Program
(2010 SIAM Great Lakes conference)

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2010 SIAM Great Lakes Conference on Modeling and Numerical PDEs in Mathematical Biology

April 17, 2010
University of Michigan-Dearborn

Invited Speakers

Leonard Sander
Univ. of Michigan

Avner Friedman
MBI, Ohio State Univ.

Mark Alber
Univ. of Notre Dame

Organizing Committee
Yangjin Kim, Michael Lachance, Joan Remski
University of Michigan-Dearborn

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For more information, visit http://www.engin.umd.umich.edu/glsiam/spring10.htm
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<td><em>(What is mathematical biology and how useful is it?)</em></td>
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<td>5:15 - 6:00</td>
<td>Plenary talk (Leonard Sander)</td>
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Table 1: Tentative Schedule

**Speaker List**

(P) = Plenary speaker, (I) = Industry
Alber, Mark S. (P) (Center for the Study of Biocomplexity, University of Notre Dame)
Denton Bobeldyk (I) (Davenport University and DJB Consulting L.L.C.)
Chou, Ching-Shan (Mathematics, Ohio State University)
Friedman, Avner (P) (Mathematical Biosciences Institute, Ohio State University)
Gurarie, David (Mathematics, Case Western Res University)
Jackson, Trachette (PA) (Mathematics, University of Michigan-Ann Arbor)
Jain, Harsh (Mathematical Biosciences Institute, Ohio State University)
Kang, Yeona (Applied Mathematics, SUNY at Stony Brook)
Kao, Chiu-Yen (Mathematics, Ohio State University)
Khain, Evgeniy (Physics, Oakland University)
Kohandel, Mohammad (Applied Mathematics, University of Waterloo)
Lim, Sookkyung (Mathematics, University of Cincinnati)
Liu, Di (Richard) (Mathematics, Michigan State Univeristy)
Matzavinos, Anastasios (Mathematics, Iowa State University)
Rong, Libin (Los Alamos National Laboratory, Mathematics @ Oakland University)
Sander, Leonard M. (P) (Physics, University of Michigan-Ann Arbor)
Spagnuolo, Anna (Mathematics, Oakland University)
Srinivasan, Parthasarathy (Mathematics, Cleveland State University)
Abstracts

(Alphabetical order)

1 Plenary Speakers

Alber, Mark S. (Center for the Study of Biocomplexity, U of Notre Dame)
- Title: Multiscale Modeling in Biology
- Abstract:
A multiscale model of blood clot formation will be described which combines a detailed tissue factor pathway submodel of blood coagulation, a blood flow submodel and a stochastic discrete cell submodel [1,2]. It will be shown that low levels of FVII in blood result in a significant delay in thrombin production demonstrating that FVII plays an active role in promoting clot development at an early stage. We will also describe a new subcellular element method for simulating cellular blood components. In addition, multiscale models of chemotactic cell motion [3] and bacterial swarming will be discussed [4].

2 Speakers in a special session

Bobeldyk, Denton (Davenport University and DJB Consulting L.L.C.)
-Title: Biometrics - Applications and Challenges
-Abstract:
Biometrics is the science of teaching machines (computers) to identify unique biological characteristics or traits in humans; these identifications are then used to authenticate people or pick out known terrorists in a crowd. Uniquely identifying people based on biological traits can be quite a challenge. Some modalities provide high accuracy such as iris or fingerprint, while other modalities provide the ability to identify from large distances such as gait (the way you walk). A brief overview of the algorithms currently being used for each of the modalities will be discussed as well as areas that require further mathematical research.

Chou, Ching-Shan (Mathematics, Ohio State University)
- Title: Spatial Dynamics of Stem Cells and Multi-Stage Cell Lineages in Tissue Stratification

- Abstract:
In developing and self-renewing tissues, differentiated cell types are typically specified through the actions of multistage cell lineages. Such lineages commonly include a stem cell and multiple progenitor (transit amplifying; TA) cell stages, which ultimately give rise to terminally differentiated (TD) cells. Typically, as the tissue reaches a tightly controlled steady-state size, the cells at different lineage stages also assume distinct spatial locations within the tissue. Although significant genetic information are revealed on locations of different type of cells, the underlining mechanisms that cause the spatial heterogeneity are not yet completely understood. In this talk, I will present modeling and simulations to explore several plausible strategies that can be utilized to create stratification during development or regeneration of olfactory epithelium (OE) in mouse.

