20.430 / 2.795 / 6.561 / 10.539

Fields Forces and Flows in Biological Systems

Fall 2015

Instructors: Mark Bathe, Alan Grodzinsky

Textbook:

Fields Forces and Flows in Biological Systems

Garland Science, March 2011

Book cover removed due to copyright restrictions.
Source: Grodzinsky, Alan. Field, Forces, and Flows in Biological Systems. Garland Science, 2011.

<u>Plus</u>:

- Additional readings from primary (research) literature
- Supplementary materials throughout

20.430 Scope and Purpose

- Describes the fundamental driving forces for transport: chemical gradients, electrical interactions & fluid flow, applied to the biology and biophysics of molecules / cells / tissues

Philosophy of the Subject

- Primary objective: to integrate principles of coupling between chemical, electrical, & mechanical forces and flows intrinsic to tissues, membranes, macromolecules, and biomaterials.
- Focus: Topics in biology, biophysics & medicine motivate quantitative engineering approaches: molecular scale through complex structural organization of tissues and organs.
- Lectures focus on current problems in biology, biophysics, and medicine, and then use text material as the basis for understanding measurement, modeling, and analysis

FFF: Assignments and Grading

Homework: (~eight 1-week assignments during the term)

You are *encouraged to form teams* with other class members to discuss the underlying concepts and approaches. (Of course, the work turned in must be your own.)

Term Paper Project:

- **Critical review** of a journal article from the literature
- Collaboration: ***Teams of 3 people***

Two take home quizzes: (~ middle and end of term)

Grading:

Homework	30%
Term Paper Project	30%
Take Home Quizzes	40%

Term Paper Project

Enzymatic Targeting of the Stroma Ablates Physical Barriers to Treatment of Pancreatic Ductal Adenocarcinoma

Cancer Cell
2012

Paolo P. Provenzano,[1] Carlos Cuevas,[4] Amy E. Chang,[1] Vikas K. Goel,[1] Daniel D. Von Hoff,[5] and Sunil R. Hingorani[1,2,3,*]
[1]Clinical Research Division
[2]Public Health Sciences Division
Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA
[3]Division of Medical Oncology, University of Washington School of Medicine, Seattle, WA 98195, USA
[4]Department of Radiology, University of Washington, Seattle, WA 98195, USA
[5]Clinical Translational Research Division, Translational Genomics Research Institute, Scottsdale, AZ 85259, USA
*Correspondence: srh@fhcrc.org
DOI 10.1016/j.ccr.2012.01.007

Screenshot removed due to copyright restrictions.
Source: Prof. Paolo Provenzano's website.

Cancer Research 2000

Role of Extracellular Matrix Assembly in Interstitial Transport in Solid Tumors[1]

Paolo A. Netti,[2] David A. Berk,[3] Melody A. Swartz,[4] .... Rakesh K. Jain[5]

Steele Laboratory for Tumor Biology, Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114 [D. A. B., M. A. S., R. K. J.], and Department of Electrical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139 [A. J. G.]

ABSTRACT

- **The extracellular matrix may contribute to the drug resistance of a solid tumor by preventing the penetration of therapeutic agents. We measured differences in interstitial resistance to macromolecule (IgG) transport in 4 tumor types and found an unexpected correspondence between transport resistance and the mechanical stiffness.**

- **The interstitial diffusion coefficient of IgG was measured *in situ* by FRAP……**

Term Paper Project

Enzymatic Targeting of the Stroma Ablates Physical Barriers to Treatment of Pancreatic Ductal Adenocarcinoma

Cancer Cell 2012

Paolo P. Provenzano,[1] Carlos Cuevas,[4] Amy E. Chang,[1] Vikas K. Goel,[1] Daniel D. Von Hoff,[5] and Sunil R. Hingorani[1,2,3,*]
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[5]Clinical Translational Research Division, Translational Genomics Research Institute, Scottsdale, AZ 85259, USA
*Correspondence: srh@fhcrc.org
DOI 10.1016/j.ccr.2012.01.007

Hyaluronan, fluid pressure, and stromal resistance in pancreas cancer

British J of Cancer 2013

P P Provenzano[1,4] and S R Hingorani[*,1,2,3]
[1]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA; [2]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA; [3]Division of Medical Oncology, University of Washington School of Medicine, Seattle, WA 98195, USA

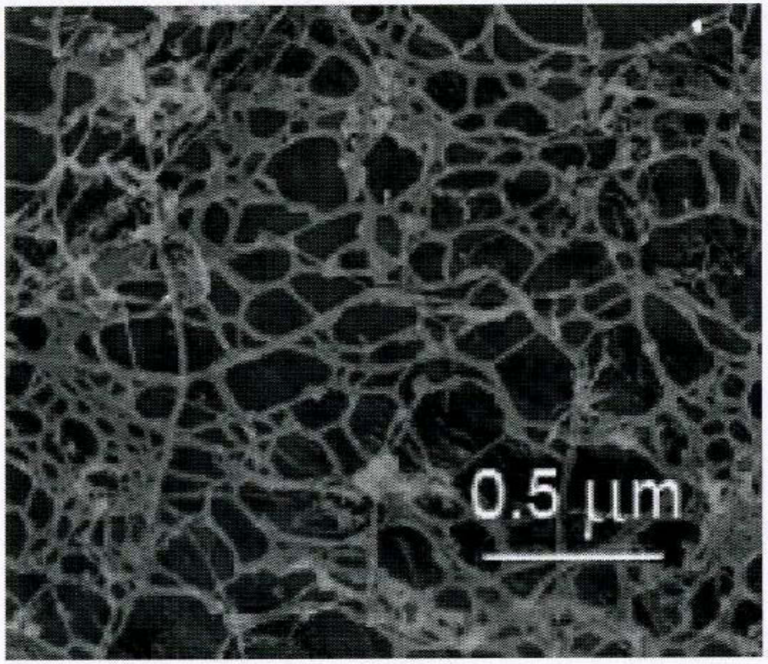
Fields Forces & Flows: Syllabus

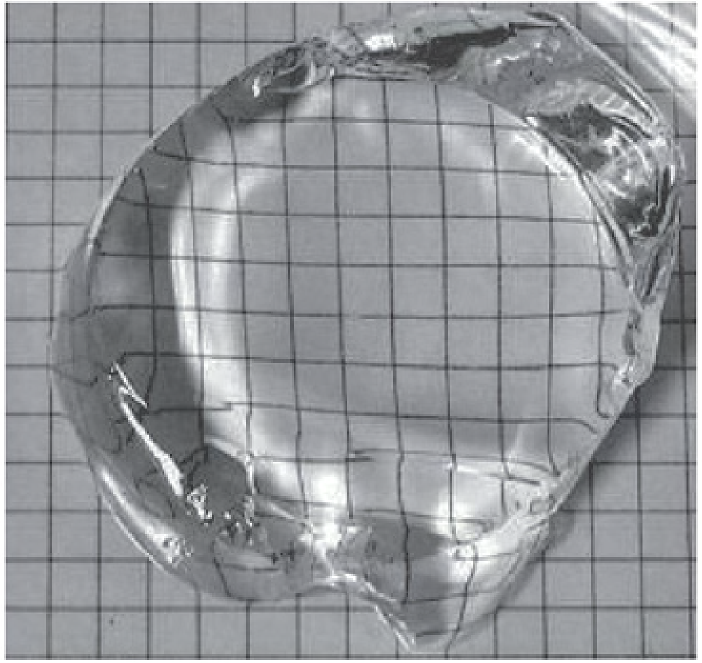
I. CHEMICAL SUBSYSTEM
II. ELECTRICAL SUBSYSTEM
III. MECHANICAL SUBSYSTEM
IV. INTEGRATIVE CASE STUDIES: PHYSICOCHEMICAL, BIOPHYSICAL

Lect	Date	Topic
1	Sep 9	Course introduction, overview, and objectives
		I. CHEMICAL SUBSYSTEM
2	Sep 14	Diffusion as a random walk; Stokes-Einstein relation for diffusion coefficient; Examples of diffusion
3	Sep 16	Constitutive equations for diffusion (Fick's Laws); Conservation of mass for a control volume; Differential form; Steady diffusion (1D); Boundary conditions
4	Sep 21	Diffusion and reaction; Reaction rates, order, molecularity and mechanisms; Scaling and the Damköhler number; Solution procedures
5	Sep 23	Examples of diffusion-reaction: Diffusion of a ligand through tissue with cell receptor-ligand interactions; Diffusion-reaction kinetics
6	Sep 28	More examples of diffusion-reaction
7	Sep 30	Case study: IGF-1 diffusion-reaction within tissues and cell seeded scaffolds; binding to IGF binding proteins & cell surface receptors; experimental methods

