BIRS-CMO Workshop 15w5095:
Viral Dynamics and Cancer: Modeling Oncogenic and Oncolytic Viruses
Oaxaca, Mexico, August 2-7, 2015

MEALS

*Breakfast: 7:30 – 9:00 am, Monday–Friday, Restaurant Hotel Hacienda Los Laureles

*Lunch: 13:30 – 15:00 pm, Monday–Friday, Restaurant Hotel Hacienda Los Laureles

*Dinner: 19:30 – 22:00, Sunday; 20:00 – 22:00, Monday; 19:00 – 21:00 pm, Tuesday–Thursday; Restaurant Hotel Hacienda Los Laureles

*Continuous Coffee Breaks: Conference Room San Felipe, Hotel Hacienda Los Laureles

MEETING ROOMS

All lectures will be held in the Conference Room San Felipe at Hotel Hacienda Los Laureles. An LCD projector, laptop, document camera and blackboards are available for presentations.

SCHEDULE

Sunday

16:00	Check-in begins (front desk at your assigned hotel - open 24 hours)
19:00–21:00	Dinner, Restaurant Hotel Hacienda Los Laureles
20:00	Informal gathering Hotel Hacienda Los Laureles. A welcome drink will be served by the hotel.

Monday

7:30–9:00	Breakfast
9:00–9:10	Introduction and welcome
9:10–10:00	Dominik Wodarz: Overview, viral dynamics modeling
10:00–10:40	Marcos Capistrán: The role of fitness and replication dynamics on virus invasion
10:40–11:20	Stanca Ciupe: Mathematical models of hepatitis B infection
11:20–11:50	Coffee break
11:50–12:40	Rafael Meza: Overview, epidemiology & cancer epidemiology
12:40–13:30	Breakout sessions
13:30–15:00	Lunch
15:00–15:40	Elamin Elbasha: Global Control and Regional Elimination of HCV
15:40–16:10	Panel discussion
16:10–16:30	Group picture
16:30–17:00	Coffee break
17:00–20:00	Field trip: Oaxaca City Tour
20:00–22:00	Dinner

Tuesday

7:30–9:00	Breakfast
9:00–9:50	Rafael Meza: Overview, cancer modeling
9:50–10:30	Andrew Brouwer: Modeling the connection of disease prevalence to cancer incidence: HPV and oropharyngeal cancer
10:30–11:10	Coffee break
11:10–11:50	Carmen Lia Murall: Understanding the evolutionary ecology of viral oncogenesis
11:50–12:30	Marisa Eisenberg: Interacting Scales in Modeling HPV and Oropharyngeal Cancer
12:30–13:30	Breakout session
13:30–15:00	Lunch

Tuesday (cont'd)

15:00–16:30	Research & collaboration time
16:30–17:00	Coffee break
17:00–17:40	Marc Ryser: HPV clearance and the neglected role of stochasticity
17:40–18:20	Anna Miller: A quantitative comparison of high-risk and low-risk human papillomavirus manipulation of the epithelial cell cycle
18:20–18:50	Panel/focused discussion
19:00–21:00	Dinner

Wednesday

7:30–9:00	Breakfast
9:00–13:00	Field trip to Monte Albán
13:30–15:00	Lunch
15:00–16:30	Research & collaboration time
16:30–17:00	Coffee break
17:00–17:40	Edwin Juarez Rosales: Using Systems Identification to build a digital cell line library
17:40–18:20	Moises Santillán: Dynamic effects of extrinsic noise in a simple oscillatory gene network with delayed negative-feedback regulation: an electronic modeling approach
18:20–18:50	Panel/focused discussion
19:00–21:00	Dinner

Thursday

7:30–9:00	Breakfast
9:00–9:50	Jean Simon Diallo: Overview, oncolytic virotherapy
9:50–10:40	Natalia Komarova: Overview, oncolytic modeling
10:40–11:20	Coffee break
11:20–12:00	Adrianne Jenner: Mathematical modelling of oncolytic virotherapy and immunotherapy using deterministic and stochastic models
12:00–13:00	Breakout sessions
13:00–13:30	Research & collaboration time
13:30–15:00	Lunch
15:00–16:30	Research & collaboration time
16:30–17:00	Coffee break
17:00–17:40	Amber Miller: The use of mathematical modeling to predict and assess oncolytic virotherapy optimizations
17:40–18:20	James K. Ooi: A systematic perturbation approach identifies novel strategies to improve the efficacy of oncolytic virus therapy
18:20–18:50	Panel/focused discussion
19:00–21:00	Dinner

