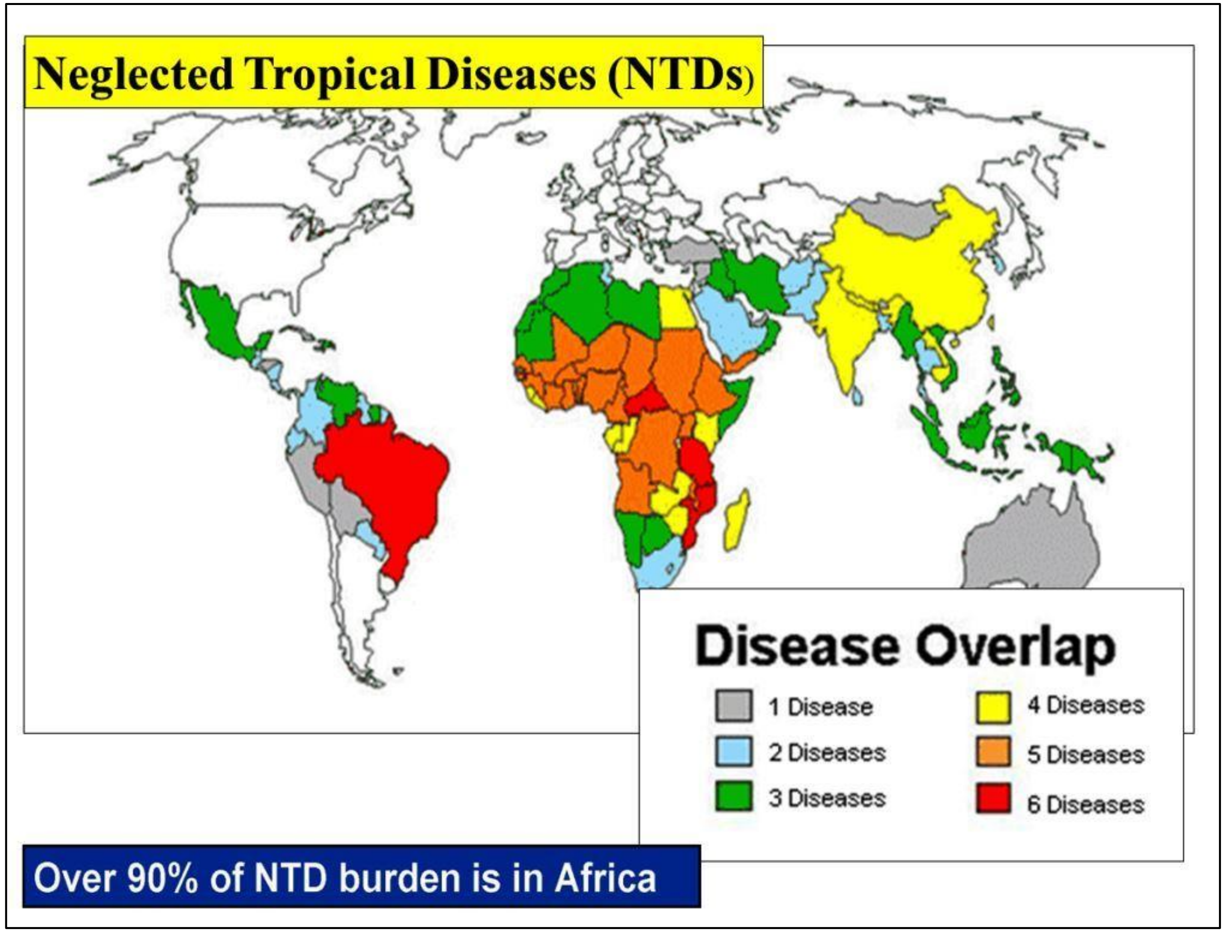
Why is biophysics important for Africa?

2. Inaccessibility to cost-effective healthcare





Africa needs low-cost innovations to address local needs!

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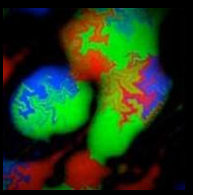



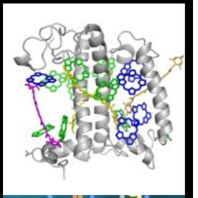


Why is biophysics important for Africa?

3. Physics brings the understanding of biology to a deeper level

IOP PUBLISHING — PHYSICAL BIOLOGY

Phys. Biol. **10** (2013) 040201 (2pp) doi:10.1088/1478-3975/10/4/040201

EDITORIAL

We need theoretical physics approaches to study living systems

Krastan B Blagoev
National Science Foundation, Arlington, VA 22230, USA

Department of Radiology, Massachusetts General Hospital, Harvard Medical School and the Martinos Center for Biomedical Imaging,

Living systems, as created initially by the transition from assemblies of large molecules to self-reproducing information-rich cells, have for centuries been studied via the empirical toolkit of biology. This has been a highly successful enterprise, bringing us from the vague non-scientific notions of vitalism to the modern appreciation of the biophysical and biochemical bases of life. Yet, the truly mind-boggling complexity of even the simplest self-sufficient cells, let alone the emergence of multicellular organisms, of brain and consciousness, and to ecological communities and human civilizations, calls out for a complementary approach.

In this editorial, we propose that theoretical physics can play an essential role in making sense of living matter. When faced with a highly complex system, a physicist builds

Why is biophysics important for Africa?

3. Physics brings the understanding of biology to a deeper level

"You will not be able to successfully develop vaccines without biophysics!"

~ Dr. Martin Friede (World Health Organisation)

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Why is biophysics important for Africa?

3. Physics brings the understanding of biology to a deeper level

EDITORIAL

nature physics Vol.2 No.4 April 2006 www.nature.com/naturephysics

An eye on biophysics

imaging techniques for biomolecules. But in the modern era of molecular biology, understanding not just individual structures but dynamics and collective phenomena in out-of-equilibrium systems are at issue. Physicists are recognizing the challenge, and rising to it.

Biophysics is firmly part of the remit of *Nature Physics*. But, as a journal for physicists, our interests are necessarily in those areas where physics is genuinely explored; less so in, say, the application of physics techniques. The increasing sophistication of imaging methods was clear at the March Meeting. Infrared spectroscopy, NMR, and picosecond X-ray crystallography using a pump–probe setup at synchrotron sources — all are contributing to our understanding of biology. But in other areas of biophysics, there is a need for physical insight. Indeed, in one of the final sessions of the meeting, 'Synchrony and complexity in brain activity and function', neurobiologist Steven Schiff (George Mason Univ.) made a straight appeal to his physics audience for help in making sense of the data.

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Why is biophysics important for Africa?

4. Biology offers a perfect testbed for some theories of physics

NATURE PHYSICS | VOL 11 | FEBRUARY 2015 COMMENTARY

"Diverse Phenomena, Common Themes" by Christopher Jarzynski

"Biology provides a natural setting for applying and refining the tools of non-equilibrium statistical physics. If an equilibrium state is one in which nothing seems to be happening, then living organisms— which grow, move and multiply— seem to be the exact opposite. Just how does a living organism maintain itself away from equilibrium? Processes such as growth and motion arise from intricate networks of chemical reactions driven by chemical imbalances, that is, chemical potential differences."

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Why is biophysics important for Africa?

5a. It drives critical innovative developments

- We're living in the "Century of Biology"
- Biophysics contributes significantly to
  - Medical science & innovation
  - Environmental management (pollution / climate change)
  - Agribusiness / food security
  - Nanotechnology
  - Even energy security and telecommunications / computing

Why is biophysics important for Africa?

5b. Examples from Quantum Biology

Various EU Key Enabling Technologies are based on quantum-mechanical phenomena and find examples in nature.

Key Enabling Quantum Technology	Research field	Examples in nature
Single-photon detection in a low-voltage electrochemical system	Photonics	• Eye • Photoreceptors • Light-harvesting complexes
N_2 fixation at room temperature and pressure	Nanotechnology	Certain bacteria
Chemically powered transport of ions and electrons across nanometers with low dissipation	Nanoelectronics	Transmembrane ion transport across basically every (sub)cellular membrane
H_2 from H^+ without noble metals at 0 V SHE	Advanced Materials	Many organisms, e.g. cyanobacteria
Photobiological charge separation with near-unity quantum efficiency	Photovoltaics	Photosynthetic photosystems

Why biophysics works for me?

http://www.iop.org/careers/workinglife/articles/page_53286.html

1) **Deborah Fygenson (Associate professor at the University of California, Santa Barbara, US)**

   Research: DNA origami to recreate some of the nanostructures we see in biology.

   For Fygenson, it is the "immediacy" of biophysics that makes the subject so attractive. "It's the potential for impact on human life, the phenomena being close by," she says. "I think that if we start to better understand the physical limitations imposed by biomaterials, we'll have fundamental insights into why biology is constructed the way it is."

   https://www.physics.ucsb.edu/news/announcement/608

2) **Thomas Krauss (Head of the School of Physics and Astronomy, University of St Andrews, UK)**

   Thomas Krauss is a great example of biophysics' interdisciplinary nature. An engineer by training, he spent his early career developing photonics for Internet applications. [e.g. data transmission]

   … Krauss has several interests in the field. One is … the nascent field of "optogenetics" – a process that makes certain nerve cells light-sensitive by infecting them with a virus, so that biologists can learn how they transmit signals at a cellular level. "Combining optogenetics with my interest of controlling light at the nanoscale, you can imagine an array of light emitters firing at neurons, controlling their function at an array type of scale," explains Krauss.

   "I was starting to get bored of telecoms," he adds. "When you do something for 10 years, you start to know most of it. Of course, you never know everything, but the factor of learning gets smaller and smaller. Whereas in biophysics there is so much I have yet to learn."

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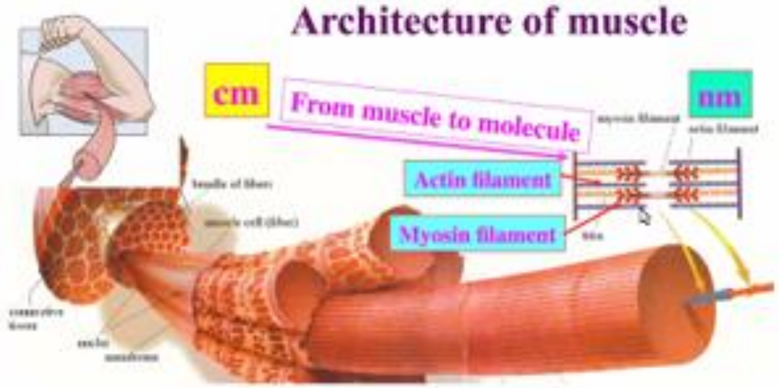
Biophysics at different scales

Macroscopic scale (“macroscale”)

Deterministic Hamiltonian dynamics

Classical mechanics: Newton’s laws

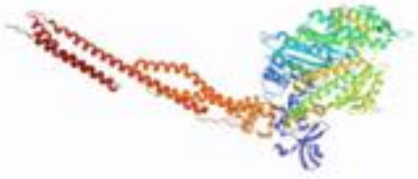


Mesoscopic scale (“mesoscale”)

Stochastic dynamics

Noise and fluctuations

Myosin motor



Atomic scale

Molecular dynamics simulations
Quantum dynamics

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Main branches of biophysics

- Bioacoustics
- Bioelectricity
- Bioenergetics
- Biophotonics
- Biomechanics
- Computational Biophysics
- Genomics
- Imaging/Microscopy
- Medical physics
- Molecular biophysics
- Membrane biophysics
- Nanobiophysics
- Neuroscience
- Plant biophysics
- Protein engineering
- Quantum biology
- Statistical biophysics
- Structural biology
- Theoretical biology

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Physical theories relevant in biology

- Fluid dynamics
- Electrostatics
- Electrodynamics
- Classical mechanics (e.g. cell dynamics)
- Quantum mechanics
- Statistical mechanics
- Thermodynamics (e.g. non-equilibrium / stochastic)
- Optics
- Acoustics

… and this doesn't even include the experimental methods used to study them!

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What can be studied?

- Organism?
  - Humans
  - Animal kingdom
  - Plants (~320,000 species)
  - Bacteria (>30,000 named species)
  - Fungi (2-3 million species)
  - Viruses (several million types, only ~7000 have been described so far)
  - …
- Cells: >2300 cell types
- Proteins: >85 million records (only ~180k structures resolved experimentally)
- Processes?
- Spatial & temporal scales?
- Interaction between organisms,
  e.g. diseases (develop vaccines?)

The Biological Cell

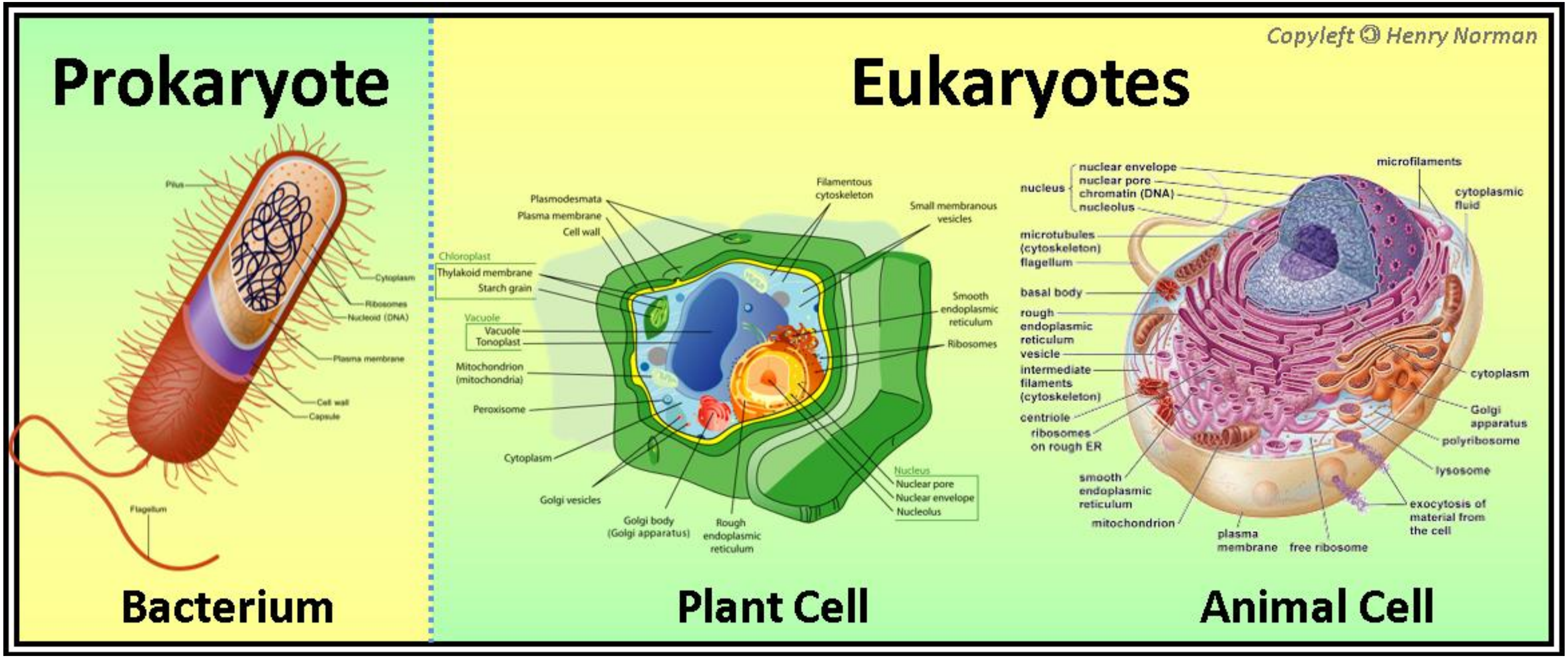

Image credit: Creative Commons

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The Plant Cell

DNA and gene expression
(City Hall)

Transportation system
Contains ribosomes for protein synthesis
(factory / construction site)