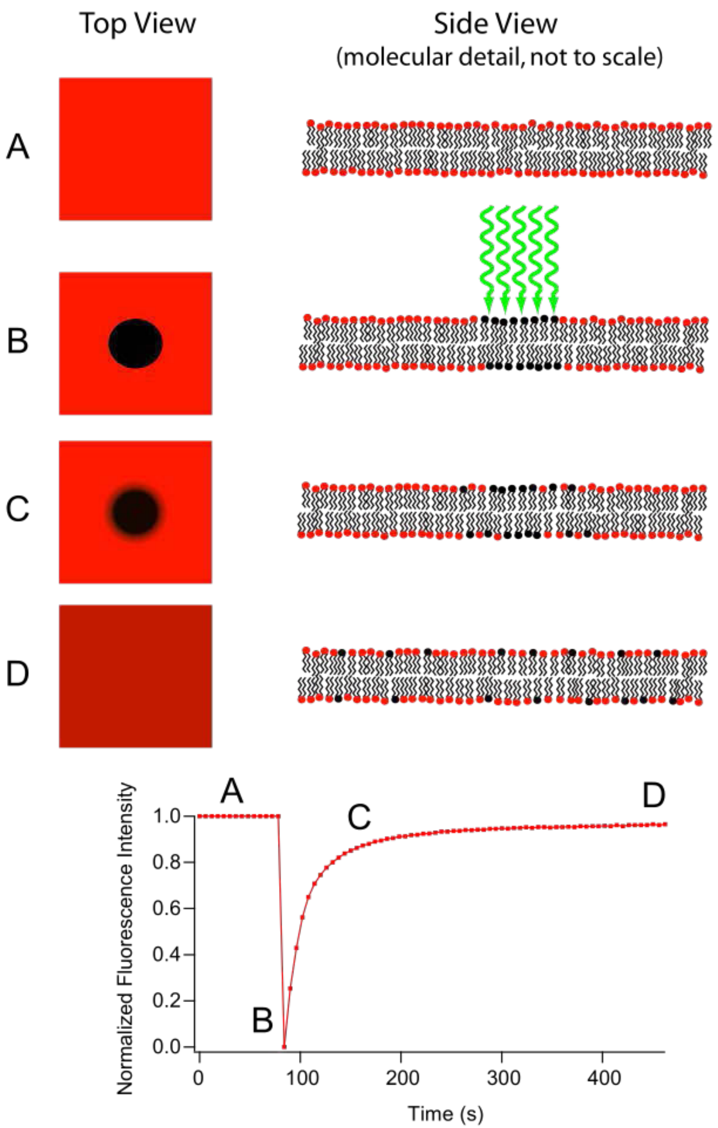
Solute Flow in & across "Bio Porous Materials:

Molecular Networks, Gels….



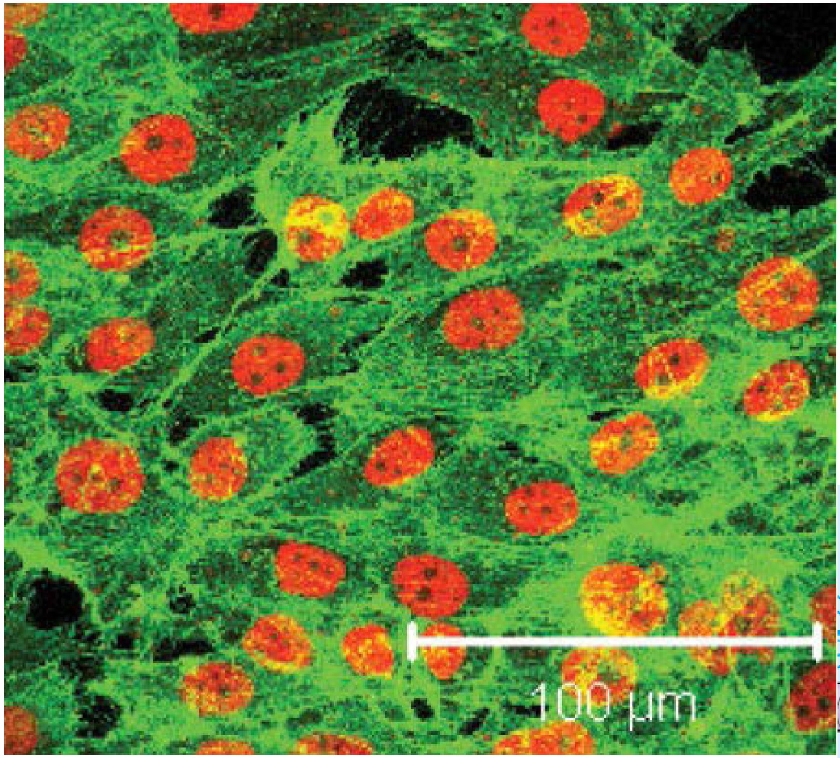


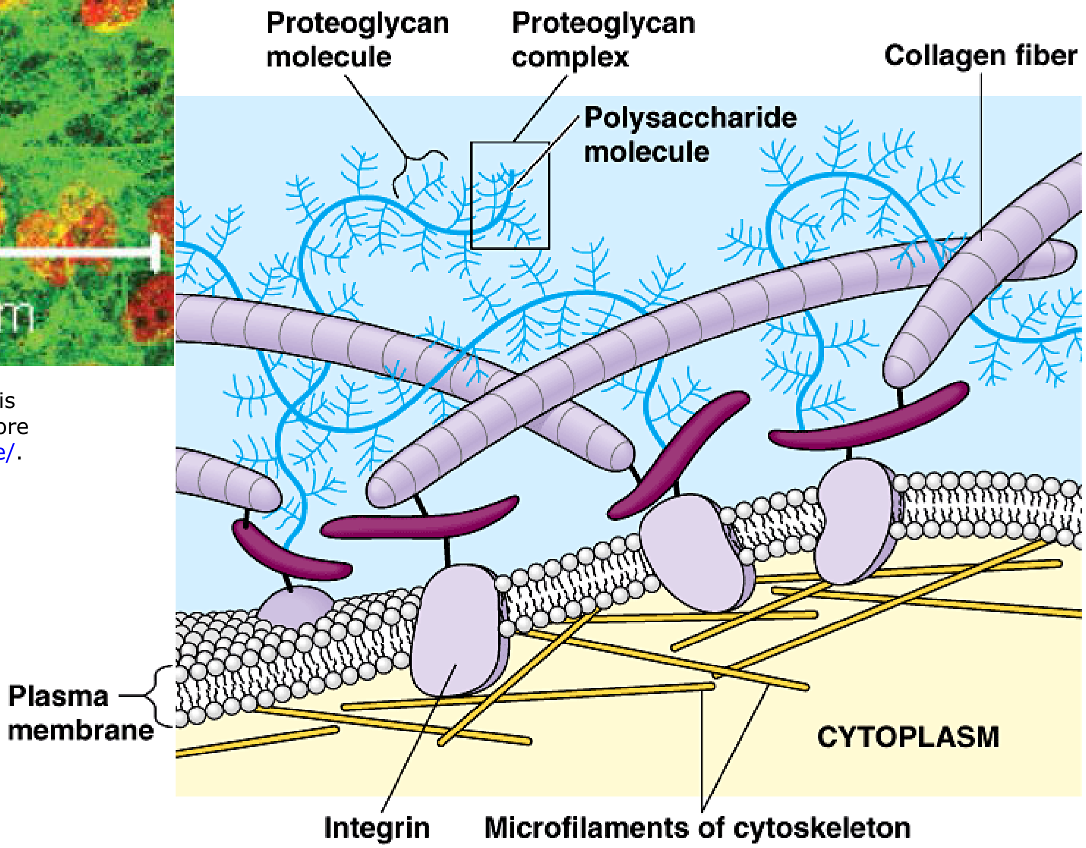
"Measure and Model": Find Diffusivity D_i



Courtesy of MDougM; in the public domain.

Growth factors (e.g., IGF-1) and cytokines (e.g., TNFα) can bind to Extracellular Matrix molecules as well as cell receptors

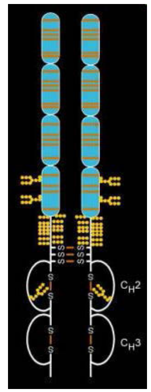




"Biologic" TNF-α Blockers: >$20 Billion/year

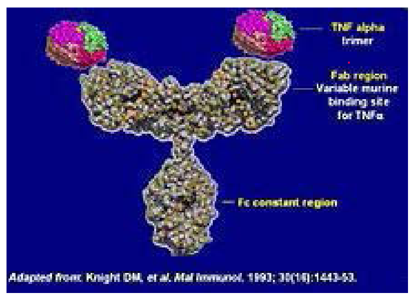
Enbrel® etanercept

(*Amgen / Pfizer*)
(1998 RA)

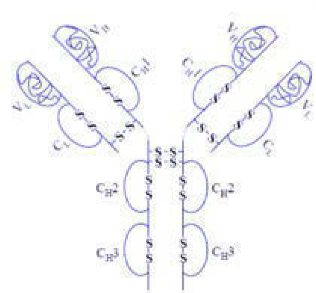


Remicade

INFLIXIMAB
(*Centocor / J&J*)
(1998 Crohn's)



HUMIRA® adalimumab
(*Abbott*)
(2002 RA)

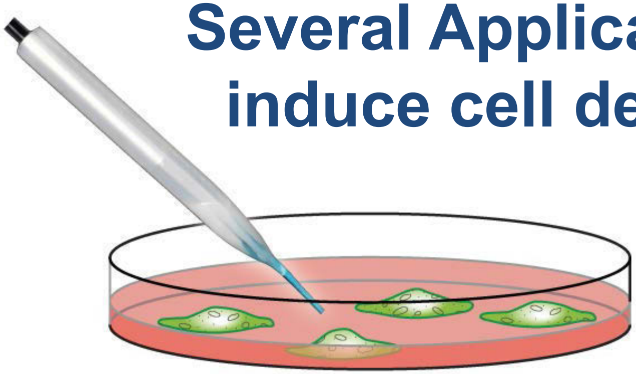


Autoimmune-Inflammatory Diseases

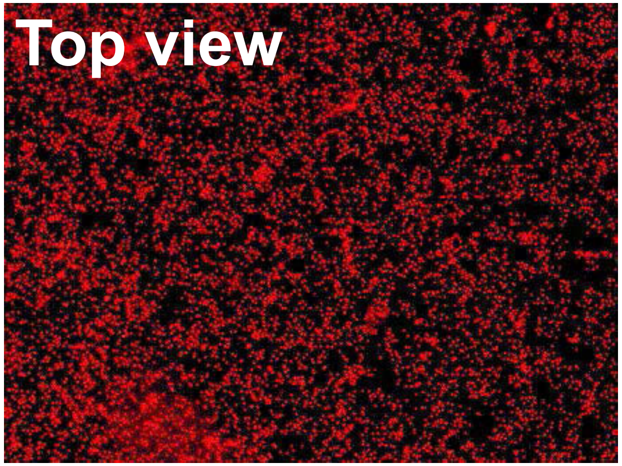
- Rheumatoid Arthritis
- Crohn's Disease (IBD)
- Ulcerative Colitis (IBD)
- Ankylosing Spondylitis
- Psoriatic Arthritis
- Psoriasis

