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

Plus:
• Additional readings from primary (research) literature
• Supplementary materials throughout

Book cover removed due to copyright restrictions.
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%
Enzymatic Targeting of the Stroma Ablates Physical Barriers to Treatment of Pancreatic Ductal Adenocarcinoma

Paolo P. Provenzano,1 Carlos Cuevas,4 Amy E. Chang,1 Vikas K. Goel,1 Daniel D. Von Hoff,5 and Sunil R. Hingorani1,2,3,*

1Clinical Research Division
2Public Health Sciences Division
Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA
3Division of Medical Oncology, University of Washington School of Medicine, Seattle, WA 98195, USA
4Department of Radiology, University of Washington, Seattle, WA 98195, USA
5Clinical 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.
Role of Extracellular Matrix Assembly in Interstitial Transport in Solid Tumors

Paolo A. Netti, David A. Berk, Melody A. Swartz, Rakesh K. Jain

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……
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DOI 10.1016/j.ccr.2012.01.007

Hyaluronan, fluid pressure, and stromal resistance in pancreas cancer

P P Provenzano and S R Hingorani

1Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA; 2Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA; 3Division 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

<table>
<thead>
<tr>
<th>Lect</th>
<th>Date</th>
<th>Topic</th>
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<tbody>
<tr>
<td>1</td>
<td>Sep 9</td>
<td>Course introduction, overview, and objectives</td>
</tr>
<tr>
<td>2</td>
<td>Sep 14</td>
<td>Diffusion as a random walk; Stokes-Einstein relation for diffusion coefficient; Examples of diffusion</td>
</tr>
<tr>
<td>3</td>
<td>Sep 16</td>
<td>Constitutive equations for diffusion (Fick’s Laws); Conservation of mass for a control volume; Differential form; Steady diffusion (1D); Boundary conditions</td>
</tr>
<tr>
<td>4</td>
<td>Sep 21</td>
<td>Diffusion and reaction; Reaction rates, order, molecularity and mechanisms; Scaling and the Damköhler number; Solution procedures</td>
</tr>
<tr>
<td>5</td>
<td>Sep 23</td>
<td>Examples of diffusion-reaction: Diffusion of a ligand through tissue with cell receptor-ligand interactions; Diffusion-reaction kinetics</td>
</tr>
<tr>
<td>6</td>
<td>Sep 28</td>
<td>More examples of diffusion-reaction</td>
</tr>
<tr>
<td>7</td>
<td>Sep 30</td>
<td>Case study: IGF-1 diffusion-reaction within tissues and cell seeded scaffolds; binding to IGF binding proteins &amp; cell surface receptors; experimental methods</td>
</tr>
</tbody>
</table>
Solute Flow in & across "Bio Porous Materials: Molecular Networks, Gels....
"Measure and Model": Find Diffusivity $D_i$
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

(Remicade) (2002 RA)

(Amgen / Pfizer) (1998 RA)

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

(Abbott) (2002 RA)

Autoimmune-Inflammatory Diseases

• Rheumatoid Arthritis
• Crohn’s Disease (IBD)
• Ulcerative Colitis (IBD)
• Ankylosing Spondylitis
• Psoriatic Arthritis
• Psoriasis

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

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

Monolayer cell culture

Top view

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

• pl ~ 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)

© American Chemical Society. All rights reserved. This content is excluded from our Creative Commons license. For more information, see http://ocw.mit.edu/help/faq-fair-use/. 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.
Partial reversal of Rett Syndrome-like symptoms in MeCP2 mutant mice

PNAS 2009

Daniela Tropea, Emanuela Giacometti, Nathan R. Wilson, Caroline Beard, Cortina McCurry, Dong Dong Fu, Ruth Flannery, Rudolf Jaenisch, and Mriganka Sur

4Picower Institute for Learning and Memory and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139; 5Whitehead Institute for Biomedical Research, Cambridge, MA 02142; and 6Department 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 autism spectrum disorder.
Experimental Setup: Transport

\[125\text{I-IGF-1}\]

Stirrers

Gamma Counter

\[\text{continuous recirculation } \Rightarrow \text{ "real-time" } c_2(t)\]
IGFBP-3 Binding Slows entry of IGF-1 into Tissue!

<1nM $^{125}$I-IGF-1 added upstream

$\tau_{\text{lag}} = 267\text{min}$

slow reaction, or slow diffusion compared to reaction???
II. ELECTRICAL SUBSYSTEM

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

(Chap 2): E-fields

- What are sources of $E$ fields
- Where do they come from
- What can $E$ do (applications)
<table>
<thead>
<tr>
<th>Name</th>
<th>Differential form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gauss’ law</td>
<td>$\nabla \cdot \varepsilon \mathbf{E} = \rho_e$</td>
</tr>
<tr>
<td>Ampère’s law</td>
<td>$\nabla \times \mathbf{H} = \mathbf{J} + \frac{\partial \varepsilon \mathbf{E}}{\partial t}$</td>
</tr>
<tr>
<td>Faraday’s law</td>
<td>$\nabla \times \mathbf{E} = -\frac{\partial \mu \mathbf{H}}{\partial t}$</td>
</tr>
<tr>
<td>Magnetic flux</td>
<td>$\nabla \cdot \mu \mathbf{H} = 0$</td>
</tr>
<tr>
<td>Charge conservation</td>
<td>$\nabla \cdot \mathbf{J} = -\frac{\partial \rho_e}{\partial t}$</td>
</tr>
</tbody>
</table>
### Table 2.8 Quasistatic laws for linear media.

