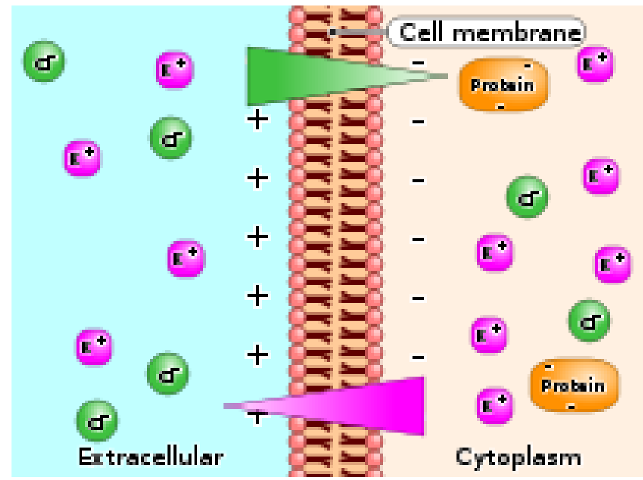
Frederick G Donnan
(1870 – 1956)

Courtesy of Journal of Chemical Education; photo in the public domain. Source: "The chemical department at University College, London." Journal of Chemical Education 4, no. 7 (1927): 819.

Irish physical chemist known for work on membrane equilibria. Most of career at University College London

Donnan Equilibria describes ionic transport in cells; "Donnan-Potential"



Courtesy of Biezl on wikipedia; in the public domain.

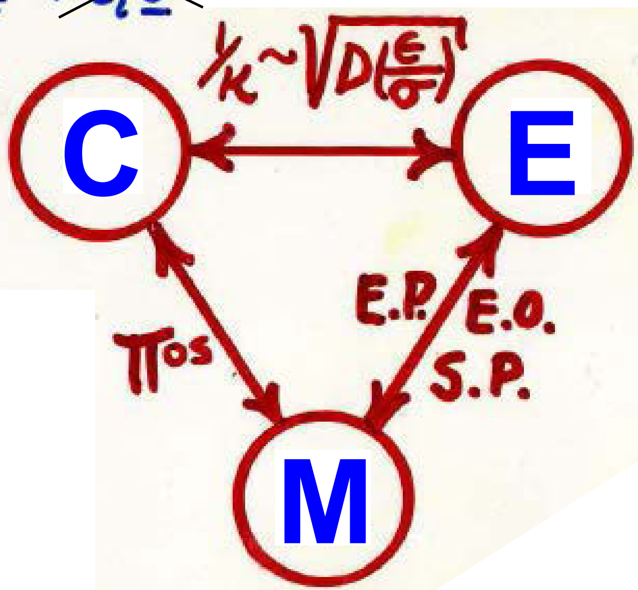
Donnan's 1911 paper on membrane equilibrium important for leather and gelatin technology ☺, but even more so for understanding transport between living cells and their surroundings.

FFF: Complete Description of Coupled Transport and Biomolecular Interactions

$$\underline{N}_i = -D_i \nabla c_i + \frac{z_i}{|z_i|} u_i c_i \underline{E} + \cancel{c_i \underline{v}}$$

$$\frac{\partial c_i}{\partial t} = -\nabla \cdot \underline{N}_i + R_{vi}$$

Diffusion-Reaction



$$\nabla \cdot \epsilon \underline{E} = \rho_e = \sum_i z_i F c_i$$

$$\left(\underline{E} = -\nabla \Phi\right)$$

$$\nabla \cdot \underline{J} = -\frac{\partial \rho_e}{\partial t}$$

$$\underline{J} = \sum_i z_i F \underline{N}_i$$

"E.Q.S."

Navier
Stokes
(Fluid Transport)

Lecture, Reading & PSets:

Chap 2: E-fields -- sources, "kinetics"

- What are E and H fields ....in BioSystems….
- Concepts: (1) *QuasiStatics*; (2) *Charge Relaxation*
- Some important & useful applications

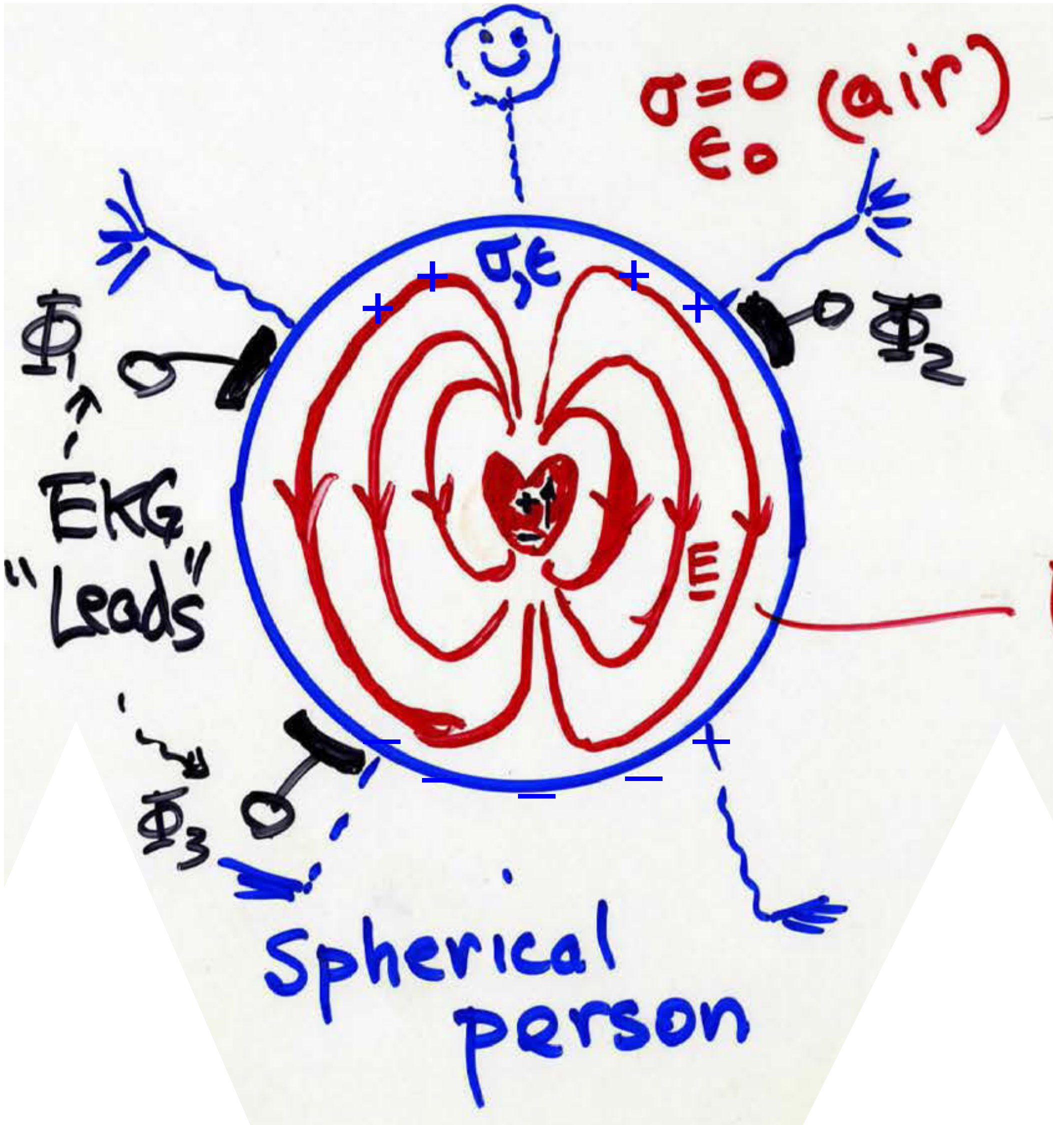
Chap 3: Transport & Electrochemical Interactions