Effects of a cell signaling (kinase) blocker (Merck BI-78D)

Several Applications: diabetes; purposely induce cell death (apoptosis) in tumors



Monolayer cell culture



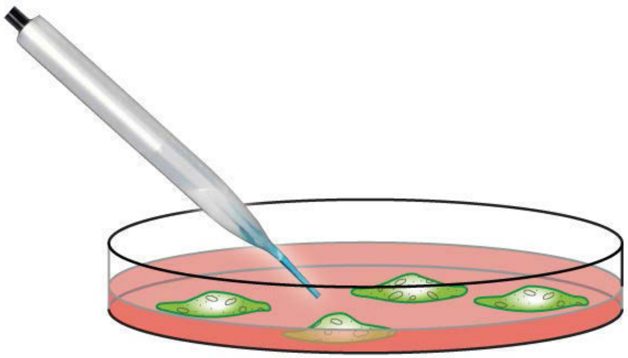
Day 1 of culture

- Added kinase inhibitor on Day 0
- Use fluorescent markers to assess cell viability:

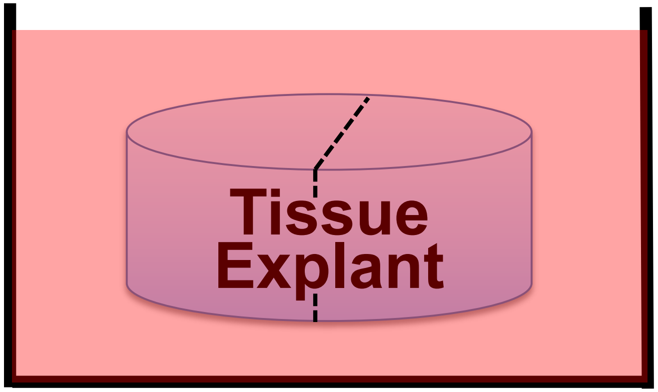
RED = Dead cells

GREEN = Live cells

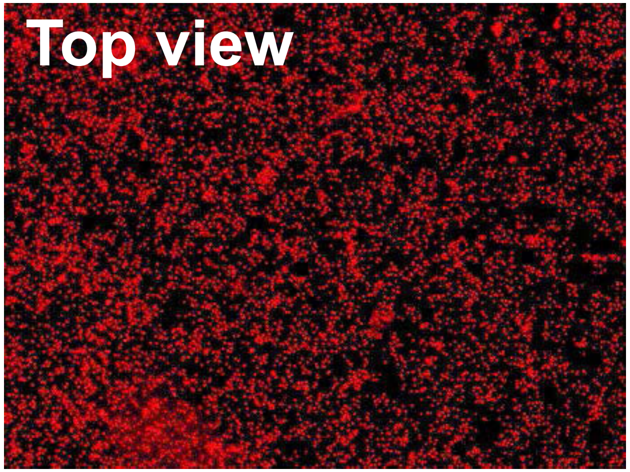
Effects of a cell signaling (kinase) blocker (Merck BI-78D)



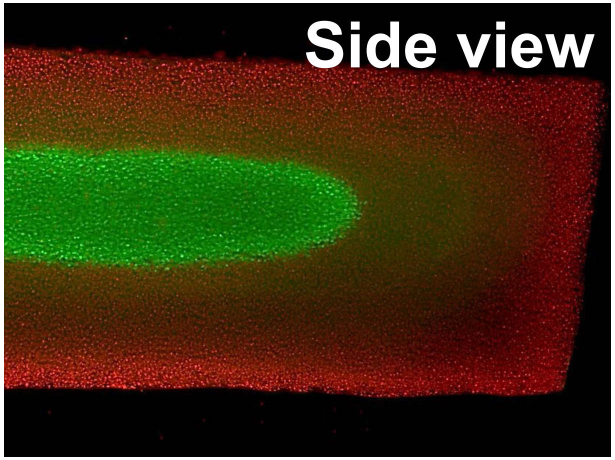
Monolayer cell culture



Tissue with same cells



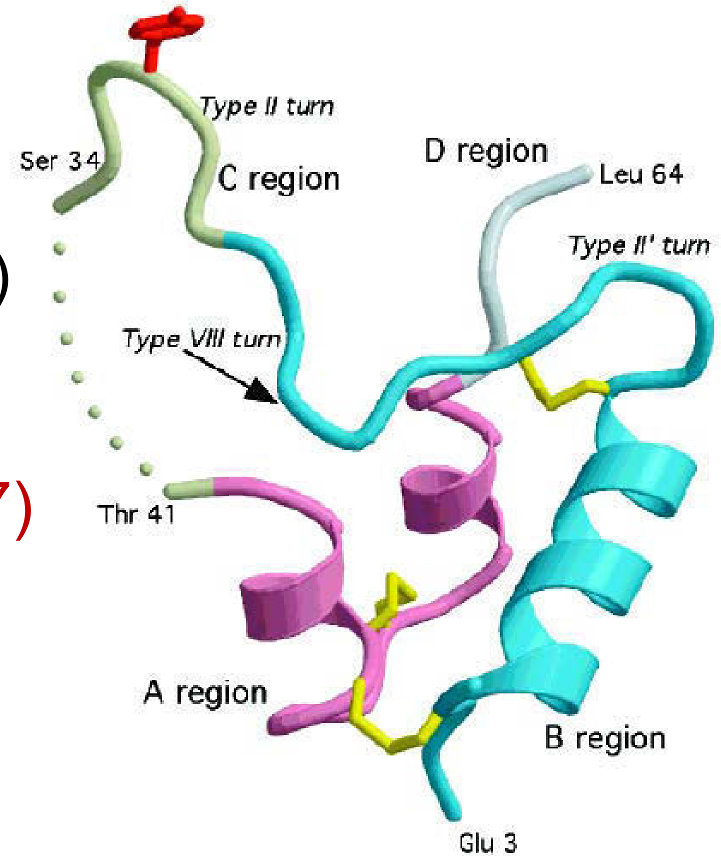
Day 1 of culture



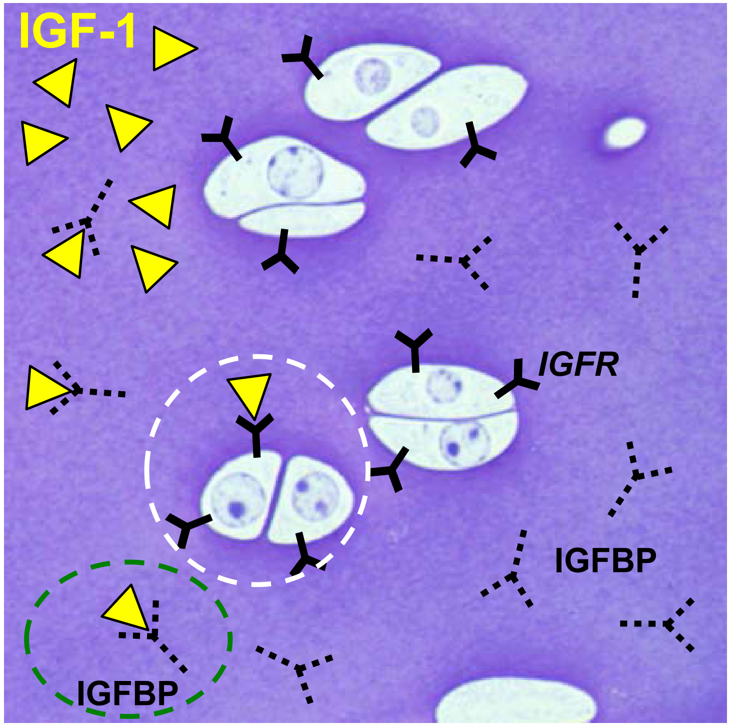
Day 6 of culture

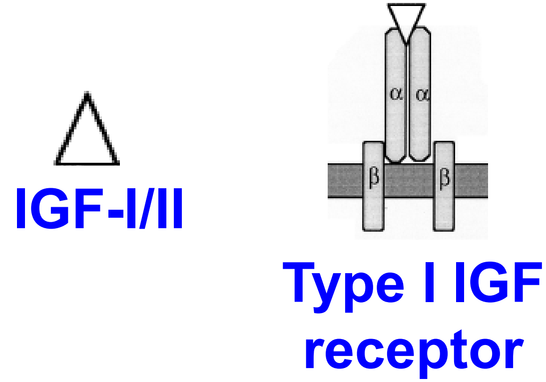
Insulin-like Growth Factor-1 (IGF-1)

