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

Here is a (partial) list of wishes

- **Protein folding and functioning**
- Protein docking and recognition
- Immunological recognition
- Gene expression and regulation
- **Metabolic networks**
- System biology
- etc.

- Protein/DNA interactions
- **Amyloid aggregation**
- Memory and networking
- miRNA/siRNA
- Signal transduction
- **Nano-bio devices**
- etc.

Not to talk about the ultimate goal,
of curing all possible diseases

What we would like to know about METABOLIC NETWORKS

A

Structure → Dynamics

Network topology, kinetic properties, enzyme amounts

Steady states, transitions, oscillations, chaos

time scale of a living organism
10^{-3} - 10^{2} years

B

Physical constraints

Free energy changes, upper limits for concentrations

Biological function

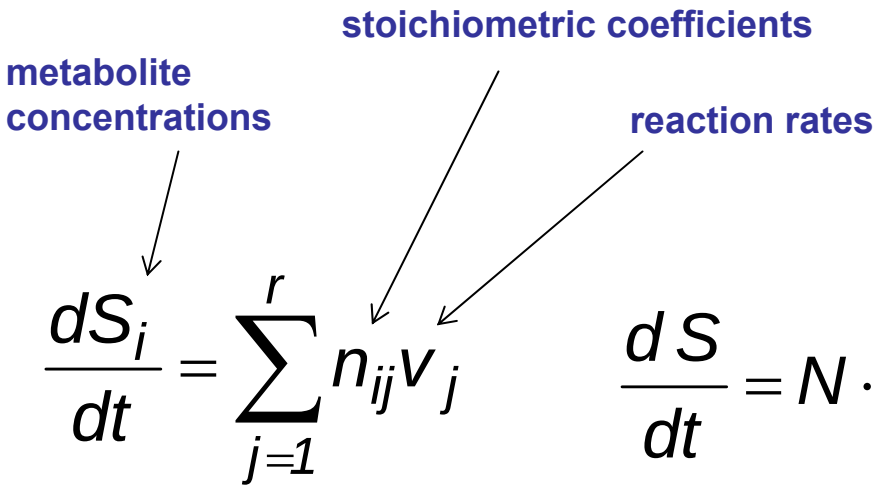
ATP-production, special chemical conversions (e.g. hexoses into pentoses) fitness properties

→ Structure

Network topology, kinetic properties, enzyme amounts

evolutionary time scale
10^{8} – 10^{9} years

SIMULATION MODELS



Attractors, Chaos (?)

Robustness

Recovery of function

Kinetic parameters

large number 10-1000 of variables

large number 10-1000 of equations

non-linearity

regulatory loops

separation of time scales

natural selection of kinetic parameters

What we would like to know about PROTEINS

even tiny atomic displacements matter

- primary structure → folding → function
  linear 3D conform. switches
  - predict geometry and dynamics of folding and conformational changes
    3D times e.g. heme, rhodopsin
  - predict function
    motif conservation, structural similarity
- evolution/selection → #10^7 among $(\#10^2)^{20}$ possibilities
  folding vs aggregation?
  - understand mis-folding and aggregation
    Mad cow (Prion), Amyloidosis (e.g. β-amyloid in Alzheimer disease)
- recognition/docking
  Ab *vs* Ag, …, transcription factors, promoters, …
  - characterize macromolecules binding
  - clarify molecular mimicry and auto-immune reactions

SIMULATION MODELS

Coarse grained models

- **how general is folding?**
  - Geometrical considerations
  - Lattice models
  - Statistical Mechanics

→ **spin glasses**

Atomistic models

- **classical**
  - Minim. of config. energy (no entropy)
  - Canonical/micro-canonical simulations
  - Multi-canonical simulations
- **QM/MM**

→ **"right" ensemble?**
"right" thermodynamic variables?