Effects of Molecular Charge on:

- Donnan Partitioning into tissues, gels, cells, ECM
- Electrostatics ↔ Binding (to ECM / ICM, receptors)
- Osmotic Pressure in tissues/gels
- Diffusion (D_{eff}): effects of electrostatic interactions

(Come back to this at end: “Integrative Case Studies)

EKG: Centric Dipole Model of the Heart



f ~ 1 Hz
low enough for EQS!

$$\nabla^2 \Phi = 0$$

Beating Heart is still a solution of Laplace: $\nabla^2\Phi = 0$

Table 2.8 Quasistatic laws for linear media.

Electroquasistatic (EQS)
$\nabla \cdot \epsilon \boldsymbol{E} = \rho_e$
$\nabla \times \boldsymbol{E} = 0$
$\nabla \cdot \boldsymbol{J} = -\frac{\partial \rho_e}{\partial t} \simeq 0$

Charge Relaxation

$\leftrightarrow$ "Steady" Conduction (sec 2.7.1)

(since $\tau_{\text{heart}} >>> \tau_{\text{relax}}$)

~1 sec (τ_{heart})

~10^{-9} sec in physiologic media (τ_{relax})

$\boldsymbol{J} = \sigma \boldsymbol{E}$

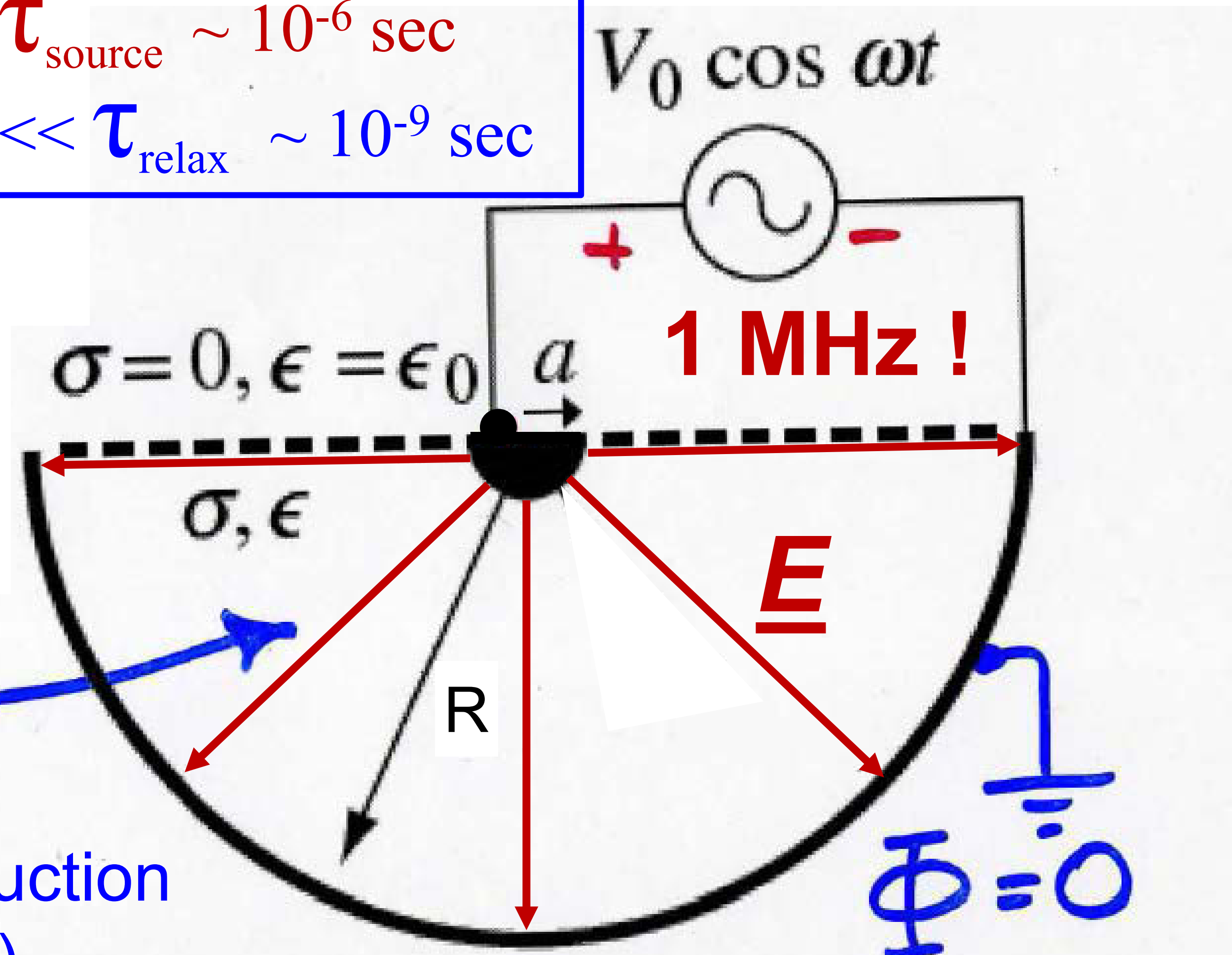
$\nabla \bullet J = \sigma \nabla \bullet E = 0$

$\nabla^2\Phi = 0$ (Laplace)

Electrosurgery: Cutting and Coagulation

$$\tau_{source} \sim 10^{-6}\ \text{sec}$$
$$<< \tau_{relax} \sim 10^{-9}\ \text{sec}$$

Universal
Hemi-
cylindrical
Patient



"Steady" Conduction
(sec 2.7.1)

