# Membrane models

History : lipids / amphiphiles

## Gorter and Grendel 1925

- Membrane frame = bilayer
found by monolayer experiment : lipid extract of RBC, of known surface area (microscopy)
↳ dense monolayer area : 2× of RBC area !!

## Danielli – Dawson 1935

- proteins are part of the membrane (hydrophobic areas !)
- Sandwiching the bilayer (from lipids)
modified by Robertson ~60's

## Singer – Nicholson 1972

- integral(i) and peripheral(ii) proteins (EM results)
a bound by hydrophobic(i) and polar(ii) interactions
- proteins float in a fluid sea (spectroscopy of liquid crystalline membranes)

## Refinements

- Israelachvili: - accounts for lipid - protein adjustment to each other ('hydrophobic mismatch')
  - separated species of lipids
- Sackmann: - cytoskeleton + glycocalix influence

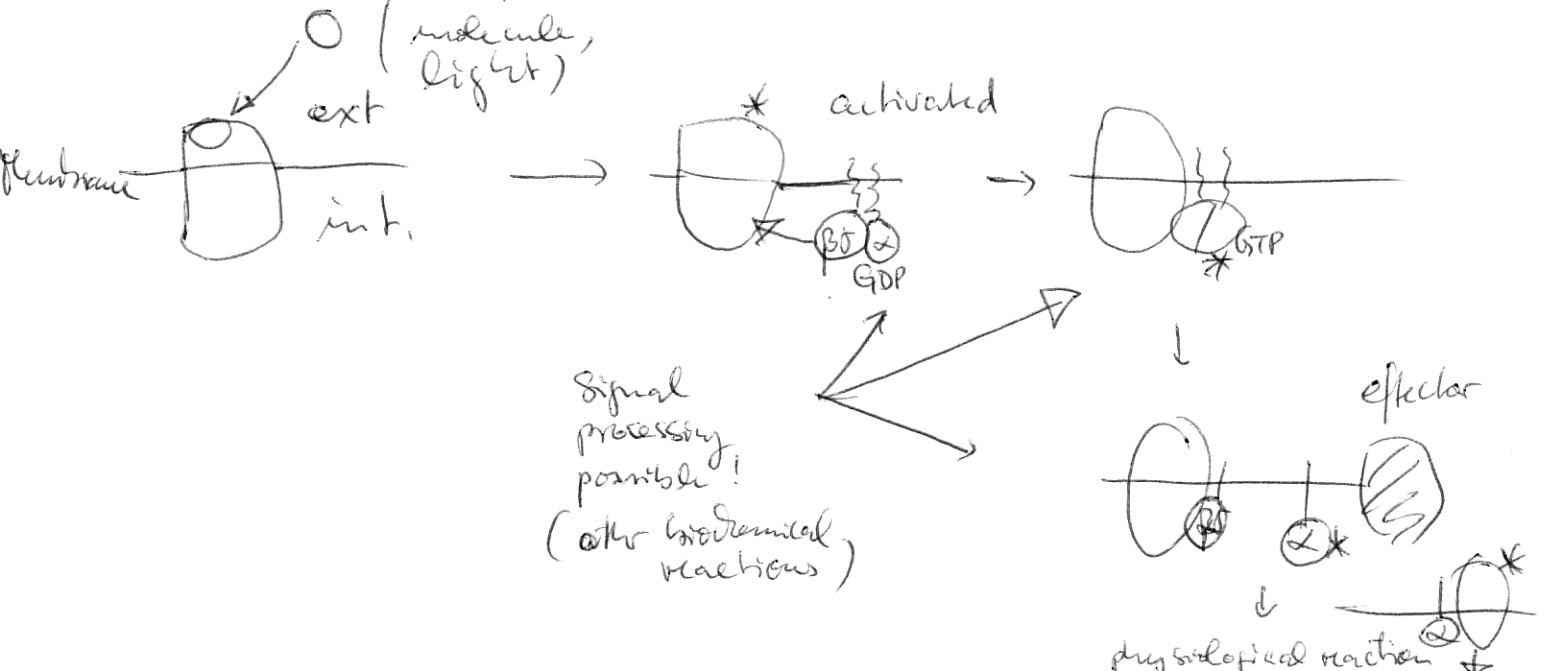
~~[illegible]~~

## Proteins working in membranes

example: receptors, receive signals from outside the cell → signal processing → cellular reaction

→ GTPase

class of receptors: G-protein coupled receptors



## Diffusion trick within the membrane (E. Sackmann)

→ reduction of dimensionality:
reactions in the two dimensions of the membrane occur faster than in the three dimensions of the cytoplasm!