- **QM**
  - Quantum Chemistry
  - DFT
  - Car-Parrinello dynamical simulations

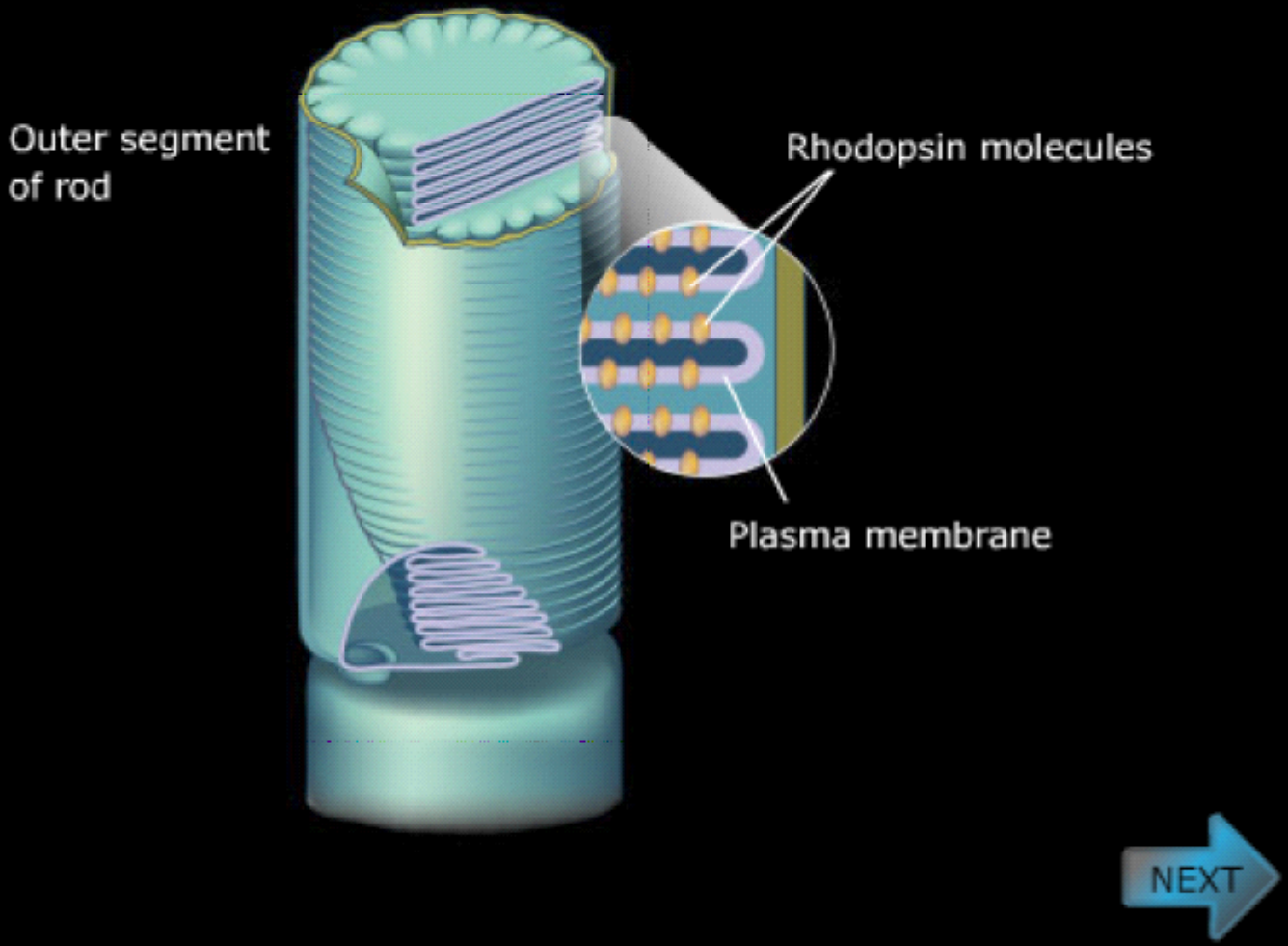
even tiny atomic displacements matter

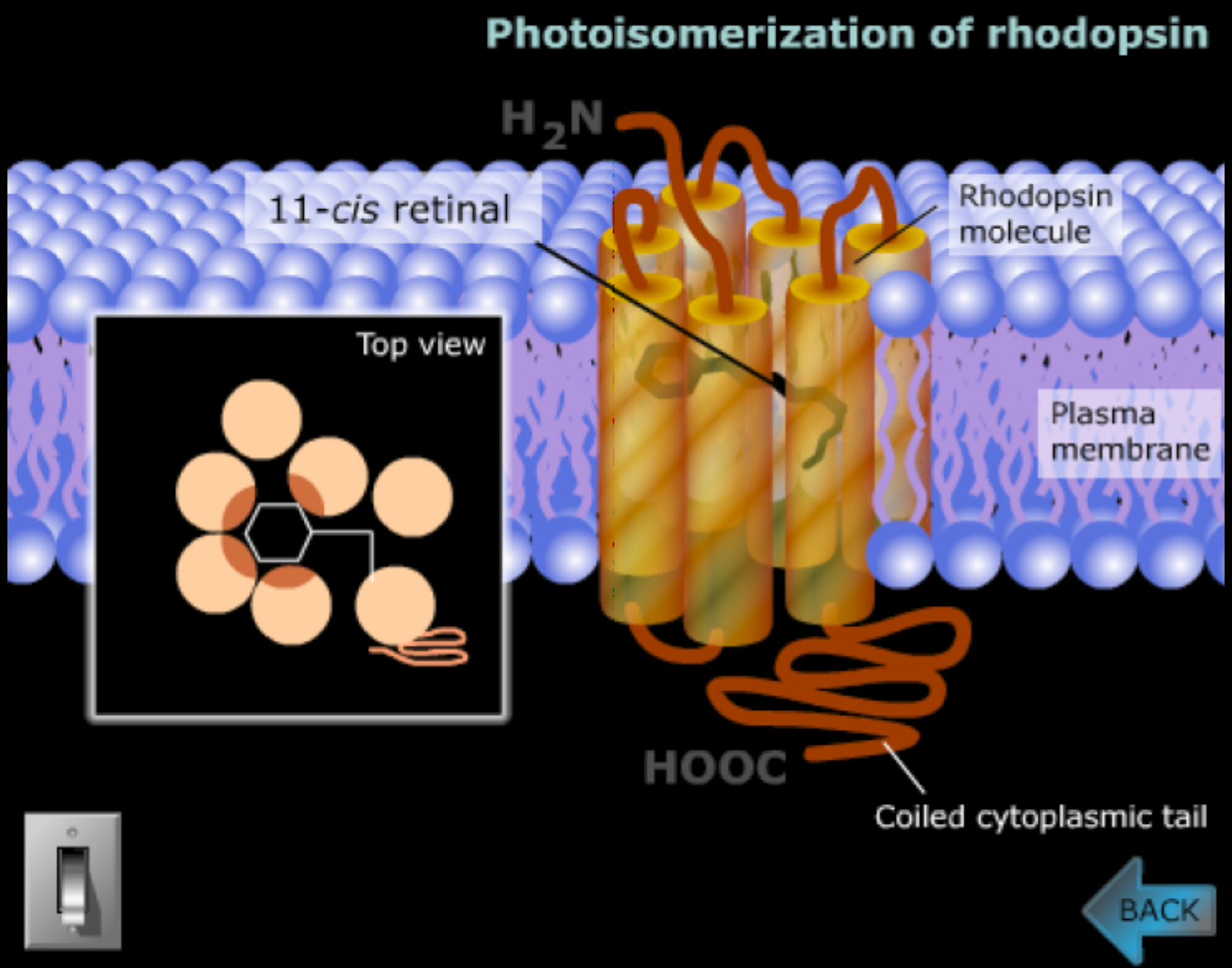
Two examples, among ∞-ly many

I. Cis →Trans isomerization of 11-cis retinal

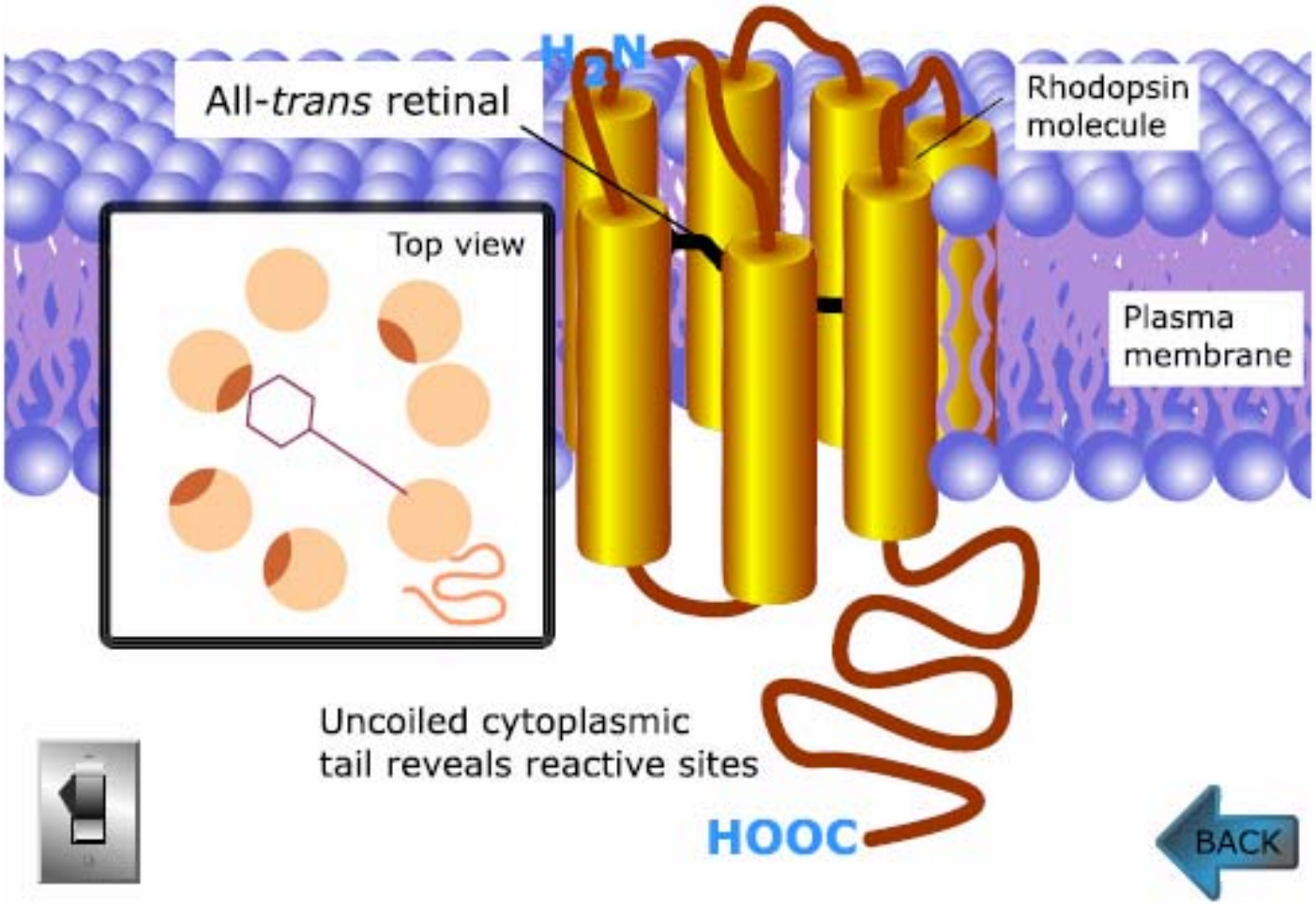
