Mathematical Modeling in the Medical Sciences

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Contents

Field-induced motion of a ferrofluid droplet through immiscible viscous media

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Ferrofluids consist of magnetic nanoparticles in a colloidal solution. Recent developments in the synthesis and characterization of ferrofluids are motivated by biomedical applications, where the treatment of retinal detachment is one example. A small amount of ferrofluid is injected into the vitreous cavity of the eye and guided by a permanent magnet inserted outside the scleral wall of the eye. The drop travels toward the side of the eye, until it can seal a retinal hole. The time taken for the drop to migrate is an important quantity which needs to be predicted, and which must be relatively short for the feasibility of this procedure. Here, the motion of a hydrophobic ferrofluid droplet placed in a viscous medium and driven by an externally applied magnetic field is investigated numerically in an axisymmetric geometry. Initially, the drop is spherical and placed at a distance away from the magnet. The governing equations are the Maxwell equations for a non-conducting flow, momentum equation and incompressibility. A numerical algorithm is derived to model the interface between a magnetized fluid and a non-magnetic fluid via a volume-of-fluid framework. The time taken by the droplet to travel through the medium and the deformations in the drop are investigated and compared with experimental studies.

The effect of bacteria on wound angiogenesis

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We present a mathematical model of the healing rate of an epidermal wound that contains bacteria. The purpose of the model is to investigate the effect of bacteria on the process of wound angiogenesis. In addition to bacteria and angiogenesis, the model incorporates the influences of growth factors and oxygen. The model is formulated mathematically as a system of reaction-diffusion equations. We present the results of simulations of the healing of simply-shaped wounds based on the model.

Zoonotic diseases carried by rodents: seasonal fluctuations

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Hantavirus, a zoonotic disease carried by wild rodents, is spread among rodents via direct contact and indirectly via infected rodent excreta in the soil. Spillover to humans is primarily via the indirect route through inhalation of aerosolized viral particles. Rodent-hantavirus models that include direct and indirect transmission and periodically varying demographic and epidemiological parameters are studied. The models are applied to two rodent populations, reservoirs for a New World and an Old World hantavirus. The numerical examples show that periodically varying demographic and epidemiological parameters may substantially increase the basic reproduction number. Also, large variations in the viral decay rate in the environment may lead to outbreaks in rodent populations and possible spillover to humans.

Elucidating tissue microstructure with diffusion MRI

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Measuring clinically or biologically useful microstructural features of tissues is challenging in vivo. Yet determining these properties is critically important in following normal and abnormal development, diagnosing diseases and disorders, and even guiding therapeutic procedures. Tissue is optically turbid, constantly in motion, and hierarchically organized. One approach that has proven successful in elucidating tissue microstructure is diffusion MRI. It entails measuring the distribution of net displacements of water molecules in tissue on a voxel-by-voxel basis. Using these distributions, along with mathematical models of water migration in different tissue compartments, one can estimate or infer gross anatomical characteristics, such as muscle or nerve orientation, and even microscopic anatomical features, such as the axon diameter distribution in nerve bundles. The basic diffusion MRI experiment will be described, and then some models of diffusion in idealized tissue compartments will be presented. The relationship between microstructure and the measured MRI signal will be presented, and the general strategy for measuring or characterizing microstructural features of tissue from these MR displacement distribution measurements will be explained.

Conceptual paths from system biology to modelling mutations and progression of tumor cells Nicola Bellomo, Politecnico di Torino
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This Lecture deals with a critical analysis on the mathematical kinetic theory of active particles [1] applied to the modelling of the early stage of cancer phenomena, specifically mutations, onset, progression of cancer cells, and their competition with the immune system [2]. The mathematical theory describes the dynamics of large systems of interacting entities whose microscopic state includes not only geometrical and mechanical variables, but also specific biological functions. Applications are focused on the modelling of complex biological systems where two scales at the level of genes and cells interact generating the heterogeneous onset of cancer phenomena. The analysis also refers to the derivation of tissue level models from the underlying description at the lower scales. The review is constantly linked to a critical analysis focused on various open problems including the ambitious objective of developing a mathematical theory for complex biological systems.

[1] N. Bellomo, Modelling Complex Living Systems - A Kinetic Theory and Stochastic Game Approach, (Birkhäuser, Boston, 2008).