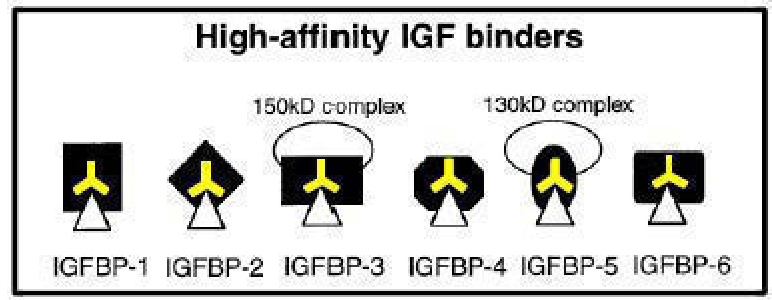
- Peptide Growth Factor:
  - ♦ Stimulates cellular biosynthesis;
  - ♦ Inhibits catabolic degradation of ECM
  - ♦ Anti-Apoptotic
- Protein: **7.6 kDa** (**70 amino acids**)
- "Folds" like Insulin in Aq. Solution
- **pI ~ 8.4** ("basic" **+ charged** @ pH 7)
- **Found in: Nerve, Muscle, Connective, & Epithelial Tissues**
  - ♦ Serum (50-200 ng/ml)
  - ♦ Joint Fluid (20-50 ng/ml)
  - ♦ Tissue (1-10 ng/ml)
  - ♦ CSF; Brain (~5 ng/ml; ~5 pg/mg)

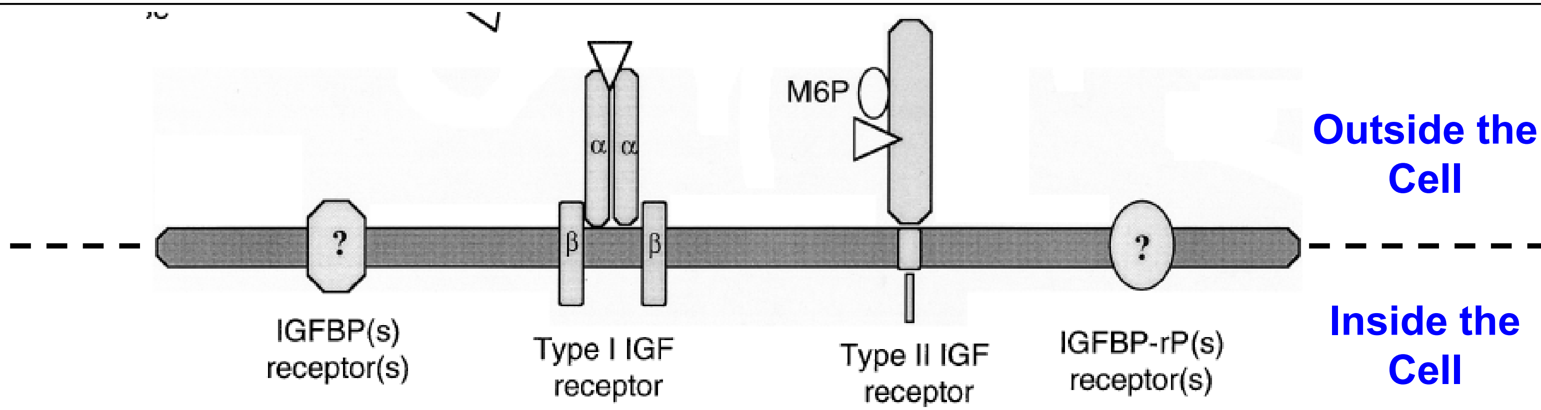


Source: Vajdos, Felix F. et al. "Crystal structure of human insulin-like growth factor-1: detergent binding inhibits binding protein interactions." Biochemistry 40, no. 37 (2001): 11022-11029.


IGF-1
IGFR
IGFBP
IGFBP


α α
β β
IGF-I/II
Type I IGF receptor


High-affinity IGF binders
150kD complex
130kD complex
IGFBP-1
IGFBP-2
IGFBP-3
IGFBP-4
IGFBP-5
IGFBP-6


M6P
α α
β β
?
?
IGFBP(s) receptor(s)
Type I IGF receptor
Type II IGF receptor
IGFBP-rP(s) receptor(s)
Outside the Cell
Inside the Cell

SIMONS CENTER FOR THE SOCIAL BRAIN

SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

Partial reversal of Rett Syndrome-like symptoms in MeCP2 mutant mice

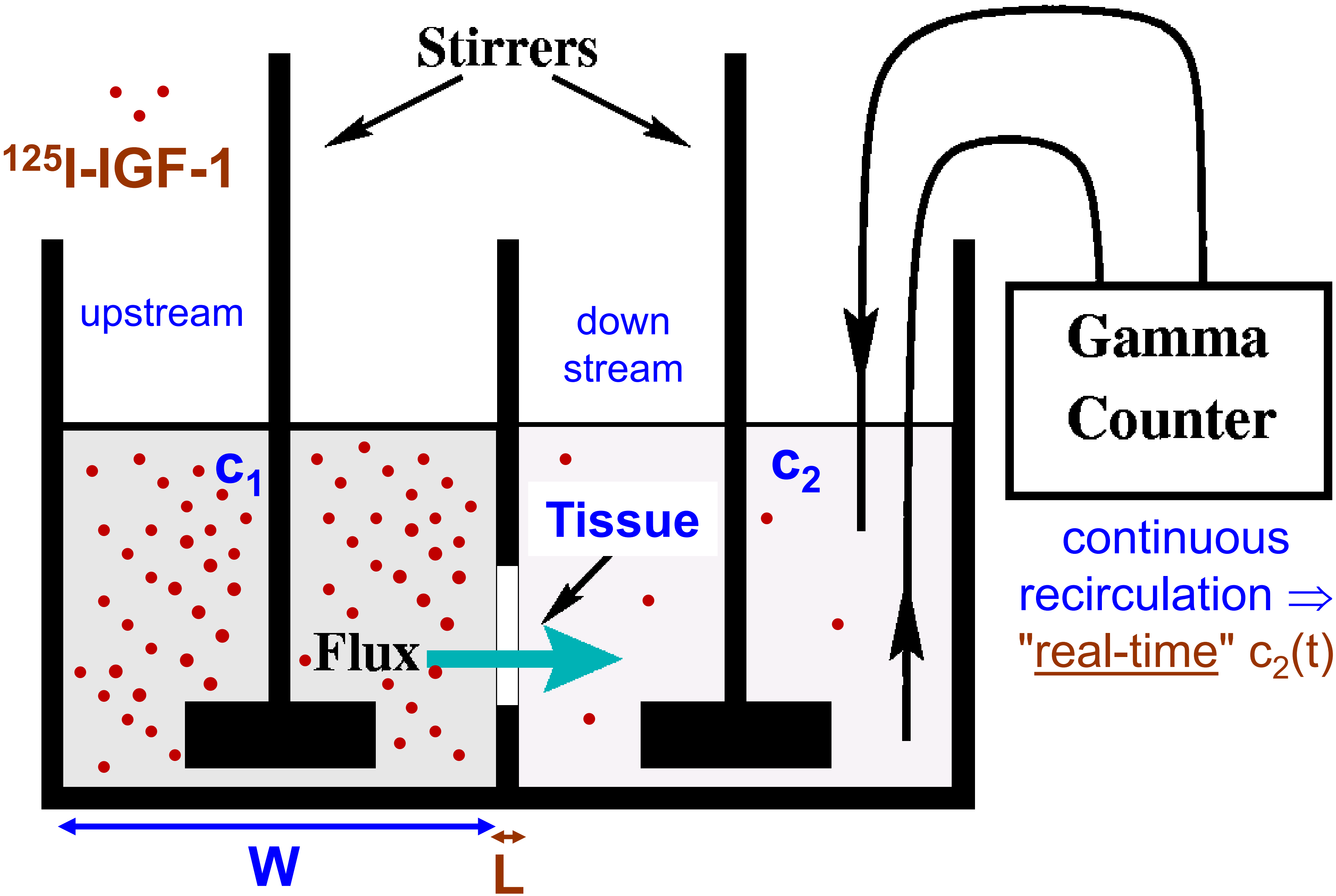
PNAS 2009

Daniela Tropea[a,1], Emanuela Giacometti[b,1], Nathan R. Wilson[a,1], Caroline Beard[b], Cortina McCurry[a], Dong Dong Fu[b], Ruth Flannery[b], Rudolf Jaenisch[b,c,2], and Mriganka Sur[a,2]

[a]Picower Institute for Learning and Memory and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139; [b]Whitehead Institute for Biomedical Research, Cambridge, MA 02142; and [c]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139