$\nabla^2\Phi = 0$ (Laplace)

Power $\propto$ ***J•E*** ~ $|\sigma E^2|$

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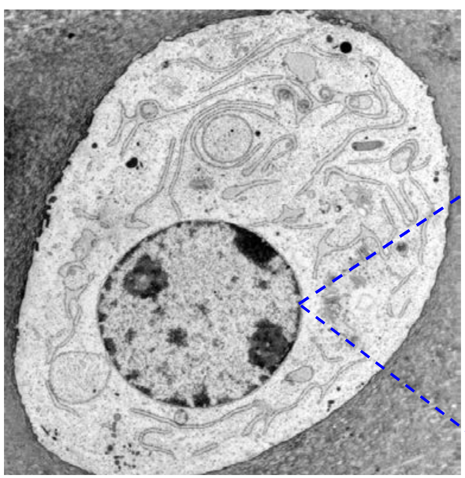
(Come back to this at end: "Integrative Case Studies)

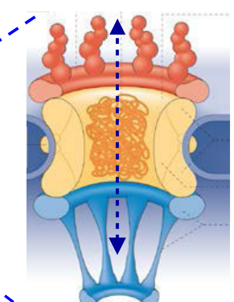
A Saturated FG-Repeat Hydrogel Can Reproduce the Permeability Properties of Nuclear Pore Complexes

Cell, 2007

Steffen Frey[1] and Dirk Görlich[1,*]
[1] Max-Planck-Institut für Biophysikalische Chemie, Am Fassberg 11, D-37077 Göttingen and Zentrum für Molekulare Biologie der Universität Heidelberg (ZMBH), INF 282, D-69120 Heidelberg, Germany

Cell nuclei lack protein synthesis and therefore import all their proteins from the cytoplasm. In return, they supply the cytoplasmic compartment with nuclear products such as ribosomes, tRNAs, and mRNAs. The nuclear



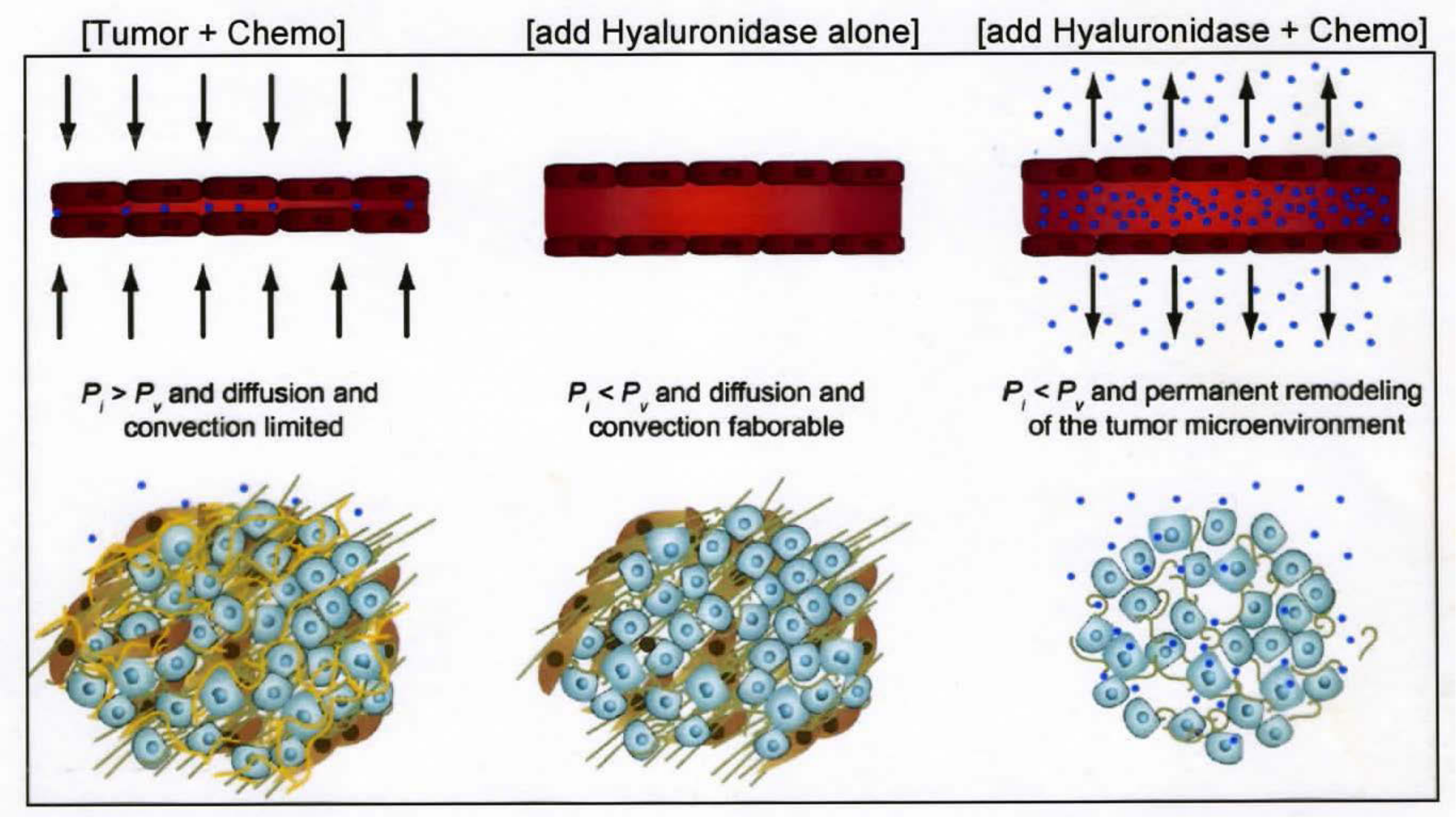


- hydrophobic and hydrophilic interactions mediate transport
- "Hydrophilic" : lots of **lysines (+ charge)**
- ~1000 translocations / sec

Source: Toyama, Brandon H. and Martin W. Hetzer. "Protein homeostasis: live long, won't prosper." Nature Reviews Molecular Cell Biology 14, no. 1 (2013): 55-61.

P. Provenzano et al., Cancer Cell, March 2012: Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma

From Fig. 7 in paper: **Blue spheres represent small chemotherapy molecules**, vessels are shown in **red**, carcinoma cells in **light blue**, activated PSC in **brown**, collagen in **green**, and **Hyaluronic acid (hyaluronan, HA) in yellow**. Pi, interstitial ("intra-tissue") fluid pressure; Pv, intravascular fluid pressure. (The examiner cannot confirm or deny the color scheme.)



Source: Provenzano, Paolo P. et al. "Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma." Cancer Cell 21, no. 3 (2012): 418-429.

