INTERNATIONAL WORKSHOP ON MATHEMATICAL BIOLOGY 2019

JANUARY 6-10, 2019

IWOMB 2019

BOHOL BEE FARM

PANGLAO ISLAND, BOHOL, PHILIPPINES

PROGRAMME

DAY 0: JANUARY 6, 2019

12:00 NN	Arrival
04:00 - 06:00	Registration
06:00 - 09:00	Welcome Dinner

DAY 1: JANUARY 7, 2019

08:30 - 09:00	Opening Program
09:00 - 10:00	Pattern formation, forces, and crawling cells *Leah Edelstein-Keshet*, University of British Columbia
10:00 - 10:40	Understanding human genome structural variation at population scale using whole genome sequencing *Robert Handsaker*, Broad Institute
10:40 - 11:10	AM Snacks/Poster Presentations
11:10 - 11:50	A sensitive method for detecting chromatin-altering polymorphisms *Ricardo del Rosario*, Broad Institute
11:50 - 01:00	Lunch
01:00 - 02:00	Modeling the Coupled Leukemic-Inflammatory Responses with application to treatment planning *Johnny T. Ottesen*, Roskilde University
02:00 - 02:40	Dynamical Models of the 2009 A/H1N1 Influenza and Effective Intervention Strategies in the Republic of Korea *Eunok Jung*, Konkuk University
02:40 - 03:00	PM Snacks/Poster Presentations
03:00 - 03:40	Insights from 3,000 rice genomes *Dmytro Chebotarov*, International Rice Research Institute
03:40 - 04:20	When can we use Michaelis-Menten equation for stochastic simulations? *Jae Kyoung Kim*, KAIST
04:20 - 05:20	Gong Show
05:20 - 05:45	Importance of Pollinators and Plant-Pollinator Networks *Neelendra Joshi*, University of Arkansas
05:45 - 07:30	Student Workshop

DAY 2: JANUARY 8, 2019

08:15 - 08:30	Announcement
08:30 - 09:10	Chemical Reaction Network Theory in Systems Biology *Editha C. Jose*, UP Los Baños
09:10 - 09:50	Controlling cell fate specification system based on network structure *Atsushi Mochizuki*, Kyoto University
10:00 - 04:00	Tour

DAY 3: JANUARY 9, 2019

08:30 - 08:55	Special talk on exploring genotype *x* environment interaction using photosynthesis models *Kusum Naithani*, University of Arkansas
08:55 - 09:00	Announcement
09:00 - 10:00	Efficient scientific inference for stochastic dynamical systems *Aaron A. King*, University of Michigan
10:00 - 10:40	Some challenges in modeling imperfect vaccines *Felicia Maria G. Magpantay*, Queen's University
10:40 - 11:10	AM Snacks/Poster Presentations
11:10 - 11:50	Noises and dynamics in cells: Mathematical modeling in systems biology *Chao-Ping Hsu*, National Taiwan University
11:50 - 12:30	White Noise Functional Analysis for Stochastic Biological Phenomena with Memory *Christopher C. Bernido*, University of San Carlos
12:30 - 02:00	Lunch
02:00 - 02:40	Eco-evolutionary game dynamics: from cells to societies *Chaitanya S. Gokhale* Max-Planck-Institute for Evolutionary Biology
02:40 - 03:00	PM Snacks/Poster Presentations
03:00 - 06:00	Student Workshop
07:00 - 08:00	Roundtable Discussion

DAY 4: JANUARY 10, 2019

08:30 - 09:00	Announcement
09:00 - 11:00	Student Presentations
11:00 - 12:00	Closing

KEYNOTE AND PLENARY TALKS

Pattern formation, forces, and crawling cells

Leah Edelstein-Keshet
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In this talk, I will describe research carried out in my group on the topic of cell motility. Why do cells move? Immune cells have to move around the body to find sites of infection and kill pathogens. How do cells move? That is a fascinating question that my group has been studying and modeling for over 15 years. Biologists have found that the distribution of specific signaling proteins (Rho GTPAses) inside a motile cell govern the polarity and direction of motions, as well as regulate the machinery (actin cytoskeleton) that powers that crawling cell motion. (A high level of the GTPAse Rac leads to local actin assembly and cell edge protrusion, whereas a high level of Rho leads to myosin activation, and local cell edge contraction. In combination, protrusion of the cell front and contraction of the back leads to cell motility.) I will review mathematical models we have studied (reaction-diffusion partial differential equations) for the patterns formed by these proteins inside a cell, describe some of the mathematical methods, and present examples of biological experiments that the models could explain. I will end with recent work that depicts how mechanical forces are coupled to the signaling proteins, and what this implies about the dynamics of both single cells and multicellular tissues.