Gurarie, David (Mathematics, Case Western Res University)

- Title: Immune regulation of malaria infection: model calibration and Agent-Based Communities

- Abstract:
The talk will outline basic biology of malaria infection within host, and develop mathematical models that account for parasite growth and its immune regulation. We shall discuss how such models can be calibrated using malaria-therapy data, and present some recent results. Our calibrated in-host model can serve as a building block for Agent-based Communities (ABC). We shall demonstrate a few examples of such ABC, and look at the effect of transmission intensity on the resulting patterns of parasitemia. Our long-term goal is to apply 'agent-based' methodology to study parasite transmission and control in realistic environment, as an alternative to the standard population-based SIR approach (Ross-Macdonald).

Jain, Harsh (Mathematical Biosciences Institute, Ohio State University)

- Title:
- Abstract:

Kang, Yeona (Applied Mathematics, SUNY at Stony Brook)

- Authors: Yeona Kang∗ and C. M. Fortmann
- Title: A structural basis for the Hodgkin and Huxley relation

- Abstract:
Neural channel transport was analyzed using a previously reported relation for charged particle transport in two energy-type gradients: the electric field and here a water/structural deformation energy. Neural channels are lined with α-helix structures filled with water vapor and sequestered hydrophobic amino acids arranged to present minimum water vapor and water-hydrophobic interface. Cation point charges generate enormous electric fields on sub-nanometer distances. Electrostatic energy reduction is characterized by dielectric water being pulled toward the transporting ion deforming the neural channel. An ion-water-structure coupling energy is induced by changes in channel diameter width. The resultant two energy gradient relation for cation transport: reduces to the Hodgkin-Huxley relation [A. L. Hodgkin and A. F. Huxley, J. Physiol. (London) 116, 449 (1952)], explains channel selectivity and environmental sensitivity, predicts fast non-dispersive transport under a narrow range of conditions, and produces current-voltage characteristics consistent with observation.

Kao, Chiu-Yen (Mathematics, Ohio State University)

- Authors: Anastasios Matzavinos, Chiu-Yen Kao, J. Edward F. Green, Alok Sutradhar, Michael Miller and Avner Friedman
Modeling oxygen transport in surgical tissue transfer

Abstract:
Reconstructive microsurgery is a clinical technique used to transfer large amounts of a patient’s tissue from one location used to another in order to restore physical deformities caused by trauma, tumors, or congenital abnormalities. The trend in this field is to transfer tissue using increasingly smaller blood vessels, which decreases problems associated with tissue harvest but increases the possibility that blood supply to the transferred tissue may not be adequate for healing. It would thus be helpful to surgeons to understand the relationship between the tissue volume and blood vessel diameter to ensure success in these operations. As a first step towards addressing this question, we present a simple mathematical model that might be used to predict successful tissue transfer based on blood vessel diameter, tissue volume, and oxygen delivery.

Khain, Evgeniy (Physics, Oakland University)
-Authors: E. Khain, C. M. Schneider-Mizell, M. O. Nowicki, E. A. Chiocca, S. E. Lawler and L. M. Sander

Clustering of brain tumor cells: theory and experiment

Abstract:
We investigate clustering of malignant glioma cells [1]. In vitro experiments in collagen gels identified a cell line that formed clusters in a region of low cell density, whereas a very similar cell line (which lacks an important mutation) did not cluster significantly. We hypothesize that the mutation affects the strength of cell-cell adhesion. We investigate this effect in a new experiment, which follows the clustering dynamics of glioma cells on a surface. We interpret our results in terms of a stochastic model and identify two mechanisms of clustering. First, there is a critical value of the strength of adhesion; above the threshold, large clusters grow from a homogeneous suspension of cells; below it, the system remains homogeneous, similarly to the ordinary phase separation. Second, when cells form a cluster, we have evidence that they increase their proliferation rate. We have successfully reproduced the experimental findings and found that both mechanisms are crucial for cluster formation and growth.