Friday

7:30–9:00	Breakfast
9:00–10:00	Breakout sessions: full group discussion
10:00–10:30	Coffee break
10:30–11:00	Focused discussion: what's next?
11:00–11:10	Final remarks & check out

BIRS-CMO Workshop 15w5095:
Viral Dynamics and Cancer: Modeling Oncogenic and Oncolytic Viruses

Oaxaca, Mexico, August 2-7, 2015

$\sim$ ABSTRACTS $\sim$

(in alphabetical order by speaker surname)

Andrew Brouwer, University of Michigan

Title: Modeling the connection of disease prevalence to cancer incidence: HPV and oropharyngeal cancer

Abstract: HPV is the etiological agent for over 90% of anogenital cancer and an increasing percentage of oral cancer. Modeling the connection of HPV prevalence and cancer is challenging because going from population-level data of prevalence to population-level data of cancer incidence crosses many spatial and temporal scales. Infection and clearance takes place locally and on the scale of months to years while progression to cancer takes place within an individual over a decade or more. Here, we use multistage clonal expansion (MSCE) models of cancer biology coupled with epidemiological age–period–cohort (APC) models to model oral cancer in the SEER cancer registry. We also investigate extensions of MSCE models that may be used to directly and mechanistically connect disease prevalence and cancer incidence.

Marcos Capistrán, CIMAT Guanajuato

Title: The role of fitness and replication dynamics on virus invasion

Abstract: In this work we use mathematical modeling to disentangle the roles of replication dynamics, contact rate between virus and target cells and initial viral load on virus invasion. A branching process model shows that a large contact rate determines invasion. Later, we assume that during early infection the contact rate is proportional to the probability that the contact gives rise to an infected cell. The arising mean field equations for the dynamics of the system exhibit bistability. The virus free state is locally unconditionally stable. There are two endemic equilibria if the basic reproductive number $R_0 > 1$, one of them stable and the other one unstable. This model allows to discuss competition of strains. We use our findings to discuss HIV infection.

Stanca Ciupe, Virginia Tech

Title: Mathematical models of hepatitis B infections

Abstract: Infection with hepatitis B virus results in acute hepatitis followed by recovery in most human adults and in chronic hepatitis in non-vaccinated infants. It is believed that the dynamical interactions between the virus and the immune system can explain the infection outcome. We developed mathematical models for the virus-host interactions in human adults and made predictions on the mechanisms leading to viral clearance or persistence. This talk will focus on the modeling process, the stability analysis of the models, and the fitting of the models to human data. Our results suggest that transition from acute to chronic disease can be explained by a bi-stable switch and we will discuss the hypotheses leading to such bifurcations. Lastly, we will present the additional challenges in inducing viral clearance in infants by modeling the strategies that the virus employ to escape the recognition of an immature immune system.

Jean-Simon Diallo, Ottawa Hospital Research Institute

Title: Overview, oncolytic virotherapy

Marisa Eisenberg, University of Michigan

Title: Interacting Scales in Modeling HPV and Oropharyngeal Cancer

Abstract: Human papillomavirus (HPV) is a sexually transmitted infection which is associated with several forms of cancer, including cervical and oropharyngeal cancer. Interactions between HPV and cancer form an inherently multi-scale problem, with population-level disease transmission driving within-host carcinogenesis, yielding overall population-level cancer trends. In this talk, I will discuss our group's recent work examining the dynamics of HPV and oropharyngeal cancer, both at the mechanistic/cellular level, and combining scales between population and within-host.

Elamin Elbasha, Merck

Title: Global Control and Regional Elimination of HCV

Abstract: The highly transmissible Hepatitis C virus (HCV) causes significant morbidity and liver disease-related deaths (due to complications of cirrhosis and hepatocellular carcinoma) worldwide. The availability of safe and highly effective, ribavirin-free, all-oral, direct-acting antiviral (DAA) agents ushered a new dawn of HCV treatment where HCV elimination is within reach. Using mathematical models calibrated to a few representative countries, this study assesses the possibilities of and discusses the barriers to regional elimination and global control of HCV. Several insights are gleaned from the mathematical analysis of the models: 1) the focus should be on high transmitters (e.g., persons who inject drugs), 2) treatment scale up alone is not enough (it has to be coupled with screening and diagnosis efforts), and 3) whereas it is easier to eliminate the less prevalent genotypes (e.g., G4, G5, and G6), it is more difficult to eliminate the highly prevalent genotypes (e.g., G1 and G3).