Understanding human genome structural variation at population scale using whole genome sequencing

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Human genomes vary at small scales (changes to single DNA bases) and also at large scales involving the addition or subtraction of DNA segments containing many thousands of bases. These large-scale changes, known as structural variation, are abundant in the general population and have been shown to have potent effects on many common phenotypes and diseases, including schizophrenia and cardiovascular disease. Whole-genome sequencing provides new opportunities to interrogate genomes at population scale, but reconstructing and measuring these large structural variations using currently available sequencing technologies poses mathematical and computational problems.

This talk will discuss the difficulties in measuring and interpreting human structural variation and the mathematical approaches and algorithms we have developed in our Genome STRiP software. I will describe some of the biological properties of human structural variation that we observe in population scale studies such as the 1000 Genomes Project and highlight examples of structural variation relevant to human disease phenotypes. I will also discuss some of our current work to build better population-scale maps of human structural variation and to improve our ability to understand and interpret the biological impact of these variants.

A sensitive method for detecting chromatin-altering polymorphisms

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Most single-nucleotide polymorphisms (SNPs) found to be associated with disease from genome-wide association studies (GWAS) lie on non-coding regions. The majority of these non-coding GWAS SNPs might not even be in in linkage disequilibrium (LD) with SNPs in coding regions, and hence it has been speculated that these variants possess regulatory functions. For example, mutations in regulatory regions such as enhancers could affect the enhancer's activity to regulate the expression of its target gene. Identifying causal variants on a large scale poses difficulties because most GWAS SNPs are merely in LD with the causal SNP and moreover, the function of SNPs in regulatory regions are mostly unknown. We present a method that simultaneously detects SNPs in regulatory regions and quantifies their regulatory impact. The method uses only one assay, chromatin immunoprecipitation-sequencing (ChIP-seq), and does not require a separate genotyping of the cohort. The regulatory regions are identified using ChIP-seq on histone H3 acetylated on lysine 27 (H3K27ac; a histone mark of active promoters and enhancers) and from the ChIP-seq reads, we detected histone acetylation quantitative trait loci (haQTLs). We developed a statistical test called the genotype-independent signal correlation and imbalance (G-SCI) test that simultaneously scores ChIP-seq peak height correlation and allelic imbalance. As proof of principle, we performed H3K27ac ChIP-seq on 57 lymphoblastoid cell lines. The G-SCI test detected 8,764 haQTLs, an order of magnitude larger than the number of SNPs detected by expression QTL analysis. Our method facilitates the detection of regulatory variants on a large-scale, using only a moderately sized cohort and provides a simple way to identify causal variants within disease associated loci.

Modeling the Coupled Leukemic-Inflammatory Responses with application to treatment planning

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Inflammation trigs and drives leukemia and the related Myeloproliferative Neoplasm (MPNs) diseases through the innate immune system while leukemia and MPNs stimulates the inflammatory responds of the adaptive immune system fighting the malign cells of the diseases. Where the two-way coupling of solid tumor cancer and the adaptive immune system has drawn some attention during the last decades and inspired to immuno- and gene-therapy, leukemia and MPNs have by the large been left unnoticed with respect to such coupling. Likewise, the two-way coupling of leukemia and MPNs, and the innate immune system is by the large left unstudied with respect to treatments and preventive measures.

We pose a novel mathematical model of development of leukemia and MPNs taking these two-way couplings into account. The model is validated against human data. It follows that the innate immune response is crucial in the development and treatment of leukemia and MPNs. Steady states and their stability are determine analytically and it is discuss how the model may be used for optimizing treatment. Geometric singular perturbation theory suggests a reduced model which shows excellent agreement with the full model.