Kohandel, Mohammad (Department of Applied Mathematics, University of Waterloo)

Electrostatic effects on the supercoiling DNA

Abstract:
We investigate the effects of electrostatic and steric repulsion on the dynamics of pre-twisted circular DNA in a viscous incompressible fluid. The DNA is modeled as a charged elastic rod represented by a three-dimensional closed axial curve and orthonormal triads embedded in each cross-section. Equations of motion of the rod, which include the fluid-structure interaction, are solved by the generalized immersed boundary method combined with the Cosserat theory of an elastic rod. We include a modified Debye-Hückel repulsive force in which the electrostatic force depends on the salt concentration and the distance between base pairs, and a close range steric repulsion force to prevent self-penetration. We find that after perturbation a pretwisted DNA circle collapses into a compact supercoiled configuration. The collapse proceeds along a complex trajectory that may pass near several equilibrium configurations of saddle type, before it settles in a locally stable equi-
The final configuration is sensitive to the initial excess link, ionic strength of the solvent, and the initial perturbation.

Liu, Di (Richard) (Department of Mathematics, Michigan State University)
- Title: Numerical methods for stochastic bio-chemical reacting networks with multiple time scales
- Abstract:
Multiscale and stochastic approaches play a crucial role in faithfully capturing the dynamical features and making insightful predictions of cellular reacting systems involving gene expression. Despite their accuracy, the standard stochastic simulation algorithms are necessarily inefficient for most of the realistic problems with a multiscale nature characterized by multiple time scales induced by widely disparate reactions rates. In this talk, I will discuss some recent progress on using asymptotic techniques for probability theory to simplify the complex networks and help to design efficient numerical schemes.

Matzavinos, Anastasios (Mathematics, Iowa State University)
- Title:
- Abstract:

Rong, Libin (Dept of Mathematics, Oakland University)
- Title: Rapid emergence of hepatitis C virus protease inhibitor resistance
- Abstract:
Telaprevir, a novel hepatitis C virus (HCV) protease inhibitor, has demonstrated substantial antiviral activity in patients with chronic HCV infection. However, drug-resistant variants emerge at frequencies of 5-20% as early as day 2 after treatment initiation. Using probabilistic and viral dynamic models, we show that such rapid emergence of drug resistance is expected. We calculate that all possible single and double mutants preexist, and that one additional mutation is expected to arise during therapy. Examining the case of telaprevir therapy in detail, we show the model fits observed dynamics of both drug-sensitive and resistant viruses, and argue that combination therapy of direct antivirals will require drug combinations that have a genetic barrier of 4 or more mutations.

Spagnuolo, Anna (Mathematics, Oakland University)
- Title: A Mathematical Model for Vibrio Cholera Colonization in the Human Intestine
- Abstract:
Vibrio cholera is a strict human pathogen that causes pandemic cholera. It is an old-world pathogen that has re-emerged as a new threat since the early 1990s. V. cholera colonizes the upper, small intestine where it produces a toxin that leads to the watery diarrhea, characterizing the disease. Colonization dynamics of the bacteria are largely unknown. Although a large initial infectious dose is required for infection, data suggests that only a smaller sub-population colonizes a portion of the small bowel leading to the disease. There are many barriers to colonization in the intestines. In this talk, I will elaborate on the dynamics of V. cholera infection by describing a mathematical model that governs the colonization process for the bacterial dynamics.

Srinivasan, Parthasarathy (Mathematics, Cleveland State University)
- Title: Estimating Biophysical Properties of Nitric Oxide
- Abstract:
Nitric oxide (NO) derived from the endothelium is a potent vasodilator, and plays a crucial role in maintaining vascular tone. Being a small diatomic molecule, it has so far been assumed that the diffusion rate of NO is the same as in solution. However, this hypothesis has not been tested
experimentally. Recent methods have enabled us to measure the flux of NO across the aortic wall directly. We present a simple mathematical model from which we can obtain the diffusion and partition coefficients of NO across the aortic wall using these measurements. Our results show that the diffusion coefficient of NO in tissues is four times slower than in solution under normal physiological conditions, which indicates that the diffusion of NO (and hence its bioavailability) in the vascular wall is crucially dependent on the environment where the molecule diffuses. We also examine the role that oxygen plays in the bioavailability of NO in the vasculature. Our results suggest that the oxygen-dependent NO consumption could play an important role in dilating blood vessels during hypoxia by increasing the effective NO diffusion distance.