Adrianne Jenner, University of Sydney

Title: Mathematical modelling of oncolytic virotherapy and immunotherapy using deterministic and stochastic models

Abstract: Cancer has been an ongoing problem in our society for many years and combined oncolytic virotherapy and immunotherapy are fields investigating possible treatments. Two mathematical models using ordinary differential equations are developed for both of these areas and optimised to current experimental data. In addition, a stochastic simulation based on the Gillespie algorithm is created based on the previous optimisations to simulate the effects of randomness and investigate what changes could be made to the treatment to possibly improve its effectiveness. Modifications to the lysis rate and infectivity of the virus are shown through the stochastic simulations to provide improvements to the effectiveness of the treatment.

Edwin Juárez Rosales, University of Southern California

Title: Using Systems Identification to build a digital cell line library

Abstract: A current challenge in data-driven mathematical modeling is identifying mathematical model parameters from sparse and often noisy experimental data of mixed types. For example, experiments may measure a time series of total cell counts from a first set of replicates, viable cell fractions with endpoint immunostains from other replicates, and cell cycle distribution via flow cytometry on yet another set of replicates. In this talk, we will apply systems identification techniques to two cell cycle models that describe cell behavior. After presenting those cell cycle models and describing how they complement each other, we define (nonlinear) error measures based upon the difference between simulated and experimental data points, and then iteratively minimize these error measures to estimate the best parameter values for each model. We will assess the relative quality of each model and show an example where this methods have been applied to quantify the effects of Doxorubicin in a drug-sensitive cell line. We will also present the insight that has been gained, through the application of this technique, about the mechanisms of action of Doxorubicin. This work is a critical step towards developing a library of digital cell lines: digital representations of the microenvironment-dependent phenotypes of real cell lines. It is our hope that such building a library of digital cell lines –along with tools to easily use them– will help encourage data sharing, resource pooling, and future models that can be combined into detailed patient simulators for planning treatments.

Mads Kaern, University of Ottawa & James K. Ooi, University of Ottawa

Title: A systematic perturbation approach identifies novel strategies to improve the efficacy of oncolytic virus therapy

Abstract: The interest in oncolytic virus (OV) as an anticancer agents has been resurrected in part due to introduction of enhanced recombinant virus vectors technology. Many engineered OV candidates has emerged; some forerunners has entered early phase clinical trials. However, the genetic heterogeneity of tumors poses a unique challenge to create novel OV and optimize its efficacy. In a previous work (Le Boeuf et al. 2013), rational OV designs were simulated and novel strategies guided by the models were experimentally validated. An indirect positive feedback loop virus (Δ51-IDE) generated through virus-mediated expression of a decoy receptor (DR) showed increased virus-mediated cytotoxicity in tumor. Simulation shows that viral efficacy of Δ51-IDE could be further optimized. Sensitivity analysis and systematic screening the model's parameter space reveals opportunities for viral efficacy improvements of this design. The screening narrows downs potential candidates based on optimal input-parameter combination for improved viral efficacy. Principal component analysis is then employed to identify parameter's attributes that are robust. We will discuss optimization of the viral efficacy through systematic perturbation and the challenges to validate the optimized model.

Natalia Komarova, University of California - Irvine

Title: Overview, oncolytic virotherapy modeling

Rafael Meza, University of Michigan

Title: Overview, epidemiology & cancer epidemiology

Title: Overview, cancer modeling

Anna Miller, University of Utah

Title: A mathematical analysis of cell cycle dysregulation due to human papillomavirus infections

Abstract: Human papillomaviruses (HPVs) are small DNA viruses that infect basal cells of squamous epithelium. HPVs can be categorized as high-risk (HR) or low-risk (LR) based on the potential to become malignant. HPVs do not encode DNA replication enzymes and thus depend on the host cell machinery for DNA synthesis. HPV E7 is a viral protein that binds to cell cycle proteins such as retinoblastoma protein (pRb) to modulate cell cycle control. Generally, HR HPV E7 binds to pRb with a higher affinity than LR HPV E7, but both are able to inactivate pRb. In addition to pRb inactivation, growth factor (GF) stimulation is also typically necessary for a cell to enter the cell cycle. Using a nonlinear system of ordinary differential equations, we examine the role that binding affinity, growth factor concentration, and HPV E7 concentration have on cell cycle progression. We will discuss our preliminary results and their implications for high binding affinity viruses.