[2] N. Bellomo, N.K. Li, and P.K. Maini, On the foundations of cancer modelling, Mathematical Models and Methods in Applied Sciences, 18 (2008) 593-646.

Role of local and long-distance travel on the dynamics of infectious diseases

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A new A/H1N1 influenza (flu) strain was identified in Mexico City on April 2009. Within weeks 590 confirmed cases with 26 deaths had been reported in Mexico; 140 cases in Canada; 403 in 38 states across the USA; and about 1500 cases in twenty-five nations in Europe, Canada, New Zealand, and Asia. The preliminary reports suggested that the 2009 A/H1N1 outbreak bore similarities to 1918 H1N1 flu outbreak and the WHO pandemic alert classification quickly rose from level 3 to 5. In this talk, distinct approaches to modeling the role of local and long-distance movement of individuals, via the use of mass transportation of other forms of travel, on disease dynamics will be discussed. Examples from various diseases including influenza will be used to illustrate these modeling approaches.

Multiscale models of infectious disease

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Humans relate in a very dynamic way with their microbial environment. Sudden modifications to this environment have resulted in a large death toll in human populations through the ages accompanied by a struggled to adapt and survive, biologically and societally. Fresh to memory is the recent scare of a swine flu pandemic. Computational modeling has impacted our understanding of Influenza A virus-human relationship and the impact of containment strategies at the host and societal levels. Yet, predicting the emergence of strains of significant pandemic potential is still at the embryonic stage. Multiscale computational models, improving local and global surveillance data, and high throughput gene sequencing of evolving viral genomes yield a set of tools that has potential to address this difficult problem effectively. We will review efforts by our transdiciplinary team to integrate such tools in the context of Influenza A virus, and guide the development of effective containment measures.

The invasion reproductive number in multi-strain infection models

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In epidemiology, we often study R_0, known as the basic reproductive number. In environments where multiple infection types cocirculate, another threshold value called the invasion reproductive number determines the stability of boundary (single-strain) equilibria. In this talk, I will introduce the invasion reproductive number by comparing two distinct two-strain coinfection models. In one system, coexistence of both strains in the population is possible, while in the other system, coexistence is not possible. I will compare the results of calculating the invasion reproductive number in both cases, while examining the implications of strain competition vs. mutualism in the application of the IRN.

The computer aided drug designing for novel diabetic target "aldose reductase"

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Diabetes is neither a disease nor it is contagious; still this metabolic disorder is threatening the well being of millions of people around the globe and devastating the physical, social and economics welfare of virtually every country in the world. The invention is based on the discovery of a new target, not previously to be linked to diabetes i.e. Aldose reductase, an enzyme, located in the eye (cornea, retina, lens), kidney, myelin sheath, and also in other tissues less involved in diabetic complications.

The enzyme can be inhibited by Aldose Reductase (AR) inhibitors, being studied as a potential treatment to prevent eye, nerve and kidney damage in people with diabetes. Keeping that in mind present study is aimed to design better analogues of Tolrestat, which may have better binding with Aldose Reductase and again can perform function against diabetes. For generating combinatorial library using SMI-LIB is used and fragmentation was done using fragmentor in J-Chem package and as a result of that five fragments were obtained. The biggest and core fragment was selected as scaffold for SMI-LIB for further library generation. These molecules were utilized for virtual screening of all drug like molecules using pharmacophoric and chemical fingerprints and molecular docking and after analyzing the docking results it was found that the molecule TOL727 thus achieved after the in silico processing in computer aided drug design is having the least docking energy as compared to the original Tolrestat molecule. As a conclusion this ligand can be used for further testing in lab and if found with good activity can be suggested as a better lead molecule for aldose reductase.

Using nonlinear model predictive control to find optimal therapeutic strategies to modulate inflammation

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Modulation of the inflammatory response has become a key focal point in the treatment of critically ill patients. Much of the computational work in this emerging field has been carried out with the goal of unraveling the primary drivers, interconnections, and dynamics of systemic inflammation. To translate these theoretical efforts into clinical approaches, the proper biological targets and specific manipulations must be identified. In this work, we pursue this goal by implementing a nonlinear model predictive control (NMPC) algorithm in the context of a reduced computational model of the acute inflammatory response to severe pathogenic infection. Our results imply that a combination of computational modeling and NMPC may be of practical use in suggesting novel immuno-modulatory strategies for the treatment of intensive care patients.