II. Hemoglobin “breathing”

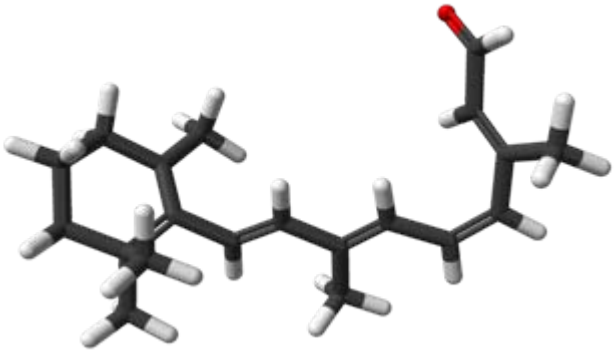
Photoisomerization of rhodopsin

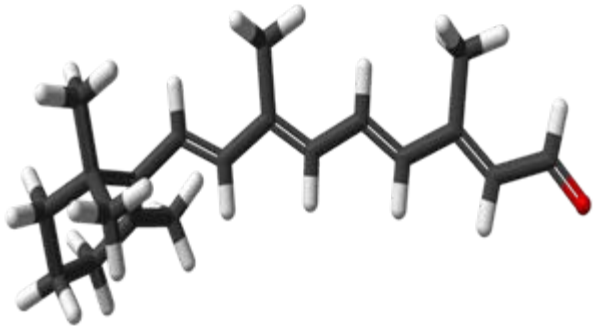


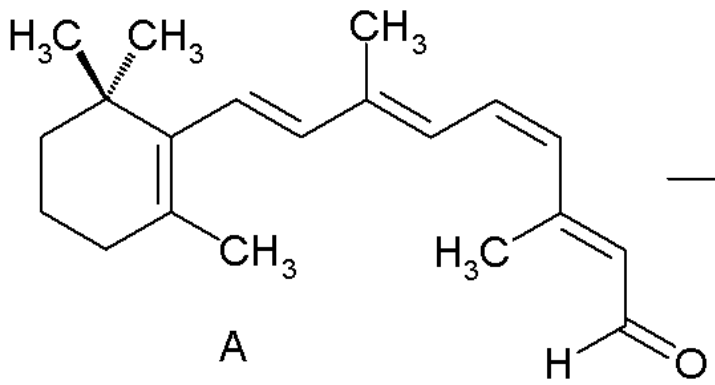

Photoisomerization of rhodopsin
H_2N
11-*cis* retinal
Rhodopsin molecule
Top view
Plasma membrane
HOOC
Coiled cytoplasmic tail
BACK