Stolarska, Magda (Mathematics, University of St. Thomas)
- Authors: Magdalena A. Stolarska
- Title: *A model of cellular movement and its effect on substrate traction patterns*
- Abstract:
Mechanical interactions between a cell and the substrate are vital for cell migration and are involved in various cellular processes, such as wound healing, embryonic development, and metastasis of cancerous tumors. As a result, understanding the nature of force generation by single cells and the mechanical interaction of a cell with the substrate is extremely important, and mathematical models are being used in furthering this understanding. In this talk, we present a continuum model of the mechanics of single cell motility in which the stresses that result from the active deformation of the cell are transmitted to a deformable substrate via adhesion sites that are modeled as either fixed connections or frictional interaction between the cell and the substrate. A finite element implementation of this model is used to numerically examine the nature of the stresses generated by the cell and the resulting traction patterns that occur at the substrate. We use the model to better understand what are the local active deformation profiles and the adhesion types necessary to replicate experimentally observed motion and traction patterns of different cell types.

Peter J. Thomas (Department of Mathematics, Department of Biology, Case Western Reserve University)
- Title:
- Abstract:

Umulis, David (Agricultural and Biological Engineering, Purdue University)
- Title: *Systems biology of tissue patterning: insights from Drosophila embryos, Zebrafish embryos, and the Drosophila germarium*
- Abstract:
The spatiotemporal regulation of cell differentiation relies on numerous extracellular cues, intracellular responses, and feedback interactions between the intra- and extracellular environment. However, the classic view of morphogen-mediated patterning considers decoupled gradient formation and cell-interpretation events. To investigate the dynamic signaling landscape of cells embedded in a tissue we focused on models of stem cell regulation and early embryo development. For each unique patterning context, we developed 3D finite element models based on available image data and employed a common approach to address the following question: How does feedback between intra- and extracellular environments impact morphogen activity and patterning? To address this question in the context of stem-cell regulation by Bone Morphogenetic Proteins (BMPs), we developed a 3D model of the Drosophila germarium. We found that positive feedback that enhances ligand endocytosis leads to cell competition for limited amounts of BMP ligands and support for only 2-3 stem cells per niche, consistent with experimental observations. We extended the study
to embryonic patterning by BMPs and found that positive feedback that leads to increased endocytosis capacity leads to a similar cell-competition event and autoregulation of the number of high BMP-signaling cells. In the context of developing Zebrafish embryos, positive feedback on an extracellular regulator called Sizzled autoregulates the morphogen distribution shape, ensuring robust patterning of multiple target genes. In summary, the autoregulation of morphogens by feedback provides a mechanism to ensure robust delineation of cell populations through competition and modification of gradient shape.

Wei, Guowei (Mathematics, Michigan State University)
-Title: Differential geometry based multiscale models for biomolecular systems
-Abstract:
This talk focuses on a new multiscale paradigm developed at MSU — the differential geometry based multiscale models of biomolecules. Under the physiological condition, most biological processes, such as signal transduction, ion channel transport and protein folding, occur in water, which consists of 65-90 percent human cell weight. Therefore, solvent and synergy of solvent-solute are important to the understanding of biomolecular structure, function, dynamics and transport. I will discuss the use of differential geometry theory of surfaces for coupling microscopic and macroscopic scales at an equal footing. The biomolecule of interest is described by discrete atomic and quantum mechanical variables. While the aquatic environment is described by continuum hydrodynamical variables. We derive the coupled geometric flow equation, Navier-Stokes equation, and generalized Poisson-Boltzmann equation (PBE) to describe the dynamics of the biomolecular systems. Applications will be discussed to protein folding, ion channels, micro/nanofluidics, and nano-bio sensors. Acknowledgment: This work was supported by NSF and NIH grants.

Xue, chuan (Mathematical Biosciences Institute, Ohio State University)
-Title: Modeling Ischemic Cutaneous Wounds
-Abstract:
Chronic wounds represent a major public health problem affecting 6.5 million people in the United States. Ischemia, primarily caused by peripheral artery diseases, represents a major complicating factor in cutaneous wound healing. In this talk, we present a mathematical model of ischemic dermal wounds. The model consists of a coupled system of partial differential equations in the partially healed region, with the wound boundary as a free boundary. The extracellular matrix (ECM) is assumed to be viscoelastic, and the free boundary moves with the velocity of the ECM at the boundary. The model equations involve the concentration of oxygen, PDGF and VEGF, the densities of macrophages, fibroblasts, capillary tips and sprouts, and the density and velocity of the ECM. Simulations of the model demonstrate how ischemic conditions may limit macrophage recruitment to the wound-site and impair wound closure. The results are in general agreement with experimental findings.