Modelling epidemics and virus mutations by methods of the mathematical kinetic theory for active particles

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The talk focuses on modelling the onset and the spread of epidemics. The mathematical approach is based on the generalized kinetic theory for active particles. The modelling includes virus mutations the heterogeneous distribution of virus levels and the role of the immune system. The structure allows the derivation of specific models and of numerical simulations addressed to highlight emerging behaviours.

An image-based reaction field method for electrostatic interactions in molecular dynamics simulations of aqueous solutions

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A new solvation model is proposed for simulations of biomolecules in aqueous solutions that combines the strengths of explicit and implicit solvent representations. Solute molecules are placed in a spherical cavity filled with explicit water, thus providing microscopic detail where it is most needed. Solvent outside of the cavity is replaced with a dielectric continuum whose effect on the solute is modeled through the reaction field corrections. With this explicit/implicit model, the electrostatic potential represents a solute molecule in an infinite bath of solvent, thus avoiding unphysical interactions between periodic images of the solute commonly used in the lattice-sum explicit solvent simulations. For improved computational efficiency, our model employs an accurate and efficient multiple-image method to compute reaction fields together with the fast multipole method for the direct Coulomb interactions. To minimize the surface effects, periodic boundary conditions are employed for non-electrostatic interactions. The proposed model is then applied to study liquid water.

Timely identification of optimal control strategies for emerging infectious diseases

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Health authorities must rely on quarantine, isolation, and other non-pharmaceutical interventions to contain outbreaks of newly emerging human diseases. A system of differential equations is used to model a generic disease caused by a pathogen apparently transmitted by close interpersonal contact, but about which little else is known. An expression for Rc, the control reproduction number, is derived, which provides threshold conditions for disease control. The sensitivity of Rc to control parameters is analyzed with biological parameters for SARS estimated from the initial case series in Hong Kong and infection rates from hospitalizations in Singapore. Using these parameter values in the model, we examined the effects of various control strategies on the reduction of both the reproductive number Rc and the final epidemic size. The results suggest that it should be possible to identify the optimal intervention early enough to facilitate effective decision-making.

The dynamics of mitosis

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Exit from mitosis requires activation of Cdc14, an essential phosphatase promoting mitotic exit. We have developed a deterministic ODE model for the control of Cdc14 release as the cells exit from mitosis. Our model provides a rigorous account of the factors affecting the dual exit pathways, called FEAR and MEN. The model captures the dynamics of mitotic exit in wild-type and mutant cells, including many details of the physiology, biochemistry and genetics of the process.

Reductions of stochastic calcium release site models

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Mathematical models of calcium release sites derived from Markov chain models of intracellular calcium channels exhibit collective gating reminiscent of the experimentally observed phenomenon of stochastic calcium excitability (i.e., calcium puffs and sparks). Calcium release site models are stochastic automata that involve many functional transitions, that is, the transition probabilities of each channel depend on the local calcium concentration and thus the state of the other channels. In order to overcome the state-space explosion that occurs in such compositionally defined calcium release site models, we have implemented several automated procedures for model reduction using fast/slow analysis. After categorizing rate constants in the single channel model as either fast or slow, groups of states in the expanded release site model that are connected by fast transitions are lumped, and transition rates between reduced states are chosen consistent with the conditional probability distribution among states within each group. For small problems these conditional probability distributions can be numerically calculated from the full model without approximation. For large problems the conditional probability distributions can be approximated without the construction of the full model by assuming rapid mixing of states connected by fast transitions. Alternatively, iterative aggregation/disaggregation may be employed to obtain reduced calcium release site models in a memory-efficient fashion. Benchmarking of several different iterative aggregation/disaggregation-based fast/slow reduction schemes establishes the effectiveness of automated calcium release site reduction utilizing the Koury-McAllister-Stewart method.