→ depend on diffusion!

### Some diffusion

- Fick's law $\frac{dx}{dt} = D \Delta n$

$n = n(r,t)$ concentration of a solute

$r, t$ : position and time

$D$ : diffusion coefficient

→ solution of Fick's law gives a probability $P(r,t)$ to find a particle at a certain position

~~initial condition $P(r,0)$~~

In two dimensions:

$$P(r,t) = \frac{1}{4\pi D t} \exp\left(\frac{-r^2}{4Dt}\right)$$

## Mean square displacement

$$MSD(t) = \langle r^2 \rangle = \int r^2 P(r,t)\, dr = \int \frac{1}{4\pi D t} \exp\left(\frac{-r^2}{4Dt}\right)$$

↑ summing up the probabilities

$$\Rightarrow \quad MSD(t) = 4Dt$$

↗ can be obtained from trajectories of high-particle tracking experiments.

Brownian diffusion follows this relation (thermal collisions)

$$D = \frac{kT}{\zeta}$$

$k$ = Boltzmann constant

$\zeta$ = ~~viscosity~~ friction coefficient

## Diffusion in cell membranes

- observations: - temporary and spatial confinement of lipids and proteins

Lipids: $t < 1s$

250 - 750 nm region size

proteins: $t = 3 - 35\,s$

100 - 1000 nm region size

reasons: obstacles: - membrane cytoskeleton anchors

- proteins;
- diffusion of proteins reduced in cell membranes by a factor of 10, compared to model membranes

- ordered domains within membranes: 'lipid rafts'

⇒ liquid-ordered / liquid-disordered phase coexistence

↓

reduced lipid diffusion coefficient (by factor of 2; $D \sim 0.5 \frac{\mu m^2}{s}$)

→ also: subdiffusion/anomalous diffusion observed: $MSD = 4Dt^{\alpha}$, $\alpha < 1$

Biochemical evidence

- detergent resistant membranes:
  resist the extraction with triton X at 4°C
  (empirical)

→ sphingolipids / cholesterol → see figure

## Important membrane proteins

- ion channels
- occur in neuron cells, control potentials and transmission

-30-

- typical membrane potentials: -70 mV, inside is more negative than the outside
- muscle/neuronal cells: controlled changes in potential
- resting potential: determined by the concentration gradient of $K^+$ ions, outside the axon: 4 mM $K^+$, inside 100 mM

→ open channels →

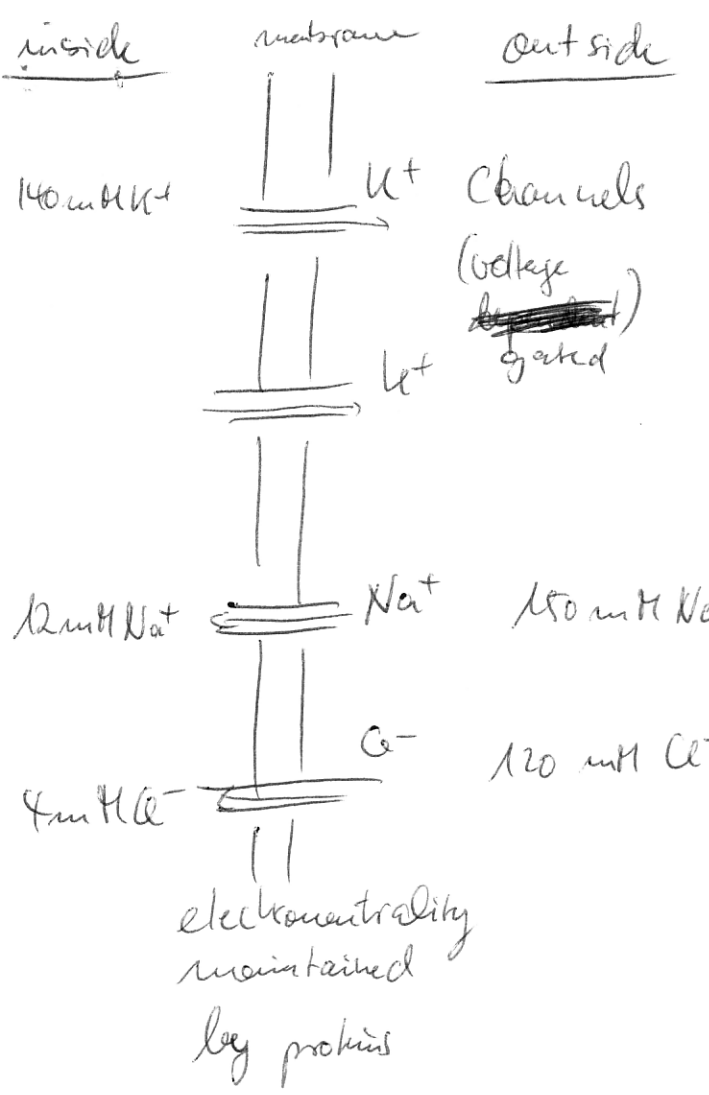
negative charge left on the inner surface