Photoisomerization of rhodopsin





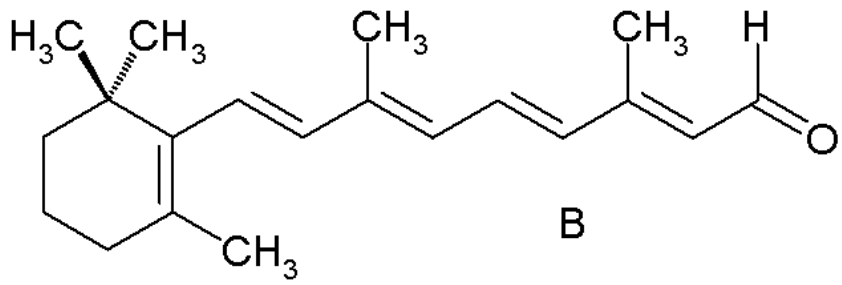




light

γ

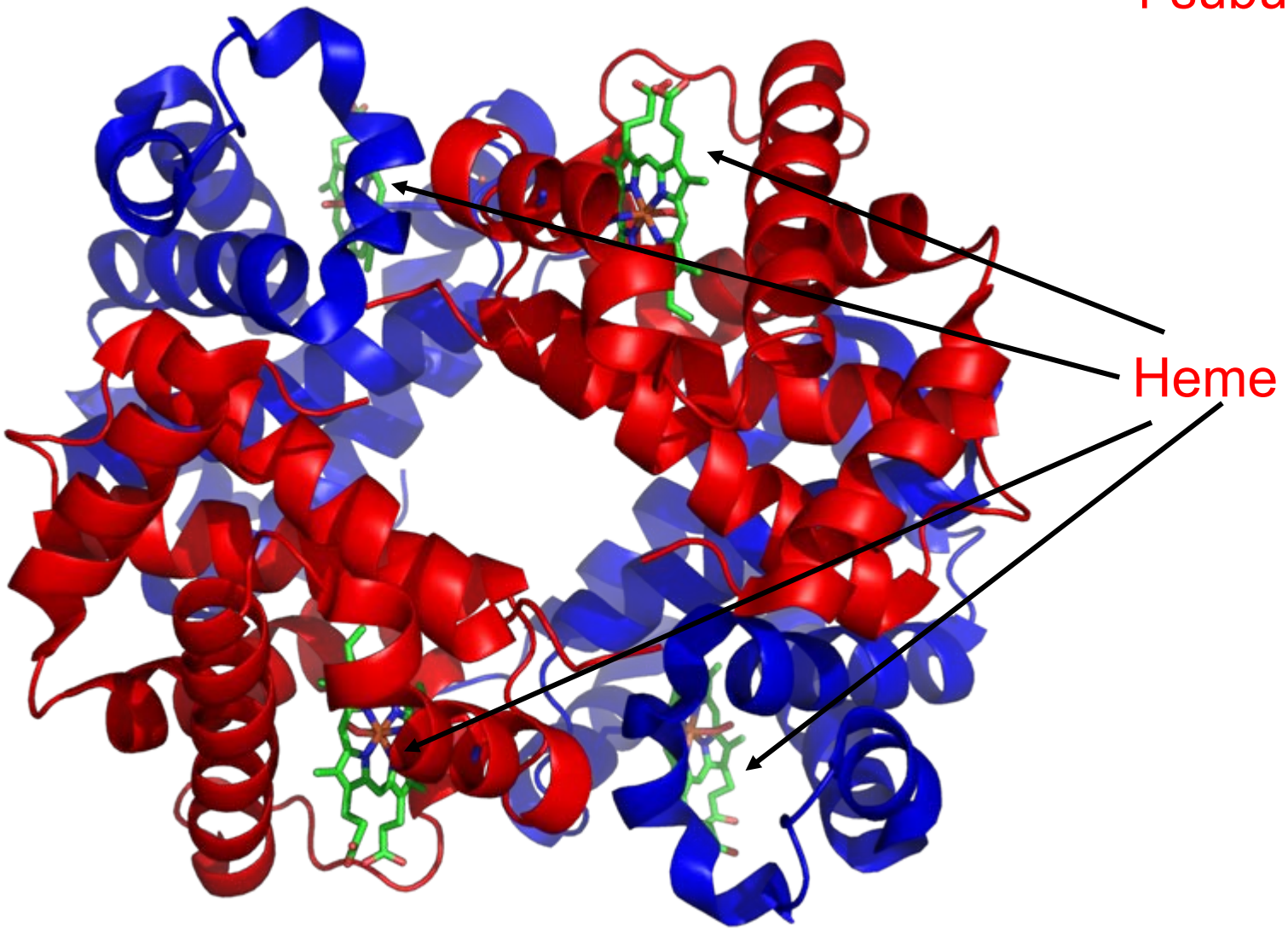
11-cis retinal

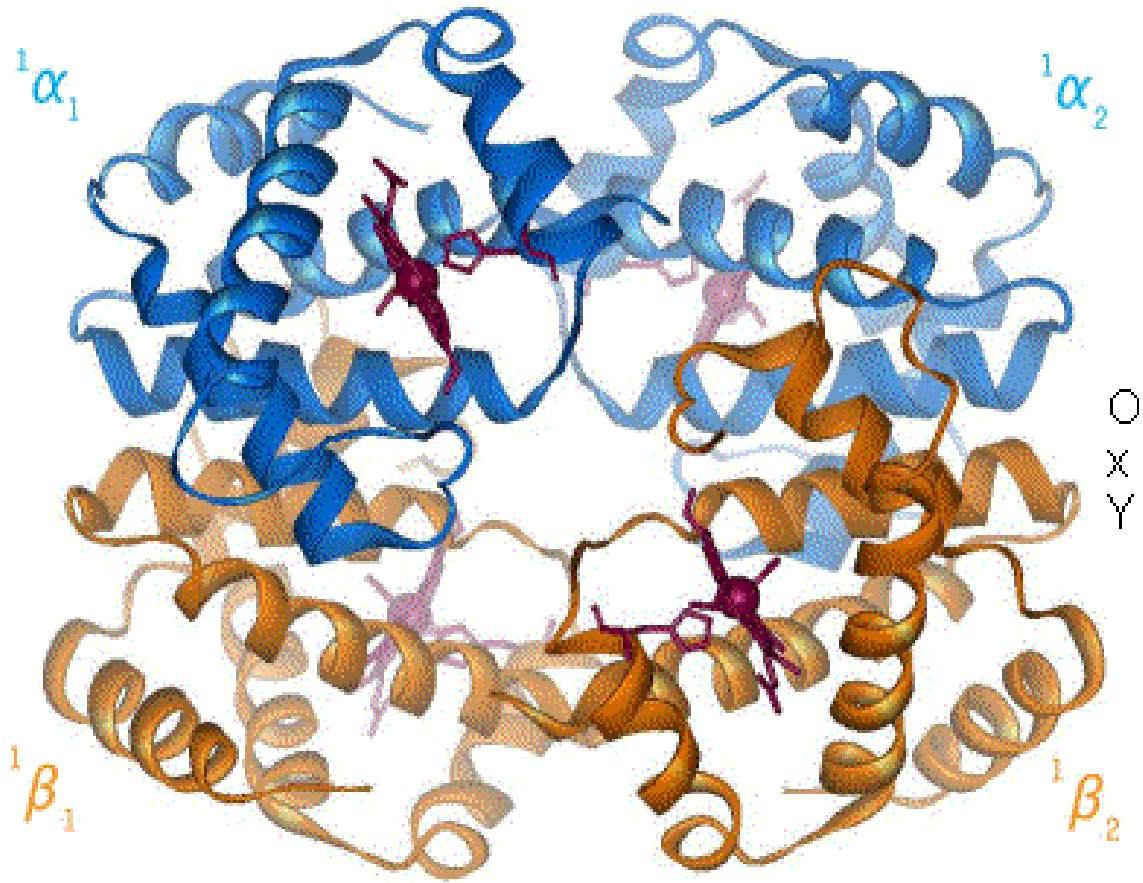


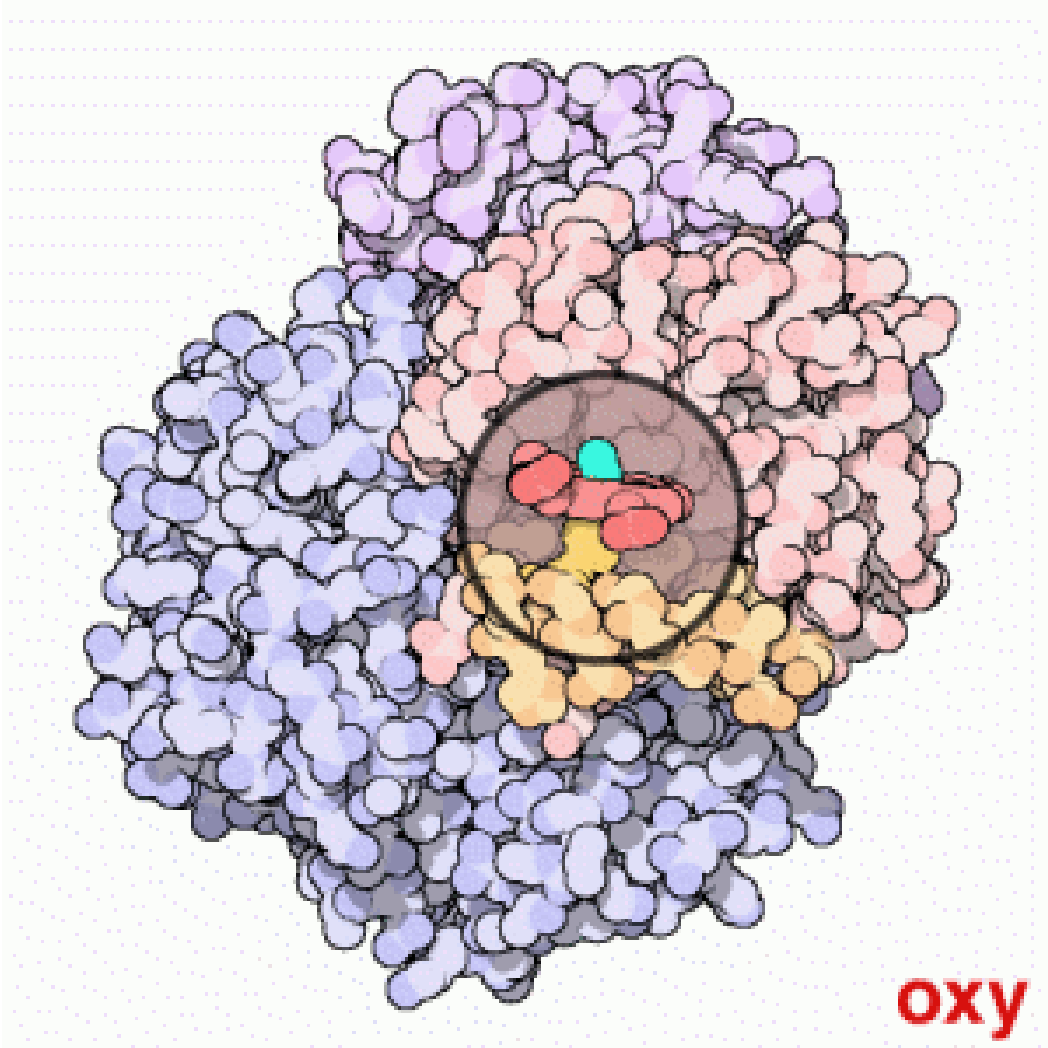
all-trans retinal

Hemoglobin

