Project Proposals:

Use this template to submit a project proposal for the Bioen 485/585 class. The proposal will be used to recruit students in the class to your project. Teams of 3 to 4 students will work for 5 weeks on a computational project that uses numeric solutions to ordinary, partial, or stochastic differential equations to address a biological or medical problem or question. If you think you have such a project, you should talk to Wendy to get an idea of whether the project seems appropriate.

Topic Title. Provide a short descriptive title that indicates the topic of the project.

Consultants. Someone who has expertise in this topic should be available to consult with the team from early May to mid-June. This person does not need to have any modeling or computational expertise, since the course instructors can provide this. Please provide the consultant's name and contact information. This person can be a student in the course or anyone not in the course. It is fine to have more than one consultant.

Importance. Describe briefly why the project is of interest.

Previous Knowledge: Describe briefly what is known already about the problem (from experiments, clinical data, or even previous models or theory). This will help the group understand, build and validate the model. One or two references would be helpful.

Question to be addressed: Why do you want the problem modeled? That is, what new information do you hope to learn from the model? (test a hypothesis, design a device, design experiments, determine novel predictions of a hypothesis, etc).

Modeling approach: If you have thought about it, suggest what methods might be used to model this problem. If you have already looked into it, please provide the relevant reference(s) for the most related modeling work, which could be different approaches to the same problem, or a similar model applied to a different problem.

For examples, the following pages show project proposals from previous years.

BIOEN 585 Project Proposal **Alissa Bleem, Spring 2015**

Topic Title: Examining the effects of diffusion, mechanical stability, and molecular composition on drug delivery to medical biofilms

Consultant: Alissa Bleem (bleema@uw.edu) is interested in this topic because is directly related to her PhD research in the Daggett Lab. She has extensive laboratory experience with bacterial biofilms and modeling in COMSOL.

Importance: Nosocomial (i.e. hospital-acquired) infections are the fourth leading cause of death in the United States, and as many as 60% of these infections result from biofilm accumulation on an implanted medical device [Klevens et al., 2007]. While prophylactic antibiotics have historically been effective in mitigating some types of bacterial infections, biofilm bacteria are particularly difficult to eradicate. Biofilms are surface-associated bacterial colonies encased in an extracellular matrix of proteins, genetic material, and polysaccharides. This matrix provides protection from antibiotics and other community threats while lending structure to the biofilm [Zhurina et al., 2014]. The Daggett lab seeks to develop a new class of antimicrobial therapies by utilizing engineered peptides to disrupt the formation of matrix proteins. However, critical design factors – such as the concentration of peptide required, its ability to transport to the interior of an existing biofilm, and to what degree these peptides may disrupt biofilm mechanical properties – remain elusive.

Previous Knowledge: Biofilms emerged as an area of major scientific importance in the early 1990's, so several studies have already been conducted describe transport phenomena within these complex structures. We can utilize some of this information to determine diffusion coefficients within the biofilm [Stewart, 2003]. Mathematical models have also previously been generated to describe the spatial arrangement of cells and structures within a biofilm, so parameters such as boundary layer thickness, system dimensions, and mechanical properties are readily available [Picioreanu et al., 2001; Picioreanu et al., 1998].

Questions to be addressed: Does mathematical modeling predict that designed peptides can be delivered to nascent biofilms in a timely, physiologically relevant manner? Additionally, does modelling yield insights to the expected degree of mechanical instability (and subsequent antibiotic susceptibility) generated by addition of these peptides? What experimental conditions are necessary to achieve the desired results?

Modeling approach: First, PDEs (and possibly some simplified ODEs) will be generated to describe the physics of the biofilm system. Next, construction and numerical solution of the model will take place in the COMSOL simulation environment. Finally, results will be analyzed and compared for various experimental parameters; this will likely involve some additional modeling and/or plot generation in MATLAB.

References:

Klevens, R. Monina, et al. "Estimating health care-associated infections and deaths in US hospitals, 2002." *Public health reports* 122.2 (2007): 160.