LETTER

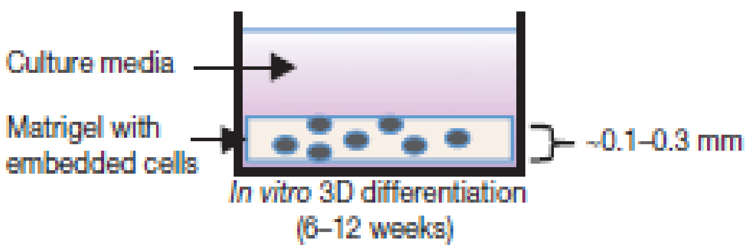
PSet 5.3

Nature, 10/12/2014

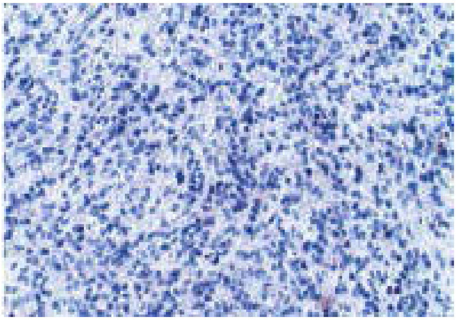
doi:10.1038/nature13800

A three-dimensional human neural cell culture model of Alzheimer's disease

Se Hoon Choi[1]*, Young Hye Kim[1,2]*, Matthias Hebisch[1,3], Christopher Sliwinski[1], Seungkyu Lee[4], Carla D'Avanzo[1], Hechao Chen[1], Basavaraj Hooli[1], Caroline Asselin[1], Julien Muffat[5], Justin B. Klee[1], Can Zhang[1], Brian J. Wainger[4], Michael Peitz[3], Dora M. Kovacs[1], Clifford J. Woolf[4], Steven L. Wagner[6], Rudolph E. Tanzi[1] & Doo Yeon Kim[1]



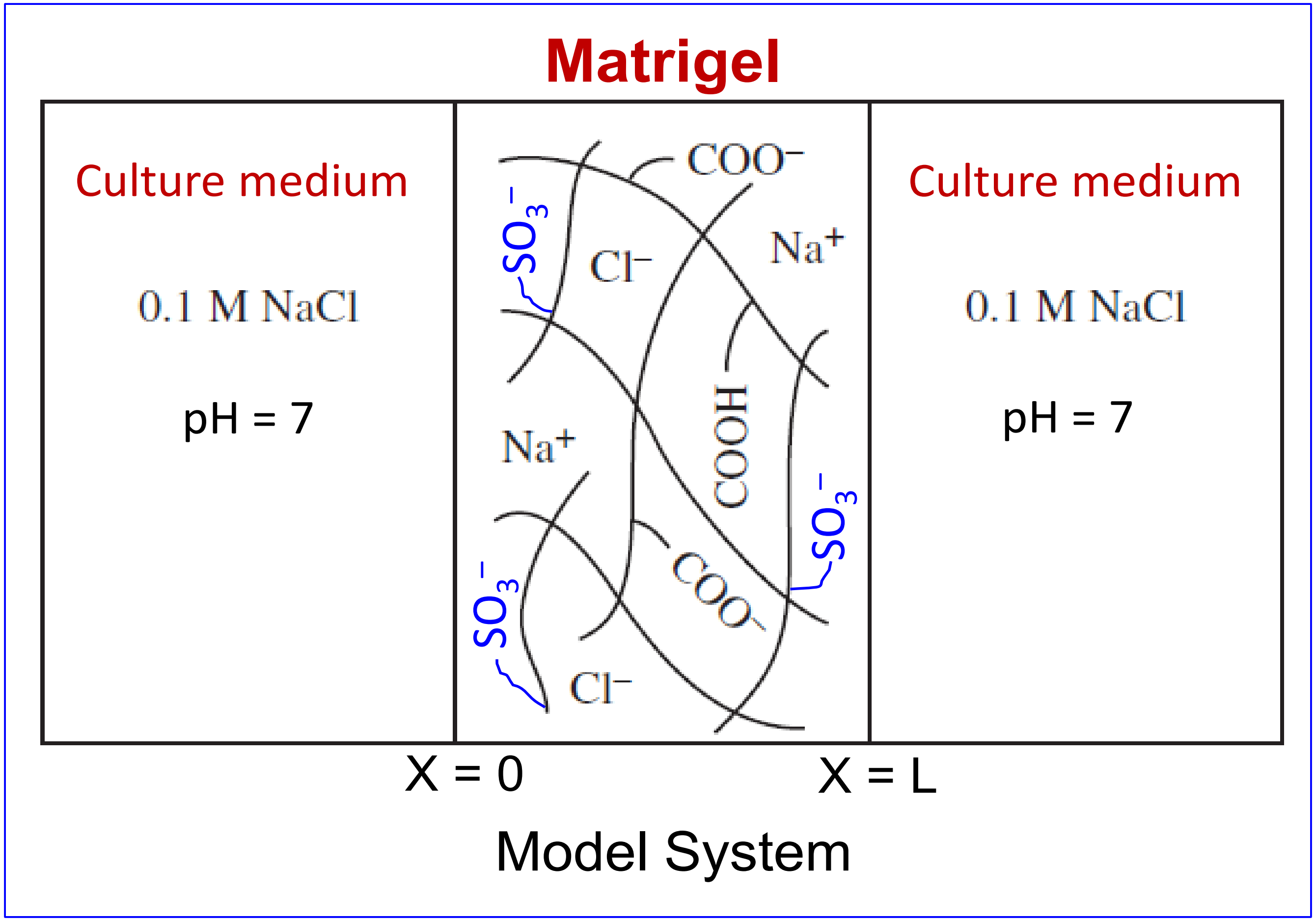
Matrigel contains many extracellular matrix proteins including highly negatively charged heparan sulfate proteoglycans....



Immunohistochemistry shows amyloid protein deposits in this 3D cell culture system

Source: Choi, Se Hoon et al. "A three-dimensional human neural cell culture model of Alzheimer/'s disease." Nature 515, no. 7526 (2014): 274-278.