Dynamical Models of the 2009 A/H1N1 Influenza and Effective Intervention Strategies in the Republic of Korea

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A novel influenza A/H1N1 is characterized by high transmissibility and low fatality. In this talk, we present mathematical models of the 2009 A/H1N1 influenza based on the reported data of the 2009 A/H1N1 influenza collected by the Korea Center for Disease Control (KCDC). First, a spatial-temporal pattern of the 2009 A/H1N1 influenza spread is studied using the metapopulation model. The SEIR-type of an influenza transmission model is used in each subpopulation linked by commuting flow. We find localized (province-level) spread by using the spatial heterogeneity such as the basic reproductive number and peak time and investigate the effect of early non-pharmaceutical interventions such as isolation and/or commuting restriction. Second, we introduce an age-dependent model of the 2009 A/H1N1 influenza by considering five age groups and suggest the best way to prioritize an age-dependent vaccination strategy for mitigating the epidemic. The estimated transmission matrix captures one of the main characteristics of the 2009 A/H1N1 influenza, the transmission rate of which is high among young people, unlike that of seasonal influenza. The impact of an age-dependent vaccination priority on the transmission dynamics of the 2009 A/H1N1 influenza is investigated. Furthermore, we quantify and analyze the Korean government vaccination policy when the vaccination started being administered 90 days (or 120 days) after the onset of the outbreak.

Insights from 3,000 rice genomes

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In this talk, I will present recent and ongoing work from 3,000 rice genomes project, from an overview of variation (SNP and structural variants), population structure, to implications for history of rice domestication and utility for uncovering genotype-phenotype associations. I will touch on open questions and discuss opportunities for collaboration.

When can we use Michaelis-Menten equation for stochastic simulations?

Jae Kyoung Kim
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Biochemical reaction networks (BRNs) in a cell frequently consist of reactions with disparate timescales. The stochastic simulations of such multiscale BRNs are prohibitively slow due to high computational cost for the simulations of fast reactions. One way to resolve this problem uses the fact that fast species regulated by fast reactions quickly equilibrate to their stationary distribution while slow species are unlikely to be changed. Thus, on a slow timescale, fast species can be replaced by their quasi-steady state (QSS): their stationary conditional expectation values for given slow species. As the QSS are determined solely by the state of slow species, such replacement leads to a reduced model, where fast species are eliminated. However, it is challenging to derive the QSS in the presence of nonlinear reactions. In this talk, I will describe under which condition such stochastic QSS can be accurately approximated by a deterministically derived QSS (e.g. Michaelis-Menten equation), which allows to use the non-elementary functions for the propensity functions of the Gillespie algorithm. Furthermore, I will also present two classes of multiscale BRNs which can be reduced by deriving an exact stochastic QSS rather than approximations: a feedforward network or a complex balanced network. Finally, I will illustrate how we used such accurate reduction to identify a novel molecular mechanism for robust circadian rhythms and improve the prediction of drug clearance in liver.

Chemical Reaction Network Theory in Systems Biology

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Chemical reaction network theory (CRNT) is an area of applied mathematics that attempts to model the behavior of real world chemical systems. It aims to understand connections between network structure and system dynamics with mathematical methods from graph theory, linear algebra, group theory and the theory of ordinary differential equations (dynamical systems). Even though the modern theory of CRNs was started in the 1970's by chemical engineers, the emergence of Systems Biology led biologists, computer scientists, mathematicians and researchers from other disciplines to pursue collaborative efforts in CRNT to understand complex biological and chemical systems. CRNT has become a tool to study complex biology independent of rate parameters, that is, certain behaviors of networks are examined by analyzing their structures only.

In this talk, we will present some basic concepts of CRNT and apply these to study some biochemical systems. We will feature some Filipino contributions to this field focusing on power law kinetic systems and biological applications. We also describe our current and future research directions.

Controlling cell fate specification system based on network structure

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By the success of modern biology, we have many examples of large networks which describe regulatory interactions between a large number of genes. On the other hand, we have a limited understanding for the dynamics of molecular activity based on such complex networks. To overcome these problems, we developed Linkage Logic theory to analyze the dynamics of complex systems based on information of the regulatory linkages alone. It assures that i) any long-term dynamical behavior of the whole system can be identified/controlled by a subset of molecules in the network, and that ii) the subset is determined from the regulatory linkage alone as a feedback vertex set (FVS) of the network. We applied this theory to the gene regulatory network for cell differentiation of ascidian embryo, which includes more than 90 genes. From the analysis, dynamical attractors possibly generated by the network should be identified/controlled by only 5 genes, if the information of the network structure is correct. We verified our prediction by combinatorial experiments of knockdown and overexpression by using ascidian embryos. We found that almost all of the expected cell types, six among seven major tissues, could be induced by experimental manipulations of these five genes.