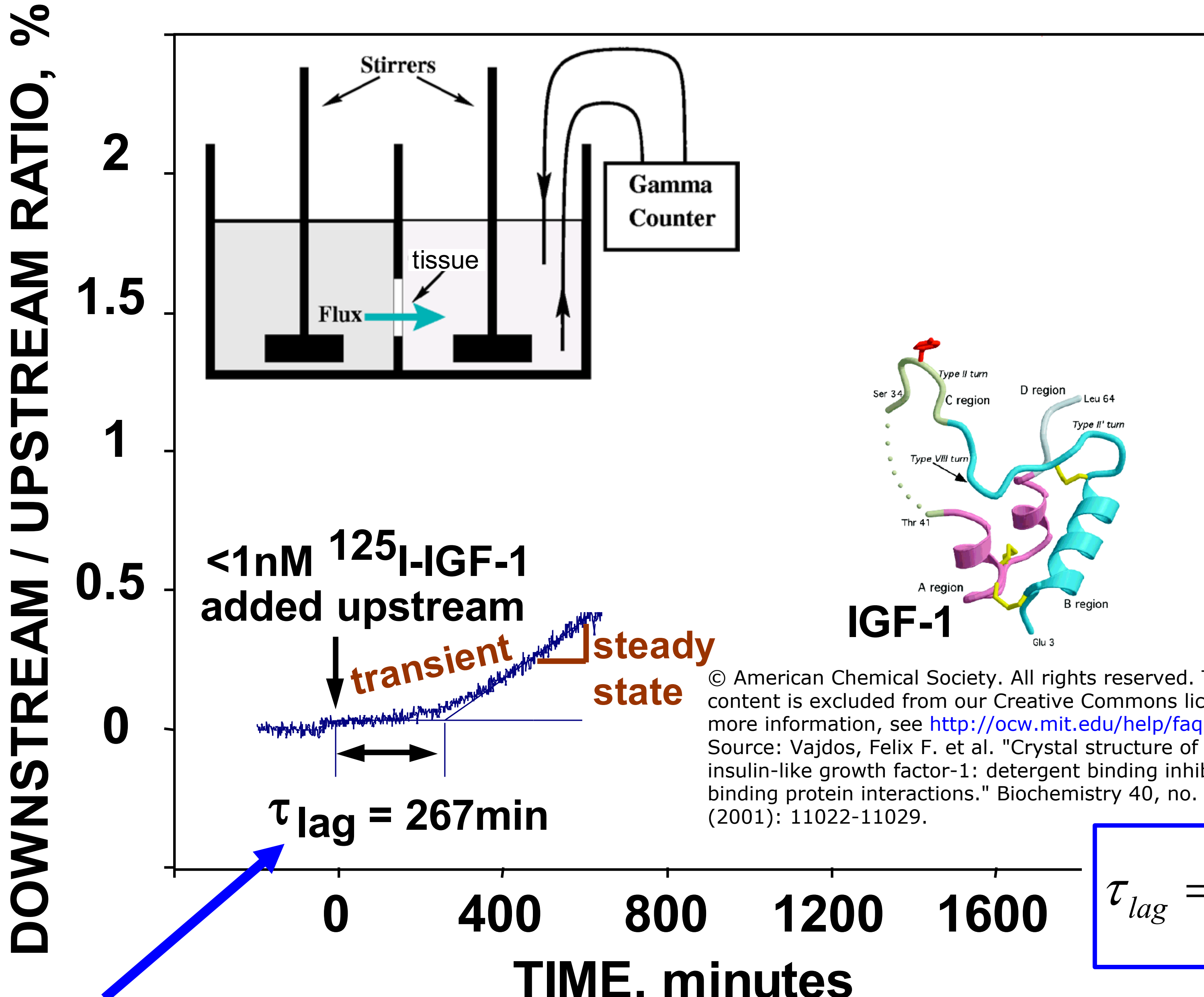
- **Rett patients express aberrantly high levels of IGFBP3, which inhibits IGF-1 signaling. Depressed IGF-1 signaling has indeed been implicated in <u>autism spectrum disorder</u>**

Experimental Setup: Transport



continuous recirculation ⇒ "real-time" $c_2(t)$

IGFBP-3 Binding Slows entry of IGF-1 into Tissue!



$$\tau_{lag} = \frac{L^2}{6D_{eff}}$$

slow reaction, or slow diffusion compared to reaction???

Lect	Date	II. ELECTRICAL SUBSYSTEM
8	Oct 5	E-fields and transport; Maxwell's equations for electric & magnetic fields
9	Oct 7	Define electrical potential; conservation of charge; Electro-quasistatics
10	Oct 13	Laplacian solutions via Separation of Variables; Electric field boundary conditions; Ohmic transport; Charge Relaxation; Electrical migration vs. chemical diffusive fluxes
11	Oct 14	Electrochemical coupling; Electrical double layers; Poisson–Boltzmann Equation
12	Oct 19	Donnan equilibrium in tissues, gels, polyelectrolyte networks
13	Oct 21	Charge group ionization & electro-diffusion-reaction in molecular networks
14	Oct 26	Case study: Insulin-like growth factor-1 transport in tissues & cell-seeded gels; IGF-1 binding to cell receptors vs. extracellular matrix; Experimental methods

(Chap 2): E-fields

- What are sources of $\underline{E}$ fields
- Where do they come from
- What can $\underline{E}$ do (applications)

Table 2.7 Maxwell's equations for linear media.

Name	Differential form
Gauss' law	$\nabla \cdot \epsilon \boldsymbol{E} = \rho_e$
Ampère's law	$\nabla \times \boldsymbol{H} = \boldsymbol{J} + \frac{\partial \epsilon \boldsymbol{E}}{\partial t}$
Faraday's law	$\nabla \times \boldsymbol{E} = -\frac{\partial \mu \boldsymbol{H}}{\partial t}$
Magnetic flux	$\nabla \cdot \mu \boldsymbol{H} = 0$
Charge conservation	$\nabla \cdot \boldsymbol{J} = -\frac{\partial \rho_e}{\partial t}$

EM Waves

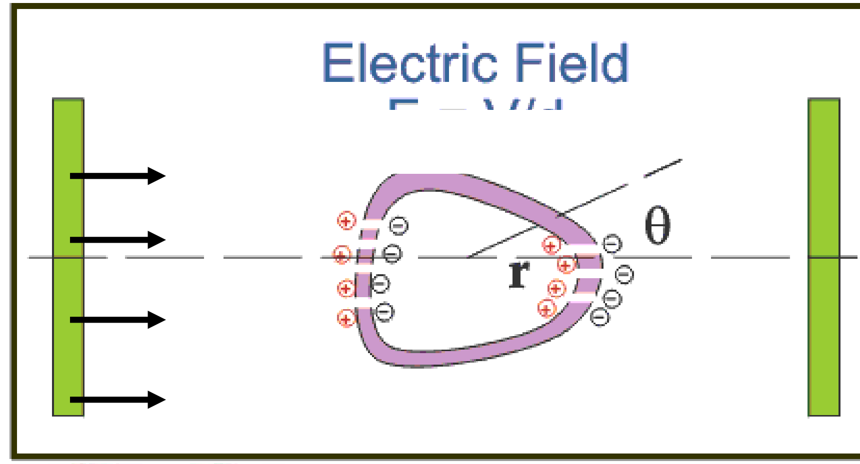
Source: Grodzinsky, Alan. Field, Forces and Flows in Biological Systems. Garland Science, 2011. [Preview with Google Books]

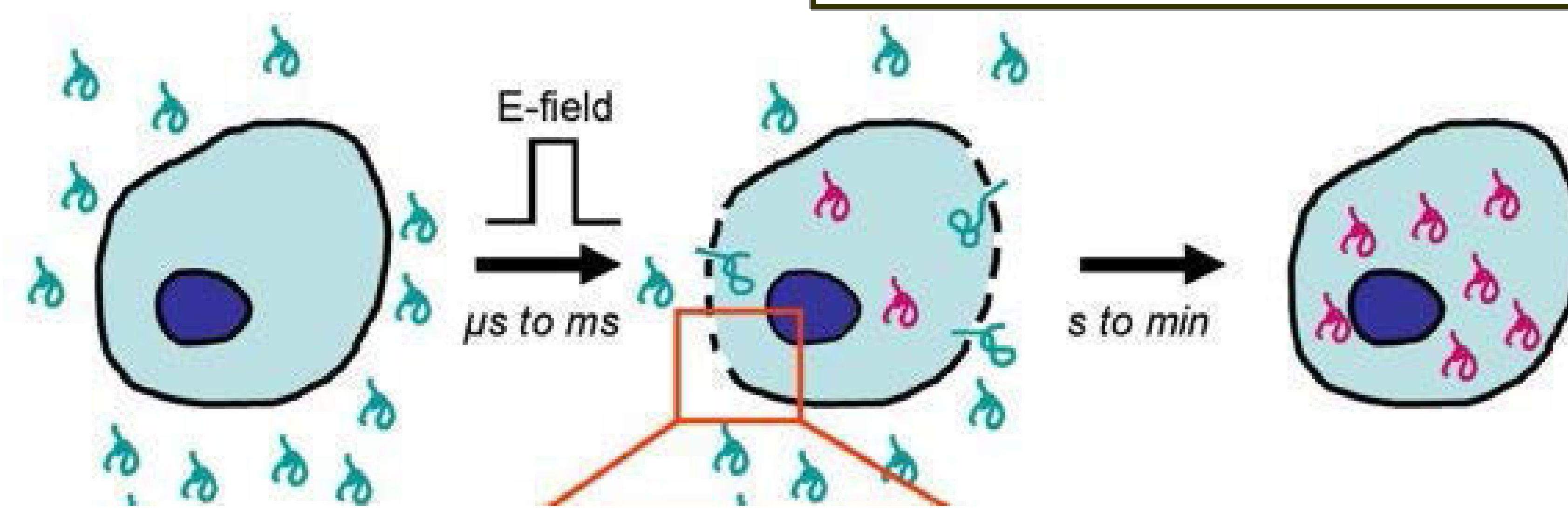
Table 2.8 Quasistatic laws for linear media.