Background from paper: Human neural progenitor cells that produce high levels of toxic amyloid-β proteins were cultured in 3D Matrigel. Authors state, "In conventional 2D cultures, secreted amyloid-β diffuses into a large volume of media (and are lost). We hypothesized that 3D culture accelerates amyloid-β *deposition* by limiting diffusion of amyloid-β out of the gel, allowing aggregation near the cells. We chose BD **Matrigel** (BD Biosciences) as a 3D support matrix since it contains **high levels of brain extracellular matrix proteins.**

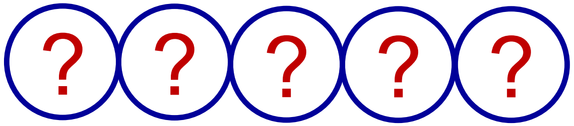


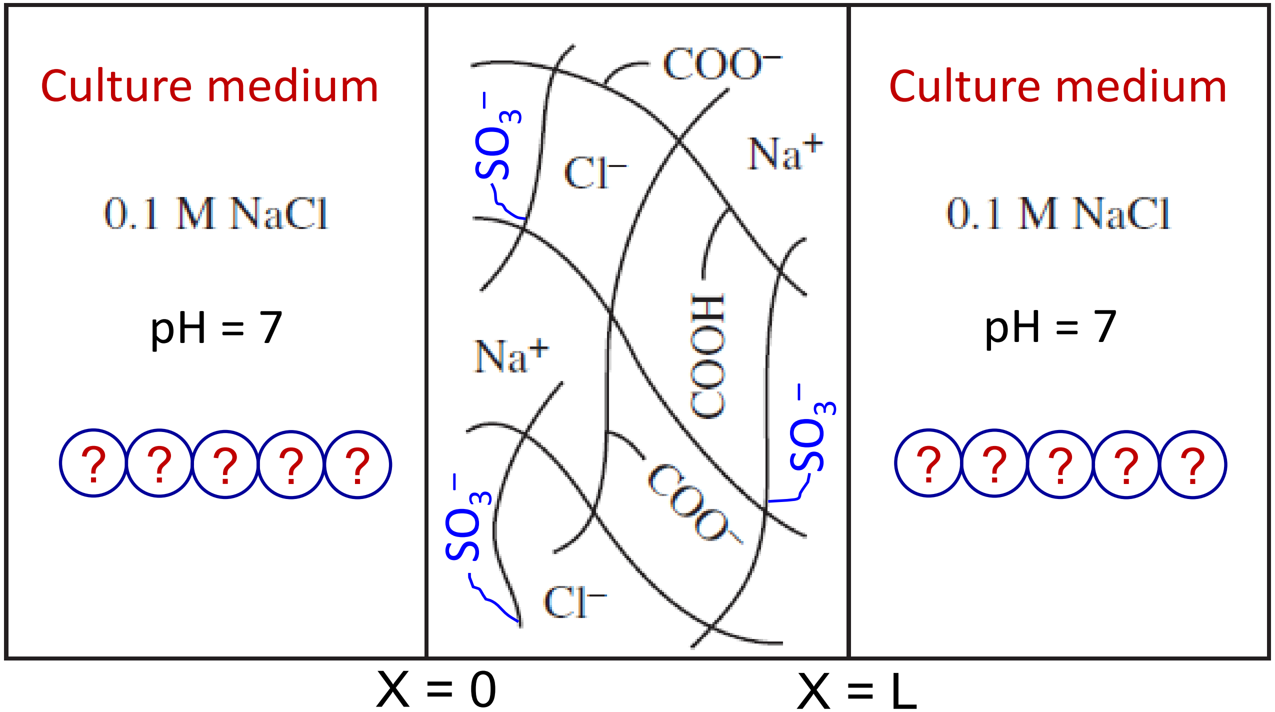
P 5.3

- Gel & fixed charge density: uniform; culture medium is C_o = 0.1M NaCl, pH 7 (for simplicity). Bath volume larger than gel. **Add positively charged drug to medium at 10 nM;** <u>let the system come to complete equilibrium</u> (concentration of all species inside the gel is uniform).
- **Use Donnan Equilibrium to find/optimize drug & drug concentration in matrigel**

Pfizer Mystery Drug: "Pf-Pep"

760 Da; pI ~ 11   ("peptide; basic")





Like
P 5.3

Can drug charge increase penetration (?) and retention (?) of drug into desired tissue (tumor…)

Boltzmann Distribution of mobile ions near charged macromolecules

$$\underline{N}_i = -D_i \nabla c_i + \frac{z_i}{|z_i|} u_i c_i \underline{E} = 0$$

Statement of thermal equilibrium

$$\frac{D_i}{u_i} = \frac{RT}{|z|F}$$

$$\bar{N}_i = -\bar{D}_i \nabla \bar{c}_i \ominus \bar{c}_i \bar{u}_i \frac{z_i}{|z_i|} \nabla \Phi = 0$$

$$-\int_{X=0-}^{X=0^+} \left(\frac{D_i}{u_i}\right) \frac{dc(x)}{c(x)} = \int_{X=0-}^{X=0^+} \left(\frac{z_i}{|z_i|}\right) d\Phi(x)$$

$$\frac{RT}{F} \ln\left(\frac{\bar{c}_i}{c_i}\right)^{\frac{1}{z_i}} = -\underbrace{\Delta\Phi_D}_{\text{(constant)}}$$

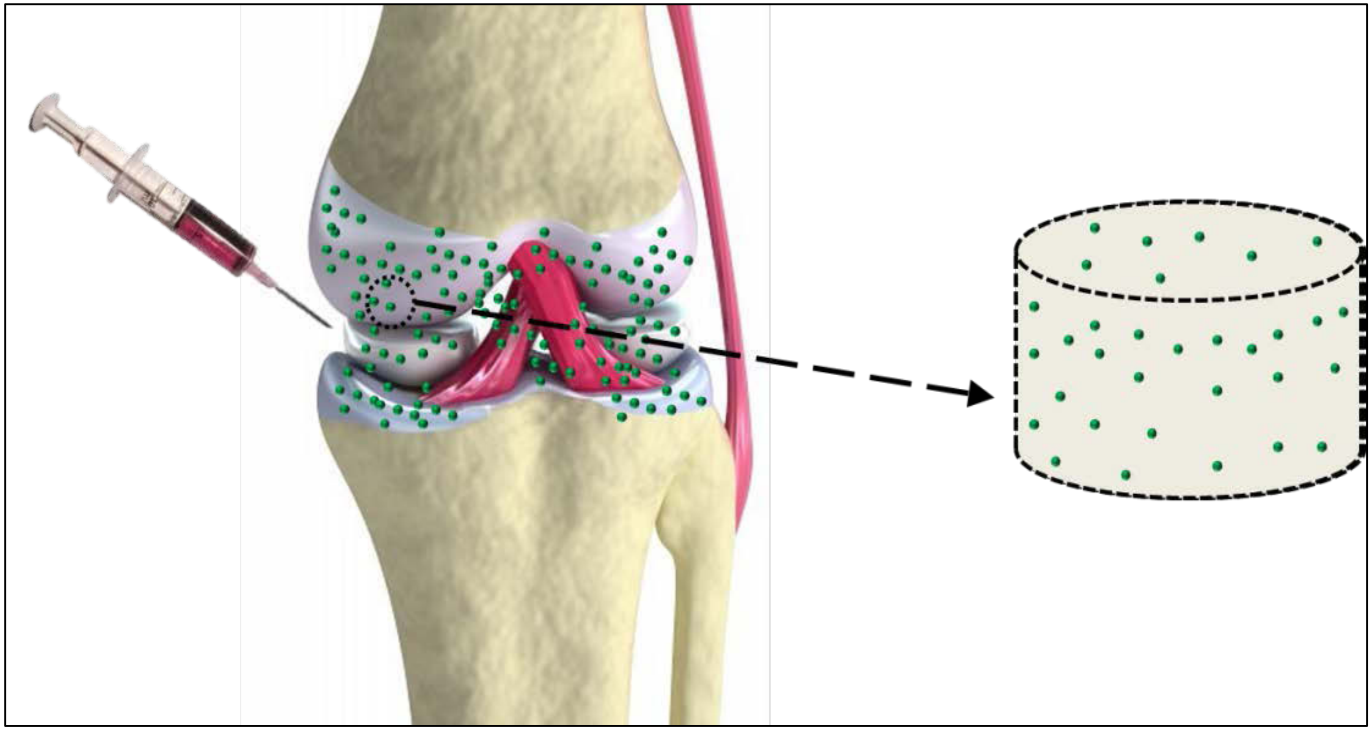
$$c_i = c_{i0}\, e^{-z_i F \Phi(x)/RT}$$