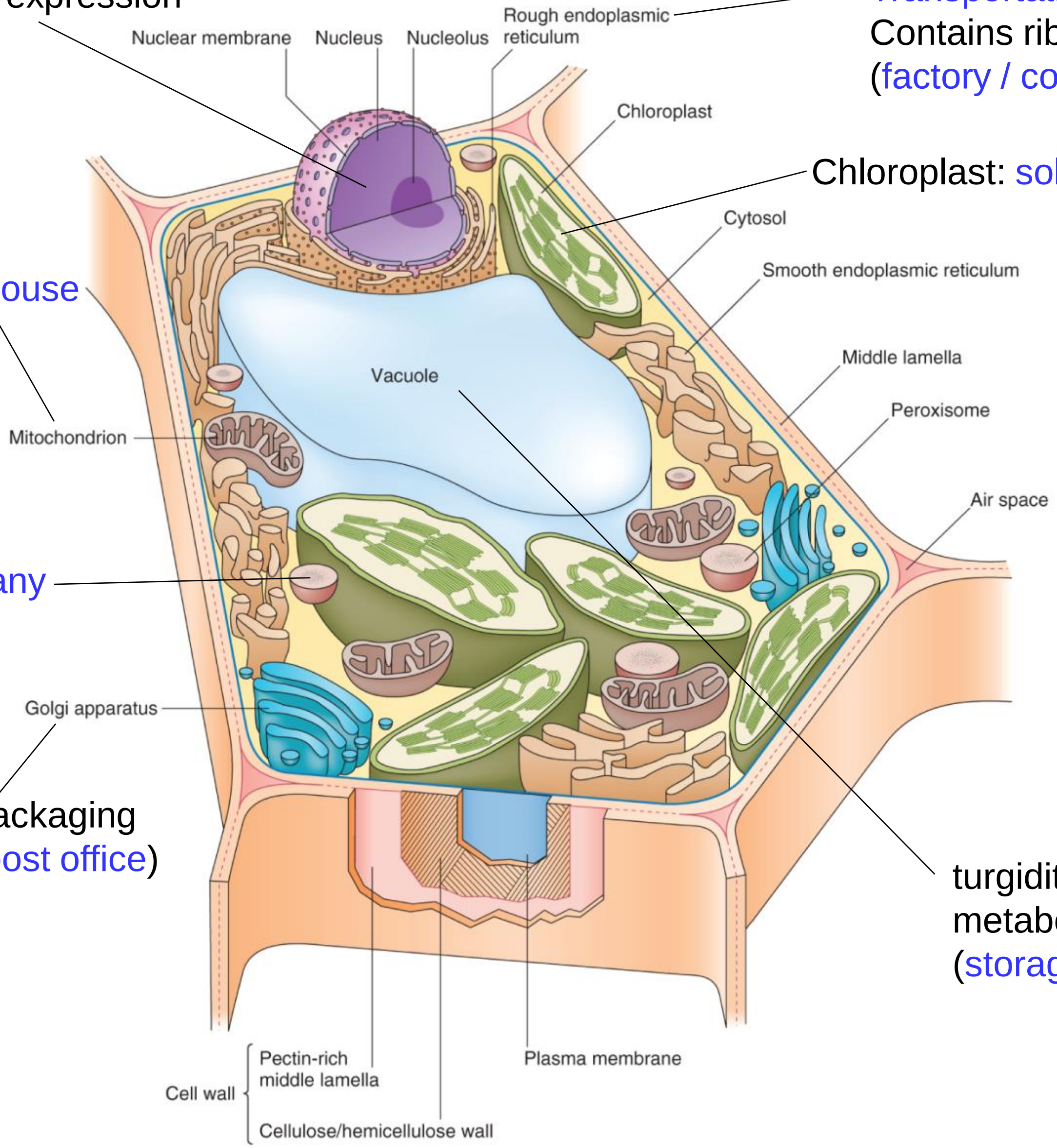
Chloroplast: solar farm

energy powerhouse

Lysosome: garbage company

Macromolecule packaging
and processing (post office)

turgidity control and
metabolite storage
(storage unit)



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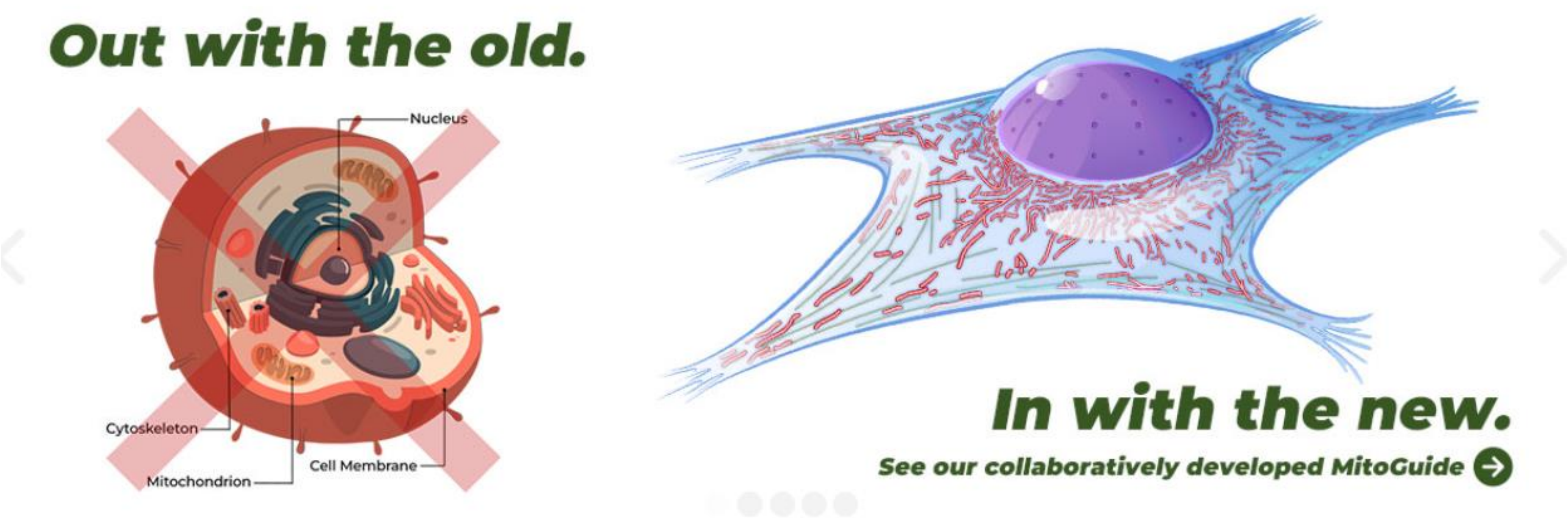
More realistic depiction of the cell



Mitochondria exist as a dynamic network inside each cell in the body and can break apart or fuse together in long chains in response to the changing demands of the cell.

https://mitoworld.org/mitomedia/mitoguide

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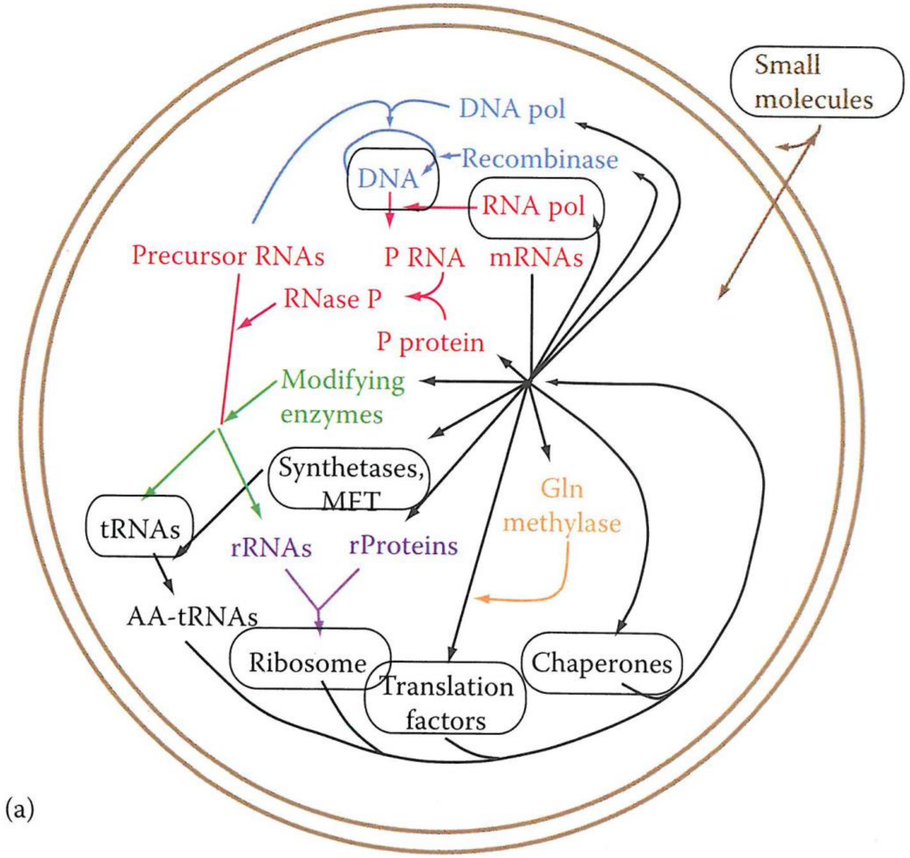
How complex is a cell?

The minimal cell



From: Quantitative Understanding of Biosystems
An Introduction to Biophysics, Second Edition
By TM Nordlund & PM Hoffmann

Simplest process is diffusion of small molecules:

$$\frac{\partial C(x,t)}{\partial t} = -D\frac{\partial^2 C(x,t)}{\partial x^2}$$ ~~+ source & sink terms~~

- Boundary conditions
- Reactions with other molecules: source & sink terms
- Feedback mechanisms: **coupled PDEs.**

Assume: every line denotes a reaction, described by a PDE.

~30 coupled PDEs!

Can Mathematica solve this for time-independent processes?

Metabolic pathways

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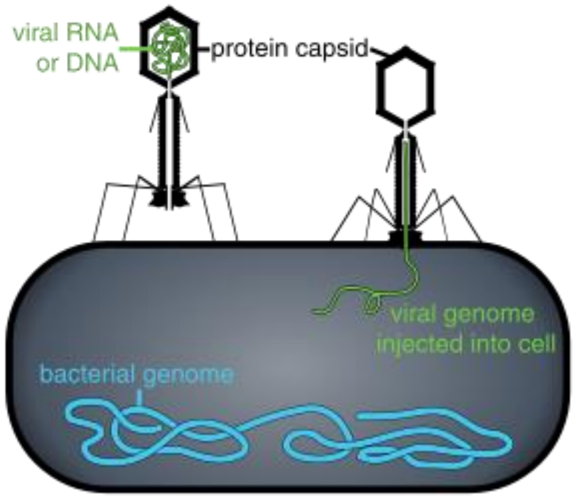
Viruses



Nature Reviews Microbiology **9**, 628 (September 2011) | doi:10.1038/nrmicro2644

1. How big are viruses?

~20 – 400 nm

2. How many viruses are there on the earth?

~10^{31} viruses!

There are more viruses on Earth than stars in the universe.
If you stacked every virus end to end, they would stretch 100,000 light years.

3. How effective are antiviral drugs?

"…you will not be able to successfully develop vaccines without biophysics…"

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Bacteria

>30,000 formally named species

Bacterial library: https://www.usmslab.com/microbiology-lab-resources-library/bacterial-library

What is the ratio of bacterial cells vs. body cells in the human body?

A. 1:100

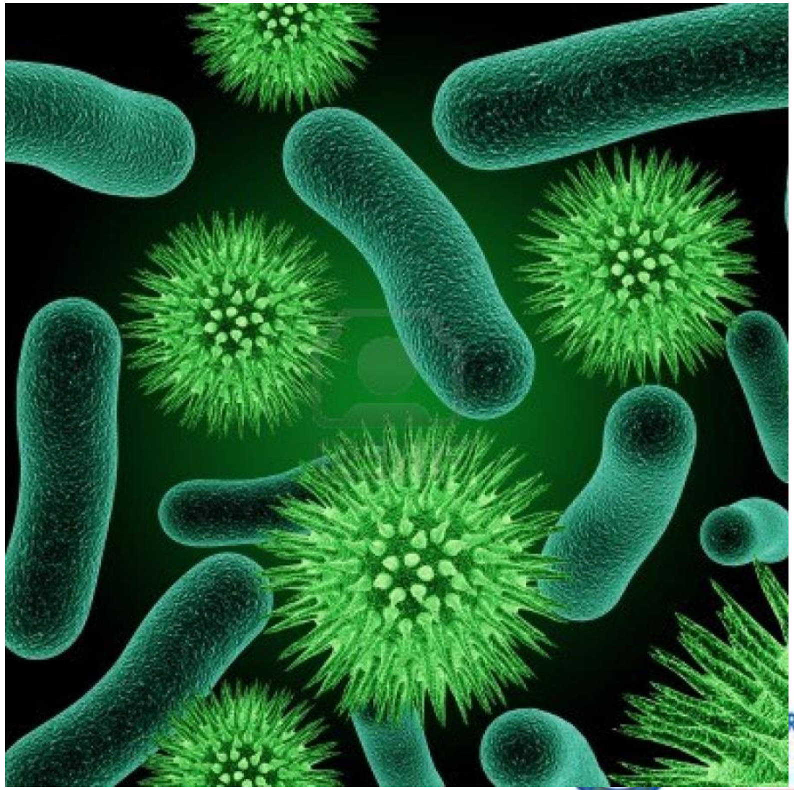
B. 1:10

C. 1:1

D. 10:1

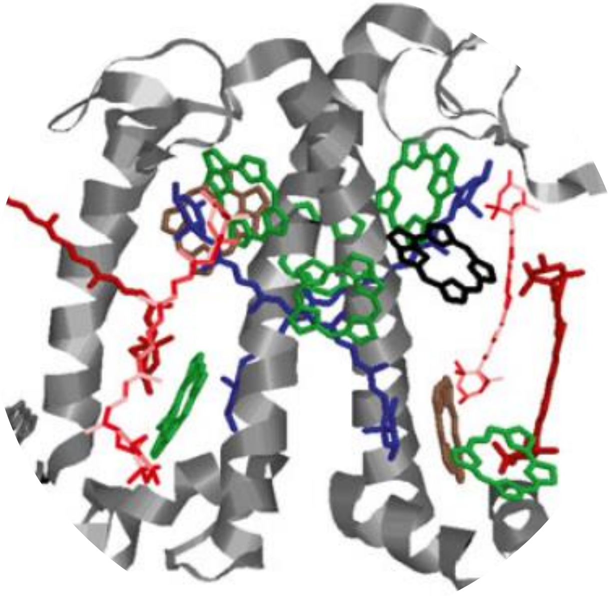
Scientists bust myth that our bodies have more bacteria than human cells

Average size = ~2 μm: 50 μm



Proteins

"Hydrogen atom" of life



>100 000 types of these "machines" in the human body!!

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Protein folding

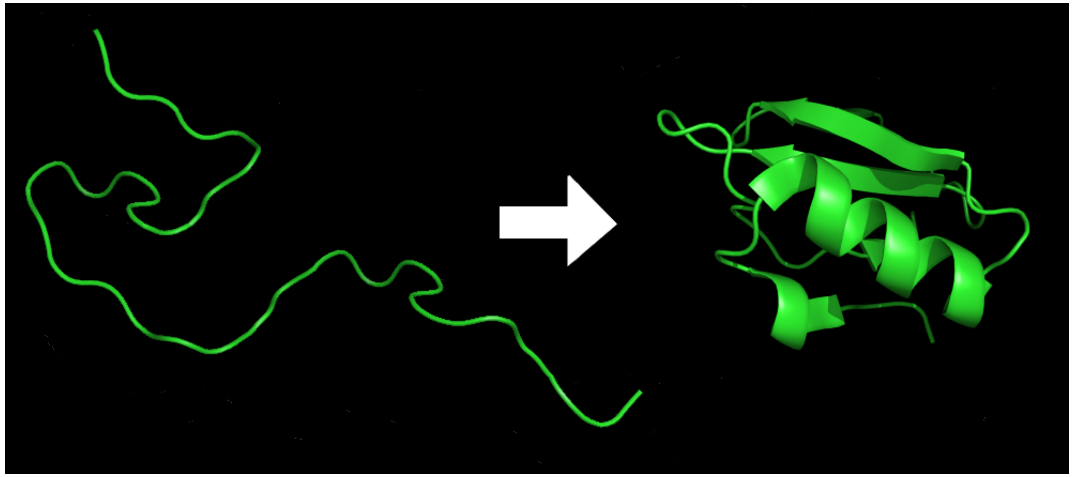

Image credit: Creative Commons license

Driving forces

- Hydrophobic & hydrophilic interactions
- Hydrogen bonds
- (other) v/d Waals interactions
- Electrostatic interactions
- Disulphide bonds

vs Conformational entropy

Misfolds can lead to severe diseases
E.g. Alzheimer’s and Cystic Fibroses

Levinthal’s paradox

Imagine that there was only a single bond between each amino acid in a protein of 101 amino acid residues. Imagine that there were only three possible configurations around each of those bonds. This means that the protein could adopt $3^{100} \sim 5 \times 10^{47}$ different conformations.
If the protein is able to sample 10^{13} different bond configurations per second then it would take 10^{27} years to sample all possible conformations of the protein.