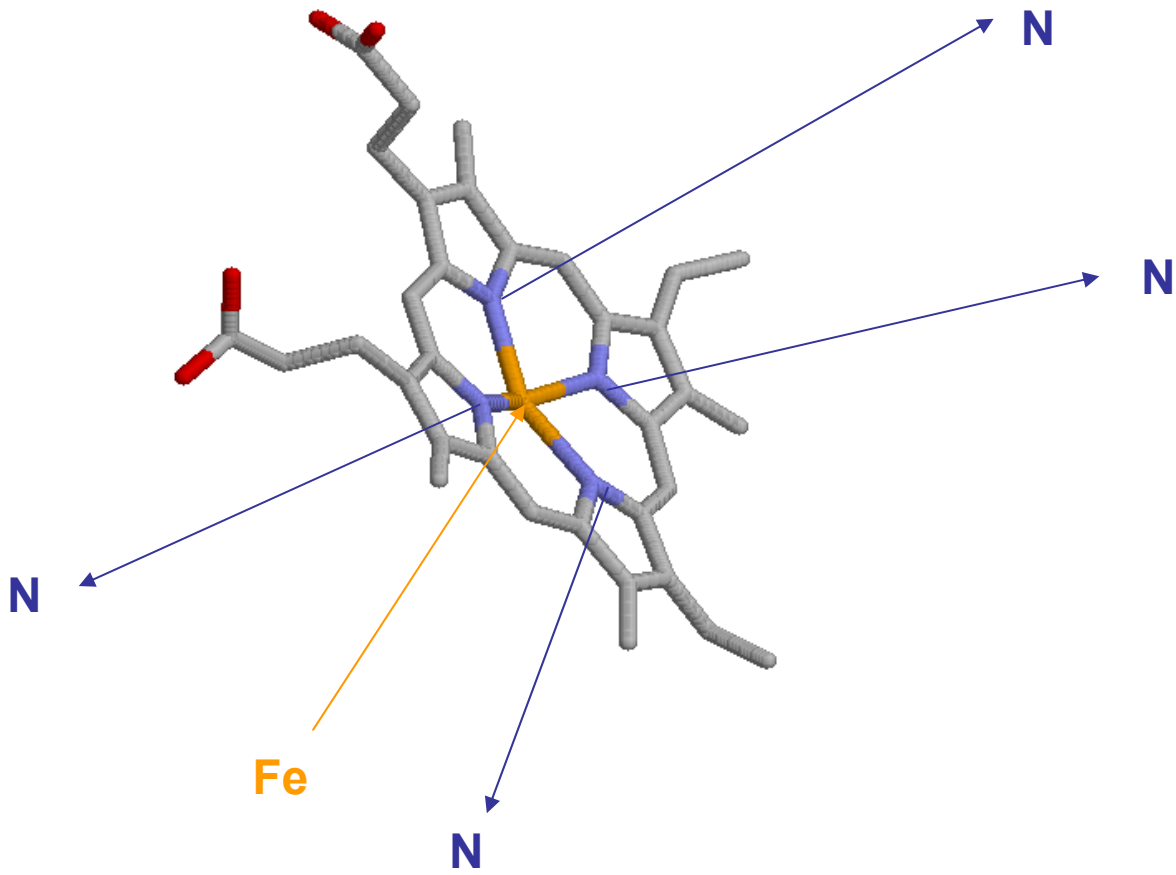
4 subunits



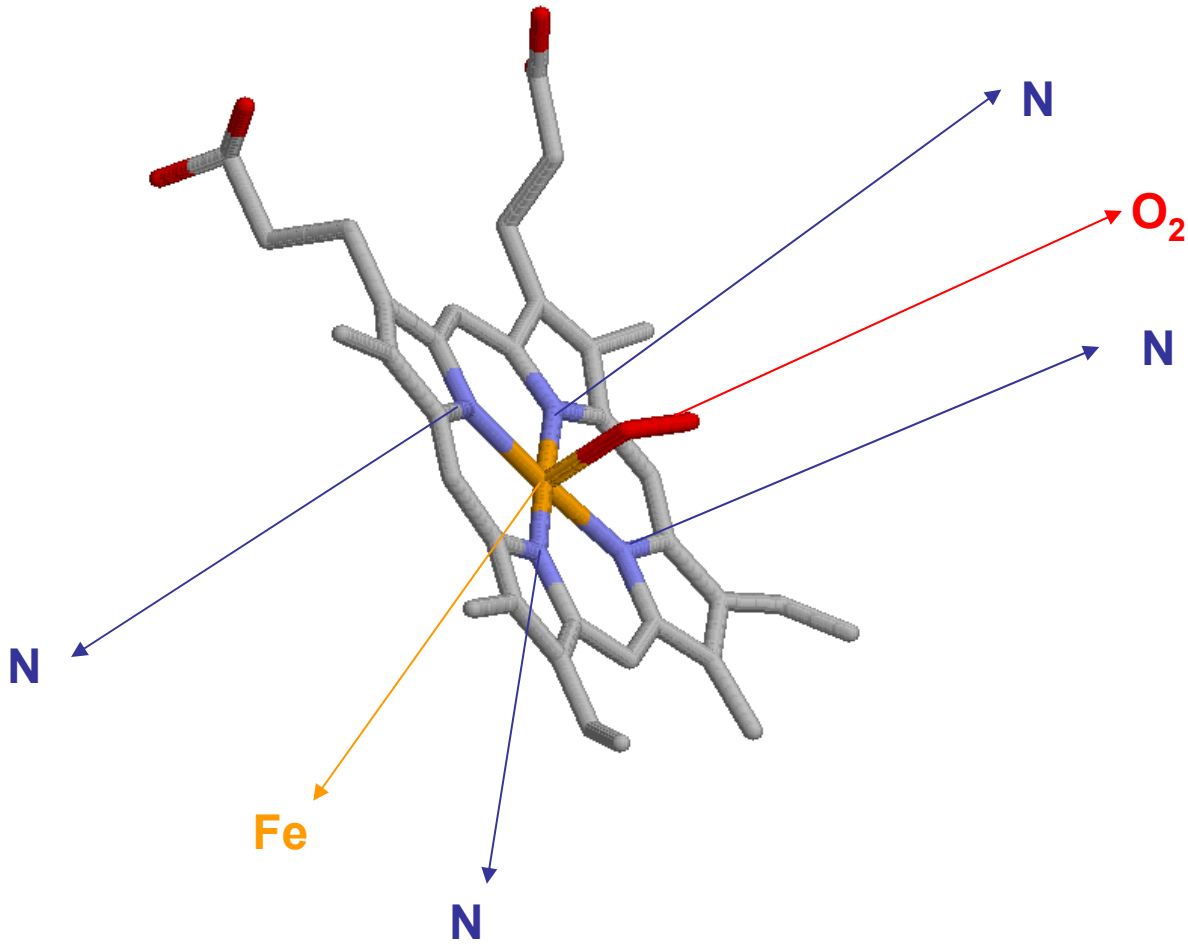

$^1\alpha_1$
$^1\alpha_2$
O
X
Y
$^1\beta_1$
$^1\beta_2$


oxy

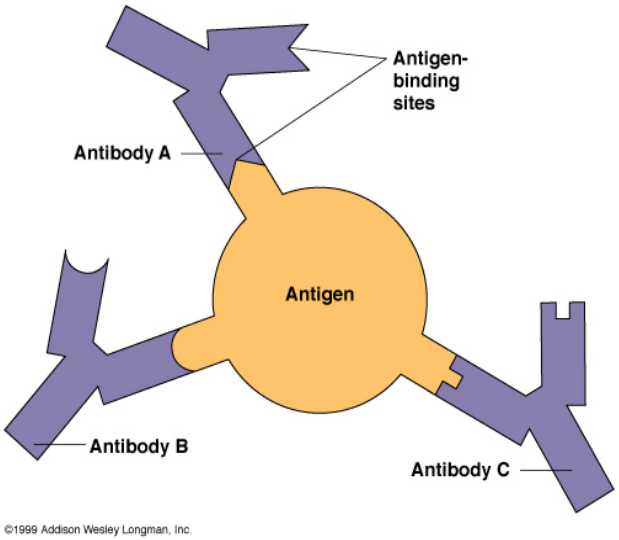
Deoxi-hemoglobin

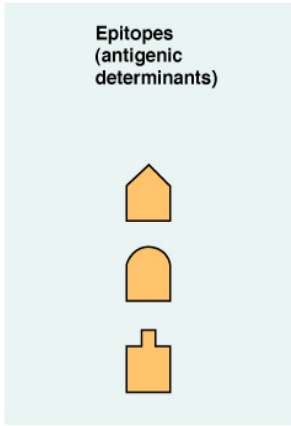


Oxi-hemoglobin