Boltzmann….consistent with equilibrium, $\boldsymbol{N_i} = 0$

Pfizer Mystery Drug: "Pf-Pep"

760 Da; pI ~ 11 (peptide; basic)

? ? ? ? ?



Courtesy of Alan Grodzinsky. Used with permission.

Can drug charge increase penetration and retention of drug into desired tissue (tumor…)

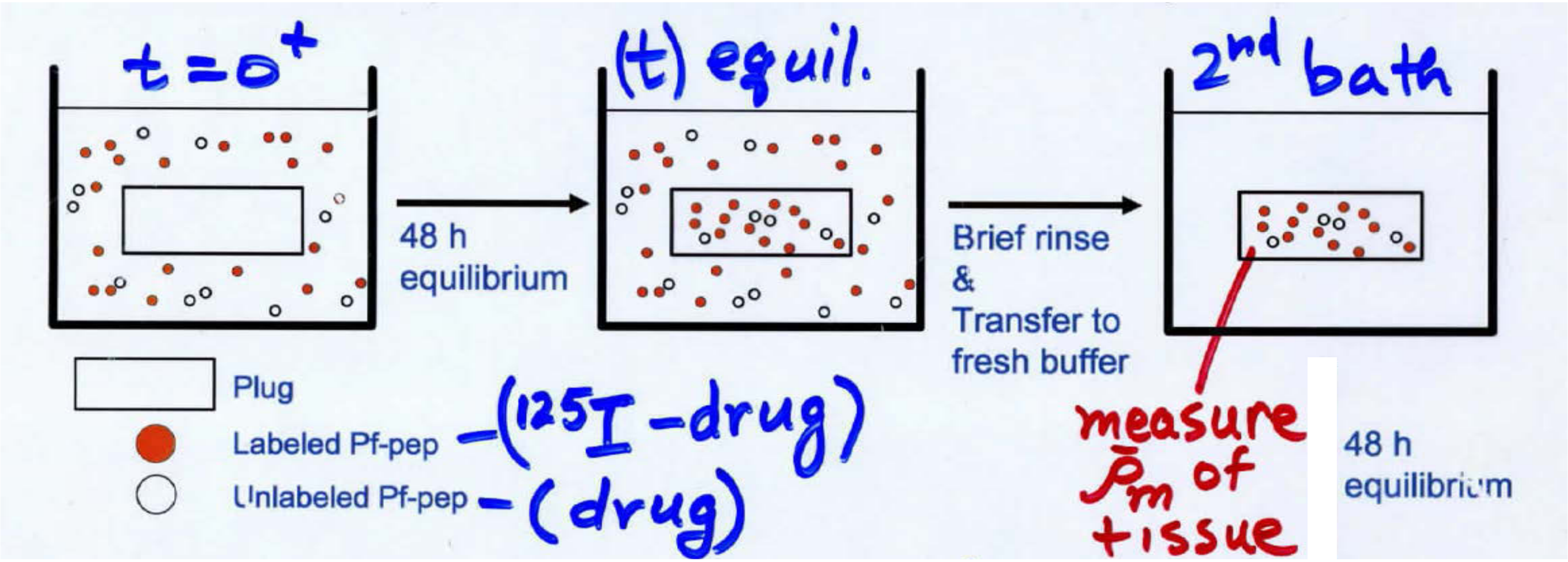
Amino acid	Abbreviations		Molecular mass (Da)	Number of atoms	Volume (A^3)	Hydropathy index
Alanine	Ala	A	89	13	88.6	1.8
Arginine	Arg	R	174	26	173.4	-4.5
Asparagine	Asn	N	132	17	114.1	-3.5
Aspartic acid	Asp	D	133	16	111.1	-3.5
Cysteine	Cys	C	121	14	108.5	2.5
Glutamine	Gln	Q	146	20	143.8	-3.5
Glutamic Acid	Glu	E	147	19	138.4	-3.5
Glycine	Gly	G	75	10	60.1	-0.4
Histidine	His	H	155	20	153.2	-3.2
Isoleucine	Ile	I	131	22	166.7	4.5
Leucine	Leu	L	131	22	166.7	3.8
Lysine	Lys	K	146	24	168.6	-3.9
Methionine	Met	M	149	20	162.9	1.9
Phenylalanine	Phe	F	165	23	189.9	2.8
Proline	Pro	P	115	17	112.7	-1.6
Serine	Ser	S	105	14	89.0	-0.8
Threonine	Thr	T	119	17	116.1	-0.7
Tryptophan	Trp	W	204	27	227.8	-0.9
Tyrosine	Tyr	Y	181	24	193.6	-1.3
Valine	Val	V	117	19	140.0	4.2

Pfizer Mystery Drug: “Pf-Pep”