AlphaFold can predict the folded structure!
Quantum Computers will do it even better!

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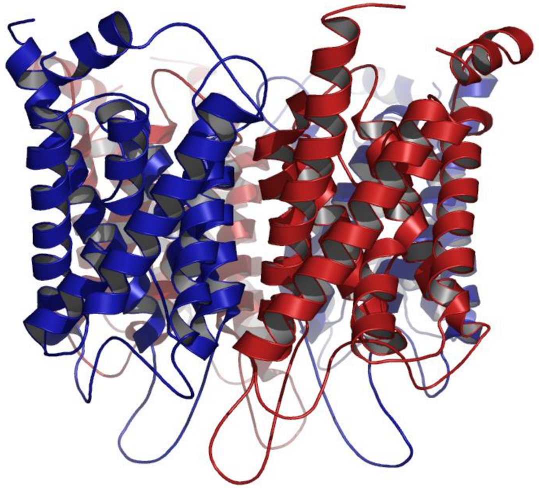
Protein functions

- Catalysing reactions (enzymes)
- Regulation of gene expression
- Building structures (skin, hair, etc.)
- Transport (across membranes or to different cellular compartments)
- Communication (receptors, signalling)
- Storage (bind specific molecules)
- Defense (antibodies bind to viruses or foreign molecules for destruction)
- Motors (generate mechanical forces, leading to torques/displacements)
- Light-harvesting (absorb light and transport photoexcitations)
- Electron and proton tunnelling (e.g. convert light into chemical energy)

pdb101.rcsb.org

Protein functions: Transport

Aquaporin = water channel



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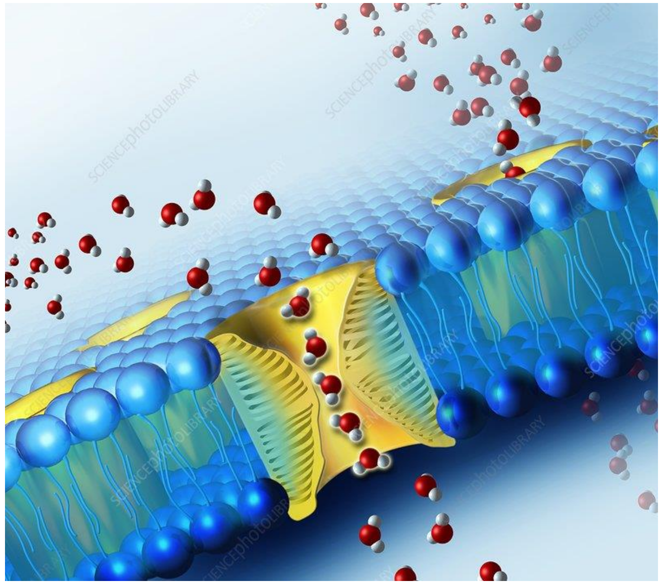
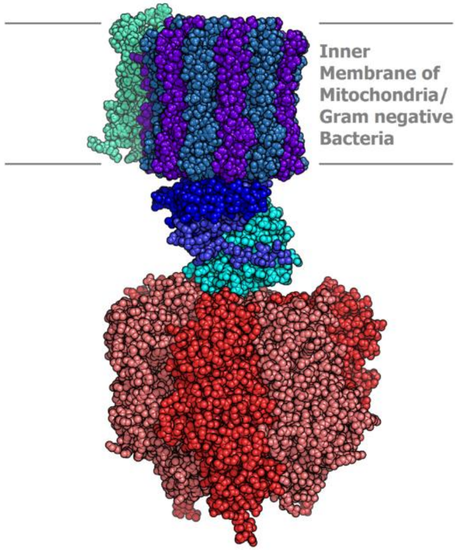


Image credit: Claus Lunau/Science Photo Library

Protein functions: Transport

ATP synthase = proton pump



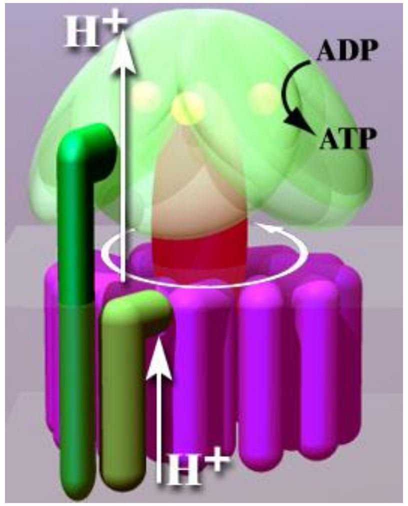


Image credit: Creative Commons

Physical mechanism: Proton gradient (potential energy) → torque → ATP synthesis

Cool animation: https://www.youtube.com/watch?v=kXpzp4RDGJI

- Spins up to 42 000 rpm! (Formula 1 engine up to 12 000 rpm)
- Our bodies turn over ~70 kg of ATP per day!

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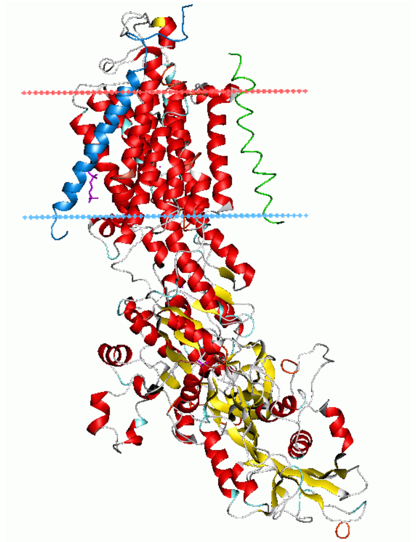
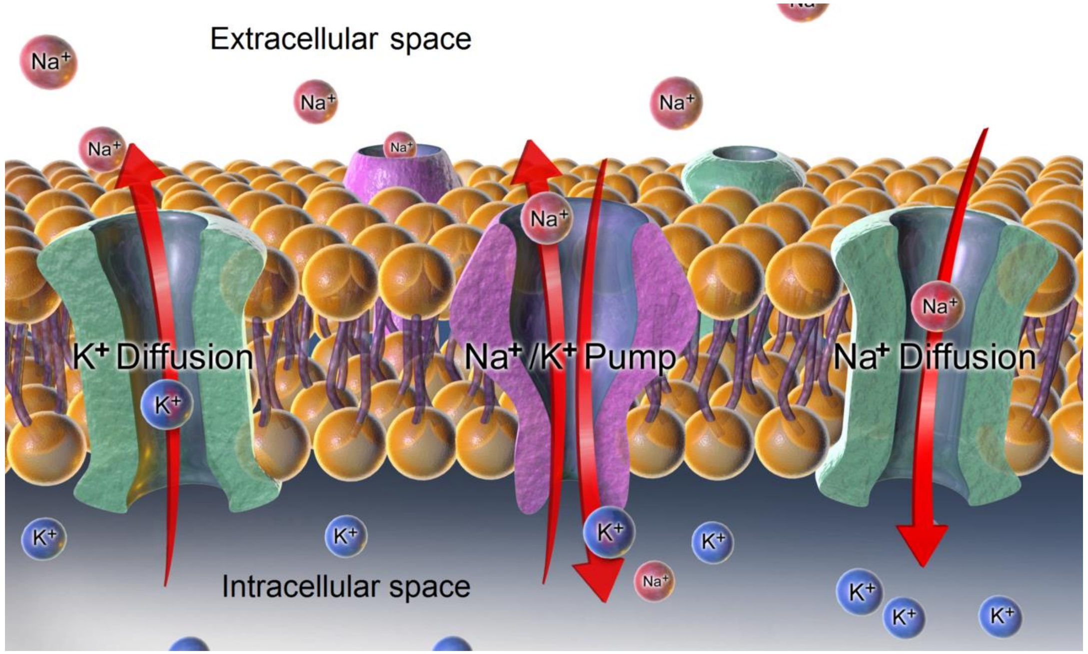
Protein functions: Transport

Fire electrical signals via charge gradients

Restore the gradients

Sodium & Potassium Channels, and Sodium-Potassium Pump





Cool animation: https://www.youtube.com/watch?v=ZKE8qK9UCrU

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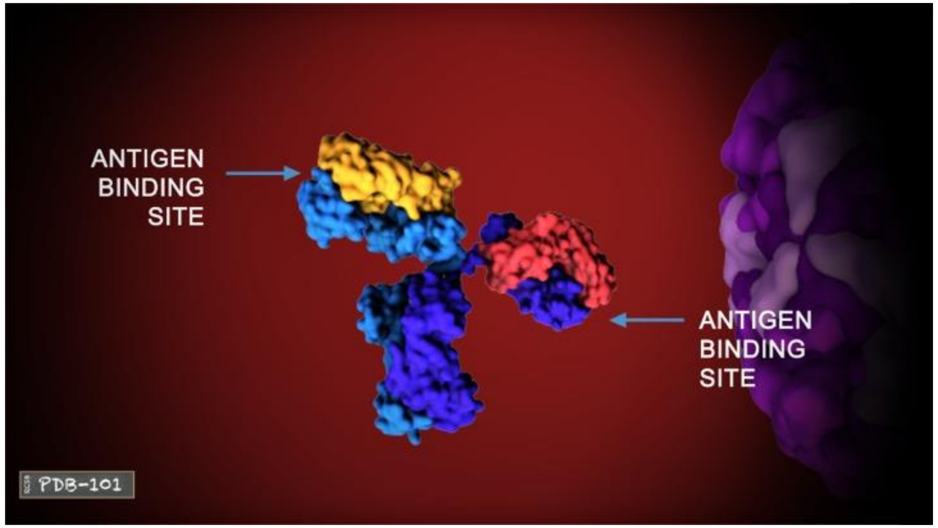
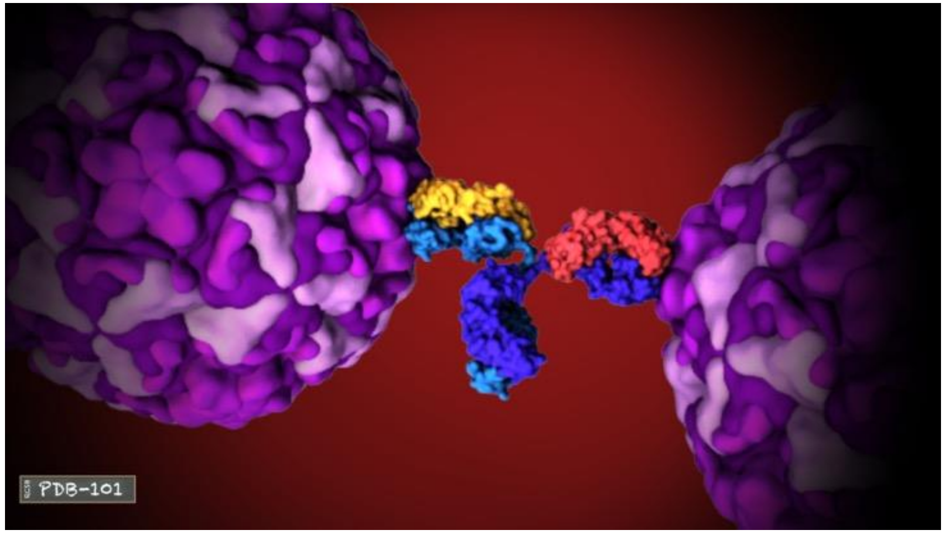
Protein functions: Defense



The flexible arms of **antibodies** protect us from disease by recognizing and binding to pathogens such as viruses, and targeting them for destruction by the immune system.



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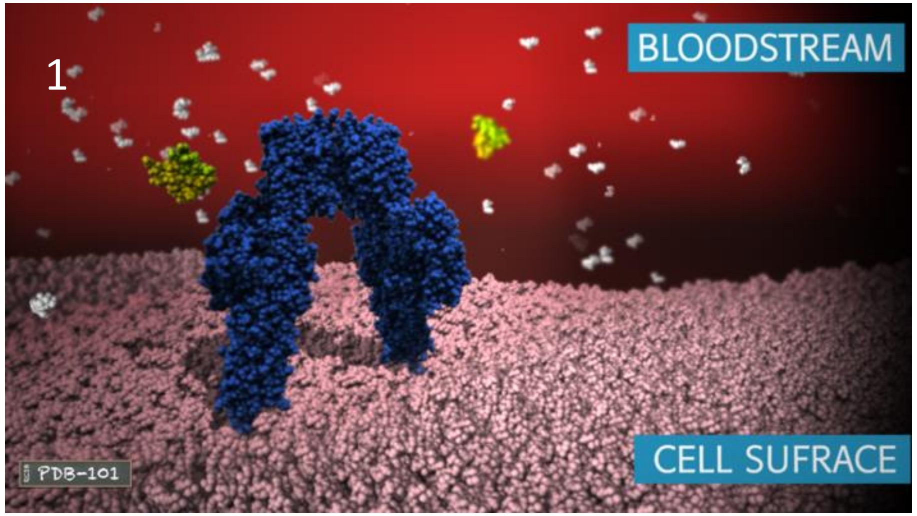
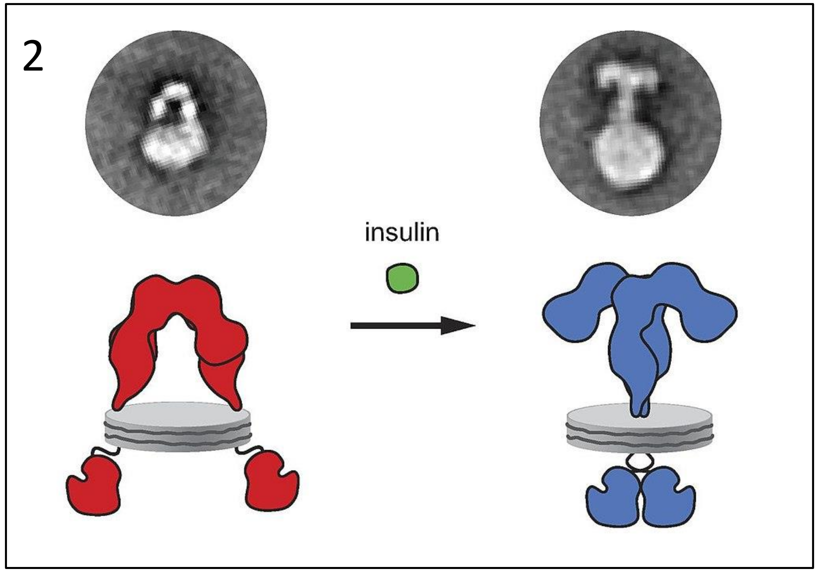
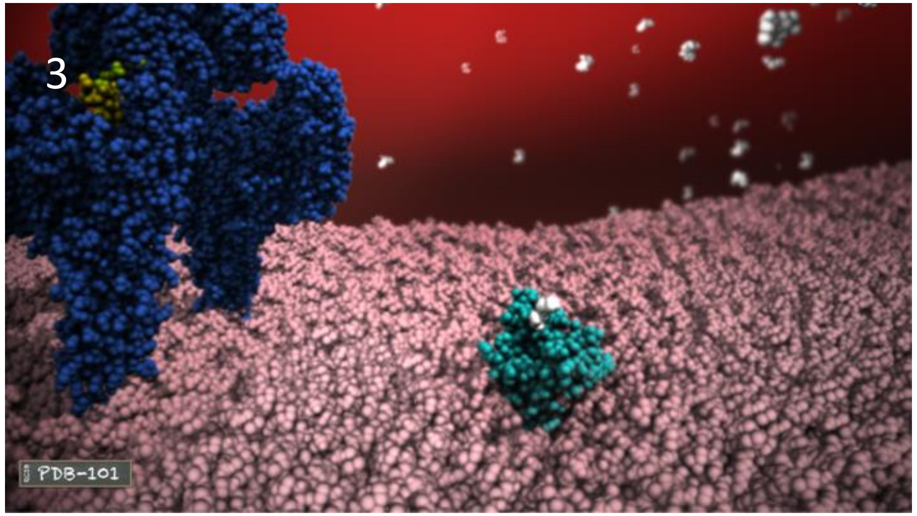
Protein functions: Communication

The **hormone** insulin (yellow) is a small, stable protein that can easily maintain its shape while travelling through the blood to regulate the blood glucose level.