Antigen-functionalized Nanotube for disease diagnosis

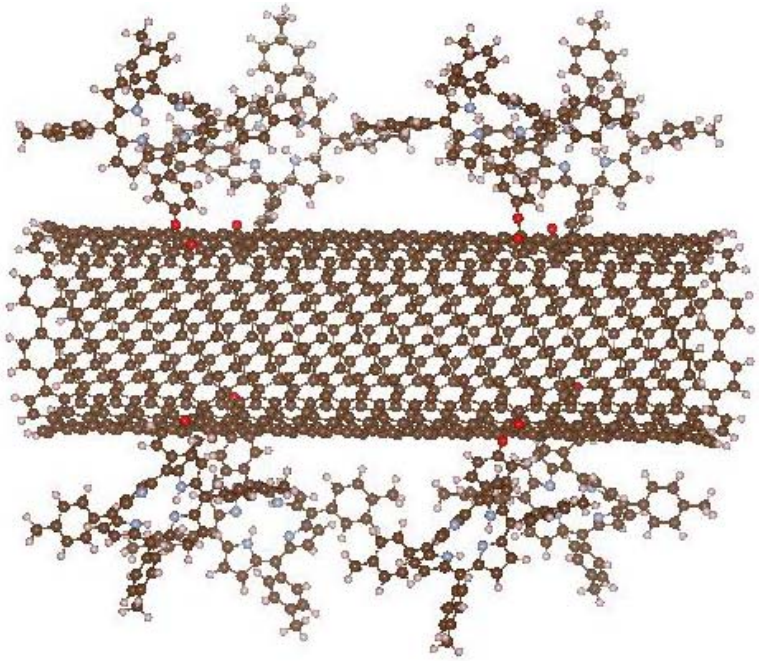




- Specific Antibodies Ab are produced in response to an external Antigen Ag (like a viral or bacterial protein)
- If you have been infected by Ag_A, you will produced Ab_A, detectable in your blood
- One would like to functionalize a nanotube with the Ag we wish to detected

- Questions
  - can all this be done?
  - will it work (specificity)?
  - can one detect a signal upon Ab_A binding the Ag_A?
  - can simulations be of help?

