School of Medical Sciences

Physiology 1A

Cell Physiology lecture #2

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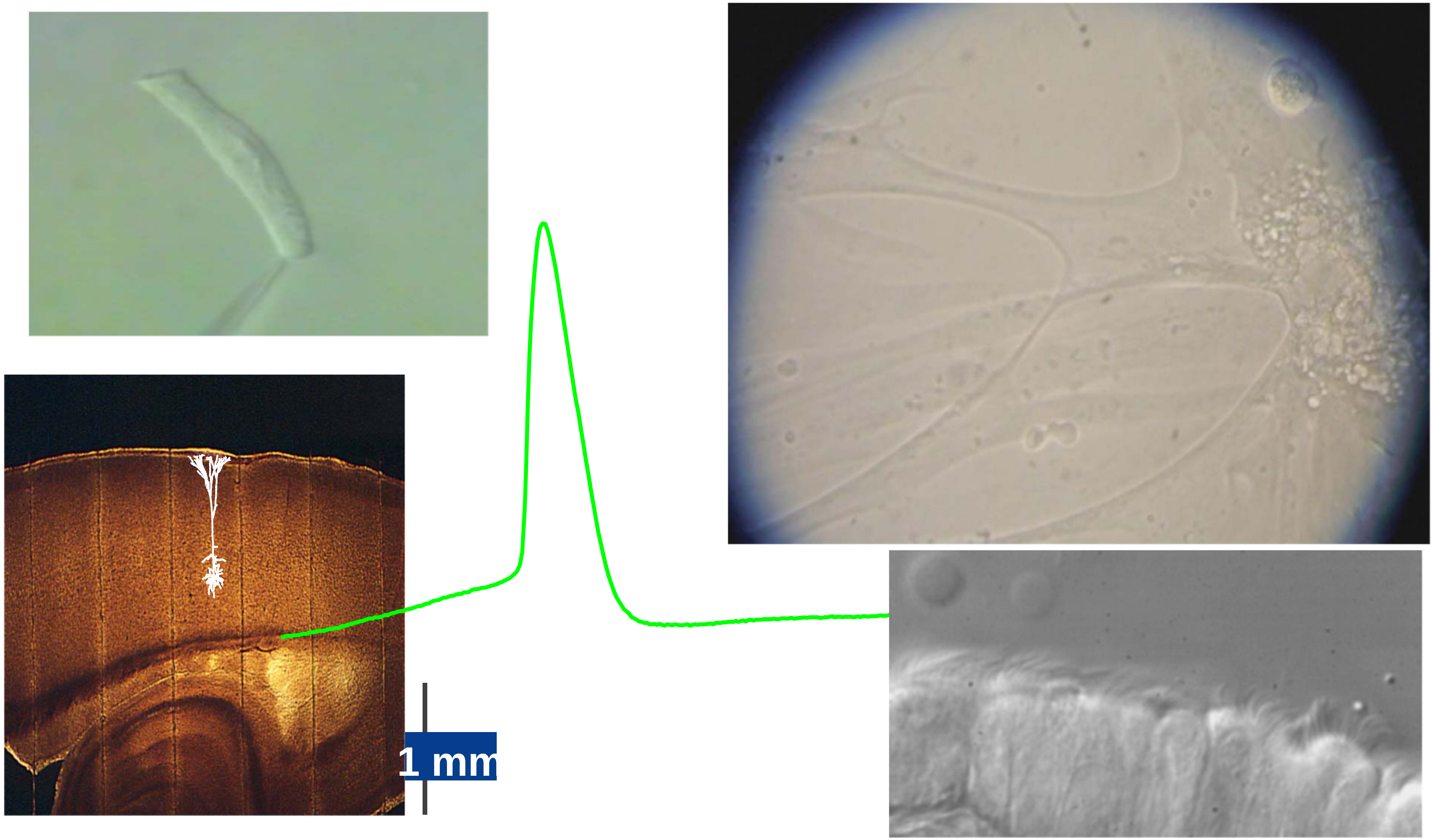
Recap: Physiology – The study of body function

生 理 学

Life　　Logic　　Study

Recap: Examples of single cell function



“Excitable Cells”:

- *Cells with **a potential difference** (or voltage) across their cell membrane*

- *Cells that use electrical and/or chemical signaling*

- *Cells that **move molecules across their membranes** using electrical and chemical forces (described later)*

- *E.g.s, nerve cells, muscle cells, epithelial cells*

- *The basic processes of all the major physiological systems*

“Excitable Cells”:

- *Cell function involves moving things (e.g., water, ions) across their cell membranes to mediate electrical and chemical signaling. Hence important questions are:*

Weds

  - *How do substances move across the membrane?*

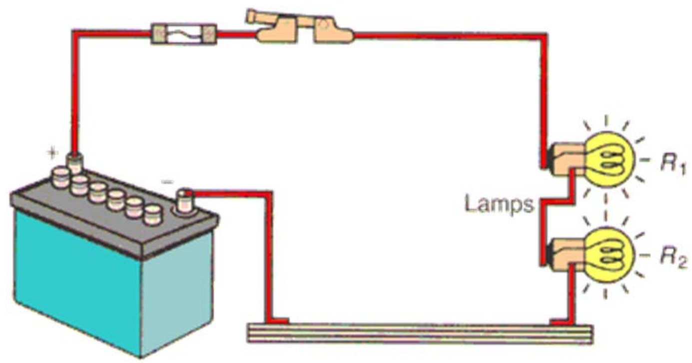
now

  - *What are the properties of the cell membrane?*
  - *Review basic physics and chemistry about solutions and membranes, and about electricity.*

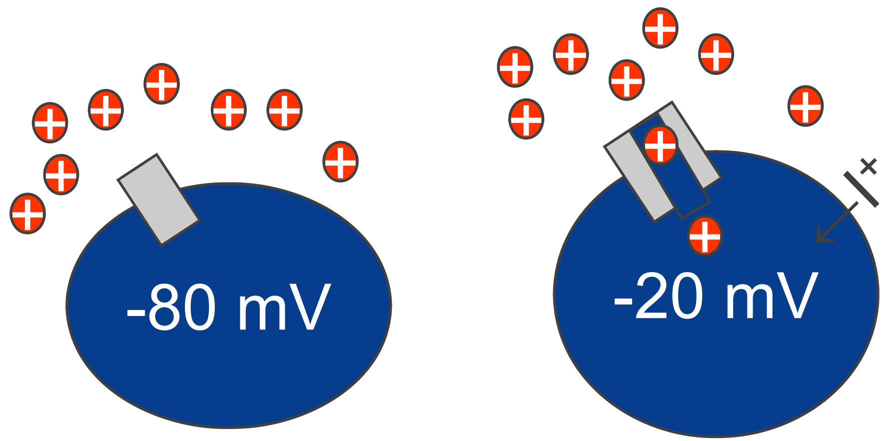
Biological electricity

- In the adjacent electrical circuits, the battery provides the driving force, the circuit is complete when the switch is closed, the current is carried by electrons flowing in a conductor (wire) and the current flows through a resistor (light bulbs) to cause some response

$e^- \rightarrow (\leftarrow I^+)$



- In excitable cells, the electrochemical potential provides the driving force, the switch is an ion channel and the current is carried by ions (a cation in adjacent figure) to results in a response (depolarization).