760 Da; pI ~ 11   (5 amino acids; basic)

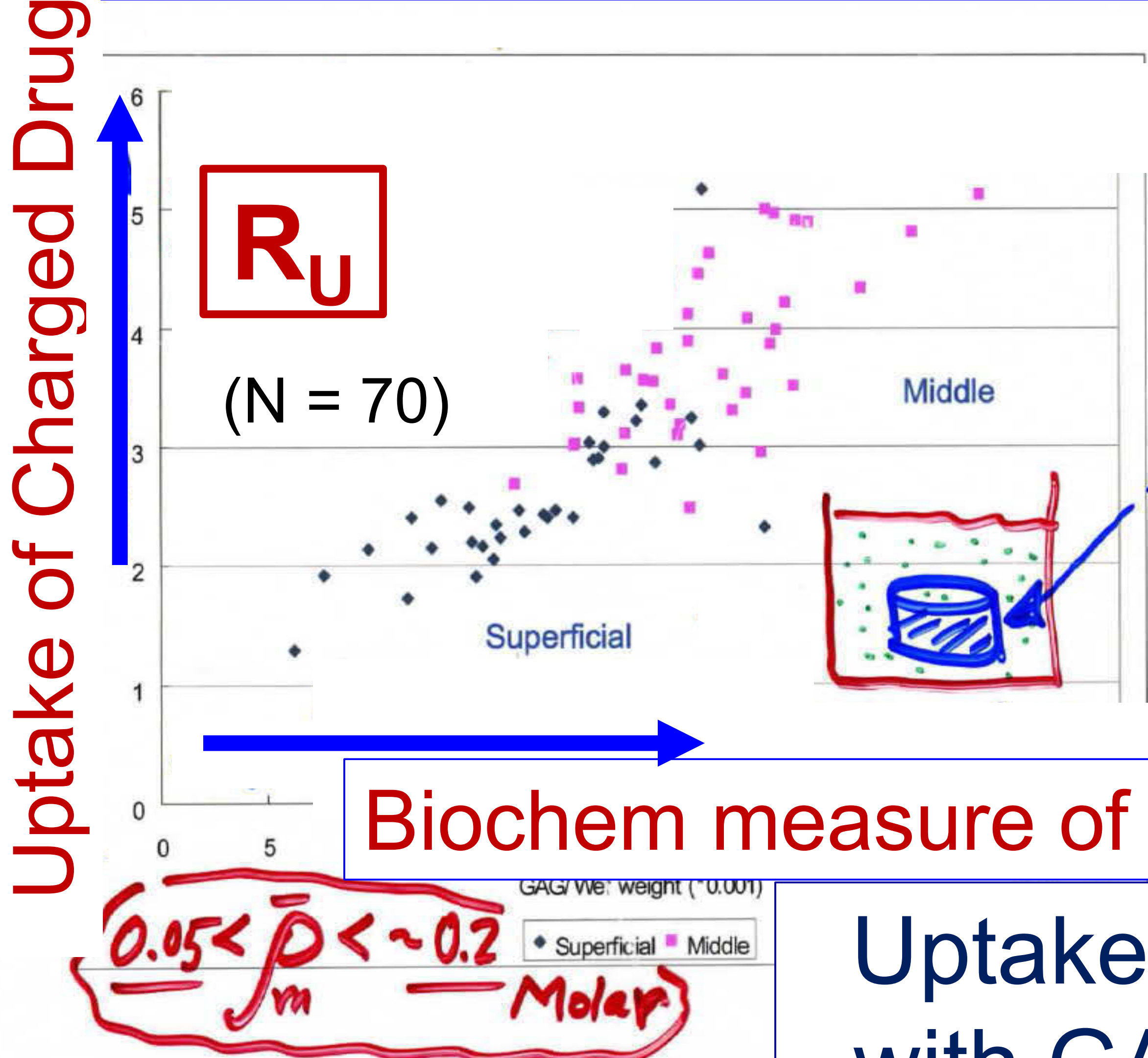
Measure Uptake of ^{125}I-Pf-pep:

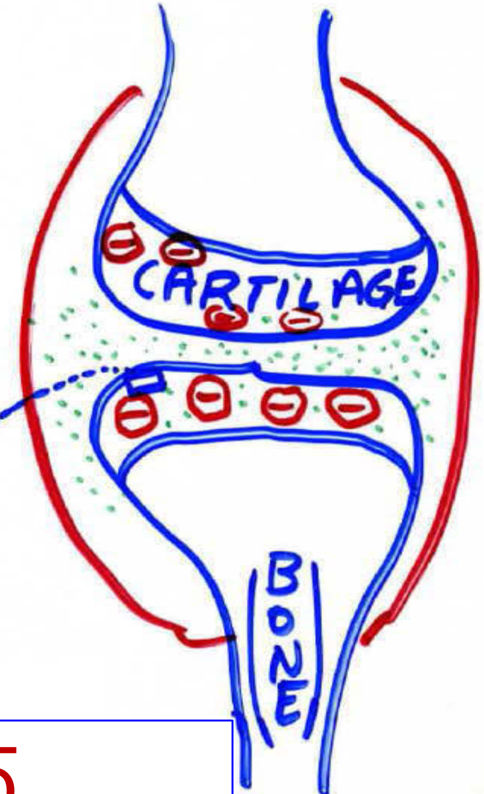
$$R_U = K_{part}\left(1 + \frac{n}{K_d + c_F}\right)$$



Pfizer Mystery Drug: “Pf-Pep”

760 Da; pI ~ 11 (5 amino acids; basic)





Uptake increased with GAG density

Can You Use Donnan to Find: Charge of the Drug ??

From (3) $\bar{\rho}_m = \dfrac{\text{GAG}}{\text{water content}} \cdot \dfrac{2}{\text{Molecular weight}_{\text{chodroitin sulfate}}}$ $\bar{\rho}_m$ measured

Also, we have $C_{Na^+} = C_{Cl^-} = C_0 = 0.15\,\text{M}$ Bath

From (1) $\dfrac{\bar{C}_{Na^+}}{C_0} = \dfrac{C_0}{\bar{C}_{Cl^-}}$ (4) (Na^+, Cl^- partitioning) (BOLTZMANN)

From (2) and (4) $\rho + \bar{C}_{Na^+} - \dfrac{C_0^{\,2}}{\bar{C}_{Na^+}} = 0$ (5) ρ and C_0 are known, thus calculate $\bar{C}_{Na^+}$

FIND

ELECTRONEUTRALITY

From (1) $\left(\dfrac{\bar{C}_{pep}}{C_{pep}}\right)^{\frac{1}{z}} = \left(\dfrac{\bar{C}_{Na^+}}{C_{Na^+}}\right)$??