Zhurina, M. V., et al. "Composition and functions of the extracellular polymer matrix of bacterial biofilms." *Microbiology* 83.6 (2014): 713-722.

Stewart, Philip S. "Diffusion in biofilms." *Journal of bacteriology* 185.5 (2003): 1485-1491.

Picioreanu, Cristian, Mark CM van Loosdrecht, and Joseph J. Heijnen. "Two-dimensional model of biofilm detachment caused by internal stress from liquid flow." *Biotechnology & Bioengineering* 72.2 (2001): 205-218.

Picioreanu, Cristian, Mark CM Van Loosdrecht, and Joseph J. Heijnen. "Mathematical modeling of biofilm structure with a hybrid differential-discrete cellular automaton approach." *Biotechnology and bioengineering* 58.1 (1998): 101-116.

Bioen485 Project Description

Topic title: An Anesthetic Vaporizer for the Developing World

Consultant: David Peeler (dj.peeler@gmail.com), Eric Swanson (eric.swanson8@gmail.com)
UW Bioengineering Graduate Students/Bioengineers Without Borders Team Leads

Importance: Constructing a novel anesthetic delivery device for the developing world would enable surgeons to perform life-saving surgeries in remote, low-resource settings. Existing draw-over anesthetic vaporizers are either too expensive, fragile, difficult to transport, dependent on electricity, or maintenance-intensive to serve the populations that need them most. We are developing a simplified draw-over vaporizer that uses phase change materials to regulate chamber temperature, which is critical to anesthetic delivery rates.

Previous knowledge: In draw-over vaporizers, air is drawn through a chamber that is saturated with vaporized anesthetic (halothane) rising from the liquid reservoir below and carried out a one-way valve to the patient. We know from thermodynamics that the energy needed to transition from liquid to gas (the enthalpy of vaporization) is lost from the liquid as heat, causing it to cool down. Because the temperature of halothane is dropping over time due to vaporization, the halothane's enthalpy of vaporization increases[1] altering the subsequent amount of halothane that is vaporized and delivered to the patient.[2] In some simple vaporizers, this heat loss is compensated by surrounding the reservoir with a massive metal heat sink that draws in heat from ambient air; these designs require additional temperature-dependent valves (bimetallic strips) that are fragile and drive up device costs. We aim to use cheap phase change materials (PCMs) to provide our replacement heat source. PCMs have extremely high latent heats of fusion and high melting points, which means that they release a significant amount of heat energy as they solidify at a specific temperature (in our case, room temperature) for an extended period of time.[3]

Questions to be addressed: We need a model that can predict how well the PCM can modulate temperature in the evaporating liquid halothane in a range of relevant operating conditions and to compare this to the modulation by a steel block. The consultants will provide the team with both the typical operating conditions and the range of operating conditions that may be encountered. The modeling work should provide the following information:

1. For a given geometry suggested by the consultants, what is the expected temperature at all locations within the device during halothane evaporation, for PCM and steel blocks? In particular, what are the model outcomes that can be compared with experiments once this device is made? (The consultants will explain what experimental measurements they will be able to make.) How robust are these outcomes with respect to parameters that will vary in actual use, such as ambient temperature and patient-specific volumetric flows?
2. How will the device performance depend on device design parameters that can be changed, such as ambient temperature, geometry, type of PCM, addition of additives that affect heat transfer, etc?

Modeling approach: COMSOL has a "phase change heat transfer" model input within the "heat transfer in solids" model and there are examples in the literature of its application.[4] Broadly speaking, it will be important to model the PCM and the evaporation of halothane separately, then together as described above. The team will need to look into how evaporation will be modeled, although the processes of vaporization and convection are easily modeled with COMSOL as well. The properties of various PCMs and halothane evaporation are well known.