On a size-structured two-phase population model with infinite states-at-birth

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We introduce and analyze a linear size-structured population model with infinite states-at-birth. We model the dynamics of a population in which individuals have two distinct life-stages: an "active" phase when individuals grow, reproduce and die and a second "resting" phase when individuals only grow. Transition between these two phases depends on individuals' size. First we show that the problem is governed by a positive quasicontractive semigroup on the biologically relevant state space. Then we investigate, in the framework of the spectral theory of linear operators, the asymptotic behavior of solutions of the model. We prove that the associated semigroup has, under biologically plausible assumptions, the property of asynchronous exponential growth.

A Monte Carlo analysis of peritoneal antimicrobial pharmacokinetics

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Peritoneal dialysis associated peritonitis (PDAP) can be treated using very different regimens of antimicrobial administration, regimens which result in different pharmacokinetic outcomes and systemic exposure levels. There is not currently a detailed pharmacokinetic framework germane to the treatment of peritoneal dialysis associated peritonitis. A mathematical model involving a system of differential equation is used as a computational framework to study the effects of different dosing regiments on the pharmacokinetic parameters, AUC/MIC and 5x MIC, and the level of systemic exposure.

Seeking Cinderella: mathematical models, life support, and medical education

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Each year, tens of thousands of patients require life support when seriously ill. The education of those who manage patients during such life support is, in general, more akin to an apprenticeship than a formal curriculum. Using mechanical ventilation as an example, we will demonstrate that mathematical models offer unique advantages for training individuals responsible for critically ill patients. Dynamic microsimulations based on simple mathematical models can be used very effectively for guided learning, self instruction, assessment of practitioner competence, and evaluation of environmental factors on provider performance.

The application of mathematical models and simulation techniques for educational purposes is an exciting area offering many near-term benefits and great opportunities for investigation.

Design and testing of an artificial neural network model to distinguish between normal and steppage gait based on kinematics data patterns

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In this research kinematics parameters obtained from motion analyzer were evaluated to distinguish between normal and steppage gait. Twenty-five drop foot subjects with steppage gait and twenty normal subjects were participated in the study. Each subject was tested in average 10±2 times for calculating kinematic parameters. The kinematics data required for modeling of patients by artificial neural network were obtained from the films of patient captured by high speed camera, and then the films were analyzed through motion analysis software. Then time parameters of three joints on the sagittal plane namely hip, knee and ankle were captured during a complete gait cycle. In other words there are six time series related to complete gait cycle. From each time series twenty Fast Furrier Transform coefficients were extracted. It means each data will be converted to a vector of one hundred and twenty members. Due to ankle joint disorder in steppage gait, the test consists of similar networks that initially were trained by a vector of forty members containing FFT coefficients of ankle joint and then trained by a vector of one hundred and twenty members containing all the coefficients. A two layer MLP neural network was applied. During implementation of neural networks the Tangent hyperbolic function was applied instead of the Sigmoid function in hidden and output layer and results better distinction. The findings of this research may extend the clinical applications of motion analyzer to classify neurologic gait. There is a need to replicate this research with more patients and normal subjects to confirm our findings.

Understanding tumor growth and angiogenesis: a multiscale modeling approach

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Cancer remains one of the leading causes of disease death for Americans. The development of prognostic tools could have immediate impact on the lives of millions of cancer patients. We have developed an integrated, cell-based modeling framework that includes a cellular model for cell dynamics (cell growth, division, death, migration and adhesion), an intracellular regulatory network for cell cycle control and a signaling network for cell decision-making, and a partial differential equation system for extracellular chemical dynamics. This model has produced avascular tumor growth dynamics that agree with tumor spheroid experiments; it has generated realistic sprout patterns and dynamics in tumor-induced angiogenesis; it has also shown potential for comparing chemotherapeutic strategies for vascular tumor. In particular, we investigate the mechanisms for tumor growth saturation and the roles of VEGF and ECM in tumor angiogenesis. Given the biological realism and flexibility of the model, we believe that it can facilitate a deeper understanding of the cellular and molecular interactions associated with cancer progression and treatment.

Evidence that natural immunity to breast cancer and prostate cancer exists in the majority of their risk populations is predicted by a novel, inherently saturated, ordered mutation model

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The series of ordered mutations that cause a specific cell to become cancerous is modeled so that the fraction of a risk population (e.g. white men) that has developed a specific cancer (e.g. melanoma) at any age can be calculated. The saturated model constructed and solved here is isomorphic to the physical model describing an ordered chain of radioactive nuclei decays with the exception that it allows for the possibility that a fraction of a risk population may be immune to developing a specific cancer.