only $K^+$ channels → membrane potential can be quantified by the Nernst equation (Boltzmann approach)

$$E_K = \frac{RT}{zF} \cdot \ln \frac{K_{out}}{K_{in}} = -91\ mV$$

→ only potassium considered

→ also $Na^+$, $Cl^-$ channels: actual potential: ~-60 mV

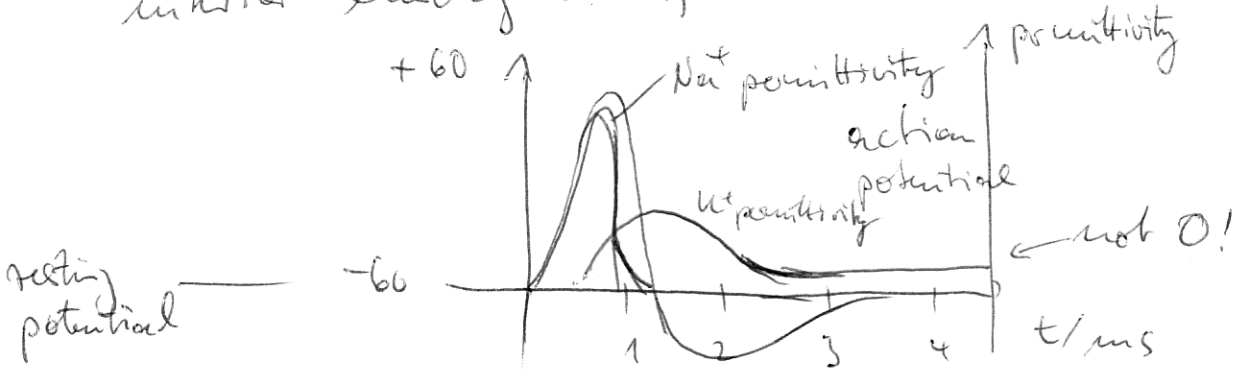



action potential:

- ~~cycle of hyperpolarisation~~, cycle of depolarisation, hyperpolarisation, return to resting value:
  transient increases in the conductance of ions
- lasts 1-2 ms
- massive influx of $Na^+$ through voltage-gated channels, depolarisation by initial potential change structure → activation → influx until $E_{Na}$ is reached (equilibrium) channel open for 1 ms, → channel closed by an inactivity structural segment
  → repolarisation.

Further channels:

- voltage gated $Ca^{2+}$ channels
- cyclic nucleotide gated channels:
  interior binding site for cAMP or cGMP




Proton pumps

- supply the fuel for ATP production
- final oxidation step in a mitochondrion:

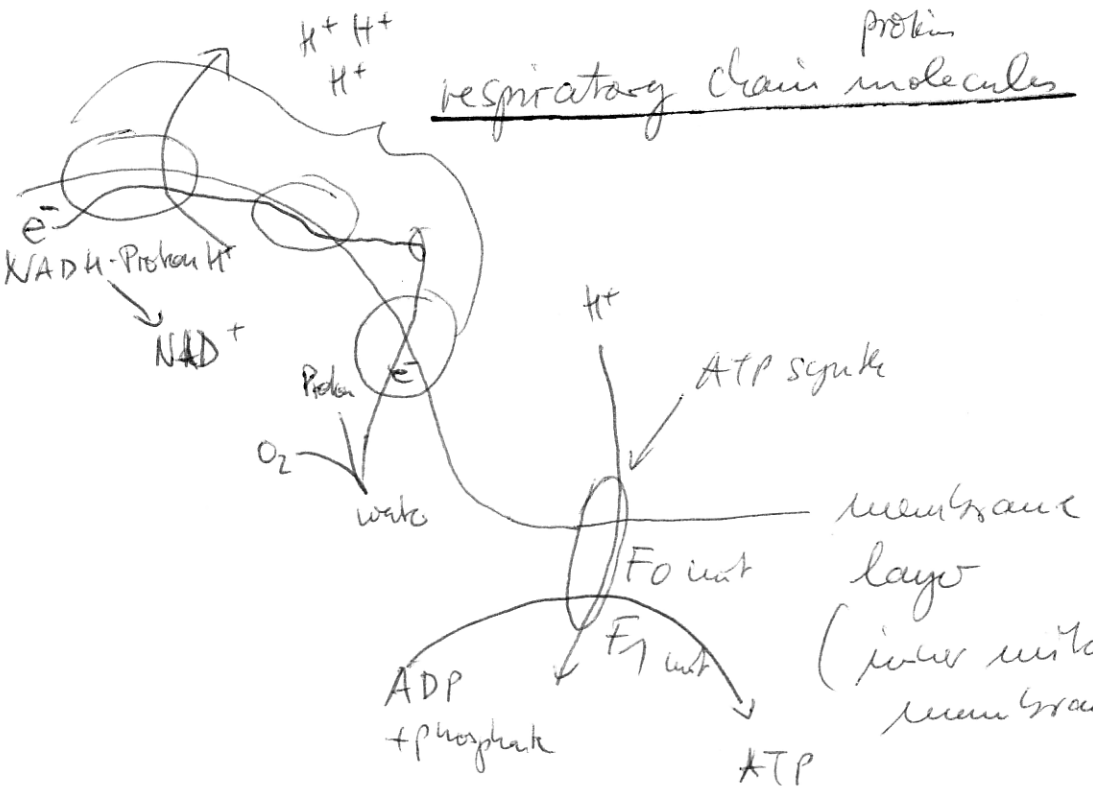
$$NADH + H^+ + \frac{1}{2}O_2 \longrightarrow NAD^+ + H_2O \qquad \Delta G = -88\,kT$$

↑ nicotinamide adenin dinucleotide

→ used for pumping of 10 protons across the inner mitochondrial membrane, potential difference can be used by a 'machine'
(membran isolater)

→ ATP synthase: membrane protein
  lets 4 protons for one ATP
↓ oxidation of 1 glucose molecule → 28 ATP molecules

Schema




ATP synthase : a 'cellular dynamo', mechanical torque achieved!

Other ion pumps

- in chloroplasts, proton gradient drives 'CFOF1'

  protons pumped by sun light - driven membrane proteins

- Halobacterium salinarium:

  light driven proton pump : bacteriorhodopsin

- calcium ATPase : powered by ATP, pumps $Ca^{2+}$

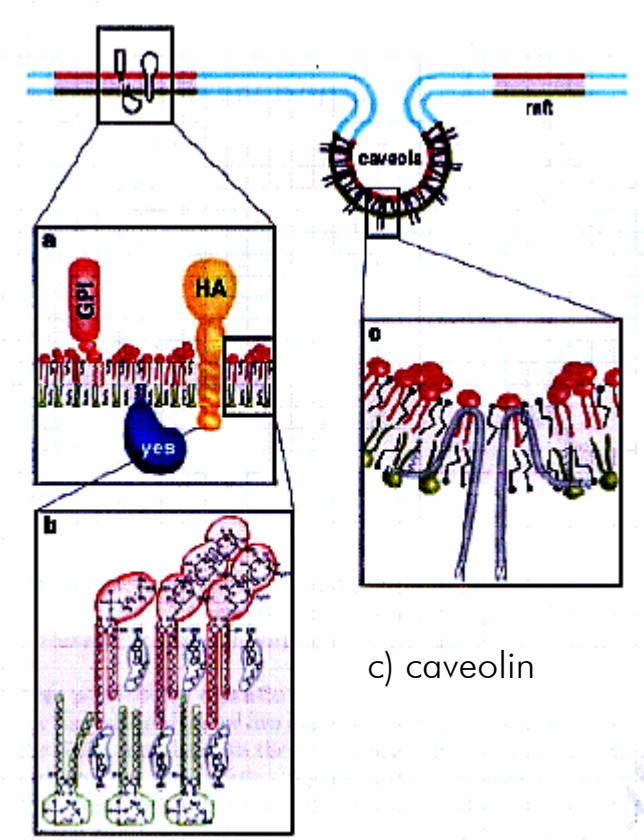
- flagellar motor of E. coli → mechanical torque by proton gradient