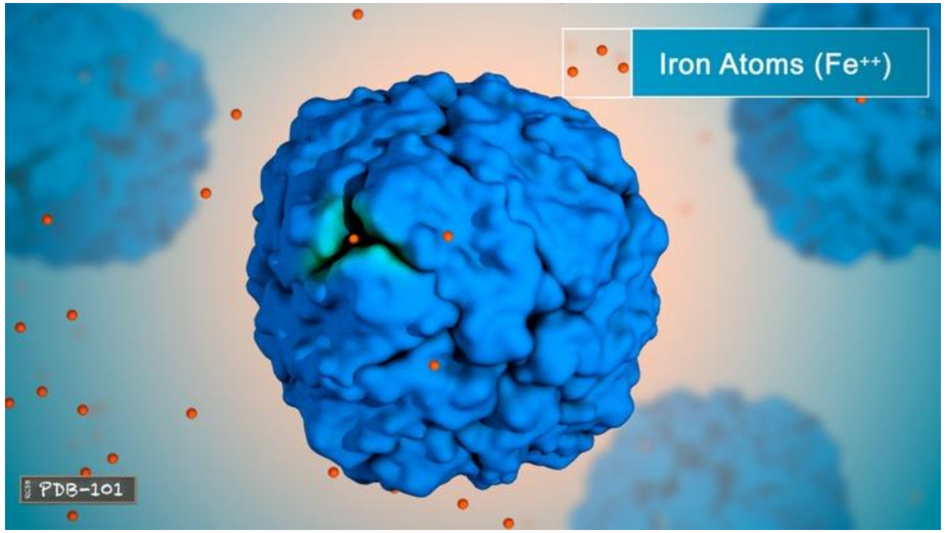
Insulin binds to the insulin receptor (navy blue) and triggers an intracellular signaling pathway.

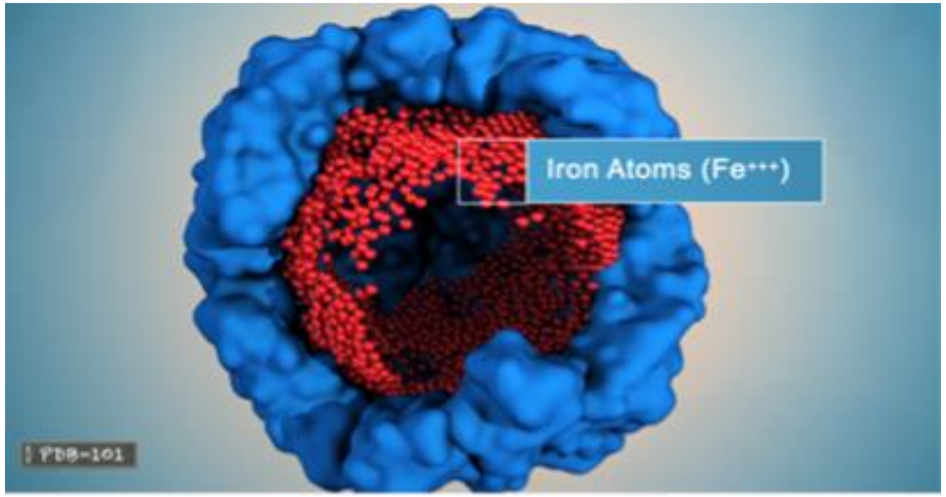


As a result, the glucose transporter (aqua) comes to the cell surface creating a channel for glucose (white) to enter the cell.

pdb101.rcsb.org

Protein functions: Storage





Ferritin **stores** iron. It is a spherical protein with channels that allow the iron atoms to enter and exit depending on the organism's needs.

On the inside, ferritin forms a hollow space with the iron atoms attached to the inner wall.

Ferritin stores iron in the non-toxic form.

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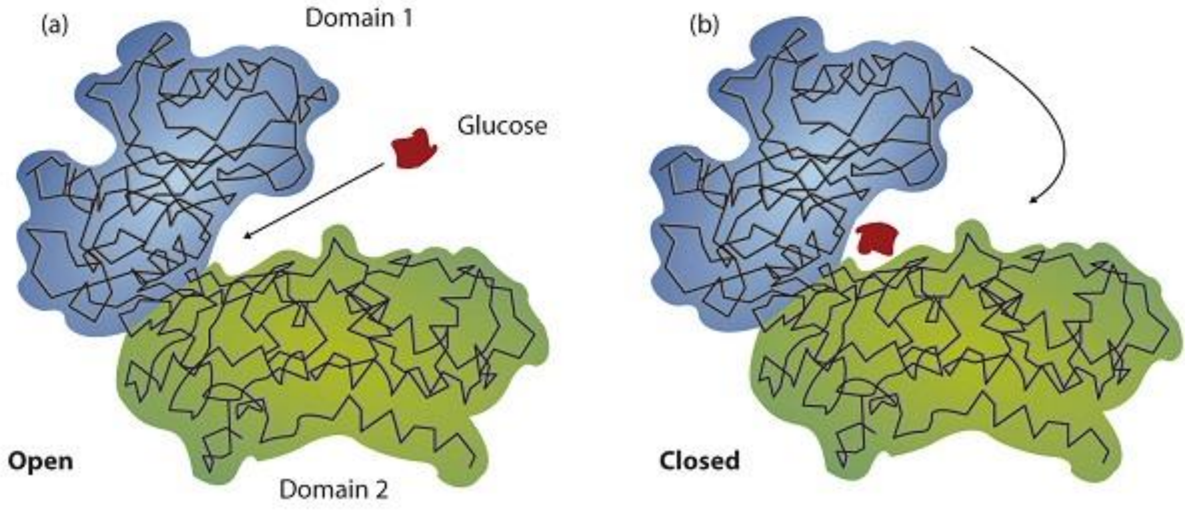
Proteins are dynamic structures



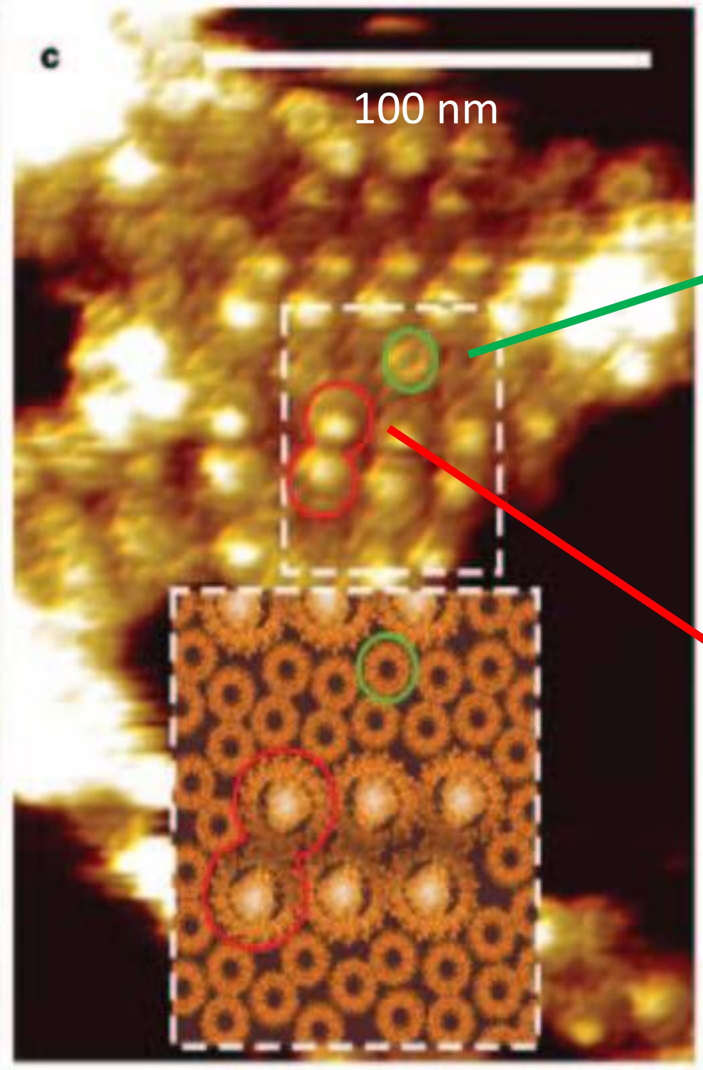
https://chem.libretexts.org/

Enzymes switch from an inactive to active conformation upon binding of an activator molecule.

Biological membranes

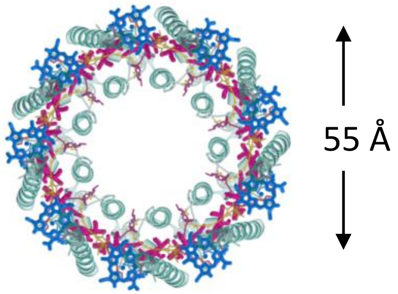
- Most of life happens in ‘soap bubbles’ (give examples)
- Transportation across the membrane:
  - Diffusion
  - Osmosis
  - Channels & carriers
  - Endo-/exocytosis
- Self-assembly

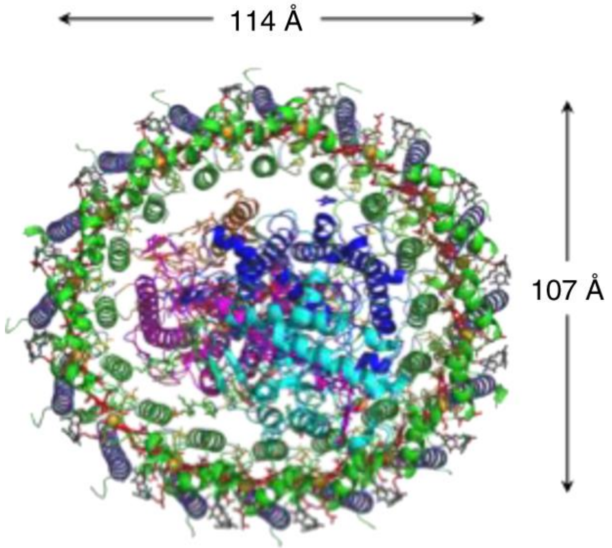
Self-assembly of light-harvesting complexes



LH2

RC-LH1

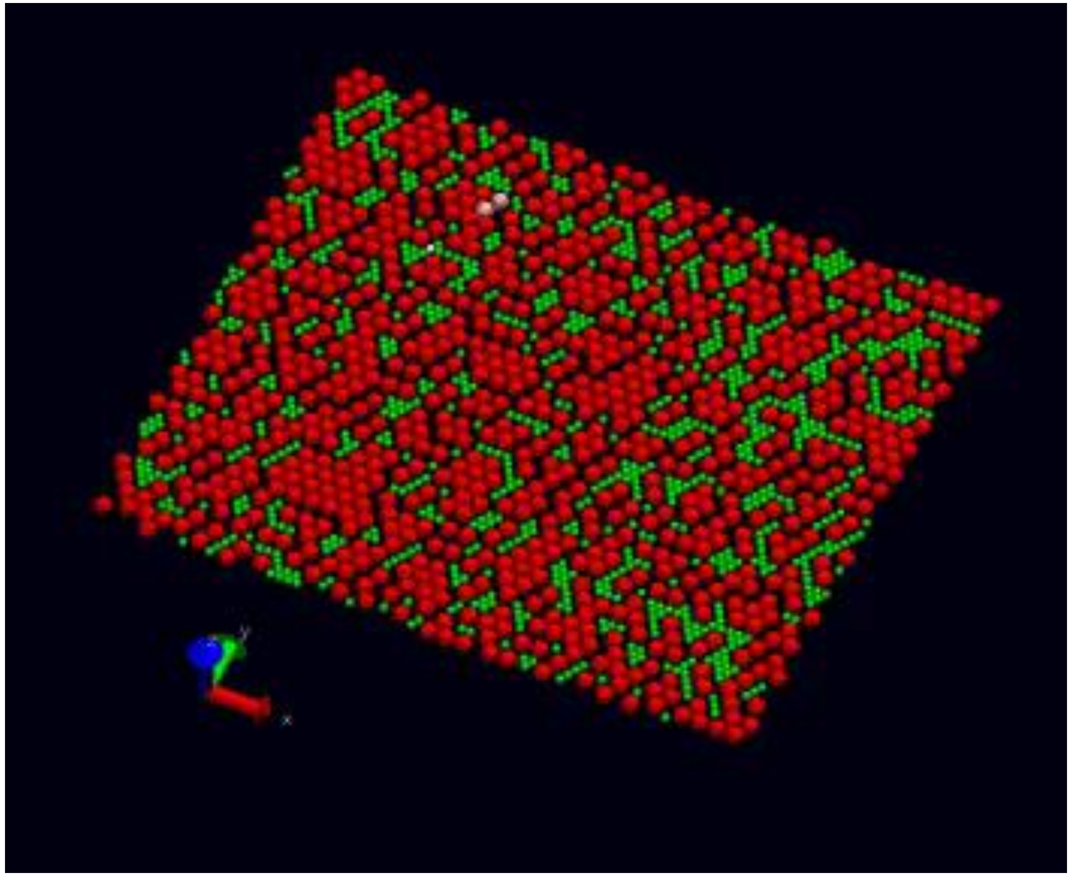




AFM

Bahatyrova et al. *Nature* 430, 1058 (2004)

Self-assembly of light-harvesting complexes



LH2
RC-LH1

Helfrich elastic energy

$$\mathcal{H} = \frac{1}{2} k_A \frac{(A - A_0)^2}{A_0} + 2k \int_A dA (J - c_0)^2$$

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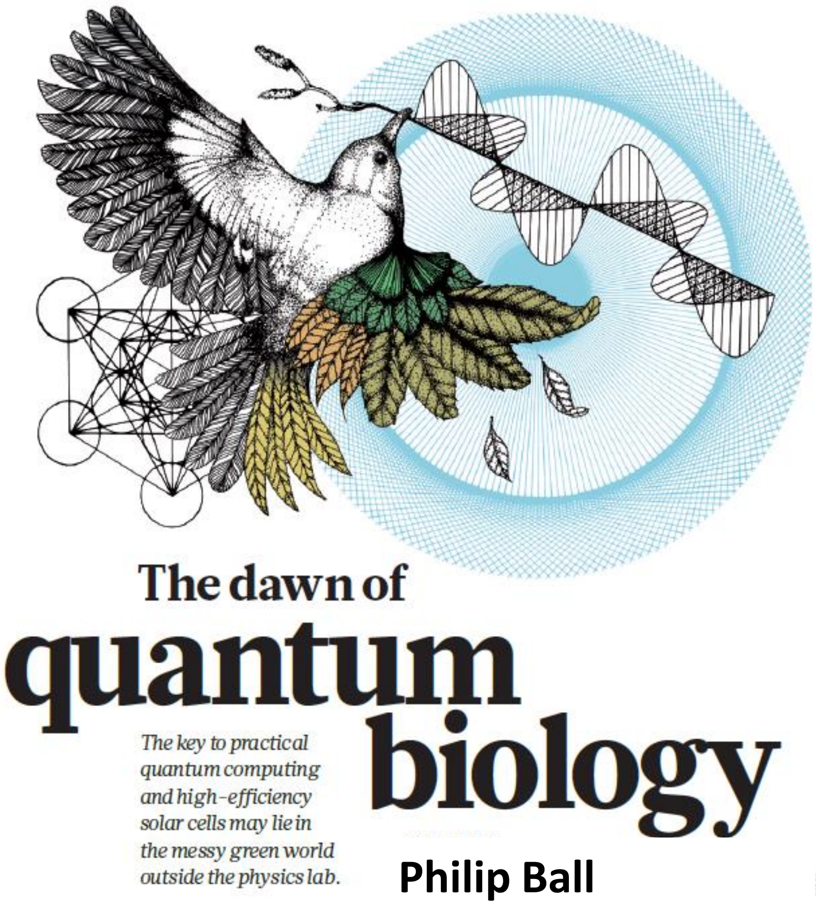
Frese et al. *Biophys. J* 94, 640 (2008)

Quantum Biology

Quantum Biology

Quantum biology is the field of study that investigates processes in living organisms that cannot be accurately described by the classical laws of physics.