The simplest model developed here depends on only three independent parameters: the number of ordered mutations necessary for a cell to become cancerous, the fraction of the risk population that is immune to developing a specific cancer, and the average time between mutations (a time defined as the mutation lifetime). The values of these independent parameters are determined by fitting the model's cancer incidence function to the cancer incidence data.

This model was applied to five widely different cancers: melanoma, pancreatic cancer, female breast cancer, non-Hodgkin lymphoma, and prostate cancer. The modeling predicts that all white males in the USA are vulnerable to developing melanoma, five ordered mutations are required to develop it, and the mutation lifetime is 48.3 years. By contrast, the modeling predicts that 80.7% of white females in the USA are immune to developing melanoma, three ordered mutations are required to develop it, and the mutation lifetime is 78.9 years. Remarkably, it was also found that about 70% of females are immune to developing breast cancer, and about 70% of males are immune to developing prostate cancer, predictions that fit in with the experimental evidence of cancer immunosurveillance and immunoediting.

Clearly, different risk populations can develop the same cancer through different pathways. Delineating the mechanism underlying the prevalence of immunity to specific cancers in specific risk populations should become a research priority. Finding ways of blocking or repairing cellular mutations and/or destroying mutated, potentially cancerous cells would prevent cancers from developing altogether and eliminate a major cause of mortality.

Calculating the number of people with Alzheimer's disease in any country using saturated mutation models of brain cell loss that also predict widespread natural immunity to the disease

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The series of mutations that cause brain cells to spontaneously and randomly die leading to Alzheimer's disease (AD) is modeled. The prevalence of AD as a function of age in males and females is calculated from two very different mutation models of brain cell death. Once the prevalence functions are determined, the number of people with AD in any country or city can be estimated.

The models developed here depend on three independent parameters: the number of mutations necessary for a brain cell associated with AD to spontaneously die, the average time between mutations, and the fraction of the risk population that is immune to developing the disease, if any. The values of these parameters are determined by fitting the model's AD incidence function to the incidence data.

The best fits to the incidence rate data predict that as much as 74.1% of males and 79.5% of females may be naturally immune to developing AD. Thus, the development of AD is not a normal or inevitable result of the aging process. These fits also predict that males and females develop AD through different pathways, requiring a different number of mutations to cause the disease. The number of people in the USA with AD in the year 2000 is estimated to be 451,000.

It is of paramount importance to determine the nature of the immunity to AD predicted here. Finding ways of blocking the mutations leading to the random, spontaneous death of memory brain cells would prevent AD from developing altogether.

Dynamics of tubuloglomerular feedback

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The tubuloglomerular feedback (TGF) system is an important regulator of the single nephron glomerular filtration rate. (The nephron is the fundamental functional unit of the kidney.) Experiments in rats (by others) have revealed that TGF can mediate regular and irregular oscillations in nephron tubular fluid flow, pressure, and NaCl concentration; moreover, the TGF systems of nephrons whose glomeruli are nearby on the vascular tree frequently exhibit coupled oscillations. Mathematical modeling indicates that the regular oscillations arise from a Hopf bifurcation; that the regular oscillations may serve to enhance NaCl delivery to the distal nephron and thereby elevate NaCl excretion; and that the irregular oscillations, which are found in hypertensive rats, and which appear to meet empirical standards for deterministic chaos, are not truly instances of deterministic chaos but instead arise from multistability, coupling, parameter lability, and episodic perturbations.