Efficient scientific inference for stochastic dynamical systems

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Questions about the mechanistic operation of biological systems are naturally formulated as stochastic processes but confronting such models with data can be challenging. In this talk, I describe the essence of the difficulty, highlighting both the technical issues and the importance of the "plug-and-play property". I then illustrate some effective approaches to efficient inference based on such models. I conclude by sketching promising new developments and describing some open problems.

Some challenges in modeling imperfect vaccines

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The dynamics of vaccine-preventable diseases depend on the underlying disease process and the nature of the vaccine. In this talk I will present a general model of an imperfect vaccine and the epidemiological consequences of different modes of vaccine failure. I will also discuss likelihood-based statistical inference methods that can be used to estimate the parameters of the model even in the presence of incomplete covariate information (such as vaccine coverage). The methods used can be extended to study and fit mechanistic models of complex phenomenon beyond those in disease ecology.

Noises and dynamics in cells: Mathematical modeling in systems biology

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Gene expression noise is ubiquitous in cells. One source of noises is that genes are expressed in bursts, as both mRNA and protein bursts were observed in the past. In order to simulate gene network dynamics with noise effects, a Langevin's equation formulism is developed that is capable to account for the effects of bursts.

This Langevin equation approach is further used in the development of model organism *C. elegans*. In this work, we study the noise propagation in a regulatory network of *C. elegans*, that regulates the distal tip cell (DTC) migration. It is a genetic network composed of multiple feedforward pathways with the capability of tight timing control. Feedforward loops are known to have the potential to filter the noise, but such noise-filtering is asymmetric, i.e. it works at either the "on" or the "off" states in the source. With multiple, interlinked feed forward loops, we show that the propagated noises are largely filtered regardless of the states in the source. Positive feedback loops are also helpful in maintaining the desired activity of the target gene. I'll also discuss our recent finding in modeling the dynamics of circadian clock for plants and implication from stochastic simulations.

White Noise Functional Analysis for Stochastic Biological Phenomena with Memory

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Biological experiments often generate a huge number of empirical data points with fluctuating values which may or may not be correlated. These data points could exhibit stochastic fluctuations which allow parametrization in terms of a probabilistic white noise variable $\omega(t)$ [1]. For instance, we can express a fluctuating observable in a biological system as,

$$x(L) = x_0 + g(L) \int_0^L f(L-s)\, h(s)\, \omega(s) ds \ , \qquad (1)$$

where x_0 is an initial value, $f(L-s)$ serves as a memory kernel, $h(s)$ depends on parameter s ($0 \leq s \leq L$) which could represent length or time depending on the system under investigation, and $g(L)$ modulates fluctuation. The probability density function (PDF) corresponding to the process described by Eq. (1), can be expressed as Feynman's sum-over-all histories that can be evaluated analytically using white noise calculus [1]. For various types of memory behaviour, the PDF for Eq. (1) is obtained in closed form given by [2],

$$P(x, L; x_0, 0) = [2\pi(MSD)]^{-1/2} exp\left\{\frac{-(x-x_0)}{2(MSD)}\right\} , \qquad (2)$$

where the stochastic variable x represents fluctuating values of data points, and MSD is the parameter s-dependent mean square deviation. The PDF, Eq. (2), satisfies a modified diffusion equation,

$$\frac{\partial P(x,s;x_0,0)}{\partial s} = \frac{1}{2}\left(\frac{\partial(\mathrm{MSD})}{\partial s}\right)\frac{\partial^2 P(x,s;x_0,0)}{\partial x^2} \ . \qquad (3)$$

This mathematical framework allows us to predict probable values of subsequent data points not yet measured, or to gain insight on complex information contained in big biological datasets.
As specific applications of this approach, we investigate two examples for big data in biological systems where fluctuating data points exhibit an underlying mathematical structure: (a) DNA sequences of four bacteria species [3,4], and (b) values of the diffusion coefficient for proteins of varying lengths [5,6].