Philip Ball
Nature 27 June 2011

Recommendable headline review:

Adriana Marais, …, Tjaart Krüger, Francesco Petruccione and Rienk van Grondelle, The future of quantum biology. *J. R. Soc. Interface* **15**: 20180640 (2018)

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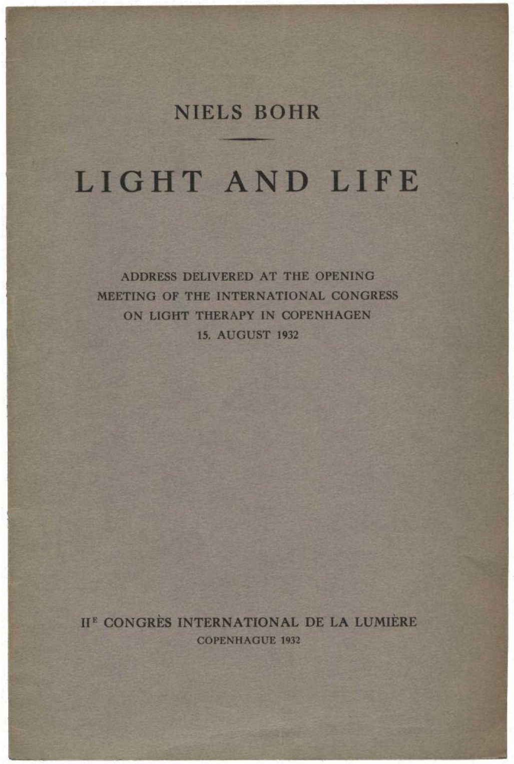
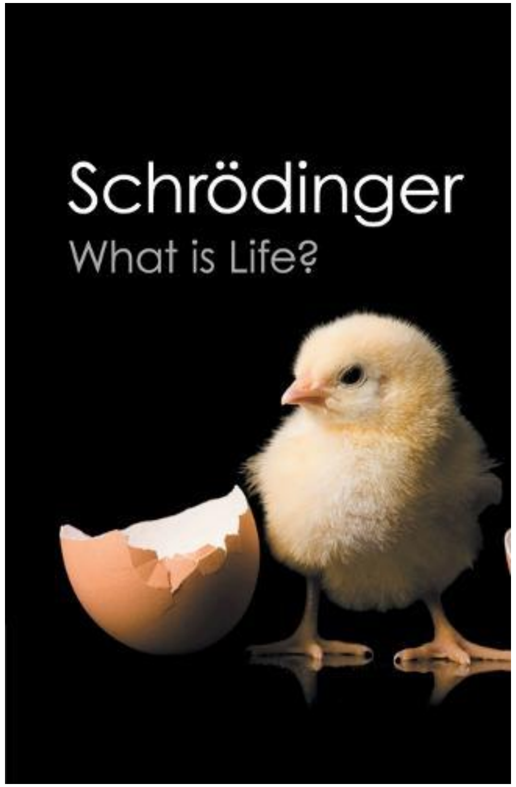
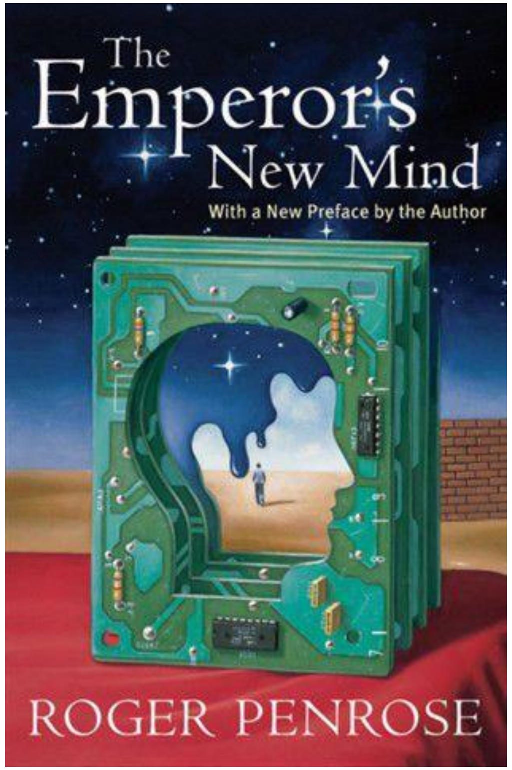
3 Historical Highlights



1932



1944



1989

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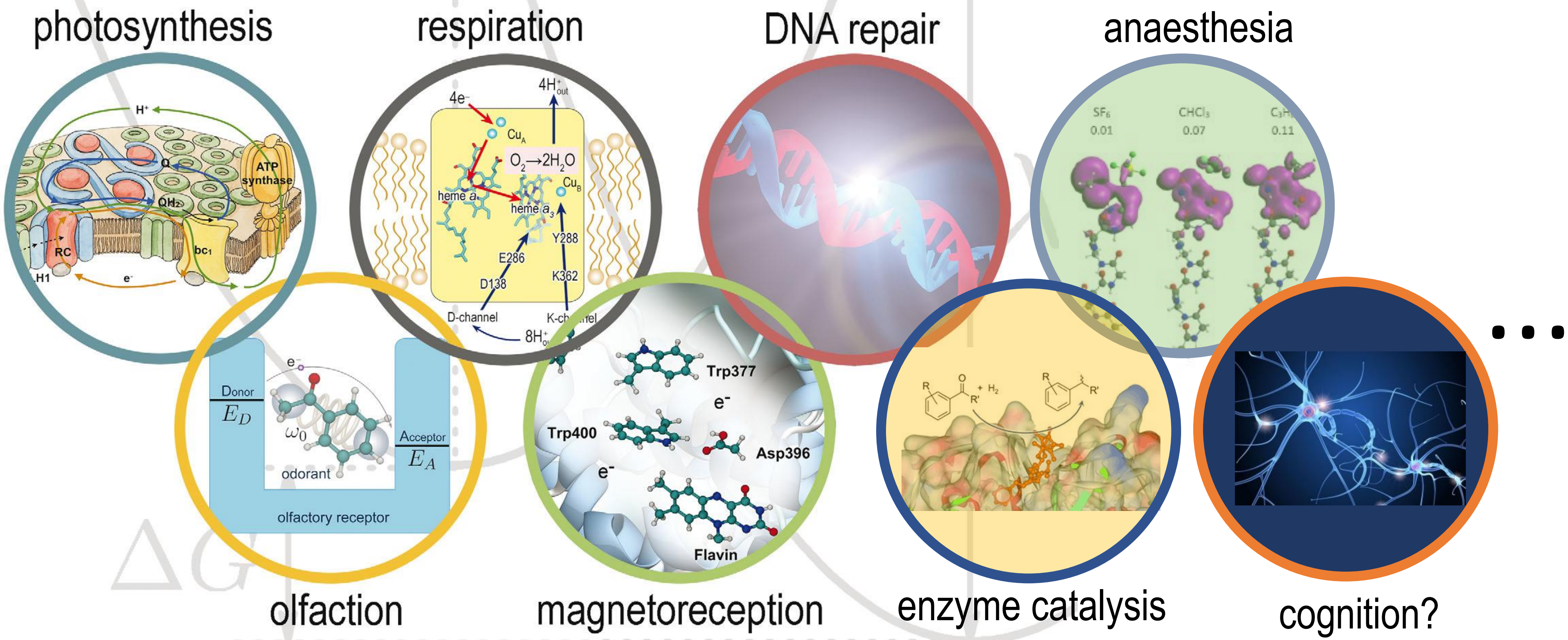
Quantum Biology

$$k_{et} = \frac{2\pi}{\hbar}|H_{AB}|^2 \frac{1}{\sqrt{4\pi\lambda k_B T}} \exp\left(-\frac{(\lambda + \Delta G)^2}{4\lambda k_B T}\right)$$



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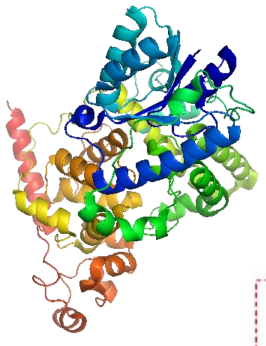
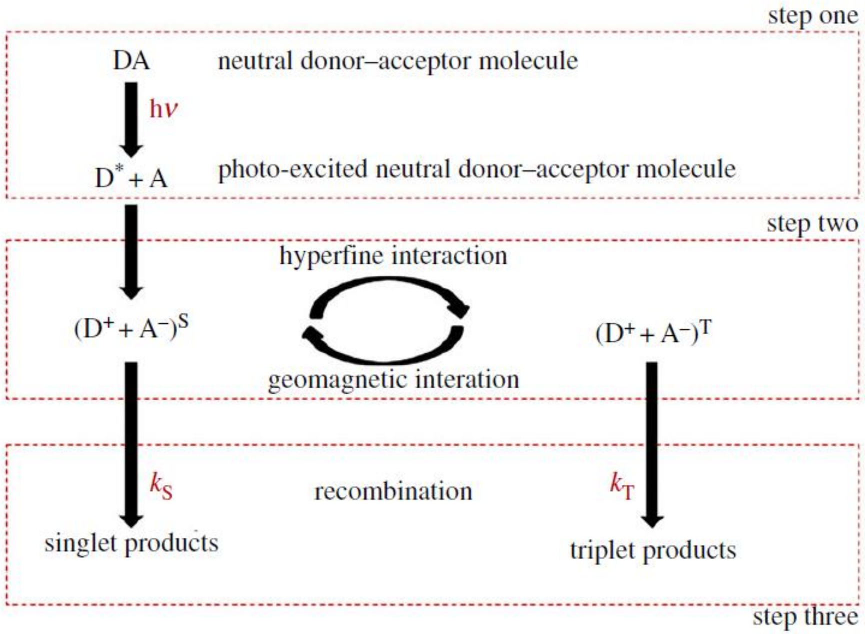
Picture adapted from the Theoretical and Computational Biophysics Group, Beckman Institute, University of Illinois at Urbana-Champaign

Quantum Biology: Magnetic Field Sensing

Breaking Symmetry with an Environment

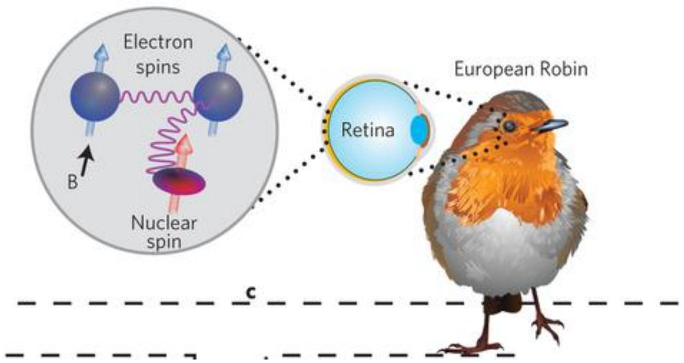


Cryptochrome



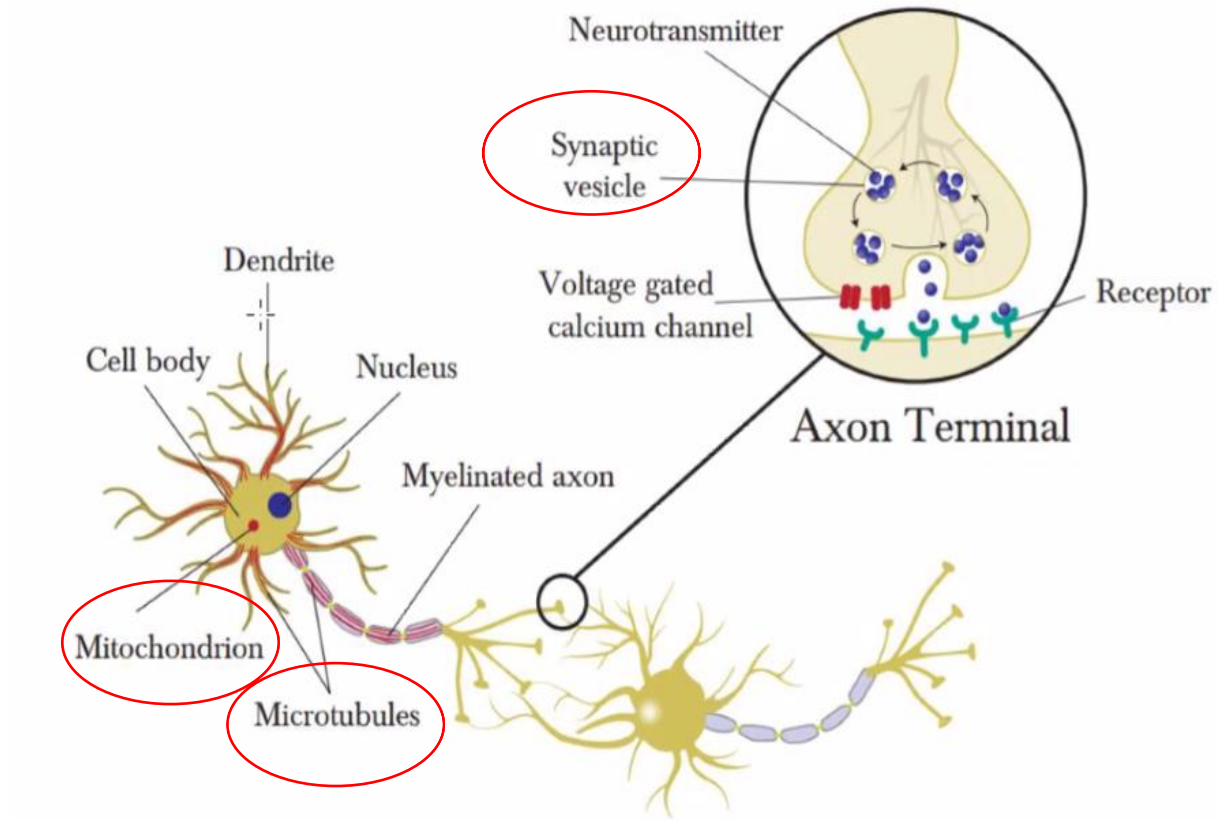
Marais et al. *J. R. Soc. Interface* **15**: 20180640 (2018)

Photon absorption creates radical pair in singlet state



Ritz, Adem, and Schulten., *Biophys. J.* (2000)

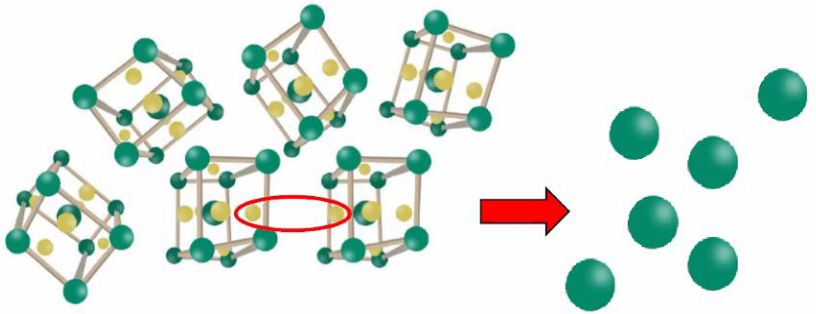
Quantum neurobiology?



- Signals are transported between nerve cells when the axon terminal of one cell connects with the dendrite of a neighbouring cell.
- The synaptic vesicles are also the site of the proposed uptake of Posner molecules during endocytosis.
- Non-trivial quantum effects may also take place in mitochondria and microtubules.