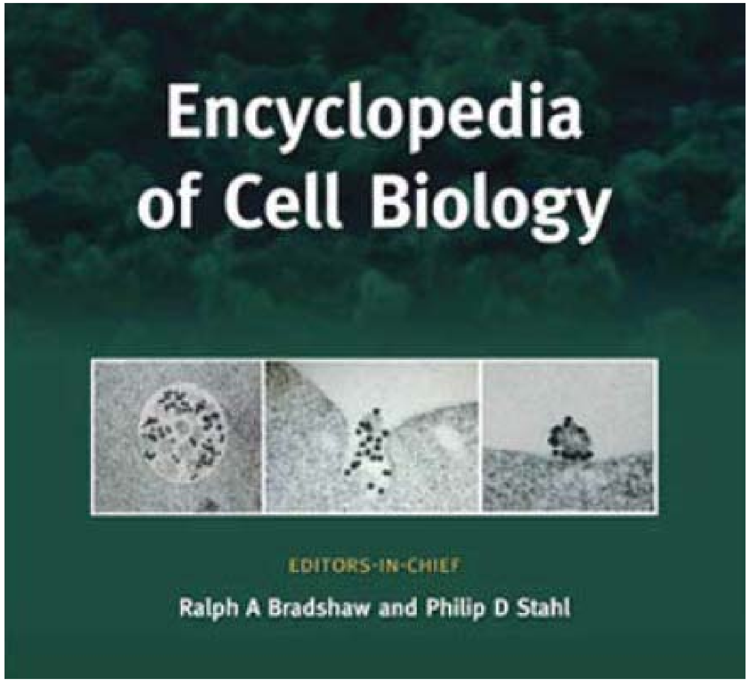
Cell at rest Activated cell

Reading Lists and Lecture Objectives on Moodle

A key resource:

Membrane Potential: Concepts

AJ Moorhouse, UNSW Australia, Sydney, NSW, Australia



UNSW library URL:
http://er.library.unsw.edu.au/er/cgi-bin/eraccess.cgi?url=http://www.sciencedirect.com/science/article/pii/B9780123944474100276

Ions in solution

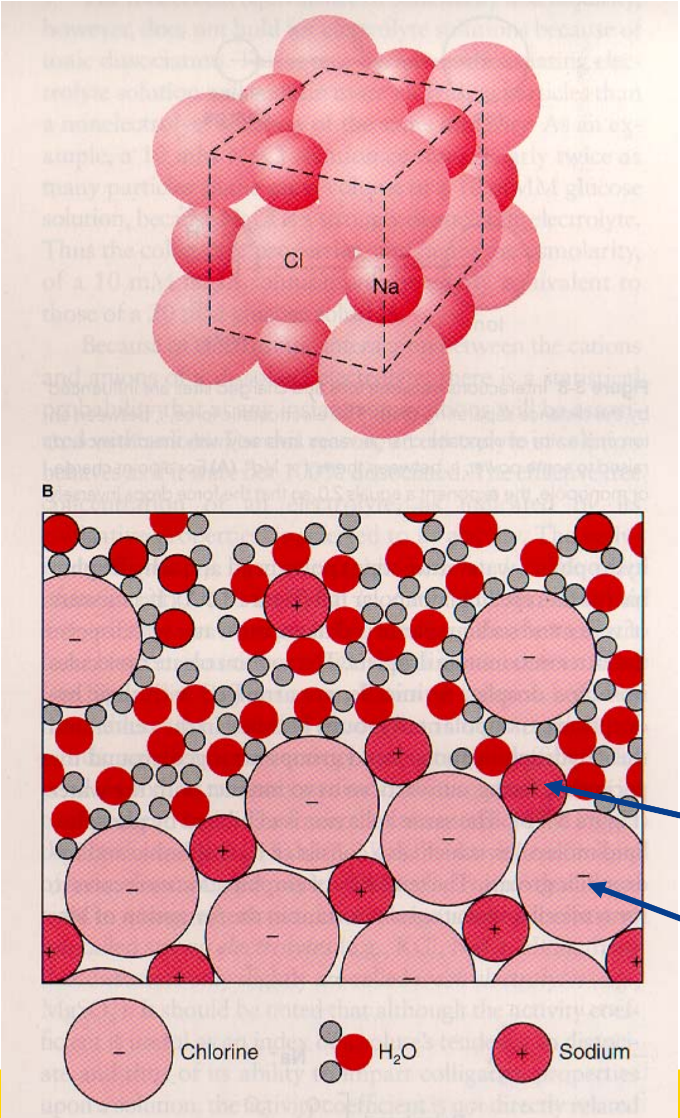
An Experiment with Copper Sulphate ($CuSO_4$)

NB Copper atoms are Blue

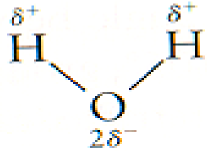
Ions in solution

ECHO+ Q…

Ions in solution



Partial charges (dipoles) on a water molecule



Ions in solution are surrounded and stabilized by water molecules (hydrated)

water loving: hydrophilic / polar

water hating: hydrophobic / non-polar

cation (positive; Na^+, K^+, H^+, Ca^{2+} **or Cu^{2+}**)

anion (negative; Cl^-, HCO_3^-, **or SO_4^{2-}**)

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How can substances cross the cell membrane?

1. Passive diffusion

2. Active Transport

3. Via incorporation into lipid vesicle ("sac")
[eg, exo- & endo-cytosis]

How can substances cross the cell membrane?