Electroquasistatic (EQS)	Magnetoquasistatic (MQS)
$\nabla \cdot \epsilon \boldsymbol{E} = \rho_e$	$\nabla \times \boldsymbol{H} = \boldsymbol{J}, \nabla \cdot \boldsymbol{J} = 0$
$\nabla \times \boldsymbol{E} = 0$	$\nabla \cdot \mu \boldsymbol{H} = 0$
$\nabla \cdot \boldsymbol{J} = -\frac{\partial \rho_e}{\partial t}$	$\nabla \times \boldsymbol{E} = -\frac{\partial \mu \boldsymbol{H}}{\partial t}$

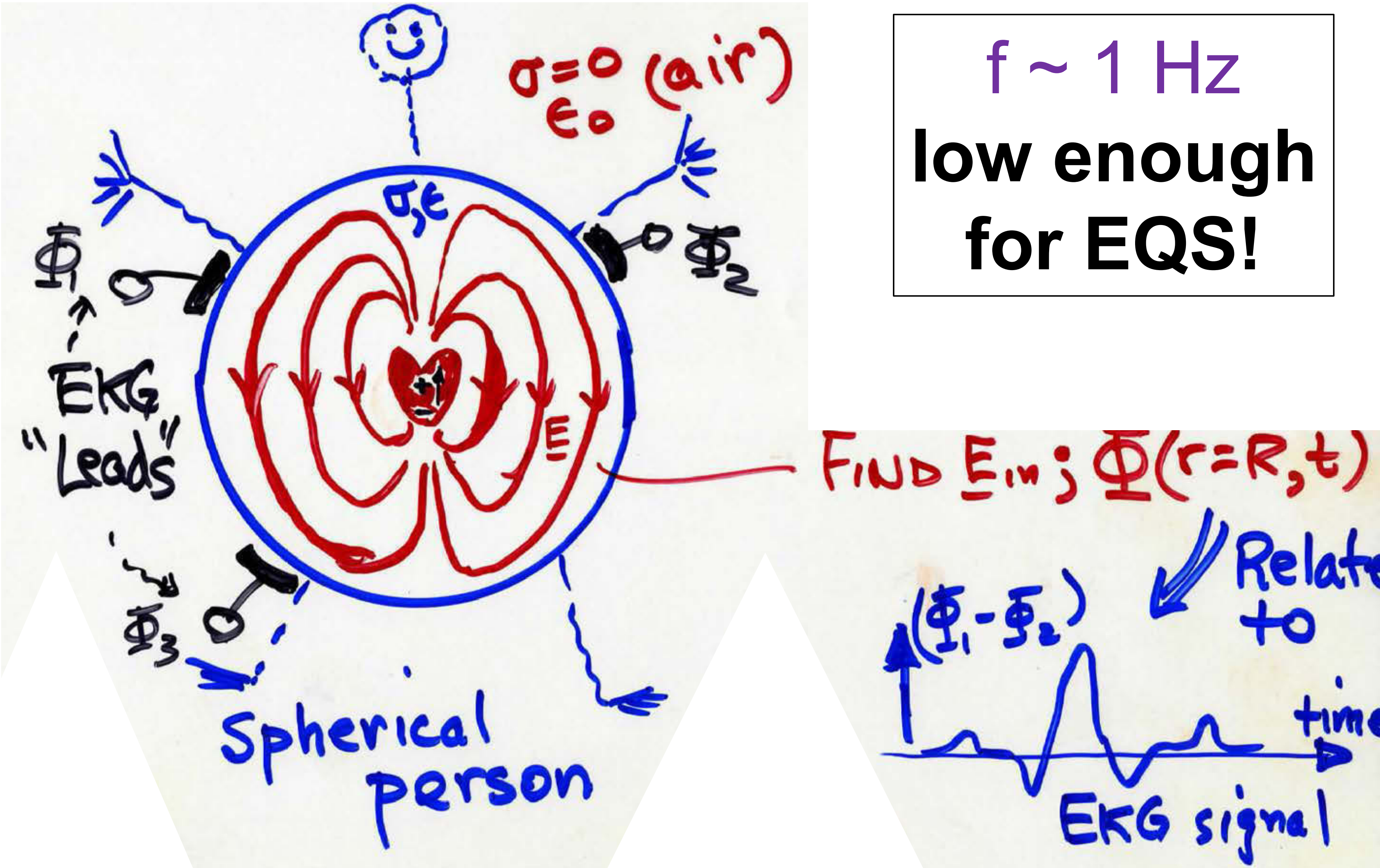
[+ Ohmic Constitutive Law ($\boldsymbol{J} = \sigma \boldsymbol{E}$)]

Electroporation: transient permeabilization of cell membrane for gene transfection/therapy; drug delivery; tumor treatment, and cell-based therapy





EKG: Centric Dipole Model of the Heart



f ~ 1 Hz
low enough for EQS!

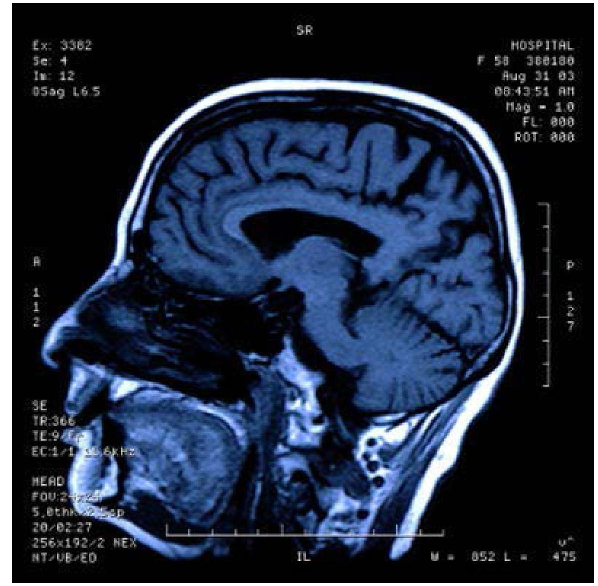
Table 2.8 Quasistatic laws for linear media.

Electroquasistatic (EQS)	Magnetoquasistatic (MQS)
$\nabla \cdot \epsilon \boldsymbol{E} = \rho_e$	$\nabla \times \boldsymbol{H} = \boldsymbol{J}, \nabla \cdot \boldsymbol{J} = 0$
$\nabla \times \boldsymbol{E} = 0$	$\nabla \cdot \mu \boldsymbol{H} = 0$
$\nabla \cdot \boldsymbol{J} = -\frac{\partial \rho_e}{\partial t}$	$\nabla \times \boldsymbol{E} = -\frac{\partial \mu \boldsymbol{H}}{\partial t}$

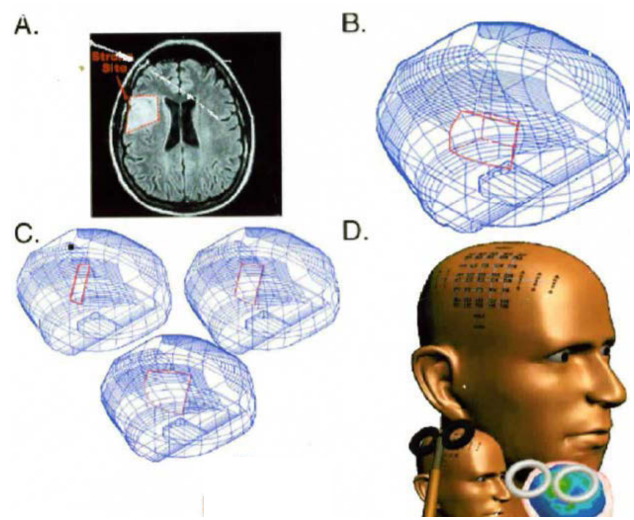
[+ Ohmic Constitutive Law ($\boldsymbol{J} = \sigma \boldsymbol{E}$)]

Source: Grodzinsky, Alan. Field, Forces and Flows in Biological Systems. Garland Science, 2011. [Preview with Google Books]

MRI



Deep Brain Stimulation via B-fields



Source: Wagner, Tim et al. "Transcranial magnetic stimulation and stroke: a computer-based human model study." Neuroimage 30, no. 3 (2006): 857-870.

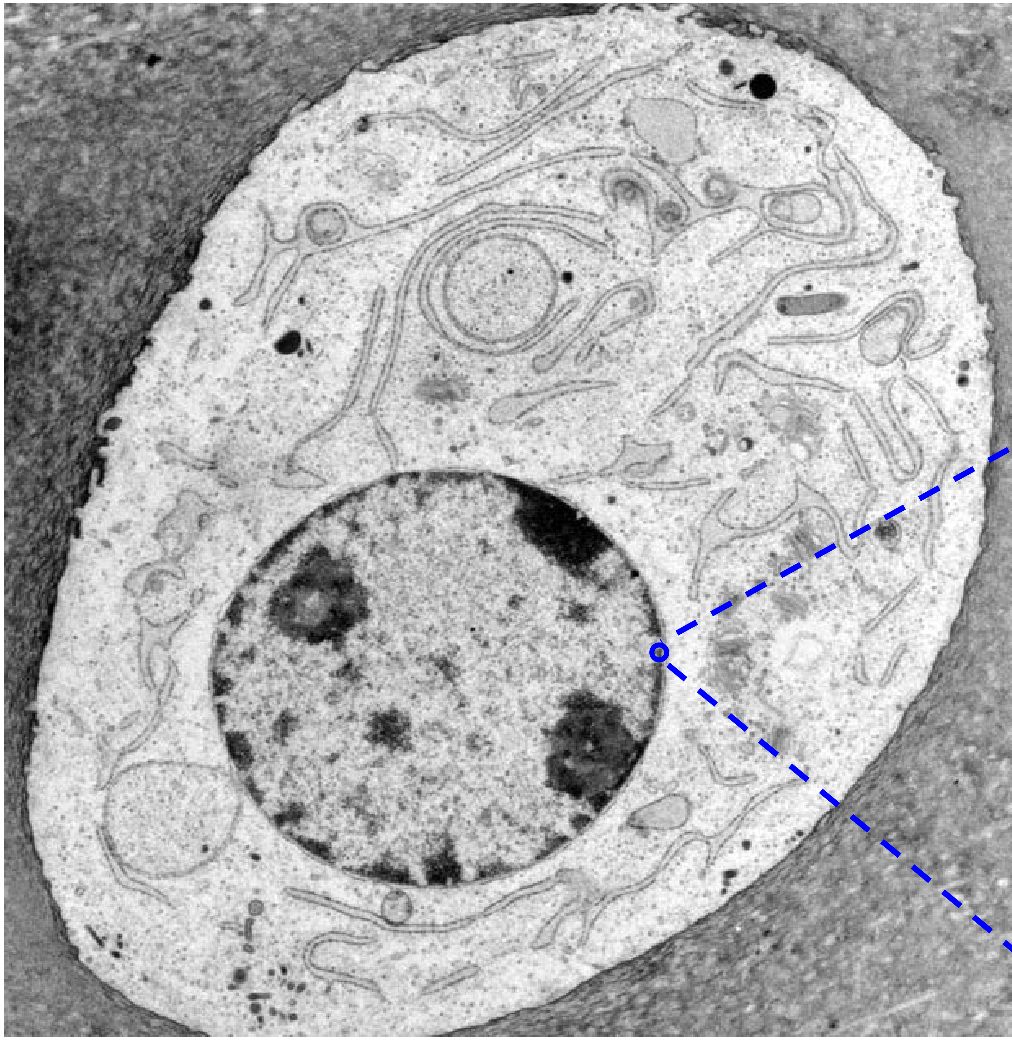
Chap 3: Electrochemical Interactions & Transport