NUCLEAR SPIN ENTANGLEMENT

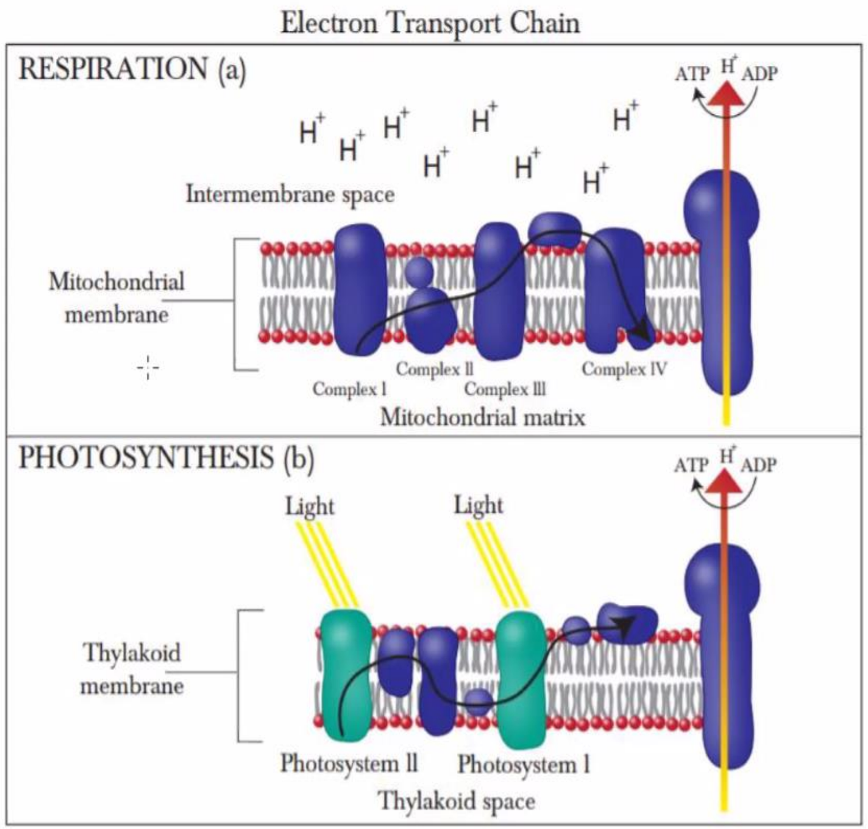
Posner molecules in extracellular fluids/nerves



Increased binding, increased calcium ions, increased neural firing

- Posner molecules are calcium phosphate clusters. Exceptionally long coherence times of the nuclear spins of these clusters have been reported.
- I.e., they may feature as “neural qubits” in a proposed mechanism for quantum processing in the brain.

Light-matter interactions

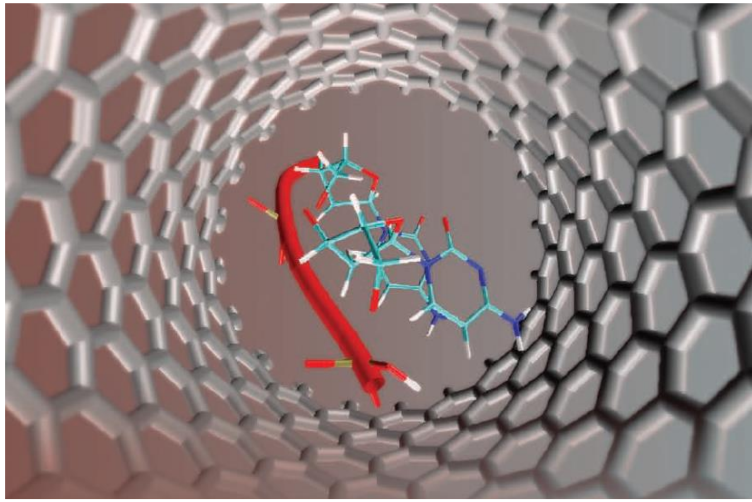


Source of biophotons:
- Lessening depression & brain damage
- Improving memory, learning & executive function
- Reducing Alzheimer’s & Parkinson’s diseases

Experimental examples

Nanobiophysics: a new thriving discipline

"Nanobiophysics is a new branch of science that operates at the interface of physics, biology, chemistry, material science, nanotechnology, and medicine."



Nanobiophysics research focuses on

1. the manipulation of single biomolecules,
2. development of interfaces between single biomolecules and single nanoparticles,
3. creation of new nanobiostructures and study of their properties,
4. bio-diagnostics and the development of biological sensing devices,
5. application of nanobiophysics in medicine and other biological applications,
6. unique experimental physical methods that are used to study nano-size biostructures.

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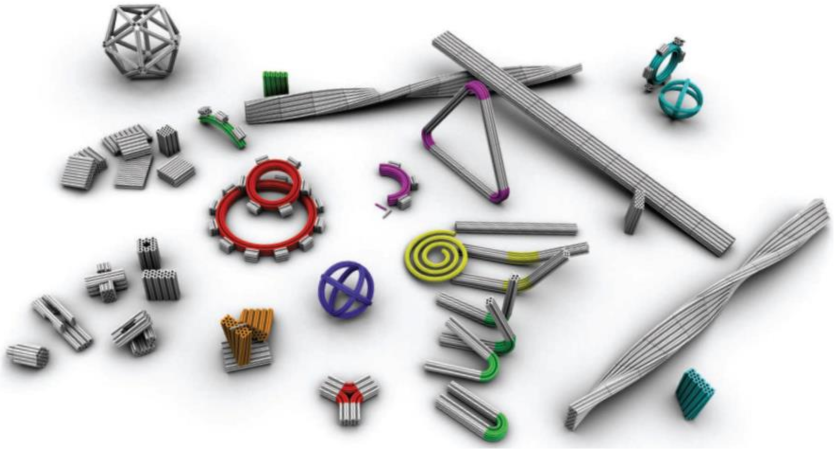
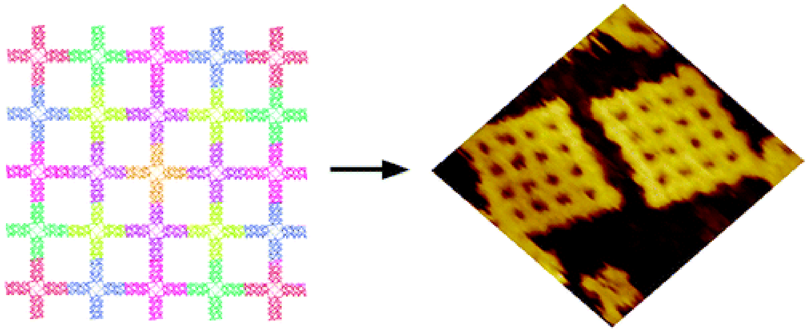
DNA Origami

Complex, self-assembling nanostructures

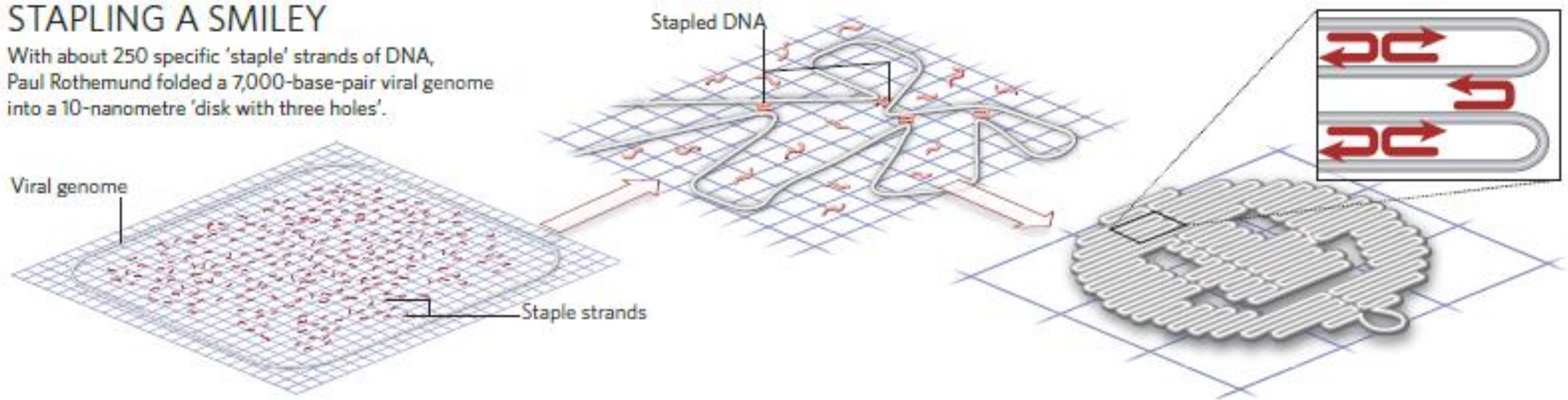


Sanderson *Nature* 464:158–159 (2010)

Self-assembly of DNA nanoarrays



Liu, Ke & Yan, *JACS* 127:17140-17141 (2005)



Rothemund *Nature* 440:297–302 (2006)

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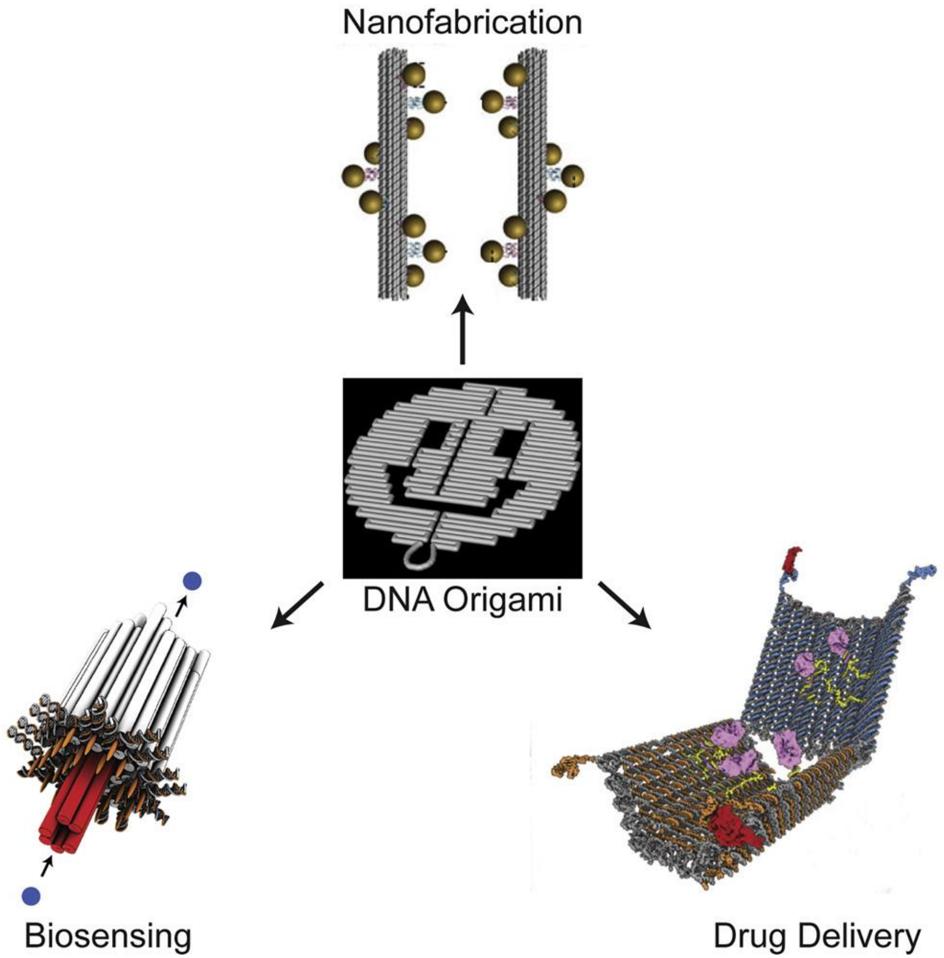
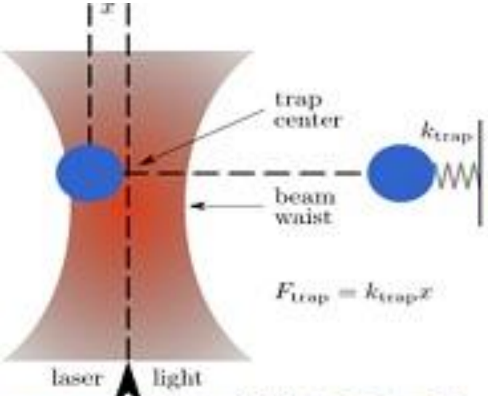
DNA Origami



Wang et al. Chem 2: 359-382 (2017)

Manipulation of single biomolecules:
Optical tweezers

Nobel Prize in Physics 2018



Arthur Ashkin

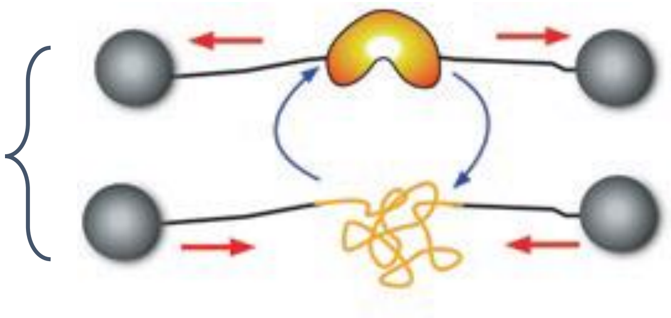
Affiliation at the time of the award: Bell Laboratories, Holmdel, NJ, USA

Prize motivation: "for the optical tweezers and their application to biological systems."

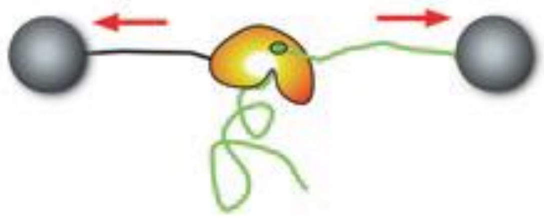
Prize share: 1/2

Manipulation of single biomolecules:
Optical tweezers

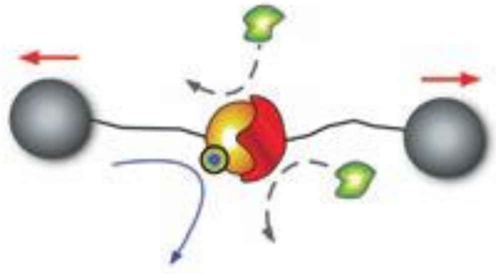
protein unfolding and folding



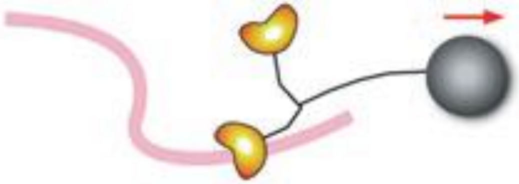
DNA binding proteins



ligand-receptor bonds

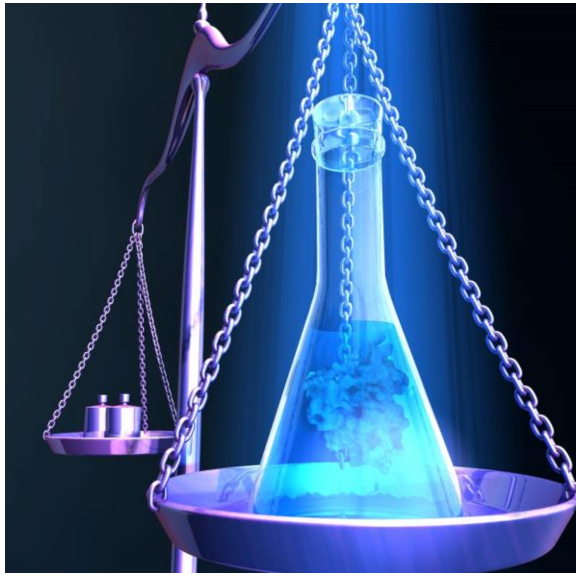


cytoskeletal motor proteins

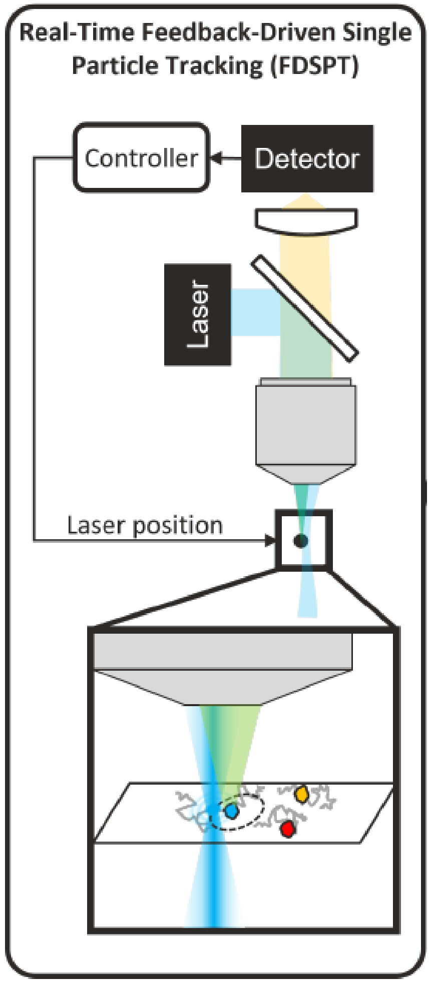


Dufrêne et al. (2011) Nature Methods

Weighing or tracking a single protein with light



Young et al. *Science* **360**, 423–437 (2018)