<table>
<thead>
<tr>
<th>Electroquasistatic (EQS)</th>
<th>Magnetoquasistatic (MQS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\nabla \cdot \epsilon \mathbf{E} = \rho_e$</td>
<td>$\nabla \times \mathbf{H} = \mathbf{J}$, $\nabla \cdot \mathbf{J} = 0$</td>
</tr>
<tr>
<td>$\nabla \times \mathbf{E} = 0$</td>
<td>$\nabla \cdot \mu \mathbf{H} = 0$</td>
</tr>
<tr>
<td>$\nabla \cdot \mathbf{J} = -\frac{\partial \rho_e}{\partial t}$</td>
<td>$\nabla \times \mathbf{E} = -\frac{\partial \mu \mathbf{H}}{\partial t}$</td>
</tr>
</tbody>
</table>

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

\[ f \sim 1 \text{ Hz} \]

low enough for EQS!
Table 2.8 Quasistatic laws for linear media.

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<td>$\nabla \cdot \varepsilon \mathbf{E} = \rho_e$</td>
<td>$\nabla \times \mathbf{H} = \mathbf{J}, \nabla \cdot \mathbf{J} = 0$</td>
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<tr>
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</tr>
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</table>

[ + Ohmic Constitutive Law ($\mathbf{J} = \sigma \mathbf{E}$)]
Deep Brain Stimulation via B-fields

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** ($D_{\text{eff}}$): 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)

"Hydrophilic": lots of lysines (+ charge)
Avidin uptake into dense negative extracellular matrix:

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

Avidin

$\mathrm{pl} \sim 10.5; \ 66 \ \text{kDa}$

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

+5 per chain; 4 chains

Total Charge +20
<table>
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<th>III. MECHANICAL SUBSYSTEM</th>
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<tr>
<td>15</td>
<td>Oct 28</td>
<td>Conservation of mass and momentum in fluids</td>
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<tr>
<td>16</td>
<td>Nov 2</td>
<td>Viscous stress-strain rate relations; Navier–Stokes equations; examples</td>
</tr>
<tr>
<td>17</td>
<td>Nov 4</td>
<td>Low Reynolds number flows; Stokes equation; Scaling and dimensional analysis; examples</td>
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<tr>
<td>18</td>
<td>Nov 9</td>
<td>Newtonian, fully developed low Reynolds number flows; Stokes drag on sphere</td>
</tr>
<tr>
<td>19</td>
<td>Nov 16</td>
<td>Diffusion and convection; The Peclet number; Convection-diffusion-reaction and boundary layers</td>
</tr>
<tr>
<td>20</td>
<td>Nov 18</td>
<td>Concentration boundary layers: fully-developed flow and transport</td>
</tr>
</tbody>
</table>
A microfluidic in vitro system for the quantitative study of the stomach mucus barrier function

Leon Li, Oliver Lieleg, Sae Jang, Katharina Ribbeck and Jongyoon Han

2012 Lab on a Chip

A microfluidic Chip

Stomach Wall Mucus Layer Gastric Juice

500µm

H+ Penetration

µ-fluidic Chip

Gastric Acid Buffer

Mucin Sample

H+ Penetration

150µm

x = 0

x = 5 mm

lots of...

COO−

SO3−
mucin glycoprotein

"...continuously secreted mucin layer hinders acid diffusion..."
### IV. INTEGRATIVE CASE STUDIES: PHYSICOCHEMICAL, BIOPHYSICAL INTERACTIONS

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<tr>
<td>21</td>
<td>Nov 23</td>
<td>Electrokinetics: Capillary electroosmosis: theory and experiments</td>
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<td>22</td>
<td>Nov 25</td>
<td>MEMs, microfluidics, cell membranes and hydrogels</td>
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<tr>
<td>23</td>
<td>Nov 30</td>
<td>Electrophoretic motion: proteins in gels, tissues, molecular networks, &amp; membranes; zeta potential</td>
</tr>
<tr>
<td>24</td>
<td>Dec 2</td>
<td>DLVO theory: double layer repulsion and Van der Waals interactions (DNA, RNA, proteins, glycoproteins, GAGs: macromolecular interactions)</td>
</tr>
<tr>
<td>25</td>
<td>Dec 7</td>
<td>Porous media flows: extracellular and intracellular</td>
</tr>
<tr>
<td>26</td>
<td>Dec 9</td>
<td>Cell/molecular electrokinetics; review of term paper project</td>
</tr>
</tbody>
</table>
Electrophoresis of individual microtubules in microchannels

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

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Zeta Potential (particle charge) Instruments

Measure $\zeta$ → Infer effective particle charge

+(applied electric field) –

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