Testing cancer stem cell hypothesis through mathematical modeling

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Cancer Stem Cells (CSCs) are believed to play a critical role in the development and progression of the disease in solid tumors and haematological cancers. The CSC compartment features specific and phenotypically defined cell population characterized with self-renewal, quiescence, overexpression of antiapoptotic proteins, multidrug resistance and impaired differentiation. As CSCs show resistance to a number of conventional therapies, this could explain why it is difficult to completely eradicate the disease. The selective targeting of CSCs may offer a new paradigm in both cancer therapeutics and diagnostics. A temporal mathematical model of eight compartments at the normal and cancer cell levels is investigated. Initially, a baseline normal stem cell model is proposed featuring populations of different cell categories, their proliferation, serial differentiation or apoptosis, and exhibiting a low stem cell compartment and a feedback from differentiated cells to normal progenitor cells. Two controlled oncogenic mutation events are also introduced. As an empirical test, the tumor grading and progression, typically collected in the pathologic lab, is used to correlate the outcome of this model with the tumor development stages. In addition, the model is able to quantitatively account for the temporal development of the population of observed cell types. Finally, several therapeutic treatment models are considered, some with for dose-density chemotherapy (a pulsatile scenario) as well as several continuous, metronomic delivery to find an optimal low dose. The model provides a number of experimentally testable predictions. The relative importance of the cell kill and survival is demonstrated through a deterministic parametric study. The significance of the stem cell compartment is underlined based on this simulation study. This predictive mathematical model for cancer stem cell hypothesis is used to understand tumor responses to chemotherapeutic agents and judge their efficacy.

Self-organization in mucociliary flow

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Mucociliary flow is an essential component of the airway defense system, evacuating many pathogens from the lung. It is also a remarkable display of cooperative behavior: thousands of dynein molecular motors move in unison to establish a cilium beat pattern and thousands of cilia beat together to form metachronal waves. A computational model linking dynein motion, cilium deformation, flow around cilia is presented. Cooperative phenomena are seen to arise naturally from an interplay between the deformable mechanics of the cilia and the fluid mechanics of the airway surface liquid.

Mosquito-borne diseases and emergence of pesticide resistance

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The dynamics of a mosquito-borne disease is studied using a system of nonlinear difference equations. It is assumed that under some conditions, the disease transmitting agents develop resistance to pesticides which are applied for mosquito control. We established the conditions which lead to a disease-free and resistance-free environment and also studied circumstances which allow the disease to be eradicated while pesticide resistance emerges. By employing analytical and numerical techniques, other possibilities such as the persistence of pesticide resistance along with endemic fixed points are also studied. The model is tested with data from malaria, a known mosquito-borne diseases and the development of resistance to commonly used pesticides.

Modelling hemodynamics of blood in a diseased coronary network

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The function of the coronary network is to supply blood to the heart; however, in cases of coronary Artery disease (CAD), the geometry has much influence on blood flow dynamics and the overall performance of the heart. In this paper, blood is modelled as a non-Newtonian fluid and the shearing stress behaviour is described using Eyring –Powell model. The momentum equation for the flow is non-dimensionalized and the non-linear dimensionless equation is then solved numerically by shooting method. Variations of different flow parameters are conducted and discussed.

Computational modeling of tumor development in bone tissue

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Purpose of this study is to investigate so-called “vicious cycles” arising during metastases formation of tumor cells to bone tissue. It is well known that bone tissue and in particular the bone marrow environment provides a preferred niche for some tumor cells to grow. There have been a number of hypotheses been put forward on how tumor cells may achieve this preference. Among these hypotheses are the actions of RANKL, PTHrP and TGF-beta in the bone microenvironment. However, due to the complex cell-cell interactions and the large number of signaling molecules involved, our current understanding of system behaviour is still fragmented. Here we extend a recently developed bone-cell population model to include a particular type of tumor, i.e. myeloma cells. In particular we focus on PTHrP production by myeloma cells and actions of Wnt, sclerostin and Dkk1 on osteoblastic cell lineages within the bone microenvironment. The proposed model takes into account the RANK-RANKL-OPG signaling system between bone cells, actions of TGF-beta, Wnt, sclerostin and Dkk1 on bone cells. Using bone cell numbers, bone volume, tumor cell number and tumor makers as output functions, we can monitor myeloma disease progression computationally over time. This model provides a framework to investigate different disease mechanisms associated with multiple myeloma (MM), and allows the investigation of each individual vicious cycle between MM cells and cells in the bone microenvironment, as well as their combined effect. Additionally, we will compare model predictions with observed experimental data on serum N-telopeptide (NTX), a bone resorption biomarker.