measured

known

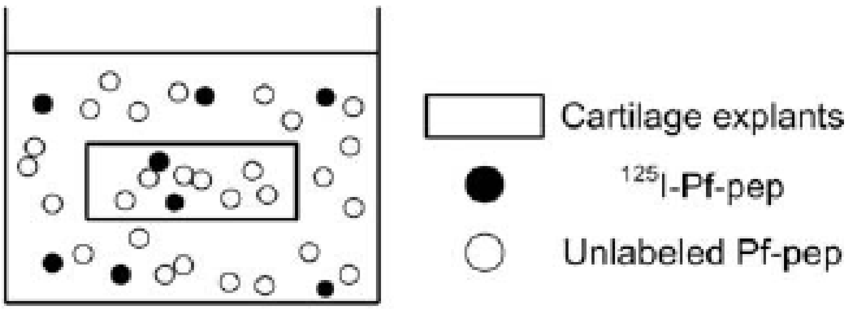
calculated (Donnan)

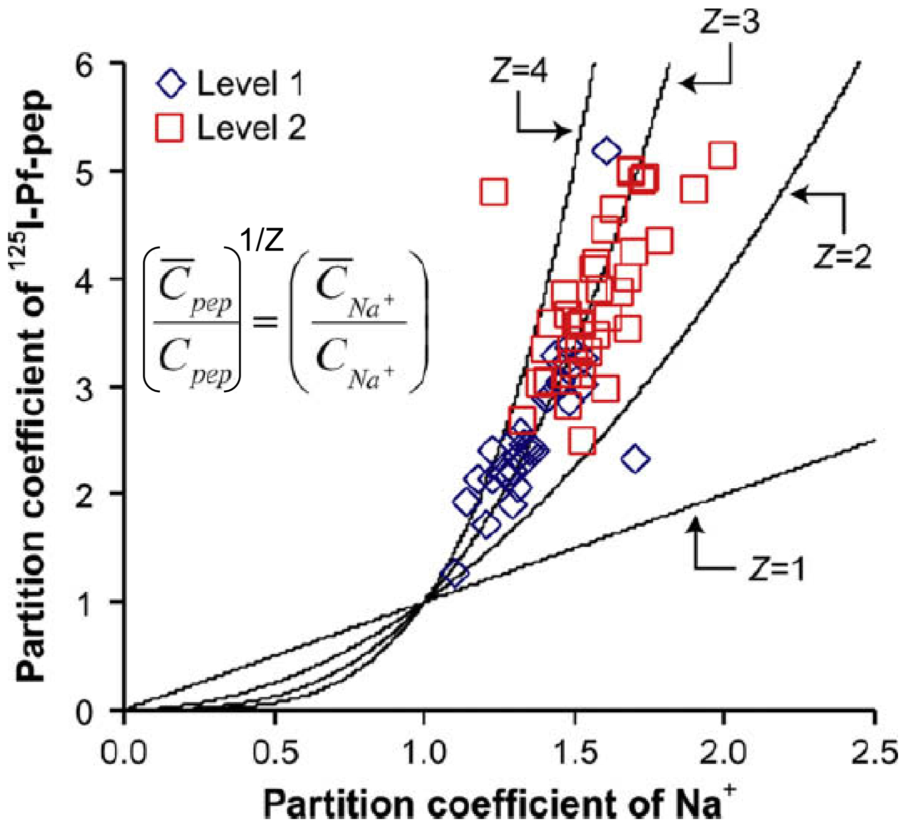
known

→ Calculate Z

FIND

- small (760 Da)
- basic (pI ~ 11)



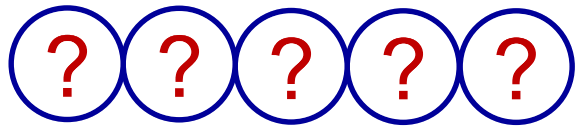


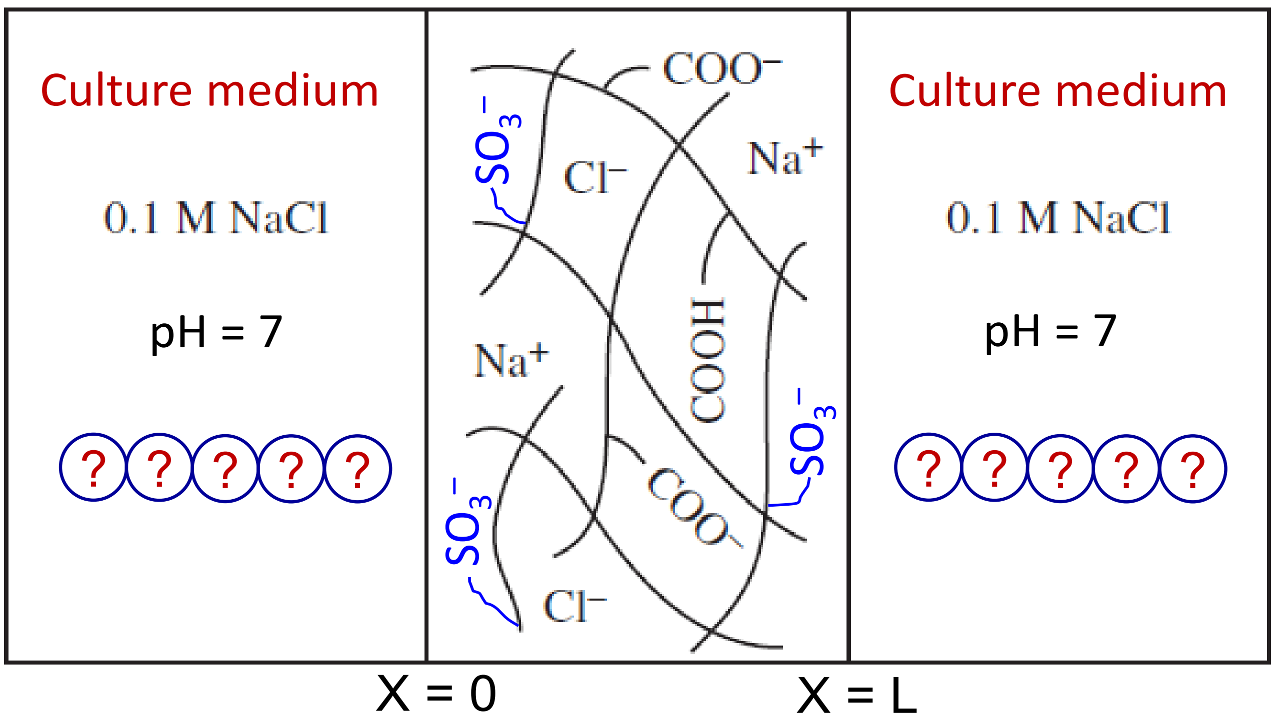
Donnan partitioning experiment

We signed a Materials Transfer Agreement:
no chemical analysis allowed ☺

Pfizer Mystery Drug: “Pf-Pep”

760 Da; pI ~ 11 (guess 5 amino acids; basic)





Can drug charge increase penetration and retention of drug into desired tissue (tumor…)