1. Passive diffusion

    1. Simple Diffusion

    2. Facilitated Diffusion

http://www.niagarafallslive.com/Facts_about_Niagara_Falls.htm, accessed 2/10/2014

Diffusion

Diffusion across the membrane:, Francisco Bezanilla home page
http://nerve.bsd.uchicago.edu/
(use explorer not chrome?)

here

https://en.wikipedia.org/wiki/Fick's_laws_of_diffusion

Diffusion

- Passive (no energy needed)

- Arises from Brownian (random thermal) motions

- Movement from high to low concentration

-rapid across small distances (e.g., within or across a single cell), but too slow for signalling over long distances (e.g., from brain to muscle, from adrenal gland to heart)

e.g:,(diffusion of some physiological molecules in body solutions, D is the "diffusion co-efficient")
- for water (D ~ 10^{-5} cm^2/s) to diffuse across a cell membrane < 0.1 ms
- for a neurotransmitter to diffuse across a synapse ~ 1 ms
- for an ion (D ~ 10^{-5} cm^2/s) to diffuse from one end of a small cell to another ~ 0.1s
- for a protein (D ~ 10^{-7} cm^2/s) to diffuse from one end of a small cell to another ~ 10s
- for a protein to diffuse along a 1 metre motor axon (spinal cord to foot) > 1,000 yrs

Fick's general law of Diffusion

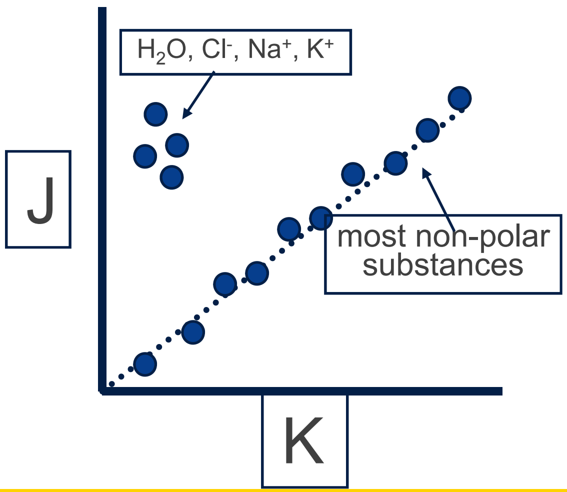
diffusion rate or flux $J = DA\,(dC/dx)$

where: A = the area of the interface
dC/dx = solute concentration gradient across the interface (width = x) D
= the diffusion coefficient
= a proportionality constant that varies directly with the speed of random motion (depends on molecule properties such as size)

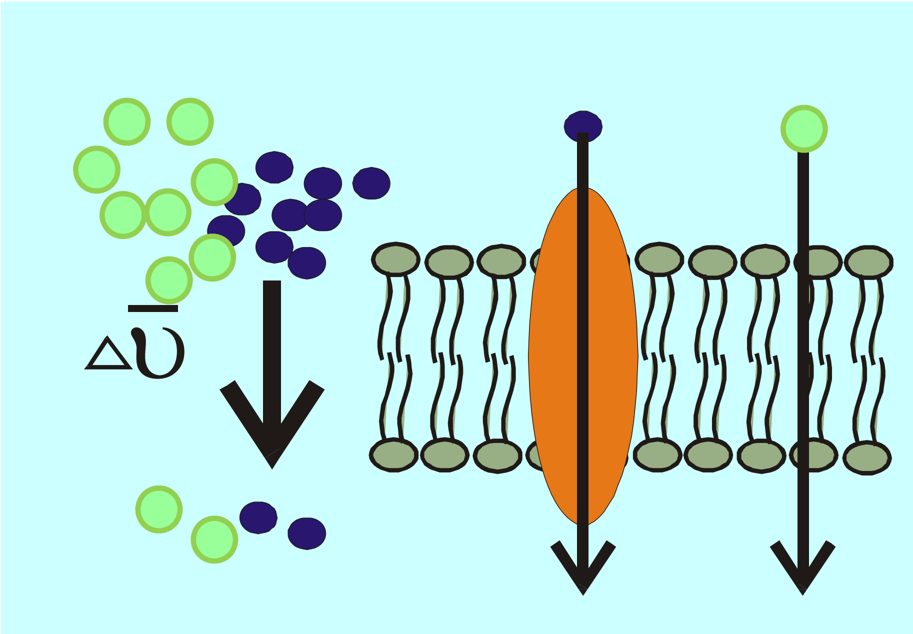
NB The above D is derived from diffusion in aqueous solution. For **membrane diffusion** an additional constant, the partition co-efficient (K; a measure of lipid solubility), is added to the equation so that:

$$J = DKA\,(dC/dx)$$

NB: Stanfield gives $J = PA\,\Delta C$; where P is permeability)



Passive Diffusion Across the Membrane



1. Simple Diffusion

- lipid soluble / hydrophobic substances
- through the membrane
- e.g. gases, steroids, hydrophobic drugs

2. Facilitated Diffusion

- water soluble / hydrophilic substances
- via a protein (carrier or channel)
- e.g. ions, glucose, amino acids

Facilitated Diffusion – Carrier Mediated

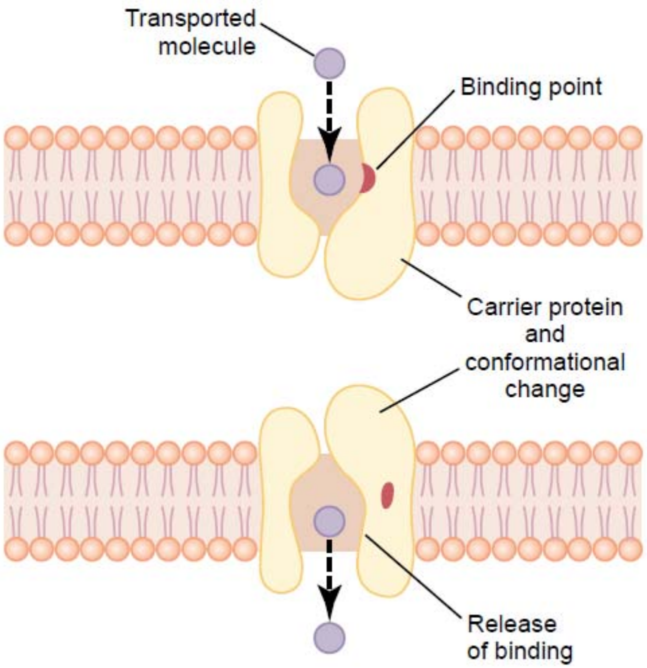


Figure 4–7

Postulated mechanism for facilitated diffusion.

“Occluded Access” model of carrier-mediated facilitated diffusion of glucose.