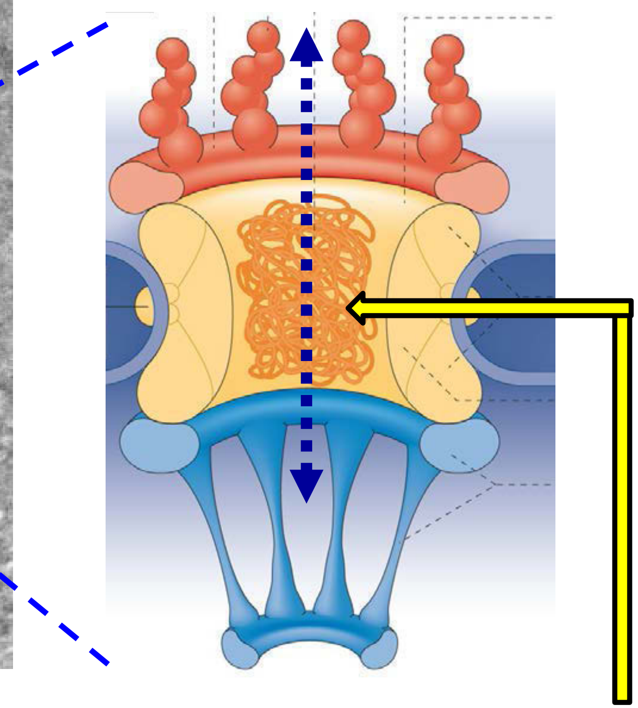
Effects of "Ligand" Molecular Charge on:

- Boltzmann Partitioning into charged tissues, gels
- Binding (to ECM / ICM, receptors.....)
- Non-Equil Diffusion (D_{eff}): do E-effects speed up or slow down transport?
- "Donnan" Osmotic Pressure in tissues/gels/cells

~2,000 nuclear pores per nucleus

per second (e.g., tRNA, mRNA)



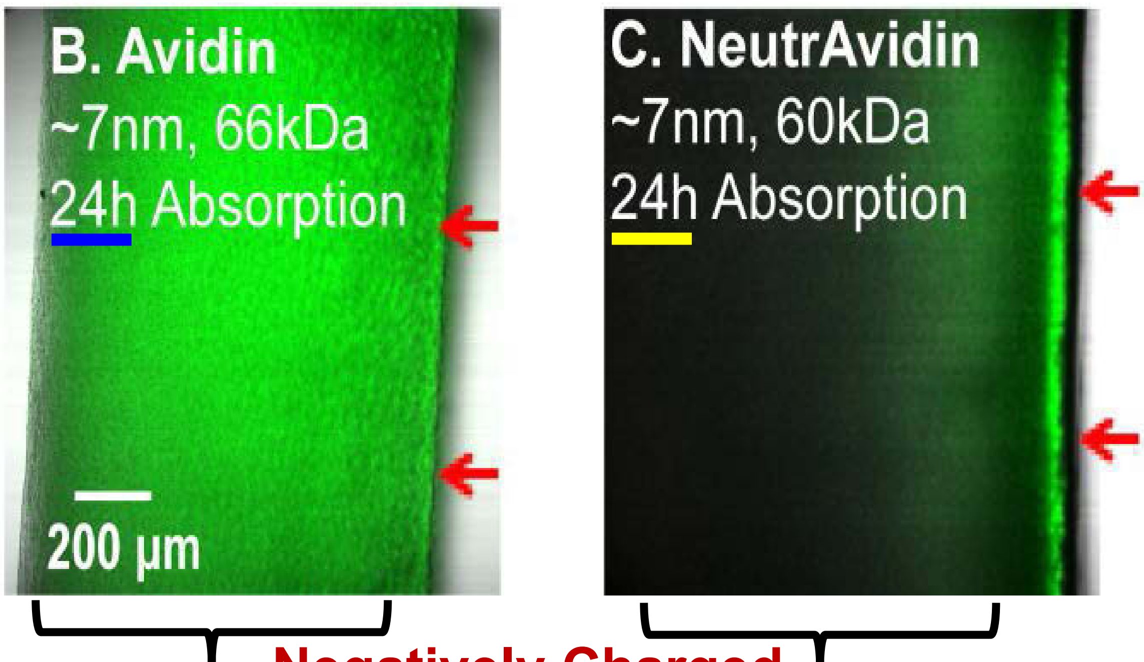


Source: Raices, Marcela, and Maximiliano A. D'Angelo. "Nuclear pore complex composition: a new regulator of tissue-specific and developmental functions." Nature Reviews Molecular Cell Biology 13, no. 11 (2012): 687-699.

"Hydrophilic" : lots of lysines (+ charge)

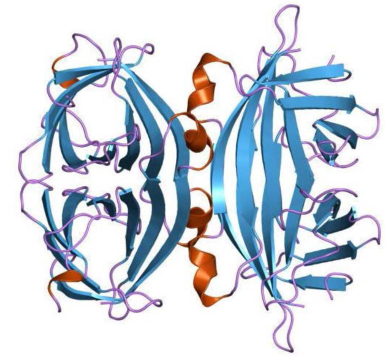
Avidin uptake into dense negative extracellular matrix:

- **Electrostatic & binding interactions: uptake ↑ by 400-fold**
- **Functionalize drugs to (+) nanoparticles, to target tissues**



Negatively Charged Connective Tissue

Courtesy of Alan Grodzinsky. Used with permission.



Courtesy of Jawahar Swaminathan and MSD staff at the European Bioinformatics Institute; image in the public domain.

Avidin

pI ~ 10.5; 66 kDa

9 lysine (+);
8 Arginine (+)
7 Glutamic (-)
5 Aspartic (-)

+5 per chain; 4 chains

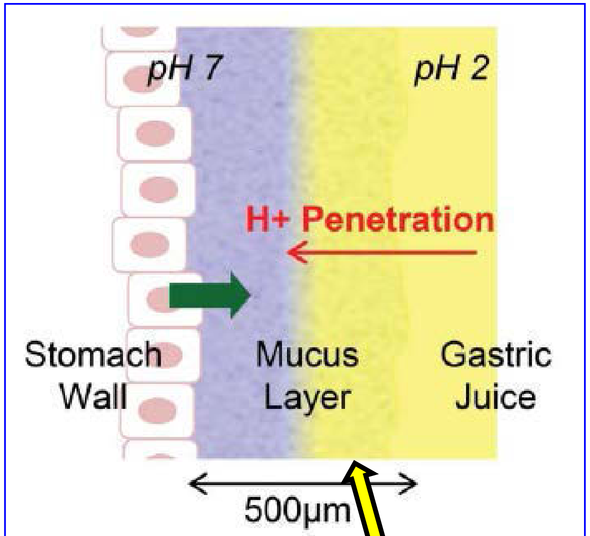
Total Charge +20

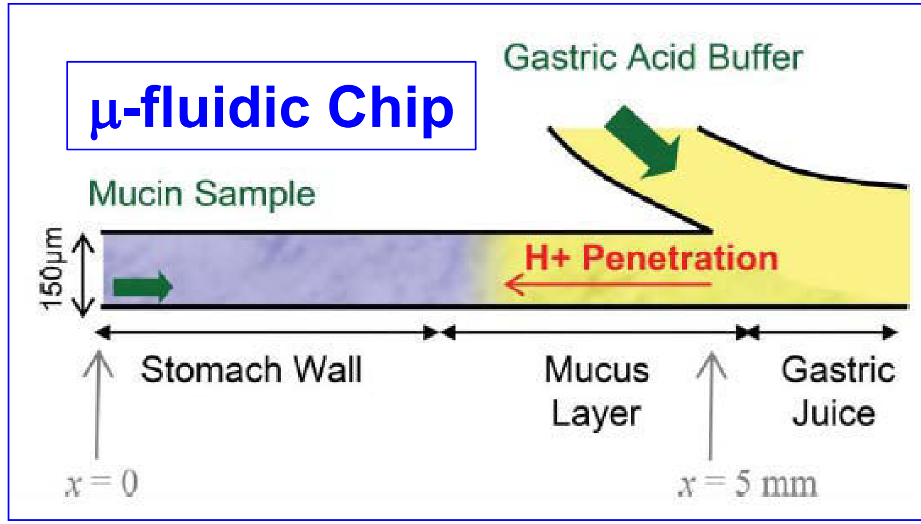
Lect	Date	III. MECHANICAL SUBSYSTEM
15	Oct 28	Conservation of mass and momentum in fluids
16	Nov 2	Viscous stress-strain rate relations; Navier–Stokes equations; examples
17	Nov 4	Low Reynolds number flows; Stokes equation; Scaling and dimensional analysis; examples
18	Nov 9	Newtonian, fully developed low Reynolds number flows; Stokes drag on sphere
19	Nov 16	Diffusion and convection; The Peclet number; Convection-diffusion-reaction and boundary layers
20	Nov 18	Concentration boundary layers: fully-developed flow and transport

A microfluidic *in vitro* system for the quantitative study of the stomach mucus barrier function

Leon Li,[ab] Oliver Lieleg,†[c] Sae Jang,[d] Katharina Ribbeck*[c] and Jongyoon Han*[bc]

2012 Lab on a Chip



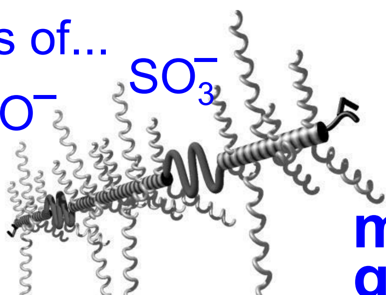


Source: Li, Leon et al. "A microfluidic in vitro system for the quantitative study of the stomach mucus barrier function." Lab on a Chip 12, no. 20 (2012): 4071-4079.

lots of...