Amber Miller, Mayo Clinic

Title: The use of mathematical modeling to predict and assess oncolytic virotherapy optimizations

Abstract: Oncolytic viruses like vesicular stomatitis virus (VSV) are experimental cancer therapies that selectively infect and kill tumor cells during an oncolytic phase and invoke anti-tumor adaptive immune responses for residual tumor clearance during a subsequent immunotherapeutic phase. A simplistic mathematical model has been developed to identify factors that influence the probability of tumor cell survival following the oncolytic phase of oncolytic virotherapy. The model uses assumptions based on detailed immunohistochemical staining of myeloma tumors explanted from mice administered systemic VSV. Analysis revealed that VSV particles extravasate into the tumor parenchyma and initiate infection by entering and propagating in multiple dispersed neoplastic cells. The infected cells serve as the origin of centrifugally expanding infected centers as the cells produce progeny virions that spread in a contact-dependent and spatially constrained manner. Virus spread is either terminated rapidly by innate immune responses (antiviral state), or continues unabated until controlled by the adaptive immune system, such that

intratumoral infection spread is arrested yielding static spheres of infected cells within the tumor. These spherical infected centers can be described in a spatial and probabilistic manner. The resulting model identifies (i) the density of initially infected cells in the tumor, (ii) the average maximum size attained by the infectious centers, and (iii) the distribution of infectious centers as key factors in predicting therapeutic outcome. In order to systematically improve upon these factors, we have developed quantitative dynamic radiohistologic approaches to assess improvements in intratumoral infection. We use noninvasive SPECT/CT imaging after the administration of recombinant virus expressing the sodium-iodide symporter (NIS) reporter gene to visualize radiotracer uptake at centers of active NIS expression correlating with intratumoral infected centers. The SPECT/CT data is analyzed using distributive distance transformation algorithms to quantitatively assess changes in delivery and intratumoral distribution as it relates to theoretically simulated random distribution. Together, our predictive survival model and quantitative analysis of intratumoral distribution via dynamic radiohistology can guide optimization of tumor coverage and ultimately tumor cure using oncolytic viruses.

Carmen Lia Murall, Max Planck Institute for Dynamics and Self-Organization

Title: Understanding the evolutionary ecology of viral oncogenesis

Abstract: In Murall, Bauch, & Day (2015), I investigated how the novel immunity environment created by the Human papillomavirus (HPV) vaccines could change the selective pressures that shape HPV's viral traits. The vaccines elicit an unnaturally strong antibody response against a capsid protein that is not the usual target in natural cellular responses that result in clearance. Using simple mathematical models of viral dynamics, I found that, in contrast to natural immunity, the vaccines' immunity favours viral strategies of high oncogene expression. This investigation has led me to ask more general questions, including: what drives the evolution of viral traits that are linked to oncogenesis? And what trade-offs shape the life-histories of oncoviruses? In this talk I will present the above mentioned results and I will discuss some of the main interests I am currently pursuing with the aim to better understand the evolutionary ecology of viral oncogenesis.

Marc Ryser, Duke University

Title: Similarities and differences between computational drug discovery in oncology and virology: lessons learned and cautionary tales

Abstract: Clearance of anogenital and oropharyngeal HPV infections is attributed primarily to a successful adaptive immune response. To date, little attention has been paid to the potential role of stochastic cell dynamics in the time it takes to clear an HPV infection. We combine mechanistic models at the cellular level with epidemiological data at the population level to disentangle the respective roles of immune capacity and cell dynamics in the clearing mechanism. We will discuss our findings in the broader context of HPV natural history and public health.

Moises Santillan Zeron, Centro de Investigacion y de Estudios Avanzados del IPN

Title: Dynamic effects of extrinsic noise in a simple oscillatory gene network with delayed negative-feedback regulation: an electronic modeling approach

Abstract: Gene expression is intrinsically stochastic due to the small number of molecules involved in some of the underlying biochemical reactions. The resulting molecule-count random fluctuations are known as biochemical noise. The dynamic effects of intrinsic noise (that originated within the system) have been widely studied. However, the effects of the noise coming from other sources the system is in contact with, or extrinsic noise, is not so well understood. In this work we introduce an electronic model for a simple gene oscillatory network, with delayed negative-feedback regulation. Notably, this model accounts for the intrinsic biochemical noise due to the slow promoter switching between the active and inactive states; but dismisses biochemical noise due to mRNA and protein production and degradation. We characterize the oscillatory behavior of this gene network by varying all the relevant parameter values within biologically meaningful ranges. Finally, we investigate how different sources of extrinsic noise affect the system dynamic behavior. To simulate extrinsic noise we consider stochastic time series coming from another circuit simulating a gene network. Our results indicate that, depending on the parameter affected by

extrinsic noise and the power spectra of the stochastic time series, the system oscillatory behavior can be either enhanced or worsen.

Dominik Wodarz, University of California - Irvine

Title: Overview, viral dynamics modeling