Glut1 – ubiquitous glucose facilitated diffusion transporter

See also Fig 4.10 in Stanfield (4th Ed)

Facilitated Diffusion – Carrier Mediated

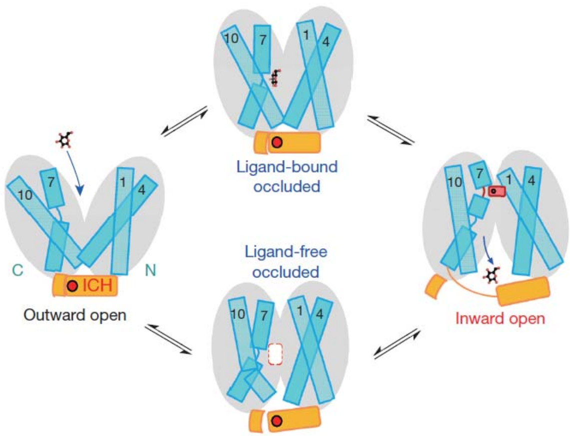
What it really looks like …… (Nature, 2014)

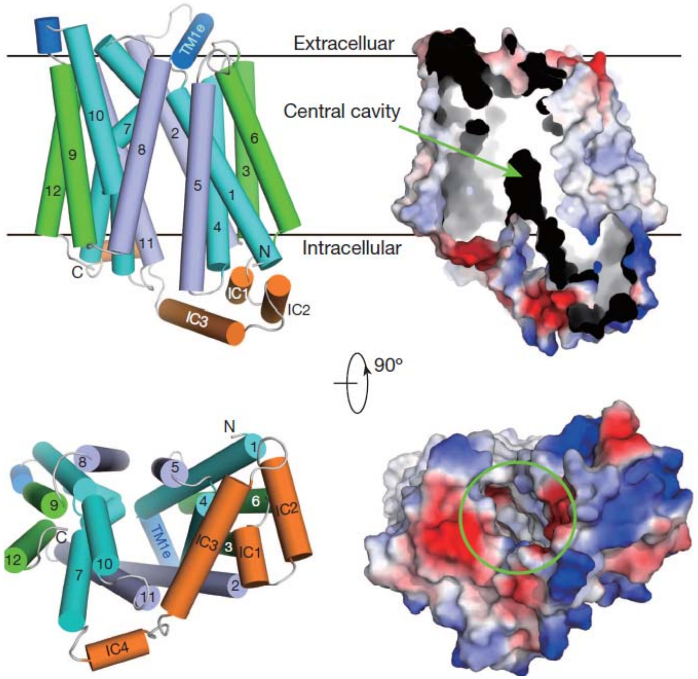
ARTICLE

doi:10.1038/nature13306

Crystal structure of the human glucose transporter GLUT1

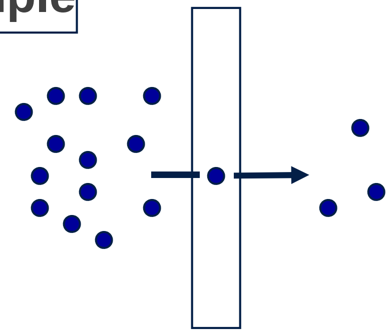
Dong Deng[1,2,3]*, Chao Xu[1,2,3]*, Pengcheng Sun[1,2]*, Jianping Wu[1,2,3]*, Chuangye Yan[1,2], Mingxu Hu[1,2,3] & Nieng Yan[1,2,3]



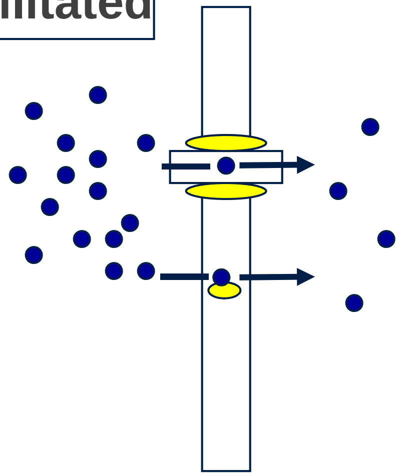


Simple Diffusion vs Facilitated Diffusion

simple

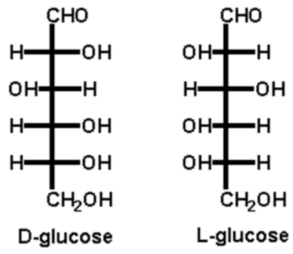


facilitated

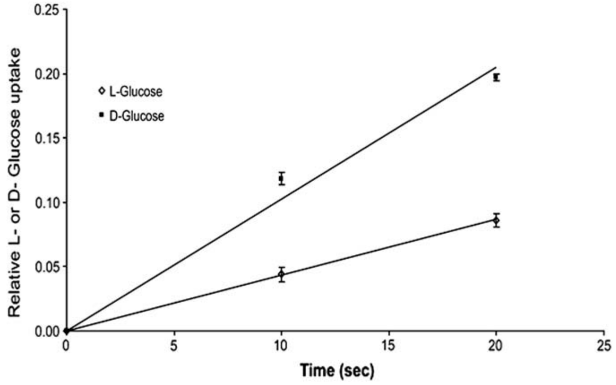


1. Specificity

e.g. L & D glucose

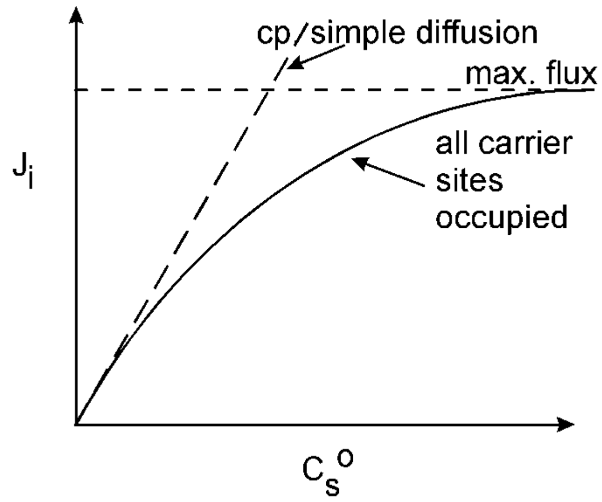


Human Glut1:
D-glucose > L-glucose
(Alisio et al., 2010)