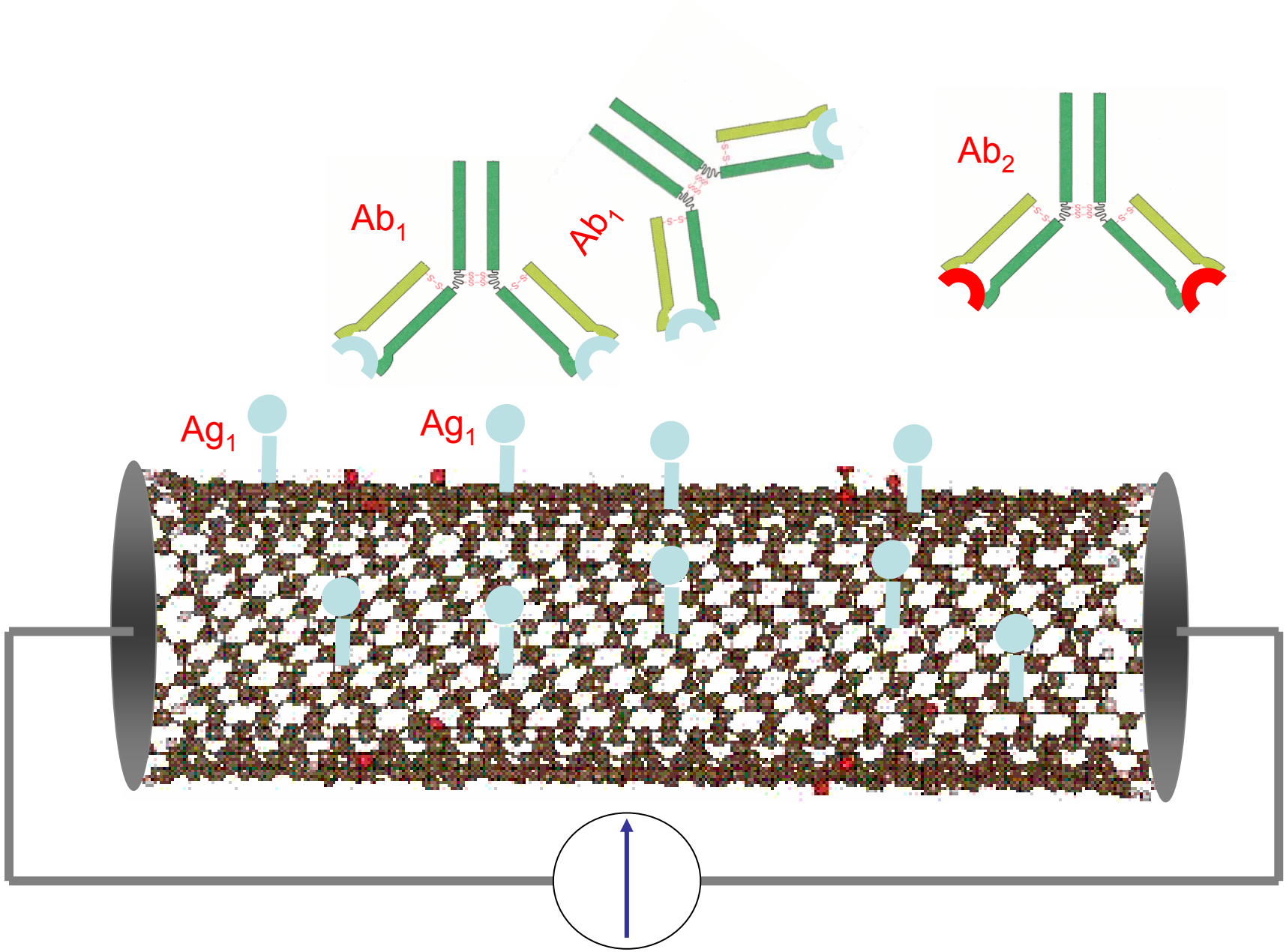
Porphyrin Functionalized Nanotube

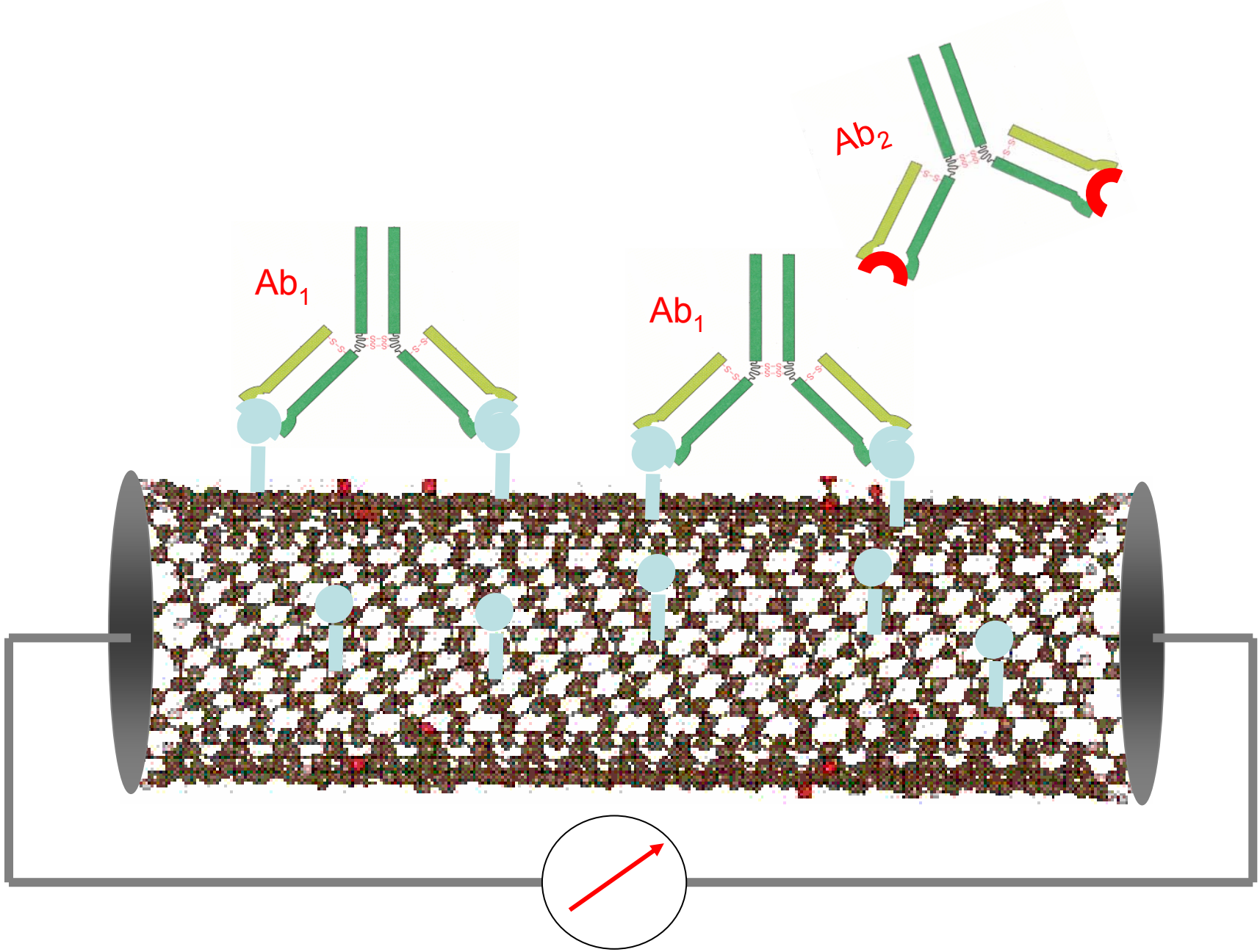


- New materials for **solar energy** applications
- Relatively simple, synthetically feasible (at ORNL-UT) mimics of light-harvesting antenna units
- **Porphyrin** molecules are the light absorbing antenna and the **nanotube** may provide a conducting channel
- Key research questions to address are:
  - How does porphyrin attach to the nanotube?
  - How does the electronic structure change as porphyrin molecules are added to the nanotube (up to 22 % in weight)?
  - How is the conductance affected by surface orientation and composition?
- Problem size **1500** (~ 60 Å) to **5000** atoms (202 Å by 60 Å)

  10 times more electrons

a case for numerical simulations


Ab1
Ab1
Ab2
Ag1
Ag1


Ab2
Ab1
Ab1

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

Two examples

IVa Metabolic networks

IVb Protein folding and aggregation