Yamada, Richard (Mathematics, University of Michigan-Ann Arbor)
-Title: Molecular Noise Enhances Oscillations in the Supra-Chiasmatic Nuclei Network
-Abstract:
In this talk, we will discuss a detailed mathematical model for circadian timekeeping within the SCN. Our proposed model consists of a large population of SCN neurons, with each neuron containing a network of biochemical reactions involving the core circadian components. Using mathematical modeling, our results show that both intracellular molecular noise and intercellular coupling (nonlinear in nature) are required to sustain stochastic oscillations in the SCN oscillator network. Our work focuses on the problem of overcoming noise in oscillator systems, and our results high-
light the importance of transcriptional noise in enhancing oscillations rather than dampening them. Surprisingly, our predictions from our model have been confirmed experimentally; we conclude with a short discussion of these results.

Zheng, Xiaoming (Mathematics, Central Michigan University)
- Authors: Trachette Jackson (Mathematics, University of Michigan), Gou Young Koh (National Research Laboratory of Vascular Biology, Korea Advanced Institute of Science and Technology)
- Title: A continuous model of angiogenesis: initiation, extension and maturation
- Abstract:
Angiogenesis, formation of new blood vessels, is essential to many physiological and pathological processes, such as wound healing and tumor growth. Angiogenesis is one of the fastest growing biomedical research disciplines in the past 20 years. However, there are very few mathematical models of angiogenesis compared with the explosion in experimental data. In this talk, we will present a brand new mathematical model of angiogenesis, which covers three critical events: endothelial cell activation (or the new blood vessel initiation), sprout extension, and maturation of new blood vessels. We investigate the regulating mechanisms of three families of growth factors: Vascular Endothelial Growth Factor (VEGF), Angiopoietins (including Ang1 and Ang2), and Platelet-Derived Growth Factor (PDGF-B). The biochemical and biophysical properties of two types of cells, endothelial cells that line the inner wall of blood vessels and pericytes that coat the outer surface of blood vessels, will be examined. These growth factors and cells form a complex multiscale system composed of molecular reactions, cellular responses and tissue growth. The numerical simulations of the mathematical model will be presented along with the main results of the study, which include: demonstrating how the balance of the angiopoietin system serves as angiogenic switch; highlighting that a proper mechanical model is necessary to address the blood vessel extension; showing that pericytes and angiopoietins are central to the maturation process.

Zhang, Yongtao (Mathematics, University of Notre Dame)
- Title: Implicit integration factor methods for PDEs on structured and unstructured meshes and their applications in morphogenesis
- Abstract:
Integration factor methods are a class of "exactly linear part" methods. In [1], a class of efficient implicit integrating factor (IIF) methods are developed for solving systems with both stiff linear and nonlinear terms, arising from numerical spatial discretization of time-dependent partial differential equations (PDEs) with linear high order terms and stiff lower order nonlinear terms. A novel property of the scheme is that the exact evaluation of the linear part is decoupled from the implicit treatment of the nonlinear part. As a result, the size of the nonlinear system arising from the implicit treatment is independent of the number of spatial grid points. The tremendous challenge in applying IIF temporal discretization for time-dependent PDEs on high spatial dimensions is how to evaluate the matrix exponential operator efficiently. I shall first present the compact IIF methods to deal with this issue for spatial discretization on structured meshes. For spatial discretization on unstructured meshes to solve PDEs on complex geometrical domains, how to apply the compact IIF approach is unclear. To solve this problem, we apply the Krylov subspace approximations to the matrix exponential operator and obtain an efficient and accurate Krylov subspace based IIF method. This novel time discretization technique is applied to Discontinuous Galerkin (DG) methods on unstructured meshes for solving reaction-diffusion equations. Numerical examples are shown to demonstrate the accuracy, efficiency and robustness of the method in resolving the stiffness of the DG spatial operator for PDEs which have high order spatial derivatives. Application of the methods to numerically solving mathematical models arising in morphogenesis during Drosophila
and zebrafish embryos development, and vertebrate limb development will be shown.