SO_3^-

COO^-



mucin glycoprotein

$$v\frac{\partial[H^+]}{\partial x} = D_{H^+}\frac{\partial^2[H^+]}{\partial x^2} - k_{on\_B1}[H^+][B_1] + k_{off\_B1}[H_{B1}] \cdots\cdots$$

"...continuously secreted mucin layer hinders acid diffusion..."

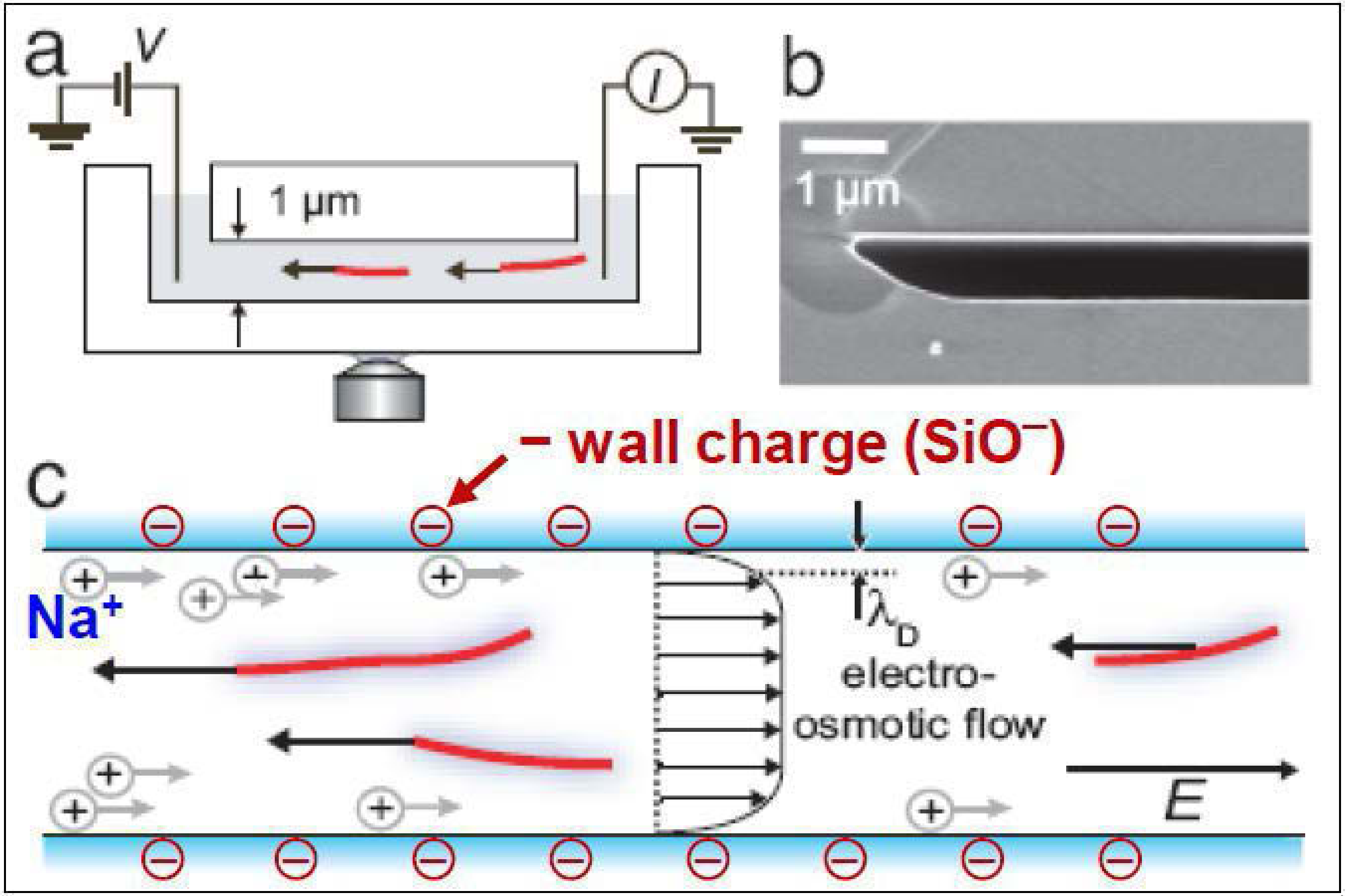
IV. INTEGRATIVE CASE STUDIES: PHYSICOCHEMICAL, BIOPHYSICAL INTERACTIONS		
Lect	**Date**	**Topic**
21	Nov 23	Electrokinetics: Capillary electroosmosis: theory and experiments
22	Nov 25	MEMs, microfluidics, cell membranes and hydrogels
23	Nov 30	Electrophoretic motion: proteins in gels, tissues, molecular networks, & membranes; zeta potential
24	Dec 2	DLVO theory: double layer repulsion and Van der Waals interactions (DNA, RNA, proteins, glycoproteins, GAGs: macromolecular interactions
25	Dec 7	Porous media flows: extracellular and intracellular
26	Dec 9	Cell/molecular electrokinetics; review of term paper project

Electrophoresis of individual microtubules in microchannels

PNAS 2007

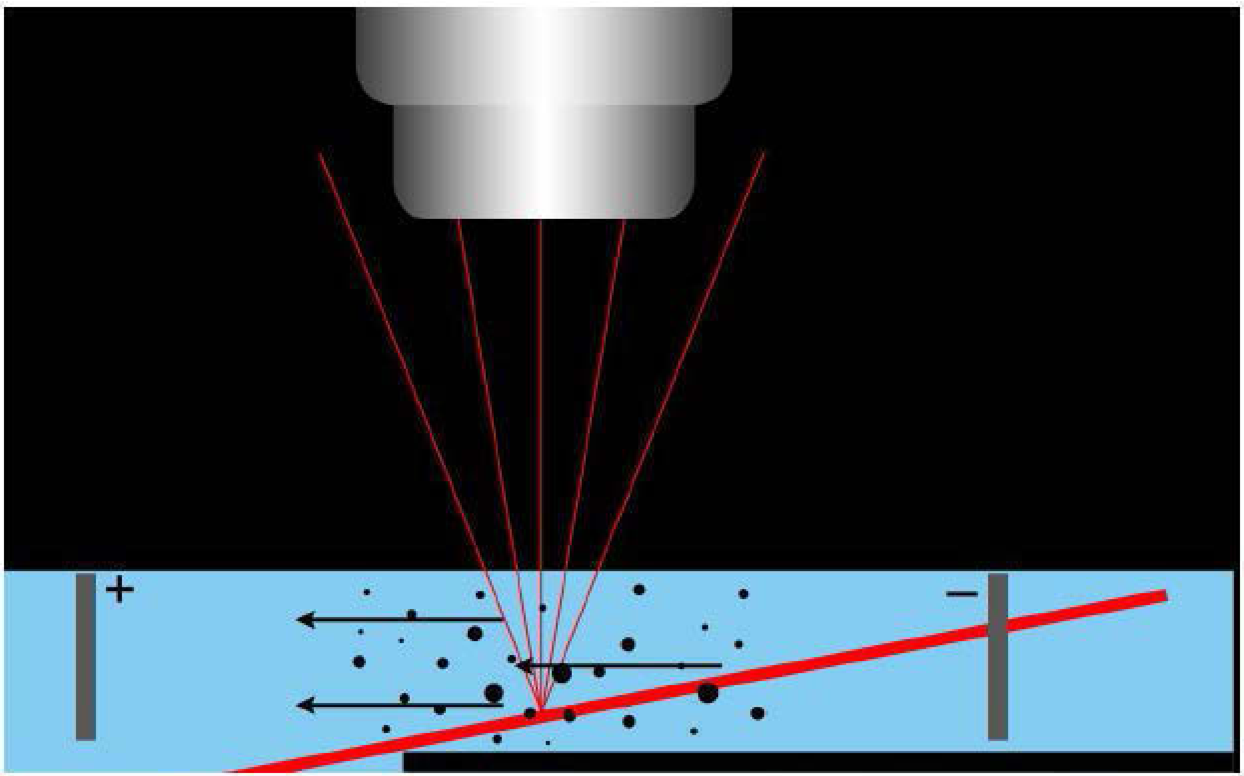
M. G. L. van den Heuvel, M. P. de Graaff, S. G. Lemay, and C. Dekker*

Kavli Institute of Nanoscience, Delft University of Technology, Lorentzweg 1, 2628 CJ, Delft, The Netherlands



Source: Van den Heuvel, M. G. L. et al. "Electrophoresis of individual microtubules in microchannels." Proceedings of the National Academy of Sciences 104, no. 19 (2007): 7770-7775.

Zeta Potential (particle charge) Instruments



+ (applied electric field) −

Measure "ζ" → Infer effective particle charge

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Source: Gelbert, William M. et al. "DNA-Inspired Electrostatics." Physics Today. 53:9 (2000): 38.

20.430J / 2.795J / 6.561J / 10.539J Fields, Forces, and Flows in Biological Systems
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