How do cells work?

from the ground up

(water and the cell)
cell biological concepts today (Alberts et al. text)

... mechanisms based on channels, pumps

channels, pumps for exchange
continuous barrier req’d

dissolved solutes
aqueous sol’n
cytoplasm
cell biological concepts today (Alberts et al. text)

... mechanisms based on channels, pumps

... channels, pumps for exchange

continuous barrier req'd

dissolved solutes

aqueous sol'n?

cytoplasm
Kellermayer et al., 1986
Cameron et al., 1996
etc.

Conclusion: K⁺ not freely diffusible
cell biological concepts today (Alberts et al. text)

... mechanisms based on channels, pumps
channels, pumps for exchange
continuous barrier req’d
dissolved solutes ?
aqueous sol’n ?
cytoplasm
microelectrode

current source

electroporation

patch-clamp
cell biological concepts today (Alberts et al. text)

... mechanisms based on channels, pumps

channels, pumps for exchange

continuous barrier req’d?

dissolved solutes?

aqueous sol’n?

cytoplasm
Pumps: require energy

- Na-pump consumes 30 - 35% of cell’s energy supply
- >100 additional cell-membrane pumps
- mitochondrial membrane pumps
- endoplasmic reticular membrane pumps
- etc.

Is there enough energy?
Evidence for channels ....

Patch-clamp experiment (Neher and Sakmann)
Sachs and Qin, 1993

Lev et al., 1993

Woodbury, 1989
Largest channels and small solutes
cell biological concepts today (Alberts et al. text)

... mechanisms based on channels, pumps

channels, pumps for exchange?

continuous barrier req’d?

dissolved solutes?

aqueous sol’n?

cytoplasm
Most abundant component of gel - Water
Water is a dipole
Bonding effect

- glue-like behavior
Is water in the cell structured?

Requirements:

• charged surfaces
• surfaces closely packed
Average surface-to-surface distance < 5 nm

Literature estimates: 1.5 - 2.5 nm

Therefore, conditions ideal for structuring

(Goodsell)
Evidence that cytoplasmic water is structured:

- Nuclear magnetic resonance
- Ultrahigh frequency dielectric dispersion
- Quasi-electric neutron scattering

Details in recent review articles (e.g., Mentre, 1995; Vogler, 1998)
Structured water differs from bulk water.

How does this impact function?
Static properties of cell

• **Ion distribution** (in vs. out)
  - partitioning: inside$_{structured}$ vs. outside$_{bulk}$
  - association: with cell proteins$_{in}$

• **Cell potential**
Partitioning between structured and bulk water

**Energy term:**
Larger solutes dig hole with more difficulty than smaller ones.

**Entropy term:**
Larger solutes more constrained than smaller ones.

**Conclusion:** Larger solutes partition more profoundly toward bulk water.
Testing size-based solute exclusion...
Ions...
K⁺

High field strength

Na⁺

Low field strength
Lower solubility in structured water

Lower affinity for charged surfaces

Less in cell

Higher solubility in structured water

Higher affinity for charged surfaces

More in cell
Testing this prediction in the cell...

$t = 0$

$t = \text{several days}$
Conclusion: origin of ion gradients

\[ \begin{align*}
K^+ & \quad 150 \\
Na^+ & \quad 10 \\
K^+ & \quad 5 \\
Na^+ & \quad 150
\end{align*} \]

\textbf{Na:} solute exclusion*

\textbf{K:} affinity to protein charges*

*similar behavior in gels
Origin of cell potential?
How much net charge in cell?

Protein
- Negative charge: 1.6 mol/kg
- Positive charge: 1.01 mol/kg
- Net protein charge: 0.6 mol/kg (-) (Wiggins, 1990)

Ions
- Potassium ion: 0.5 mol/kg (+)
- Chloride ion: 0.2 mol/kg (-)
- Net ion charge: 0.3 mol/kg (+)

- NET CYTOPLASMIC CHARGE: 0.3 mol/kg (-)
potentials in gels

(Courtesy, R. Gülch)
Summary of static features...