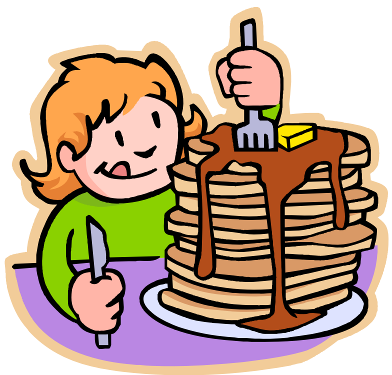


2. Competition

3. Saturation

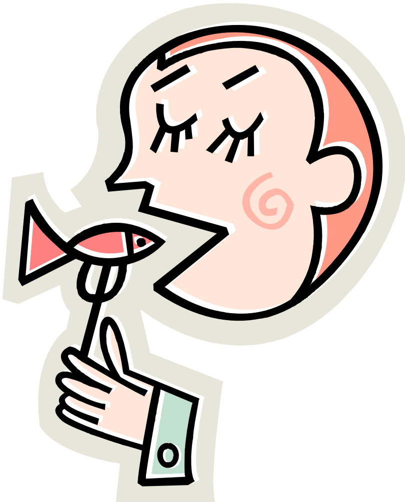


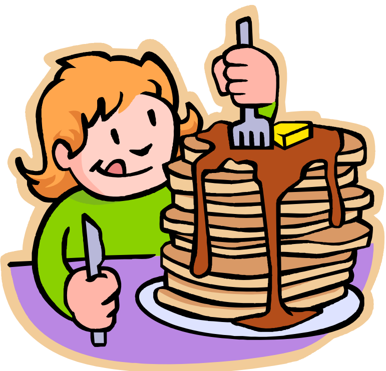
Glucose Facilitated Diffusion:
e.g., of Physiological Relevance



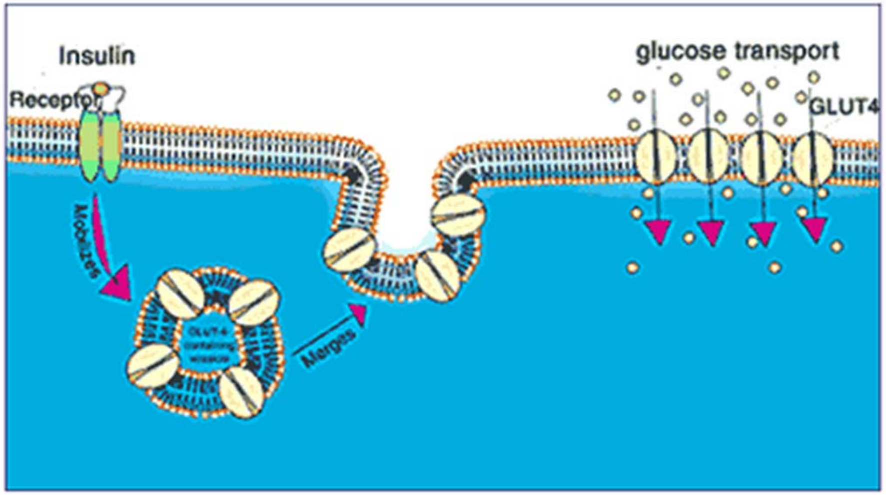
- ❑ cells need glucose to produce energy (ATP)
- ❑ glucose diffuses from blood to cells
- ❑ insulin enables us to increase the diffusion of glucose into cells

Glucose Facilitated Diffusion:
e.g., of Physiological Relevance



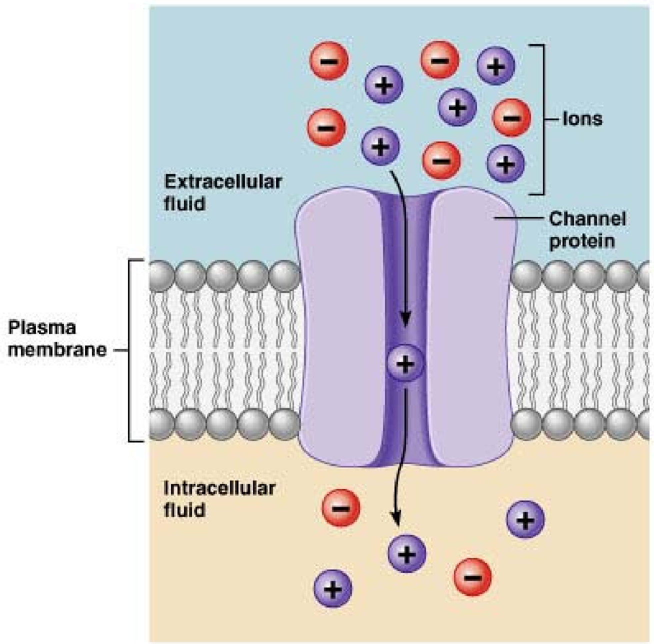


❑ insulin increases the number of facilitated diffusion transporters in muscle and fat cells so transport doesn't saturate



Facilitated Diffusion – Ion Channel Mediated

Transmembrane proteins with aqueous pores that allow diffusion of ions



Germann & Stanfield Fig. 4.13

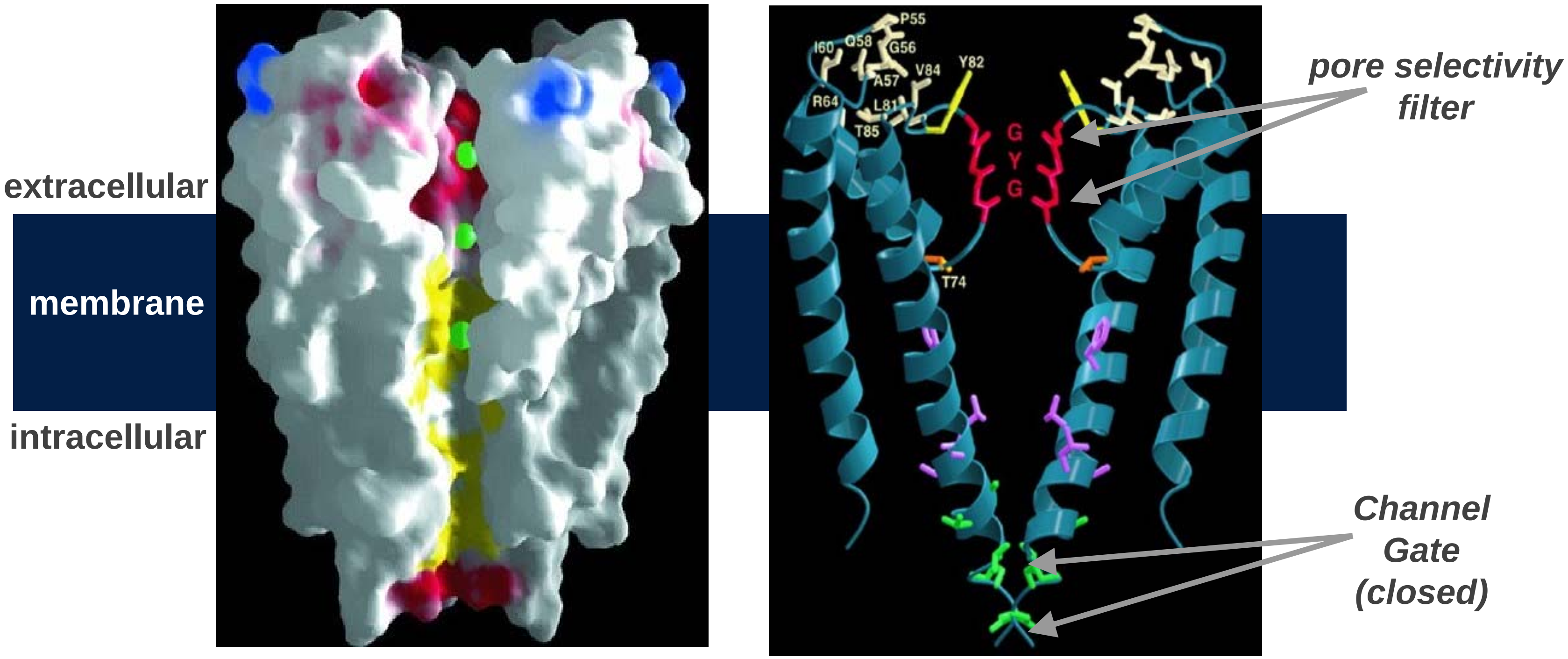
- Ion Flux is downhill (passive)
- Selective (e.g, a cation channel)
- *How does the cation influx shown affect the voltage difference across the membrane?*