# Ordered domains within a cell (plasma) membrane

Red areas: ordered microdomains
"lipid rafts" [1]

a) Membrane proteins

b) lipids: Cholesterol, Glyco- Sphingo-lipids



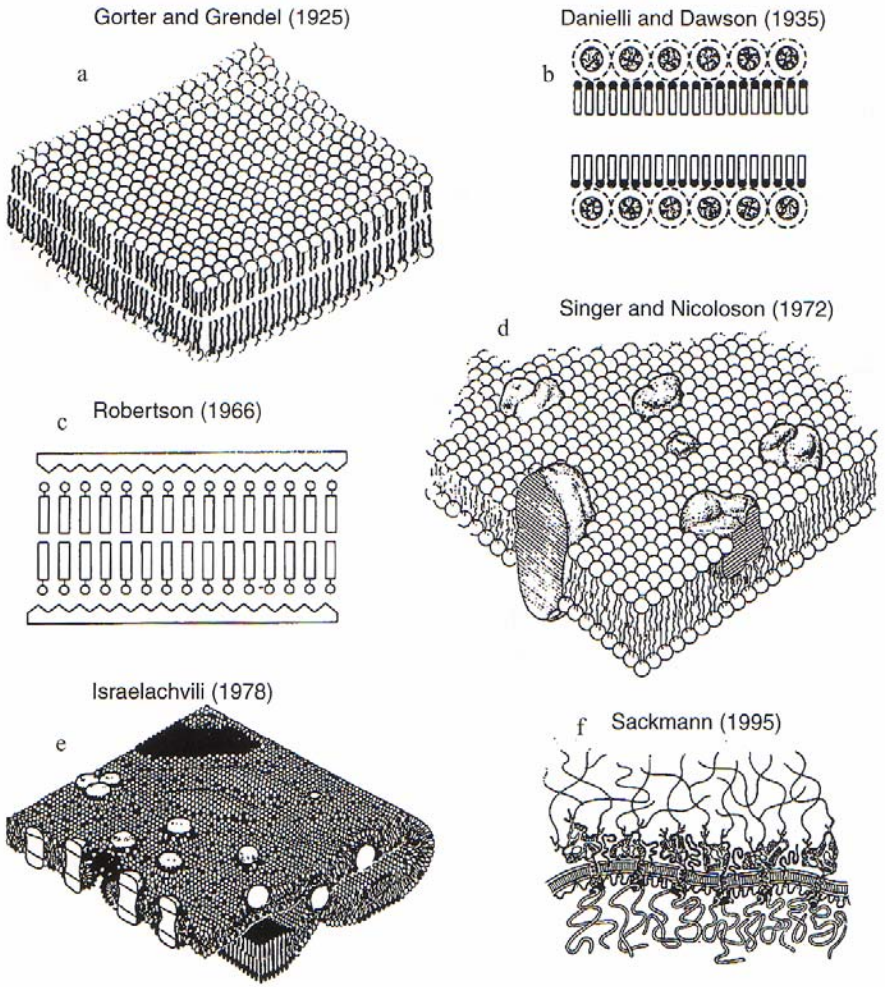

c) caveolin

1) Detergent resistent domains: Liquid-ordered ($L_o$) phase

2) Confinements found for:
-lipids: 250-750 nm size
less than a second [2]
-proteins: 100 nm to 1 $\mu$m size
from 3 – 35 s [3]


1) K. Simons and G. Ikonen, *Nature*, 1997, **387**, 569
2) G. J. Schütz et al. EMBO J., 2000, 19, 892; T. Fujiwara et al. J. Cell Biol., 2002, 157, 1071
3) E. D. Sheets et al. *Biochemistry*, 1997, **36**, 12449; A. Kusumi et al., *Biophys. J.*, 1993, **65**, 2021;C. Dietrich et al. *Biophys. J.*, 2002, **82**, 274