Pumps not required
Channels not required
Energy not required
...cell biological concepts today...

mechanisms based on channels, pumps
channels, pumps for exchange
continuous barrier req’d
dissolved solutes
aqueous sol’n
cytoplasm

real cell biological mechanisms?

...matrix adsorbs water, ions
  gel matrix
cytoplasm

standard paradigm
new paradigm
Structured water beyond gel surface?

Zheng and Pollack, PRE, 2003
Within this “new” framework, how to approach cell function?
Do gels “act”?

phase-transition
phase-transition is a “critical” phenomenon

temperature, solvent composition, pH, ions, electric field, UV light, specific molecules or chemicals
How does the phase-transition work?

Polymer-polymer affinity dominates: Condensed

Polymer-water affinity dominates: EXPANDED
Divalent cations induce condensation

(reversed by monovalent cations)
Negatively charged polymer

Polymer moves

Water moves

Ions move
divalent cations
Reverse:

\[ \text{Na}^+ \rightarrow \text{K}^+ \]

Divalent cations

(Divalent cations released)
Hypothesis: cell action occurs by phase-transitions (i.e., phase-transition within each organelle)
Processes considered today

- Secretion
- action potential
- intracellular transport
  - contraction
  - cell motility
- ciliary and flagellar action
  - mitosis
- transmembrane transport
Problem: Molecules trapped in network
How can molecules exit?

phase transition
Proposed mechanism:

(After: P. Verdugo, J. Fernandez)
Goblet Cells Before and After UTP Stimulation

Before

After

10 μm
Action potential

-60 mV
Conventional view (Na channels; K channels)

- Remove outside sodium: action potentials remain
- Remove inside potassium: action potentials remain

(numerous papers)
Na$^+$ penetrates into condensed gel: Another phase transition?
Tasaki [NIH], Matsumoto [Japan]:

- **condensed state**
- **trigger**
  - unzip
  - water entry
  - increased permeability
  - more sodium entry
  - positive swing of potential
- **network collapses**
- **initial condition reset**

Peripheral cytoskeleton

\[ \text{Peripheral cytoskeleton} \]

Ca<sup>2+</sup>

Na<sup>+</sup>
Finally...

**Linearly oriented polymers**

- Actin filaments (streaming)
- Muscle contraction
Cell movement

actin gel
sol
groping

contact point

pseudopod

Internal mass movement
Phase-transition mechanism?
Phase transition transports solutes: Zone refining

silicon, or germanium
Similar principle along actin bundle?

Requirement 1: local phase change

Requirement 2: propagation
Evidence for structural change in actin

- Length changes in streaming bundles, ~15% (Kamiya)
- Actin intra-monomer spacing changes 17% - fluorescence energy transfer (Miki & Koyama)
- Actin repeat changes by ~15% - X-ray diffraction of actin-profilin crystals (Schutt and Lindberg)
- Monomers rotate on myosin exposure - fluorescence polarization (Yanagida & Oosawa)
Evidence for propagation (#1)

gelsolin

(Prochniewicz et al., 1996)
Evidence for propagation (#2)

Actin filament translating over a bed of myosin
markers

Hatori et al. (1996, 1998)
Muscle Contraction
Contractile filaments
cf. Iwazumi, Schutt and Lindberg, Oplatka, Pollack
Propagating phase-change mechanism?
Expectations: one step per wave
step size $n \times 2.7$ nm
noise level: 5.5 nm

1

11 nm

2a

2.75 nm

2b

5.5 nm

3a

5.5 nm

3b

2.75 nm

4

2.75 nm
Backward steps

Forward steps

(Liu and Pollack, Biophys J. 2003)
Single sarcomere

(Yakovenko et al., 2002)
Conclusion

Muscle contraction could well involve a phase-transition propagating along the actin filament

(the same propagating transition that drives streaming)
Phase-transitions implicated in:

- secretion
- action potential
- intracellular transport
- contraction
- cell motility
- ciliary and flagellar action
- mitosis
- transmembrane transport
How do cells work?

Phase-transition
“A 305 page preface to the future of cell biology” Cell, July 2002

www.cellsandgels.com info