References:

1. http://webbook.nist.gov/cgi/cbook.cgi?ID=C151677&Mask=4&Type=HVAP-FORM2&Plot=on
2. http://www.anesthesia2000.com/physics/Chemistry_Physics/physics15.htm
3. V. D. Bhatt, et al. "Thermal Energy Storage Capacity of some Phase changing Materials and Ionic Liquids," 2(3): 1771–1779, 2010.
4. J Singleton, et al. "Instrument-free exothermic heating with phase change temperature control for paper microfluidic devices." Proceedings of SPIE. 2013;8615:86150R.

ODE Model for the Full Drug Delivery Pathway of Protein Complexes Carrying SiRNA-Aptamer Chimeras

Consultants: Fablina Sharara (fsharara@uw.edu)

Importance: Since the discovery of the RNA interference pathway in 2001, short double-stranded sequences of RNA known as small interfering RNA (siRNA) have been studied extensively as potential therapeutic agents for cancer treatment. SiRNA causes post-transcriptional gene silencing via mRNA degradation, and can thus suppress overexpressed proteins that are essential for cancer cell survival and proliferation. However, siRNA-based therapies have not yet achieved clinical translation, due to factors like instability, poor tumor targeting, poor cellular uptake and trapping within endosomes after uptake. The Gao Lab develops siRNA-binding protein complexes that improve the efficacy of siRNA by improving its delivery efficiency to the cellular cytoplasm. Understanding how the properties of these protein complexes affect the overall drug delivery efficiency of siRNA is essential to helping us design and evaluate them.

Previous Knowledge: Many validated models exist for many of the processes involved in the full delivery pathway that we are attempting to model. These include physiologically based pharmacokinetic (PBPK) models that predict the overall distribution of drugs throughout the body [1,2], models for the enhanced permeability and retention effect (EPR) [3-5], models for receptor-mediated endocytosis (RME) [6,7], models for the proton sponge effect [8]. These models will be used to build the subunits of the overall ODE model of the full pathway from the blood stream to the cellular cytoplasm.

Question to be addressed: How do the size, valence, endosomal escape properties, and binding affinity of the siRNA-binding protein complex affect the amount of siRNA ultimately delivered to the cellular cytoplasms of cancer cells? What combination of these parameters allows for the highest delivery efficiency? What minimum dosage of protein-bound siRNA leads to acceptable cytoplasmic siRNA levels?

Modeling approach: An ODE model of the system will be built using mass action kinetics. It will be simulated in MATLAB using built-in ODE solvers. Factors that need to be determined include compartmental volumes, permeabilities between compartments, and association & disassociation constants for binding events. Spatial variations in the system will be neglected for the sake of simplicity. Literature values for parameters will be used. Validation will be performed by predicting published data on similar systems.

References

1. Davda, J.P, et al. A physiologically based pharmacokinetic (PBPK) model to characterize and predict the disposition of monoclonal antibody CC49 and its single chain Fv constructs. *International Immunopharmacology* 8 (3): 401-413 (2008).

2. Mager, D.E., et al. General Pharmacokinetic Model for Drugs Exhibiting Target-Mediated Drug Disposition. *Journal of Pharmacokinetics and Pharmacodynamics* 28 (6), 507-532 (2001).
3. Stapletown, S., et al. A Mathematical Model of the Enhanced Permeability and Retention Effect for Liposome Transport in Solid Tumors. *PLoS One* 2013.
4. Hara, T. et al. Mathematical description of drug movement into tumor with EPR effect and estimation of its configuration for DDS. *Colloid and Surfaces B: Biointerfaces* 75 (1): 42-46 (2010).
5. Podduturi, V.P., et al. Simulation of transport and extravasation of nanoparticles in tumors which exhibit enhanced permeability and retention effect. *Computer Methods and Programs in Biomedicine* 112 (1): 58-68 (2013).
6. Krippendorff, B.F., et al . Nonlinear pharmacokinetics of therapeutic proteins resulting from receptor mediated endocytosis. *Journal of Pharmacokinetics and Pharmacodynamics* 36 (3): 239-260 (2009).
7. Gex-Fabry, M., et al. Receptor-mediated endocytosis: a model and its implications for experimental analysis. *American Journal of Physiology* 247 (5): (1984).
8. Freeman, E.C., et al. Modeling the proton sponge hypothesis: examining proton sponge effectiveness for enhancing intracellular gene delivery through multiscale modeling. *Journal of Biomaterial Science* 24 (4), 398-416 (2012).