REFERENCES:

1. T. Hida, H. H. Kuo, J. Potthoff, and L. Streit, *White Noise. An Infinite Dimensional Calculus* (Kluwer, Dordrecht, 1993).
2. C. C. Bernido and M. V. Carpio-Bernido, *Methods and Applications of White Noise Analysis in Interdisciplinary Sciences*. (World Scientific, Singapore, 2014).
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4. R. Renante, C. C. Bernido, and M. V. Carpio-Bernido, "Nucleotide Occurrences along Genomes Exhibit an Exponentially Modified Brownian Motion with Memory," (*submitted for publication*).
5. M. T. Tyn and T. W. Gusek, "Prediction of Diffusion Coefficients of Proteins", *Biotechnol. Bioeng*. **35** (1990) 327-338.
6. W. Barredo, C. C. Bernido, M. V. Carpio-Bernido, and J. B. Bornales, "Modelling non Markovian fluctuations in intracellular biomolecular transport," *Math. Biosci.* 297 (2018) 27-31.

Eco-evolutionary game dynamics: from cells to societies

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Evolutionary game theory has been applied to a variety of fields ranging from the origins of life to the evolution of language. Biologically, the theory might sometimes sound extremely simplistic. Simplicity is however precisely the power of abstraction that evolutionary games offer us to understand the immense complexity of biology. Keeping games as simple as possible we have extended it to include multiple interactions. This simple extension allows us to include some of the overlooked complexities in nature concerning the number of interacting partners. After presenting some general results of the extension, we will discuss the applications of our theory ranging from cell dynamics to belief systems. How, relatively simple games can address the questions of how complex communities can survive in equilibrium or how a belief system can evolve even when there exists no selection pressure on the belief itself. Evolution, however, requires an ecological context. Including ecological dynamics, both biotic (population dynamics) and abiotic can affect the resulting eco-evolutionary trajectory. In closing, we will report on the findings in this domain and close the discussion with our efforts in understanding the feedback between evolutionary games and ecological dynamics.

WORKSHOPS

Project 1: From pollinators to cuisine: a network analysis

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In this workshop, we will learn how to use multipartite networks in visualizing and analyzing the relationships between pollinator and plants (e.g., crops), and between plants and ingredients of Filipino cuisines. We will study the graph-theoretic properties of the derived tripartite network, and investigate how this network will change if there are disturbances in the pollination services. In addition to the mathematical knowledge that they will gain from this exercise, the students are also expected to appreciate the value of pollinators, especially in relation to the food that Filipinos usually love to consume.

Project 2: Modelling noise-induced temporal dynamics with stochastic ordinary differential equations (SDEs)

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This workshop will introduce noise-induced temporal patterns, such as noisy cycles that are observed in nature, and will present how these patterns can be generated using stochastic differential equations (SDEs). Participants will learn basic SDE model formulation of biological systems using Linda Allen's approach, Master-Equation-based approach, and Greenwood-Gordillo-Kurtz approach. Participants will also learn about deriving the theoretical power spectral density (PSD), which is a useful measure for characterizing the simulated time-series from the formulated SDEs. The theoretical PSD will be compared to the numerical PSD from MATLAB toolbox. Participants will work on a given system where they are expected to formulate SDEs using the introduced approaches and investigate their differences using the simulated sample paths as well as their associated theoretical PSD.

Project 3: Numerical Continuation and Bifurcation Analysis of Time Delay Systems

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The goal of this workshop is to introduce participants to the use of numerical continuation and numerical bifurcation analysis in time delay systems [1]. An introduction to delay differential equations (DDEs) with emphasis to applications in the life sciences will be given first to acquaint students and researchers to the basic theory of DDEs and the areas where time delays occur [2]. An example in ecology will then be examined in detail to illustrate both theoretical and numerical approaches. For the mini-project, participants will apply what they learn on a model of the cardiovascular system [3]. The author of [3] will give a plenary talk during the IWOMB 2019, so students have the unique opportunity to discuss both modelling and physiological aspects as well.

References:

[1] http://ddebiftool.sourceforge.net/
[2] Smith, Hal L. An introduction to delay differential equations with applications to the life sciences. New York: Springer, 2011.
[3] Ottesen, Johnny T. "Modelling of the baroreflex-feedback mechanism with time-delay." Journal of Mathematical Biology 36(1), 41-63 (1997).

Project 4: Chemical Reaction Network Theory (CRNT) Tools and Applications

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In this workshop, we will learn how to apply CRNT concepts in analyzing biochemical models. Fundamentals of CRNT will be discussed and available tools will be used to investigate CRNs. We will study some algorithms to represent a Biochemical Systems Theory (BST) model (in either GMA or S-system form) as a chemical reaction network (CRN) with power law kinetics. With the help of some CRNT software tools, the students will learn to analyze this BST models using the CRN representations.