Facilitated Diffusion – Ion Channel Mediated

What it really looks like …… (Science, 1998)

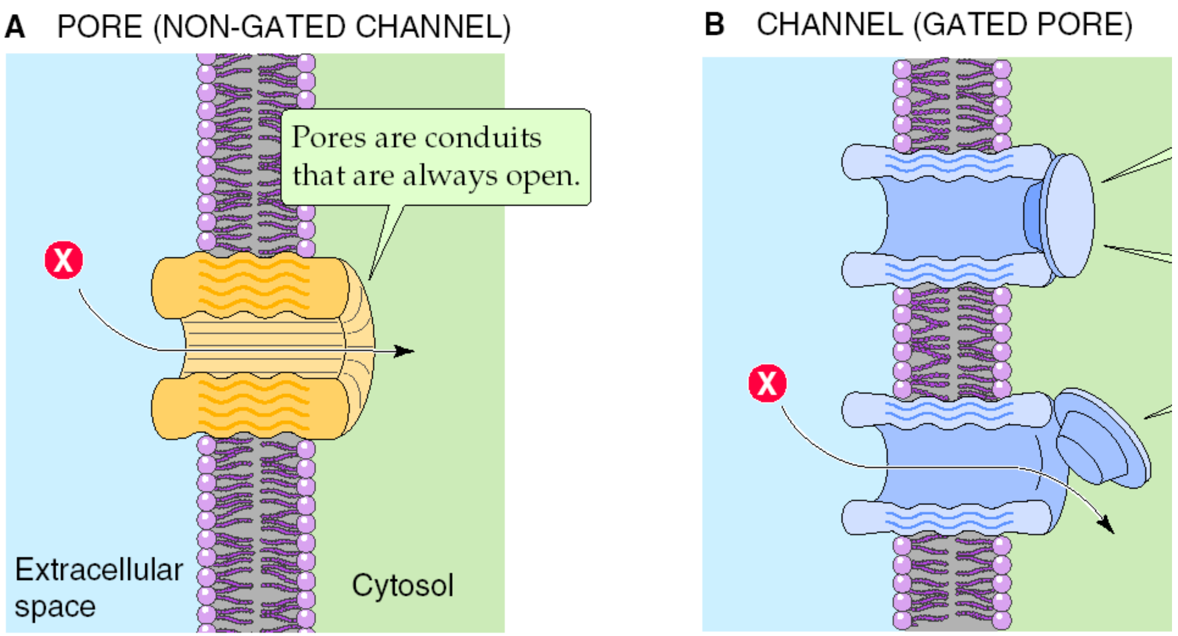
The Structure of the Potassium Channel: Molecular Basis of K^+ Conduction and Selectivity

Declan A. Doyle, João Morais Cabral, Richard A. Pfuetzner, Anling Kuo, Jacqueline M. Gulbis, Steven L. Cohen, Brian T. Chait, Roderick MacKinnon*