3 Poster presentation

Hengenius, James (Agricultural and Biological Engineering, Purdue University)
- Authors: James Hengenius*, Ann E. Rundell, Michael Gribskov, and David M. Umulis
- Title: Effects of a realistic 3D domain on models of Drosophila melanogaster gap gene regulation
- Abstract:
The fruit fly Drosophila melanogaster is a model organism for studying spatio-temporal dynamics of animal development. In the gap gene regulatory network, an initial non-uniform distribution of the transcription factor Bicoid controls downstream expression of additional interacting transcription factors. This leads to the formation of non-uniform protein distributions along the anterior-posterior axis of the embryo. Previous studies have considered gap gene regulation as a reaction-diffusion system in one dimension, fitting models to protein expression data from a limited lateral region of the embryo. While these models agree with data in the sampled lateral region, the embryo has a complex three-dimensional geometry. Because poor agreement over the full embryo geometry would indicate incomplete understanding of gap gene regulation, we evaluated existing model structures over this domain. Additionally, we optimized model parameters on the 3D domain. We first implemented a full 3D model using the finite element method with a mesh derived embryonic nuclei positions. Model output was fit to expression data from the Quantitative Spatiotemporal Gene Atlas (Fowlkes et al., 2008) by minimizing a sum-of-squared-error function. Model outputs from the best parameter sets were compared to results using previously published 1D model parameters. While previously published parameter values recapitulated data in the lateral region, the model deviated from data over most of the 3D domain. Our parameter optimization recovered parameter sets that fit the full 3D model better than previously published parameters. Our findings indicate that the current models of gap gene regulation are incomplete and must be revised to account for geometric effects and possible genetic interactions occurring outside the lateral region.

Im, Jeong-sook (Mathematics, Ohio State University)
- Title: Boundary integral method for shallow water and evaluation of the KdV equation in random wave field
- Abstract:
Consider the two-dimensional incompressible, inviscid and irrotational fluid flow of finite depth bounded above by a free interface. Ignoring viscous and surface tension effects, the fluid motion is governed by the Euler equations and suitable interface boundary conditions. A boundary integral technique (BIT) which has an advantage of reducing the dimension by one is used to solve the Euler equations. For convenience, the bottom boundary and interface are assumed to be $2\pi$-periodic. The complex potential is composed of two integrals, one along the free surface and the other along the rigid bottom. When evaluated at the surface, the integral along the surface becomes weakly singular and must be taken in the principal-value sense. The other integral along the boundary is not singular but has a rapidly varying integrand, especially when the depth is very shallow. This rapid variation requires high resolution in the numerical integration. By removing the nearby pole, this difficulty is removed. In situations with long wavelengths and small amplitudes, one of the approximations for the Euler equations is the KdV equation. I compare the numerical solution of Euler equation and the solution of KdV equation and calculate the error in the asymptotic approx-
imation. For larger amplitudes, there is significant disagreement. Indeed, the waves tend to break and the boundary integral technique still works well. The comparison is also done in random wave field. The strong nonlinearity has made a huge difference in the power spectrum between Euler equation and KdV equation.

**Jordan, Benjamin** (Organismic & Evol Biol, Harvard University)
- **Title:** Coupling tissue growth and reaction kinetics to model chick limb development
- **Abstract:**

The limb of the chicken (G. gallus) is a model organism in developmental biology used to study the patterning of tissues, cell speciation, and cell fates. The developing limb bud tissue responds to protein-gradients in a concentration-specific manner. Amongst the myriad cellular responses to these signals, division, differentiation, death, and changes to the extracellular matrix are crucial to our understanding. These responses feed back into both the chemical interactions and the material properties of the growing limb bud. To understand the interplay between growth and patterning, we have developed a model that couples the production, diffusion, reaction and advection of the relevant chemical species to the growing tissue domain. By assuming that growth is a plastic-process which occurs beyond some given yielding threshold, we model the tissue as a viscous free-boundary fluid with a volumetric source, which is in turn dependent on the concentration of specific growth factors included in the kinetics network. In this poster, I describe the mathematical model, discuss the parametrization, and explain the algorithm for the numerical solution. Specifically, details on the remeshing, convection, and split-time stepping are discussed. Preliminary results suggest that both the shape and protein distribution can be described accurately by such a model, and the next steps of this work are discussed.