Project 5: Optimal strategies for mitigating infectious diseases

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Infectious diseases pose major threats to human health and cause substantial economic burden. In this workshop, strategies to control the spread of infectious diseases will be explored in the framework of optimal control theory. In particular, intervention measures for tuberculosis and influenza transmission dynamics will be investigated. Participants of this mini-project will learn how to formulate and solve numerically optimal control problems with biological applications.

Project 6: Simulation of micro-scaled elastic swimmer using phase-field method

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In this workshop, we will study the phase-field method and its numerical simulations of a micro-scaled elastic swimmer (e.g. jellyfish). The phase-field method can be applied to model a variety of phenomena including elastic bio-membrane. Participants will learn the governing equation of the phase-field method briefly, consider the simple model of a swimmer as an example of the method coupling with a fluid equation, and finally perform some simulations based on MATLAB or Octave code.

POSTER PRESENTATIONS

Coupled within- to between-host dynamics for a viral infectious disease

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The complex processes governing an infectious disease remain an incomplete but significant area in systems medicine. Problems on the emerging dynamics at the interface of viral replication and transmission motivate the analysis of multi-scale models, especially from a mathematical standpoint. A coupled system comprising ordinary differential equations links two scales corresponding to the viral replication and transmission processes. Here, the coupling function describes disease-induced transmission: we assume that the transmission rate increases with the viral load. Bifurcation analysis captures the dynamical relationship between the two scales by evaluating the predicted epidemic size as a function of viral fitness. The results of our analysis can drive detailed studies regarding the effects of infection on epidemic progression. The poster highlights joint work with Van Kinh Nguyen and Esteban A. Hernandez-Vargas (Frankfurt Institute for Advanced Studies, Germany).

A combinatorial problem on the periodic Beverton-Holt model†

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Suppose we have a p-periodic discrete model of the form $x_{n+1} = f_n(x_n)$ with a global attractor. How does a permutation of the maps affect the global attractor? In this research, we focus on the Beverton-Holt model with p-periodic harvesting. We fix a set of harvesting quotas and give ourselves the liberty to permute them. The permutation does not change the total harvesting yield, but the population geometric-mean may fluctuate. We investigate this notion and characterize the cases in which a permutation of the harvesting quotas has no effect or tangible effect on the population geometric-mean. It has been found that as long as persistence is assured, all permutations within the dihedral group give same population geometric-mean. Other permutations may change the population geometric mean. A characterization theorem has been obtained based on block reflections in the harvesting quotas.

† Collaborative work: Asma AlGhassani, Sultan Qaboos University

Mechanistic model of macroparasite accumulation in hosts leading to aggregation

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Parasite aggregation is considered one of the "laws" in parasite ecology because it is a recurring pattern in macroparasite infections. Most models of host-parasite systems assume a phenomenological framework using the negative binomial distribution, but there is lack of mechanistic models to illustrate the aggregation of macroparasites in hosts. Here we formulate a tractable mechanistic model of host-parasite interaction considering parasite accumulation in hosts, which still arrives at an aggregated pattern without initially assuming a negative binomial distribution. Our results show that with a homogeneous pattern of parasite acquisition, parasite aggregation is still possible as a consequence of accumulation. We also discuss how our model can be used in modeling empirical data of microparasite distribution. Model analysis explains the conditions that give rise to a negative binomial distributed pattern and strengthens the claim that aggregation can indeed occur in a wide-range of scenarios in nature.

Spatiotemporal Modelling of Parasite Aggregation in Endorheic Lake Hosts

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Fishes are often hosts to various macroparasites, such as worms. In parasite ecology, it is commonly observed that the distribution of parasites among its host is aggregated. One popular method for modelling the aggregation of parasites is the use of negative binomial distribution in temporal host-parasite interaction. Analysis of this distribution helps in determining the individual host fitness, parasite transmission potential, reproduction capability of parasites, and stability of host-population dynamics. The goal of the study is to develop and analyze a spatiotemporal model to explain the possible mechanisms of parasite aggregation in endorheic lake hosts. Factors such as treatment, clustering of source of infection, reproduction of hosts and parasites, and death of hosts will be incorporated and analyzed through simulations.