Facilitated Diffusion – Ion Channel Mediated

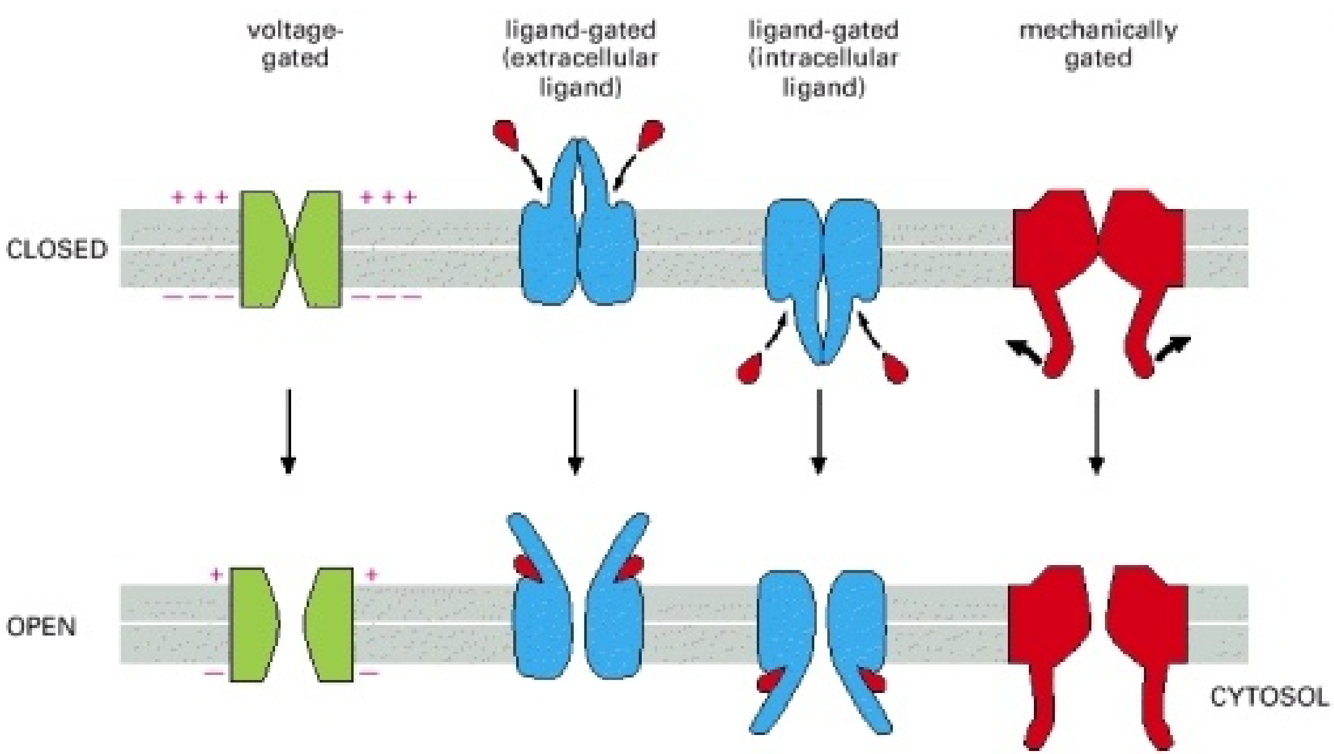
Can be always open, or can be “gated”……



from *Medical Physiology* by Boron and Boulpaep, Saunders, Philadelphia, 2003

Gating of Ion Channels

-changing between non-conducting to conducting conformations



+ non-gated, always open:

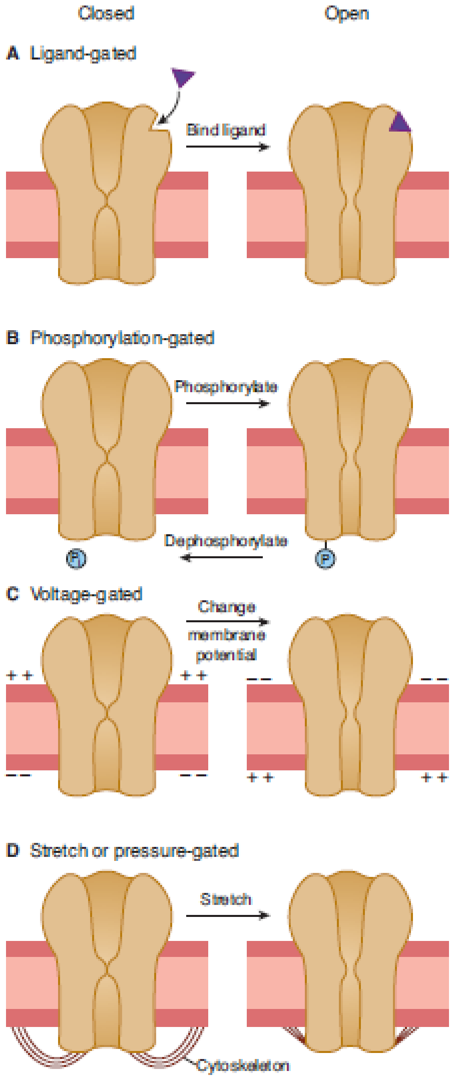
“PORES”

Particularly important for setting the resting membrane potential,

And for water flows

Gating of Ion Channels

-changing between non-conducting to conducting conformations



Main modes of ion channel gating (& examples):

extracellular ligand (Panel A in Figure)
e.g. a neurotransmitter chemical released at a synapses)

intracellular phosphorylation (B) or intracellular ligand
e.g. change in phosphorylation due to metabotropic receptors can open or close different K^+ channels; an intracellular 2nd messenger like cyclic AMP can opne channels in sensory cells.)

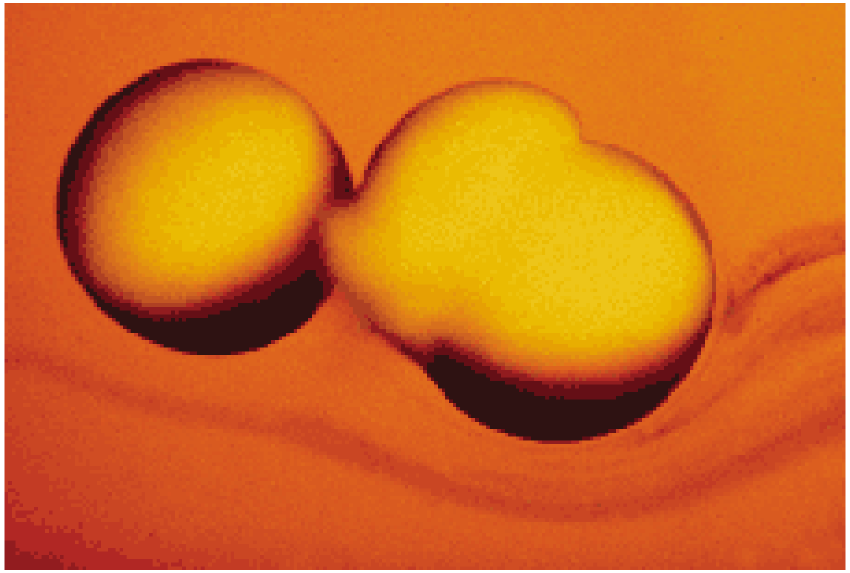
A Change in the membrane potential (C)
e.g., the voltage-gated Na+ and K+ channels involved in action potentials)

Stretch of the membrane (D)
e.g., large mechanosensitive channels that allow protozoa to adjust to different tonicity environments, channels in sensory nerve endings that detect touch)

“background”, “leak” channels or “Pores”
e.g., non-gated or weakly gated K^+ channels that help to set the resting membrane potential)

Osmosis - water diffusion

Serendipitous discovery of the water channels or "Aquaporins"