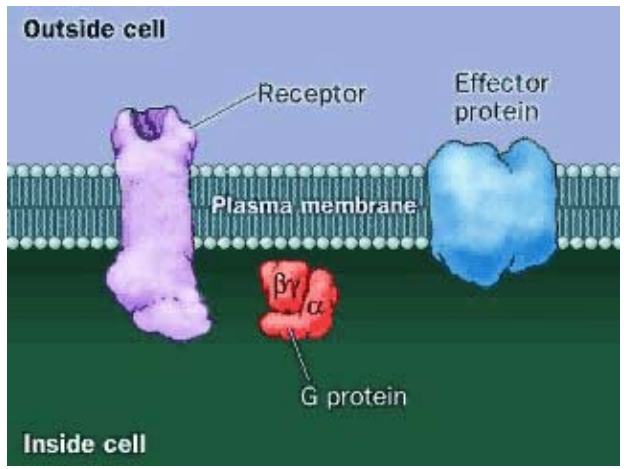
# History of membrane models




Increasing complexity!!

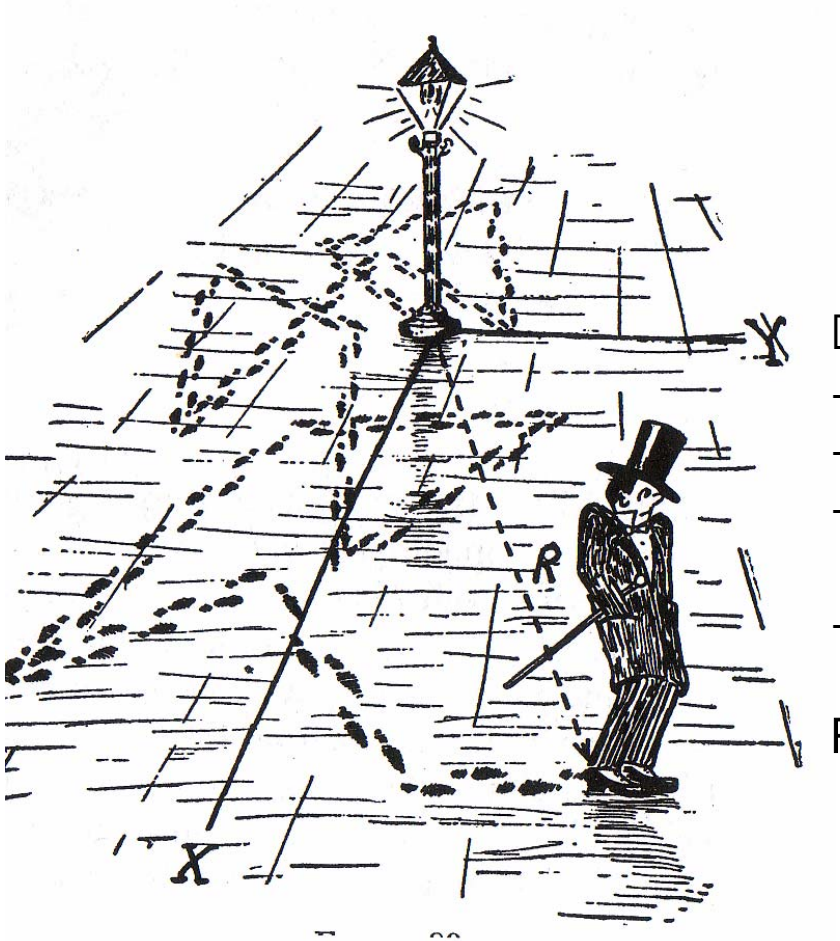
## How proteins interact in the membrane

Example: G protein coupled receptor and related effector protein




How is lateral transport adjusted in cellular membranes?

# Do membrane proteins walk randomly (like drunkards)?



$$MSD = < \mathbf{r}^2 > = \frac{kT}{2\pi\eta a}$$

Diffusion in a homogeneous system depends on:
-viscosity
-membrane thickness (after the Safman-Delbrück
-Model for proteins in membranes)

-temperature

Parameters are all biologically fixed!