**Karim, Mohammad Shahriar** (Agricultural and Biological Engineering, Purdue University)
- **Authors:** Mohammad Shahriar Karim*, Gregery T. Buzzard, and David M. Umulis
- **Title:** Secreted, receptor-associated BMP regulators reduce stochastic noise intrinsic to many extracellular morphogen distributions
- **Abstract:**

Morphogens specify cell-fate in a concentration dependent manner. Intriguingly, recent measurements of ligand-receptor binding suggest that many morphogens saturate receptors at concentrations less than 1nM or less than 20 molecules/cell. Low molecule number, combined with slow binding kinetics leads to a noisy interpretation of extracellular concentration that fluctuates on the time-scale of hours, however many morphogen patterning networks are remarkably robust. To investigate mechanisms of biological robustness and signal interpretation we developed a stochastic model of the local ligand-receptor dynamics and extended this work to consider spatial patterning and measure the errors in positional information expected for each local regulatory mechanism. We find that if a secreted non-receptor such as Crossveinless-2 (Cv-2) partially regulates ligand-receptor interactions, the amplitude of ligand-receptor fluctuations can be reduced by about 2-folds depending on specific parameter values and non-receptor concentration. Receptor-ligand regulation by secreted factors can also modify the binding dynamics to increase the frequency of fluctuations, which can be buffered out immediately downstream by the intracellular network if the time-scale for intracellular dynamics are slow relative to ligand-receptor fluctuations. This phenomenon of non-receptor imitates performance of a simple low pass filter for the system. Together, these data indicate that one of the benefits of receptor-ligand regulation by secreted non-receptors may be greater reliability of morphogen patterning mechanisms and we are developing experiments to test these conclusions.
Lee, Sang-hun (Agricultural and Biological Engineering, Purdue University)

- Authors: Sang-hun Lee*, and David M. Umulis
- Title: Dynamic simulation of Bone Morphogenetic Protein patterning in a 3D finite-element model of the Danio rerio embryo
- Abstract:

Zebrafish development relies on the spatiotemporal distribution of molecules called morphogens that pattern anterior/posterior (AP) and dorsal/ventral (DV) axes in a concentration-dependent manner. Numerous secreted regulators control the spatiotemporal distributions of BMP signaling along the DV axis, however, the mechanisms of dynamic regulation of BMP signaling remain unclear. To determine the relative contributions of the Alk8 receptors, Chordin, Tolloid-like molecules, and Sizzled, we developed and tested a full 3D mathematical model of a developing zebrafish embryo. We developed an image registration algorithm to assign point-cloud experimental data to a reference set and determine both the stage of development and the orientation of the embryo. Following development of the image registration methodology, we converted the point-cloud reference into 3D finite element meshes for each 1.5 minute time-point during growth from early blastula through gastrula stages (200-500 minutes post fertilization (MPF)). We then developed a seamless modeling strategy to test alternative hypotheses regarding the mechanism of BMP-mediated patterning on the dynamically evolving mesh and found that Sizzled-mediated regulation of Tld leads to robust mechanism to regulate gradient shape of BMP activity. We also investigated mechanisms of dynamic morphogen scale-invariance in zebrafish embryos and present a summary of these findings.

Srivastava, Prashant (IIT Kanpur, INDIA)

- Title: Dynamical Model of HIV and CD4+ T cell with drug therapy
- Abstract:

Here we shall propose and analyse a dynamical model of HIV and CD 4+ T cells under the influence of drugs Reverse transcriptase inhibitor and protease inhibitor. The infection develops as HIV infects CD4+ T cells. Infected cells are divided into two sub classes: infected cells before completion of reverse transcription and infected cells after reverse transcription. It is assumed that a fraction of infected cells revert back to uninfected class. We performed stability and also solved model numerically to analyse the analytical results.

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- Title: A NEW APPROACH TO MODELING SCHISTOSOMIASIS TRANSMISSION BASED ON STRATIFIED WORM BURDEN
- Abstract:

Multiple factors affect schistosomiasis transmission in distributed, multicommunity systems including age, behavior, and environment. Traditional modeling of macroparasite systems exploits mean worm burden formulations for humans, but this simplified approach often proves inaccurate in predicting location-specific transmission or the outcomes of control interventions. Available epidemiological data typically combine infection intensity with prevalence estimates of human and snail hosts. Both measures (burden and prevalence) reflect a worm distribution in humans that is overdispersed; classic models have had limited success, as they either ignore this over-dispersion or make ad-hoc assumptions about its pattern (e.g. negative binomial). We take a new modeling approach by stratifying human populations according to burden ("0"-group, "1"-group, etc.), and replacing mean burden dynamics with that of population strata’. The Stratified Worm Burden approach offers many advantages, in that it naturally accounts for over-dispersion and accommodates measures of human infection (burden and prevalence) along with other determining factors. Resulting projections are accessible via desktop computing, and should prove useful to regional
control programs.