Path integral formulation for stochastic resetting in an infinite potential barrier

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Resetting processes are often encountered in the field of biology, including RNA backtracking and foraging dynamics. In this study, we present a path integral approach to finding an analytic expression for the distribution function of the position of a Brownian particle diffusing in an infinite potential subject to a space-dependent resetting, analogous to a search process in a semi-infinitely bounded environment. We also provide an expression for the probability distribution of the first reset time of the particle. The obtained distribution function for the position is compared with the steady-state distribution of a free particle subject to a resetting rate. Finally, the effect of varying the resetting rate and diffusion coefficient is examined.

Highly pathogenic avian influenza epidemic in the Republic of Korea 2016-2017

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Highly pathogenic avian influenza (HPAI) subtype H5N6 caused outbreak in the Republic of Korea since November 16, 2016. More than 40 million of poultry were removed and that caused serious economic loss. In this study, we focused on two neighborhood counties, Eumsung-gun and Jincheon-gun, which had high poultry farm density and significantly high outbreak case number in 2016. There are 16 towns in that counties, and each town have different characteristics such as area or number of farms, or connectivity to other towns. To analyse spatial heterogeneity of towns and clinical heterogeneity depend on different species, we devised spatial-temporal SIR-type model for the HPAI outbreak of chicken and duck farms by using transmission kernel. As result, we found that duck farm acts key role in epidemic. Finally, we presented results of case studies which contains various controls such as pre-emptive (PE) culling or movement ban.

Dog Population Control as Key Intervention Strategy for Eradicating Rabies in Davao City, Philippines: A Policy Implication via Mechanistic and Phenomenological Models

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The call to eradicate rabies in the Philippines by 2020 led Davao City public health officials to intensify rabies control interventions. Despite the efforts done to mitigate the disease, rabies cases in dogs remain endemic. To identify the factors that significantly contributes to transmission dynamics of rabies virus between dog populations in the city, mechanistic and phenomenological modelling approaches were explored. The formulated mechanistic model follows a Susceptible-Exposed-Infected-Recovered (SEIR) compartmental framework. On the other hand, the Generalized Linear Autoregressive Moving Average (GLARMA) framework was considered to formulate a phenomenological model that empirically investigates the impacts of government-initiated interventions, weather drivers, dog characteristics, and previous monthly reported rabies cases on the monthly reported rabies cases in Davao City. The sensitivity analysis done on the mechanistic model, via the methods of Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC),

revealed that the basic reproduction number and the long-term rabies incidence are both affected positively by the annual crop of dogs and the rabies transmission rate, but negatively affected by the vaccination rate. Since high transmission occurs when there is a high number of rabid dogs, it is tantamount that lessening the number of rabid dogs, and the dog population in general, will lower the transmission rate. Empirically, dog impounding is the only government-initiated intervention that significantly decreased the monthly reported rabid dogs together with other significant weather driver and dog characteristics. Specifically, the monthly reported rabid dogs decreased by one for every 1000 impounded dogs. These parallel results recommend that the local government unit should pay attention to dog population control interventions (e.g. impounding) equally with dog mass vaccination.

Which control strategies should have been implemented for the 2017 H5N6 outbreak in the Philippines?

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In August 2017, there were outbreak reports of Highly Pathogenic Avian Influenza A (HPAI) H5N6 in the Philippines (particularly in Pampanga and Nueva Ecija). This incidence resulted to massive culling of domestic birds to control the spread of the infection. However, this control method poses a negative impact on the poultry industry. In this study, we first constructed a mathematical model for the bilinear and half-saturated incidence to compare their corresponding effect on transmission dynamics of H5N6. The simulations of half-saturated incidence model were similar to what occurred during the H5N6 outbreak (2017) in the Philippines. Instead of culling the birds, we proposed alternative control strategies such as non-medicinal (isolation) and medicinal (vaccination) ways to prevent, reduce, and control the rate of the H5N6 virus transmission in birds. For the 2017 H5N6 outbreak that occurred in the Philippines, we have shown through mathematical modeling that the poultry isolation strategy is more effective than that of vaccination strategy.

Estimating seasonal variation in Australian pertussis notifications

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In this study, we tried to understand if pertussis notifications exhibit seasonal fluctuations in Australia. We analysed the seasonality of pertussis notifications using monthly data from January 1991–December 2016, stratified by jurisdictions and age groups. Data were made available for all Australian states and territories other than the Australian Capital Territory (ACT). We formulated a generalised additive model with cosinor components to estimate the amplitude and peak timing of pertussis notifications. We found evidence that suggests peaks generally occurred from November–January, and their characteristics varied across age groups. In particular, we estimated that peaks occurred 1–2 months later for children less than 5 years. Our findings provide support to the suggestion that seasonal forcing may be useful to consider in future population transmission models of pertussis.