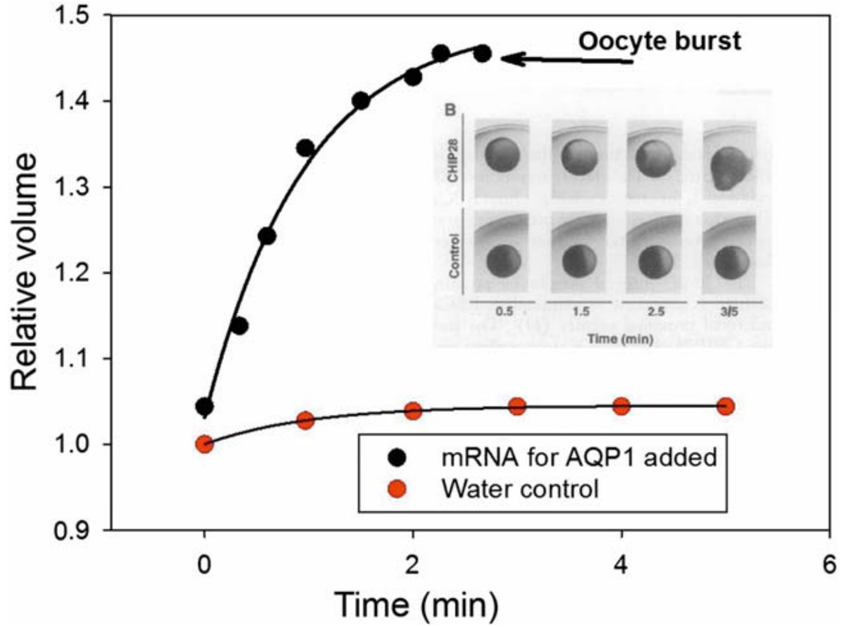
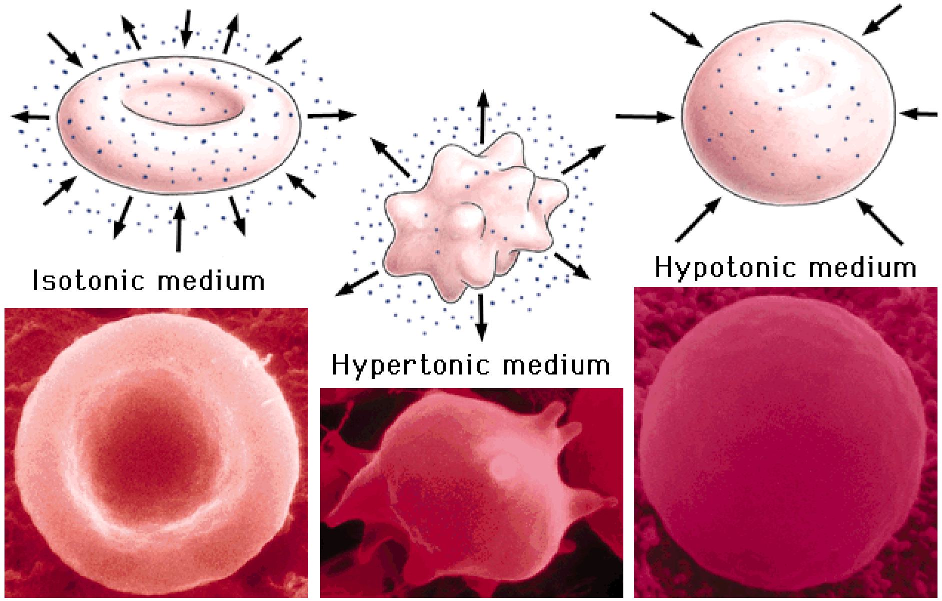


Figure 2.18 Increased osmotic water permeability of CHIP28 RNA-injected Xenopus oocytes. After 72 h, control-injected and CHIP28/AQP1 RNA-injected (10 ng) oocytes were transferred from 200 to 70 mosM modified Barth's buffer, and changes in size were observed by videomicroscopy. Osmotic swelling of representative control-injected (red circles) and CHIP28/AQP1 RNA-injected (black circles) oocytes. Time of rupture is denoted by the arrow. (Inset) Photos of injected oocytes at indicated times.
Redrawn from Preston GM, Carroll TP, Guggino WB, Agre P. Appearance of water channels in Xenopus oocytes expressing red cell CHIP28 protein. Science. 1992;256:385_7.

Osmosis - water diffusion



- If cell is placed in EXT solution that is:

isotonic (same tonicity /osmolarity):
- no change in cell volume

hypertonic (more solutes, less water) :
- cell will shrink

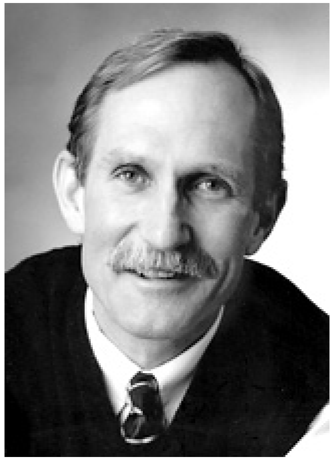
hypotonic (fewer solutes / more water):
- cell will expand

- A physiological solution contains solute (water) and osmolytes (particles) that exert an osmotic pressure. Typical values of osmolarity in physiological solutions is ~300 mOsm. When the osmolarity of the intracellular (INT) and Extracellular (EXT) solutions are equal, the cell is at equilibrium as their is no water concentration gradient across the membrane and no water will flow. When there is a different osmolarity across the membrane, water will diffuse down its concentration gradient. If a swelling cell doesn't release osmolytes (e.g. via stretch-activated channels or via the Na^+ pump) it may burst.

A Nobel Prize for Ion Channels, 2003

“for discoveries concerning channels in cell membranes”

Peter Agre
“for the discovery of water channels”



Rod MacKinnon
“for structural and mechanistic studies of ion channels”

http://nobelprize.org/nobel_prizes/chemistry/laureates/2003/index.html, accessed 16/04/2010

How can substances cross the cell membrane?

1. Passive diffusion

2. Active Transport

3. Via incorporation into lipid vesicle ("sac")
[eg, exo- & endo-cytosis]

Learning Aims – lecture 2

- To know the terms polar and non-polar and how it relates to membranes and ions. To appreciate ions are hydrated in solution.
- To relate the basic components of an electrical circuit to a potential difference across the cell membrane
- To state factors which influence the passive flux of molecules across a cell membrane, as expressed by Ficks' Law
- To distinguish simple and facilitated diffusion, and facilitated diffusion via channels and carriers
- To briefly describe an example of a facilitated diffusion transport process including physiological relevance and protein involved
- To be able to define ion channels and their basic properties of gating and selectivity
- To recognise osmosis as water diffusion and relate tonicity and water flux across cell membranes. To know what aquaporins are.

Glossary of Electrical terms used in Phys1A

- *Charge* (Q or q) is a fundamental property of matter; either positive or negative; like charges repel & opposites attract. Measured in Coulombs (C). The charge on a single electron (or monovalent ion) is $1.6 * 10^{-19}$C (the elementary charge).
An electric field emanates from any charged point or surface.

- to separate charge requires work. Once separated they possess potential energy, or a potential difference. *Voltage* (V) is an electric force exerted on charged substances (1V = 1joule/C)

- *Current* (I) is the flow of charge. Measured in amperes, A (1A = 1C/s)

- *Resistance* is a measure of how easily charge can move under a given potential difference. R=V/I (Ohm's Law). *Conductance* (g) = 1/R.

- *Capacitance* (C) is the ability to store separated charge. Two conductors separated by an insulator. C is the charge separated divided by the potential difference thus produced (C=Q/V). Accompanies the electrical potential across cells.
The units is farads (1F = C/V). Stores charge when voltage changes.