The effects of co-colonization on competition between MRSA strains in the hospital

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Historically, Methicillin-resistant Staphylococcus aureus (MRSA) infections occurred in immunocompromised hospital patients. More recently, a new strain of MRSA has been detected in the general community (CAMRSA), differing genetically from the original strain (HAMRSA) and causing infections in healthy people outside of the hospital. Initial data suggests that CAMRSA is becoming more common and is also possibly replacing HAMRSA in hospitals. Under the assumption that patients can only be colonized with one strain of MRSA at a time, previous modelers have found that competitive exclusion occurs between HAMRSA and CAMRSA strains in the hospital; the strain with the larger basic reproductive ratio will become endemic while the other is extinguished. But new studies suggest that patients can be co-colonized with multiple strains of MRSA. Here, we present a dynamical model composed of ordinary differential equations that allows patients to be colonized with both HAMRSA and CAMRSA (the co-colonization model). Converse to previous results derived from the assumption that co-colonization is insignificant, the co-colonization model rarely exhibits competitive exclusion. More commonly, both strains become endemic in the hospital. Beyond competitive exclusion, we analyze the qualitative effects of increased risk factors, as well as two interventions (decolonization efficacy and hand-washing compliance) on the percentage of patients colonized with MRSA.

Stability analysis of a model of atherogenesis

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Atherosclerosis is an immune mediated disease of the vascular system resulting in the deposition of lipid laden cells in the walls of large muscular arteries. We present a model of some bio-chemical processes involved in the early stages of the disease known as atherogenesis. In particular, we consider the role of immune cells in the presence of chemical stimuli and low density lipoproteins. The model is a system of nonlinear primarily parabolic reaction-diffusion equations. A linear stability analysis using an energy estimate approach is presented with an analysis of the stability criteria with respect to the bio-medical implications.

Model aided design: mathematics in the construction of synthetic gene networks

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Constructing predictable gene networks with desired functions remains hampered by the lack of well-characterized components and the fact that assembled networks often require extensive, iterative retrofitting for optimization. I will present an approach where network components are quickly synthesized in parallel with inherent diversity. When coupled with in silico modeling, libraries present a choice of characterized parts for gene network design, and those optimal for the desired function can be selected for network assembly, without the need for post-hoc tweaking. Our approach will be demonstrated in yeast (S.cerevisiae) by synthesizing a regulatory promoter library and using it to construct negative feedforward loop networks with different, desired input-output characteristics. I will then present the implementation of the method to produce a synthetic gene network that acts as a timer, tunable by component choice. We utilize this network to control the timing of the yeast flocculation phenotype, to illustrate a practical application of our approach.

A volume filling chemotaxis model preventing blow up

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Chemotaxis describes the oriented movement of cells in response to signals. It has significant application in many biological processes such as anagenesis. The classical chemotaxis model exhibits the blow-up behavior. However the blow up does not happen in nature. So preventing blow up mechanisms are desirable to be developed. In this talk, I will incorporate the volume filling mechanism into the model such that the resulting model prevents the blow-up and possesses the aggregation pattern formation.

A habitat-based model for the spread of hantavirus between reservoir and spillover species

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Interspecies pathogen transmission is a primary route for emergence of new infectious diseases and reservoirs in wildlife and man. Interspecies interactions among animals often result in aggressive encounters which, if a pathogen is present in its reservoir, may result in disease in a naive host or adaptation of the pathogen to create a new reservoir. Based on our recent work on hantavirus in rodent communities in Paraguay, we formulate mathematical models to account for the spread of hantavirus between two rodent species. Our Paraguayan data illustrate the spatial and temporal overlap among rodent species, one of which is the reservoir species for Jabora hantavirus and others which are spillover species. Disease transmission occurs when their habitats overlap. Two mathematical models, a system of ordinary differential equations (ODE) and a continuous-time Markov chain (CTMC), model are developed for spread of hantavirus between a reservoir and a spillover species.