van Heerden et al. *Small* 2107024 (2022)

interferometric scattering (iSCAT)

$$I_{det} \propto |rE_i + sE_i|^2 = |E_i|^2(r^2 + 2r|s|\cos\theta + |s|^2)$$

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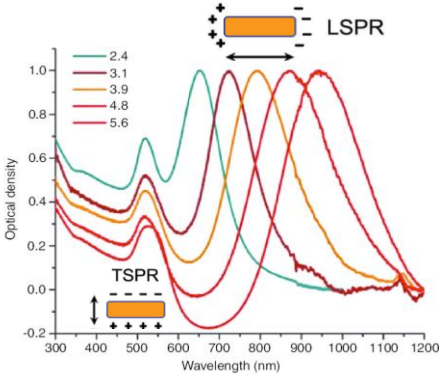
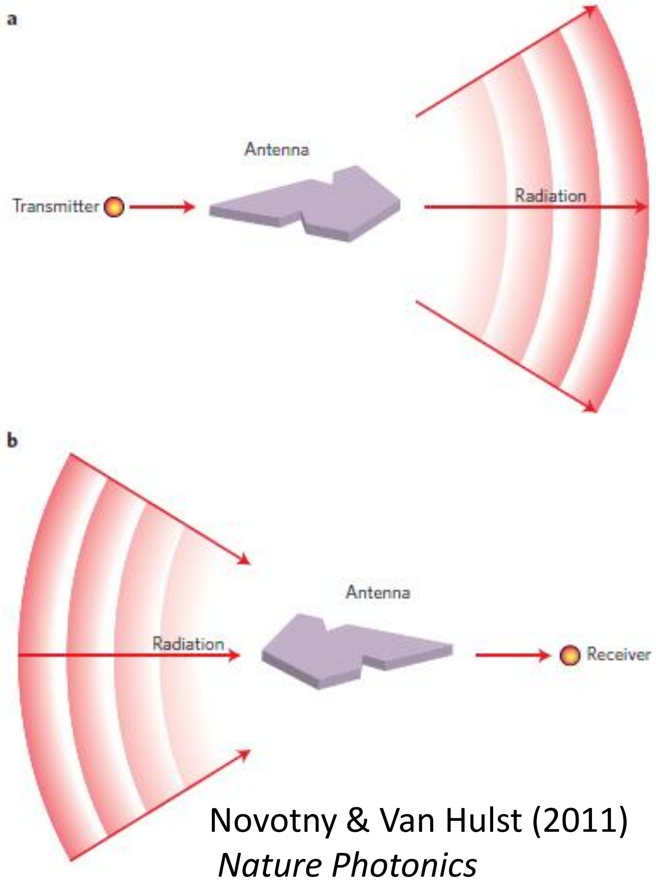
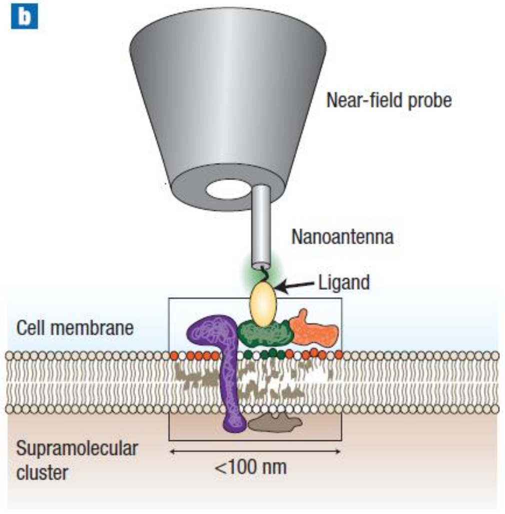
Single biomolecule–metal nanoparticle interactions

Localisation & enhancement of optical radiation at the nm scale





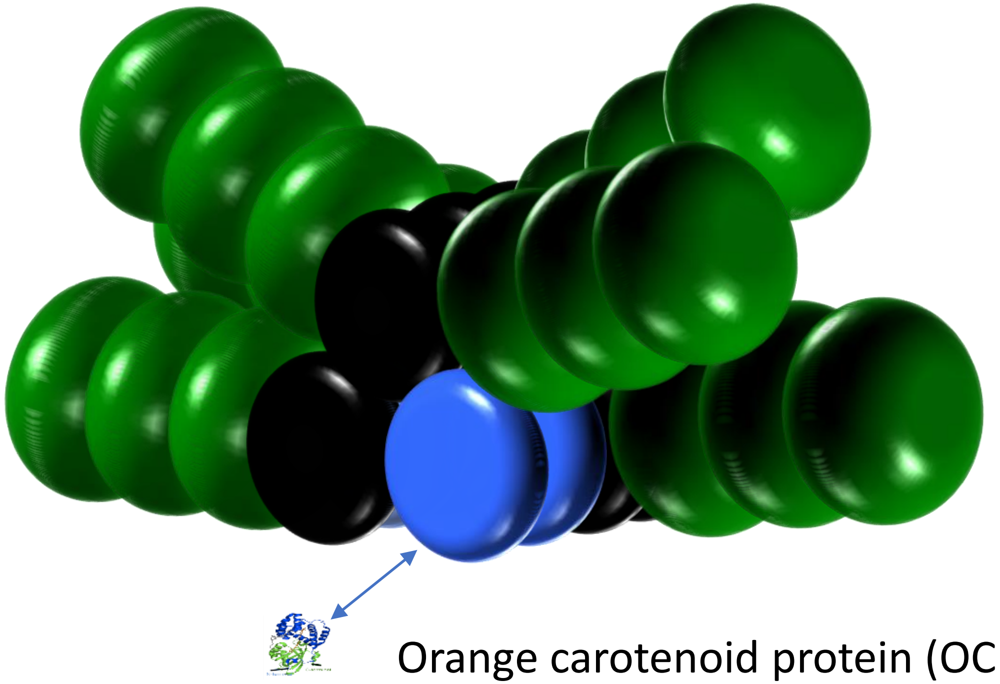
Novotny & Van Hulst (2011) *Nature Photonics*

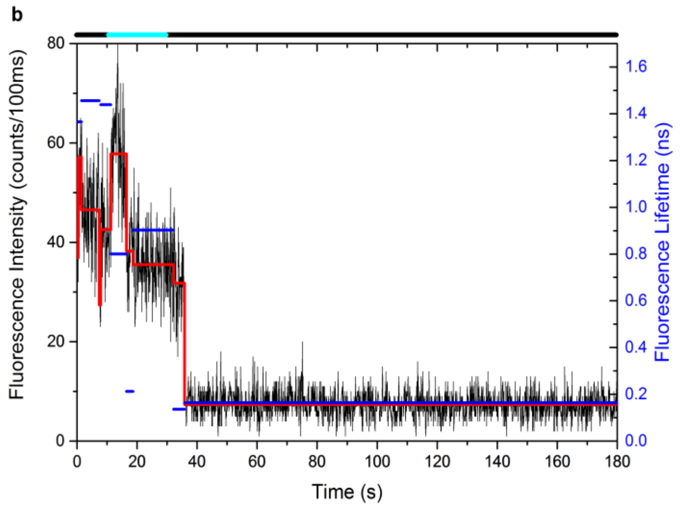


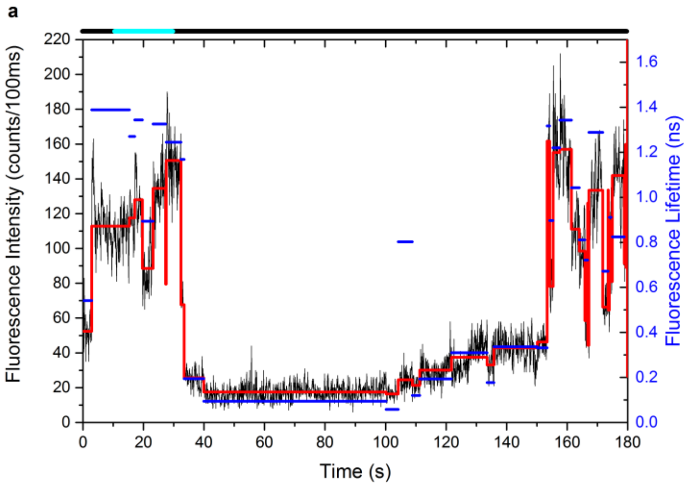
Garcia-Parajo (2008) *Nature Photonics*

Some Applications:
- Biosensors
- Optical imaging (~10 nm)
- Single particle tracking in live cells
- Photothermal therapy
- Solar cells (Light harvesting & energy conversion)
- Nanoscale optical circuitry
- Enhanced photoabsorption & emission

Switching a protein function on and off







Gwizdala, Botha, Wilson, Kirilovsky, van Grondelle & TPJK, "Switching an individual phycobilisome off and on"
J Phys Chem Lett 9:2426-2432 (2018)

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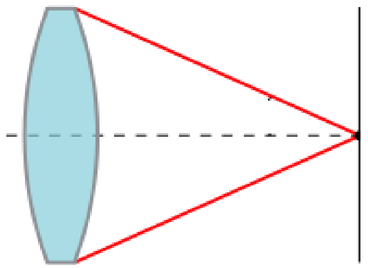
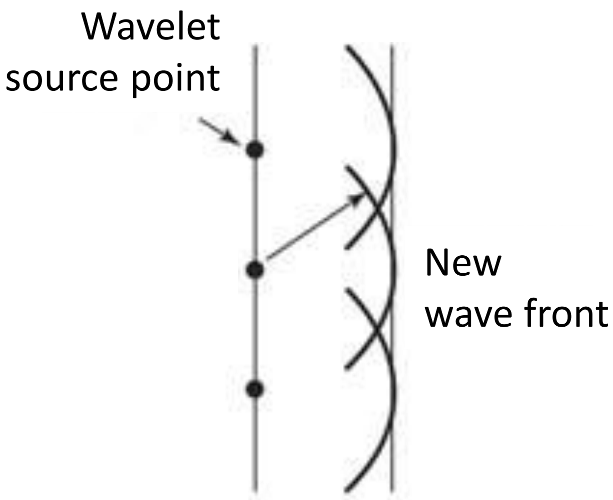
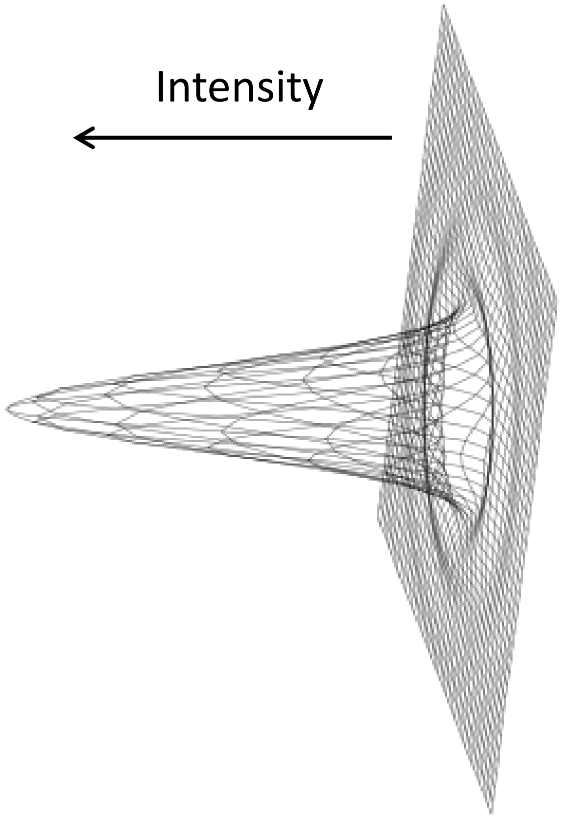
Superresolution imaging / Nanoscopy





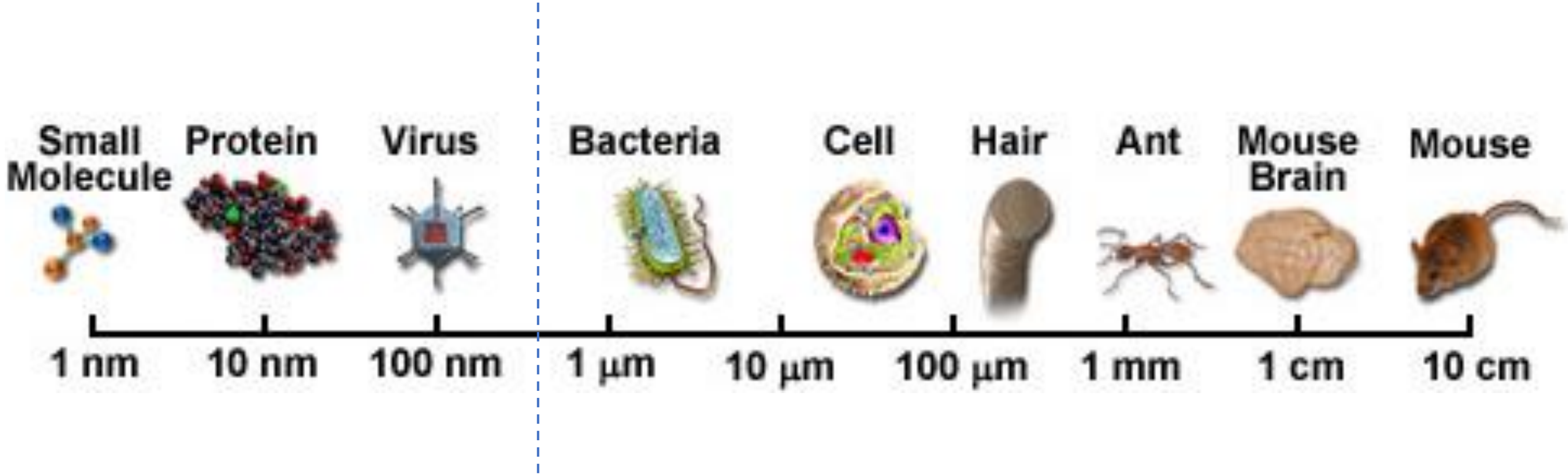
Huygens' Principle



Fraunhofer Diffraction

Superresolution imaging / Nanoscopy

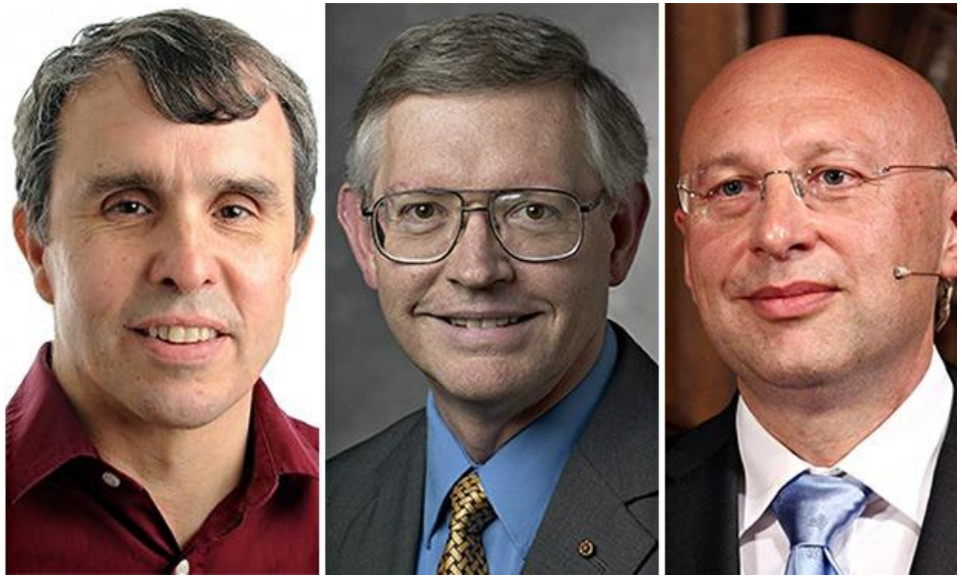
The diffraction limit



Abbè's diffraction limit ~ λ/2
I.e. ~200 nm with blue light (400 nm)

Superresolution imaging / Nanoscopy

Nobel Prize in Chemistry 2014



Eric Betzig WE Moerner Stefan Hell

Stochastic localisation microscopy (PALM/STORM)

Deterministic depletion (STED)

Both techniques can give a resolution down to ~10 nm using light!