Project Description

Topic Title. How catch bonds can create ideal bond behavior.

Consultant: Wendy Thomas (wendyt@uw.edu) is interested in this topic because she thinks it is publishable and may affect her group's research directly.

Importance. Mechanical force affects noncovalent biological bonds: it weakens slip bonds, activates catch bonds and has no effect on ideal bonds. While slip bond behavior seems most intuitive, it is now known that many if not most adhesion molecules, including integrins, cadherins, and selectins form catch bonds and/or ideal bonds. This behavior is critical to cell adhesion mechanics, which in turn is critical to most of the processes critical to medicine and bioengineering, such as tissue engineering, development, cancer, infection, and thrombosis.

Previous Knowledge: Many studies report how single bonds respond to force, and the data have been fit to models for slip, catch, or ideal bonds. However, cell adhesion mechanics is mediated by multiple bonds. There are theoretical studies calculating the strength of clusters of multiple slip bonds, such as (Isabey, Fereol et al. 2013). However, none of these address multiple catch bonds. One recent study by Jeremy Snook in William Guilford's lab showed experimentally that multiple Selectin catch bonds exhibit ideal bond behavior (Snook and Guilford 2010), but no theory has been presented to explain this quantitatively. Last year, students in this class used simulations to demonstrate that a catch bond with a single bound state cannot really explain this behavior. However, many catch bonds, including those formed by some Selectins (Waldron and Springer 2009), are known be allosteric, so may have two bound states (Thomas, Forero et al. 2006), so it is possible that this behavior could explain the Snook data.

Question to be addressed: Does mathematical modeling predict that clusters of two-state (allosteric) catch bonds can exhibit ideal bond behavior, and specifically, can the single catch bonds presented in the Snook paper explain the ideal bond behavior of their clusters? If so, is there any conditions involving experimental design or bond parameters that is necessary for clusters of two-state catch bonds to display ideal bond behavior? What is the significance of this finding to other studies, and to cell adhesion, which is mediated by clusters of (often catch) bonds?

Modeling approach: While single bonds are stochastic events, they are often modeled using ordinary differential equations for the probability of the bond being in each state. Specifically, the selectin catch bonds are often modeled with a (one state) two-pathway catch bond model (Pereverzev, Prezhdo et al. 2005), but it is possible that selectin bonds actually have bound two states, with the shorter-lived state too short-lived to be detected in experiments. In this case, it

should be modeled with a two-state model (Thomas, Forero et al. 2006), although only the long-lived state would be expected to match the experimental single molecule data, while the short-lived state need only have a lifetime below the temporal detection limit in the experiment. However, if one does not assume that force is distributed equally between multiple bonds, then stochastic chemical reaction equations may be a better approach. The project will probably use parameter estimation to fit the Snook data.

Isabey, D., S. Fereol, et al. (2013). "Force distribution on multiple bonds controls the kinetics of adhesion in stretched cells." J Biomech **46**(2): 307-313.

Pereverzev, Y., O. V. Prezhdo, et al. (2005). "The Two-Pathway Model for the Catch-Slip Transition in Biological Adhesion." Biophys J **89**(3): 1446-1454.

Snook, J. H. and W. H. Guilford (2010). "The Effects of Load on E-Selectin Bond Rupture and Bond Formation." Cellular and Molecular Bioengineering **3**(2): 128-138.

Thomas, W. E., M. Forero, et al. (2006). "Catch Bond Model Derived from Allostery Explains Force-Activated Bacterial Adhesion." Biophys J **90**(3): 753-764.

Waldron, T. T. and T. A. Springer (2009). "Transmission of allostery through the lectin domain in selectin-mediated cell adhesion." Proc Natl Acad Sci U S A **106**(1): 85-90.