Multiscale modeling of solid tumor growth and angiogenesis: the effect of the microenvironment

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We present and investigate models for solid tumor growth that incorporate features of the tumor microenvironment, including tumor-induced angiogenesis. Using analysis and efficient 2D/3D numerical simulations, we explore the effects of the interaction between the genetic characteristics of the tumor and the tumor microenvironment on the resulting progression and morphology. We account for variable cell-cell/cell-matrix adhesion in response to environmental conditions (e.g., hypoxia) and to the presence of multiple tumor cell species. The model provides resolution at various tissue physical scales and quantifies functional links of molecular factors to phenotype that for the most part can only be tentatively established through laboratory or clinical observation. This allows observable properties of a tumor (e.g. morphology) to be used to both understand the underlying cellular physiology and to predict subsequent growth or treatment outcomes, thereby providing a bridge between observable, morphologic properties of the tumor and its prognosis. This is joint work with Vittorio Cristini (SHIS; UT, Houston) and John Lowengrub (Math; UC, Irvine).

Molecular noise enhances oscillations in a supra-chiasmatic nuclei network

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The Supra-Chiasmatic Nucleus (SCN) is an an important physiological organ that is responsible for coordinating circadian rhythms and associated behaviors. 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. From our mathematical models, the 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 highlight the importance of transcriptional noise in enhancing oscillations rather than dampening them. Surprisingly, and most interestingly, our predictions have been confirmed experimentally; this confirmation highlights the importance of quantitative modeling complimenting experimental investigations in this field. We conclude with the applications of our results to understanding important problems involving the SCN: in particular the role of the SCN in cancer, depression, and bipolar disorder.

On imaging mass spectrometry data analysis

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The development of mass spectrometry (MS) such as MALDI-TOF MS, SELDI-TOF MS, and Imaging MS, greatly speeds up the proteomics research. However, the complexity and high dimension characteristic of the MS data pose great challenge for data processing. Imaging mass spectrometry (IMS), a new application area for proteome mapping which measures a large collection of mass spectra spread out over an organic tissue section and retains the absolute spatial information of the measurements for analysis and imaging, has shown great potential and is very promising for rapid mapping of protein localization and the detection of sizeable differences in protein expression. Data generated by IMS has two spatial dimensions (x-, y- dimension) and the mass-over-charge (m/z) dimension. Each pixel of MS images contains an entire mass spectrum. This means that there are 65, 536 spectra in a 256 *256 image. This in itself is a challenge for data processing. Furthermore, to fully utilize IMS data, it is desirable to not only identify the peaks of the spectrum within individual pixels, but preserve the spatial information for the whole images. The combination of spatial and mass resolution results in large and complex data sets gives a great challenge to the quantitative analysis and interpretation.
In this presentation, we'd like to report some recent improvement on the MS based proteomic data processing algorithms, especially in the denoising and peak selection steps by using wavelets. Two adaptive wavelet algorithms based on SURE (Stein Unbiased Risk Estimation) and based on GCV (Generalized Cross Validation) are proposed. Some recent results of IMS data analysis on classification and biomarkers distribution using data cube analysis tools are also presented.

Hepatitis B is endemic in China

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Hepatitis B virus (HBV) is the most common serious viral infection and a leading cause of death in mainland China. Around 130 million people in China are carriers of HBV, almost a third of the people infected with HBV worldwide and about 10% of the general population in the country; among them 30 million are chronically infected. Every year, 300,000 people die from HBV-related diseases in China, accounting for 40 -50% of HBV-related deaths worldwide. Despite an effective vaccination program for newborn babies since the 1990s, which has reduced chronic HBV infection in children, the incidence of hepatitis B is still increasing in China. We propose a mathematical model to understand the transmission dynamics and prevalence of HBV in China. Based on the data reported by the Ministry of Health of China, the model provides an approximate estimate of the basic reproduction number R0 = 3:77. This indicates that hepatitis B is endemic in China and is approaching its equilibrium with the current immunization programme and control measures. Although China has been making great progress by increasing coverage among infants with hepatitis B vaccine, it has a long and hard battle to fight in order to significantly reduce the incidence and eventually eradicate the virus.

Evolution of quantitative traits with immigration

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Ecological and genetical changes occur simultaneously but on different time scales and evolution is usually much slower than ecological changes. The interactions between them lead to the fast-slow dynamical system. In this paper, a model describing evolution of the mean value of a quantitative trait with a direct migration scheme is proposed, and numerical methods are applied to test assumptions and the robustness of the approximate equation. Finally, a fast-slow dynamical system, which relates the immigration to the ecological subsystem is set up and analyzed numerically.