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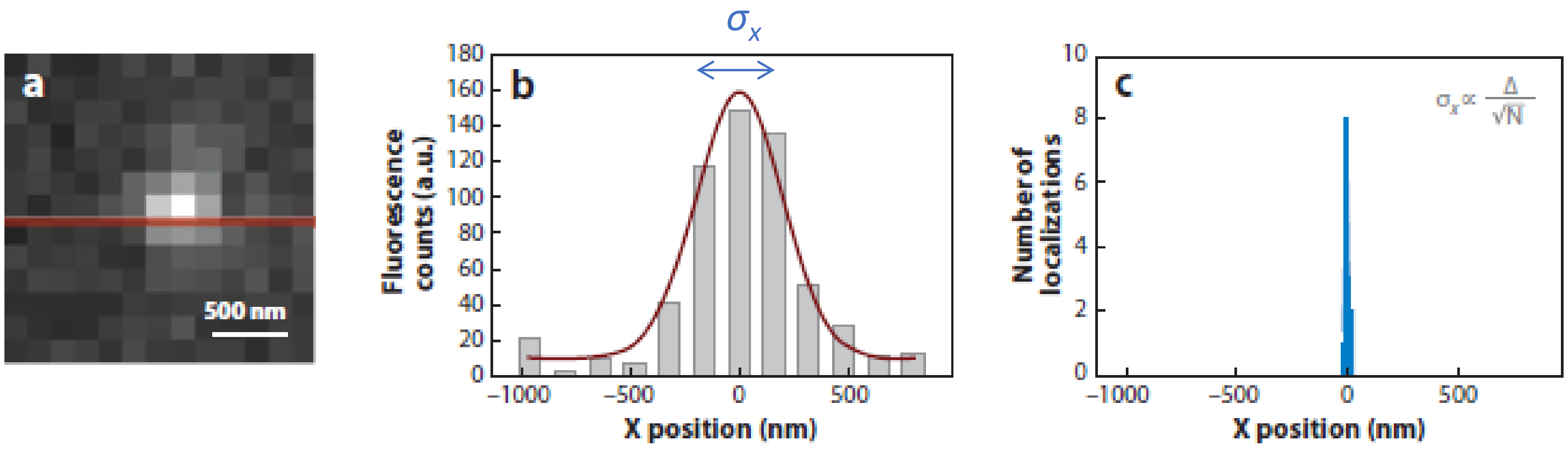
Superresolution imaging / Nanoscopy

STORM/PALM: Single molecule localisation with ~10 nm precision



Localisation ≠ resolution

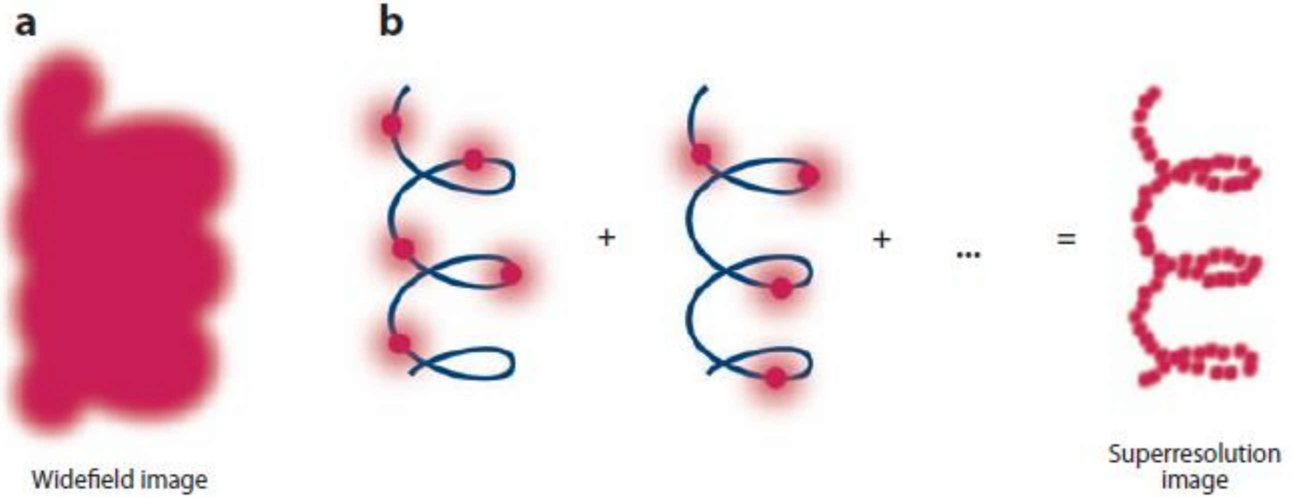
$$\sigma_x \approx \frac{1}{\sqrt{N}} \frac{\lambda}{2NA} = \frac{r_{Abbe}}{\sqrt{N}}$$

$$NA = n \sin\theta$$

Thompson MA, Lew MD, Moerner WE *Annu Rev Biophys*. 41:321-342 (2012)

Superresolution imaging / Nanoscopy

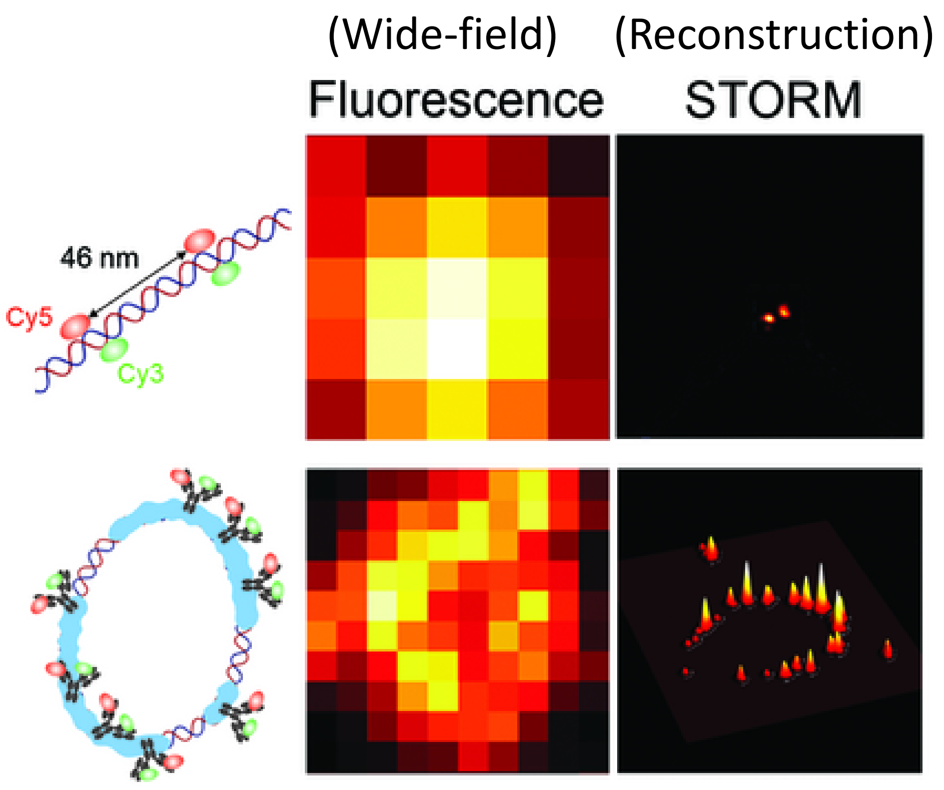
Principle of STORM/PALM:
Stochastic (de)activation of sparse subsets



Thompson MA, Lew MD, Moerner WE *Annu Rev Biophys*. 41:321-342 (2012)

Superresolution imaging / Nanoscopy

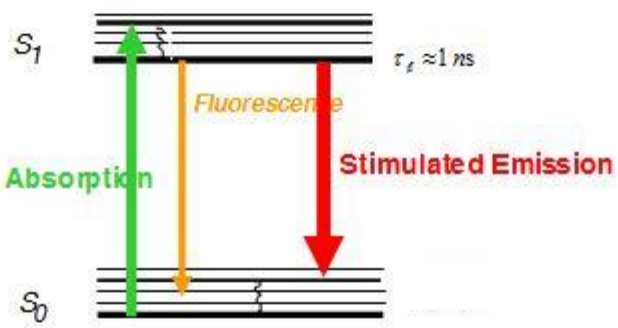
STORM: STochastic Optical Reconstruction Microscopy

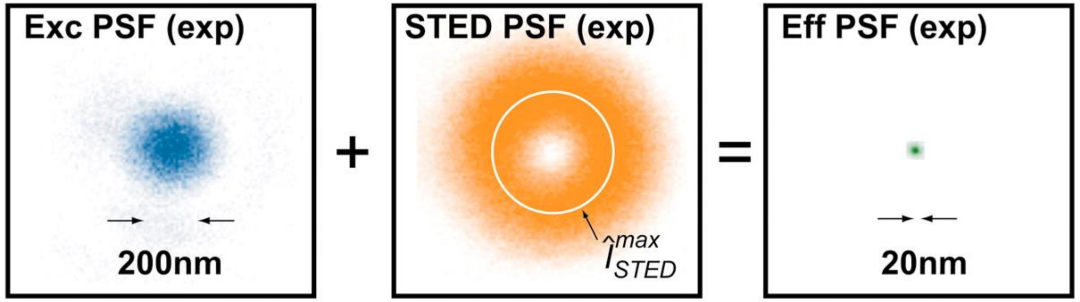


Rust et al. *Nature Methods* 3:793 (2006)

Superresolution imaging / Nanoscopy

Stimulated emission depletion (STED) microscopy

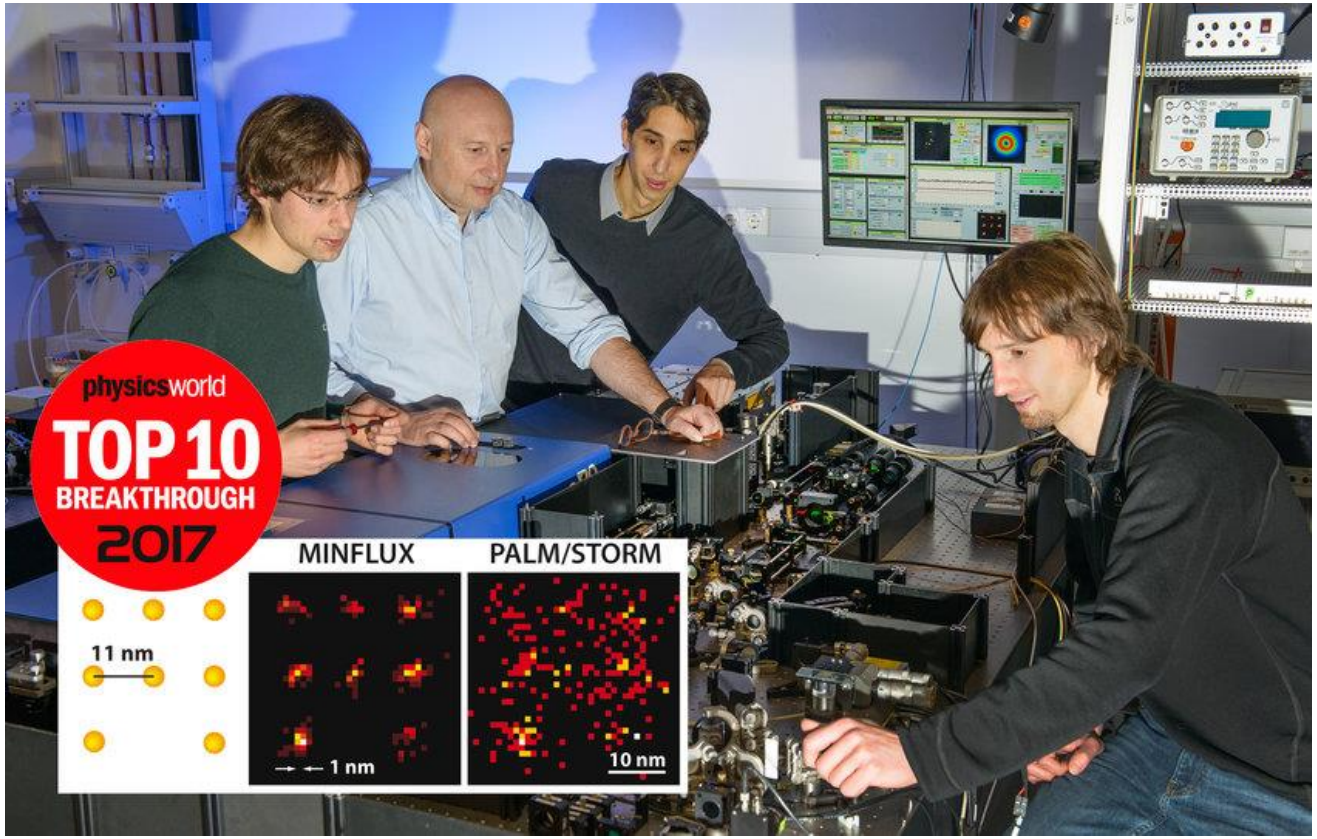




$$r_{\min} = \frac{\lambda}{2n\sin\theta}\frac{1}{1+\frac{I_0}{I_{sat}}}$$

Superresolution imaging / Nanoscopy

MINFLUX combines the two approaches to yield a resolution of 1 nm!



Balzarotti et al. *Science* 355:606-612 (2017)

Take-home messages

- Biophysics is an amazingly beautiful and diverse research discipline!
- It has already demonstrated profound advances in science and technology and is predicted to grow much further in the decades to come.
- This discipline offers an extraordinary broad range of important applications that are vital for the success of the African economy.

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A few animations to get you inspired

- The Inner Life of the Cell: https://www.youtube.com/watch?v=QplXd76lAYQ
- The Inner Life of the Cell: Protein Packing https://www.youtube.com/watch?v=uHeTQLNFTgU
- ATP synthase in action: https://www.youtube.com/watch?v=kXpzp4RDGJI
- The Molecular Basis of Life: https://www.youtube.com/watch?v=fpHaxzroYxg
- Powering the Cell: https://www.youtube.com/watch?v=ahf2HqY_vGg
- Neuronal signalling: https://pdb101.rcsb.org/learn/videos/neuronal-signaling-and-sodium-potassium-pump

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@TjaartKrueger

YouTube https://www.youtube.com/@biophysicsattheuniversityo7970/videos
(Biophysics at University of Pretoria)

Research Homepage: https://www.up.ac.za/physics/article/1821193/biophysics-research-group

- **The African Biophysics Landscape: A Provisional Status Report: https://arxiv.org/abs/2303.14456**
- **Biophysics in Africa: challenges, priorities, and hopes: https://arxiv.org/abs/2403.05609**

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