Effects of isolation, vaccination, and periodic culling against the outbreak of A(H5N6) in the Philippines

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Highly Pathogenic Avian Influenza (HPAI) A(H5N6) is a mutated virus of A(H5N1) and a new emerging infection which recently caused an outbreak in the Philippines. This A(H5N6) outbreak resulted to depopulation of 667,184 domestic birds. In this study, we incorporate half-saturated incidence (HSI) in our models and investigate three intervention strategies against A(H5N6). For the application of isolation and treatment of infected birds in our model, we emphasize that not all birds released from confinement have fully-recovered. In administering preventive vaccine to poultry, we add a waning rate for vaccine to recognize that vaccines effectiveness weakens over time. While for the modified culling of infected and susceptible birds that are high-risk to infection, we employ HSI into the culling rate. After computing for the basic reproduction number R_0, we determine the direction of bifurcation when $R_0 < 1$. All the four mathematical models presented in this paper exhibit forward bifurcation. We simulate the models and compare the consequences of utilizing different intervention strategies in the poultry population. Despite the challenges of applying each control strategy, we have shown that culling infected birds at least once a week (1/7) per day) together with culling of susceptible birds at most once every 60 days (1/60 per day) outperforms isolation and vaccination strategies in controlling an outbreak of A(H5N6).

Glycosylation-associated gene co-expression network approach for lung adenocarcinoma biomarker discovery

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Although genetic modifications have been established as a key driver on the development of cancer, post-translational modifications such as glycosylation have gained recognition in cancer research these past decades. However, the connection between these two important modifications has not yet been considered in the research community. Here we formulated a computational network-based method that links glycans to lung adenocarcinoma gene biomarkers. Using this method, MUC13 and RPN2 genes were discovered as potential novel biomarkers needed for the early detection of the disease and possible target for drug formulation. This methodology can be a template for easier and low-cost discovery of new biomarkers for any other genetic diseases.

Delay-induced stability switches in an SIRS epidemic model with saturated incidence rate and temporary immunity

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This work considers a time-delayed SIRS epidemic model with temporary immunity and nonlinear incidence rate, where the susceptible host population satisfies the logistic equation and the incidence rate is of saturated form with the susceptible. The time delay represents a period of temporary immunity where disease-recovered individuals return to the susceptible class after a fixed period of time. By analyzing the associated characteristic equation with delay-dependent coefficients and regarding the time lag as the bifurcation parameter, the local stability of the endemic equilibrium is investigated and sufficient conditions for the occurrence of stability switches via Hopf bifurcations are obtained. It is shown that the delay parameter can induce a finite number of stability switches before completely destabilizing the system. Numerical simulations are carried out to illustrate theoretical results.

On a multi-strain age-structured dengue transmission model

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We propose a mathematical model that represent the dynamics of the transmission of dengue with its four strains. Considering that dengvaxia vaccine was intended to be given only to people ages 9 to 45 years old, we divide the human population into two groups: from 9-45 years old and the rest of the population. The model is based on the Susceptible-Infected-Removed (SIR) model, but it focuses only on the number of strains a person had been infected to and not on the specific kind of strains the person was infected to, and is thus more suitable to simpler data.

Mathematical Model of the Dynamics of Lymphatic Filariasis in the Philippines

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Lymphatic filariasis is a globally neglected tropical disease which can lead to chronic morbidity in the form of elephantiasis and hydrocele when left untreated. Despite the disease elimination efforts spearheaded by the Philippine Department of Health since 2001, millions of Filipinos are still at risk of being infected. Here, we present a mathematical model describing the spread and treatment of lymphatic filariasis using mass drug administration in the Philippines. In our model analysis, we obtain a disease-free equilibrium E_0 and an endemic equilibrium E_e. We study the stability of these steady states using the basic reproduction number, $\mathcal{R}_0$, which we derive using the next generation matrix.

Mathematical model of transmission dynamics for 2015 H5N2 avian influenza among domestic geese in Yunlin, Taiwan

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Avian influenza (AI), more commonly known as "bird flu", is a viral disease that commonly infects poultry and wild birds. Recent studies have shown that the virus is capable of spreading to individuals either through direct transmission (contact with an infected individual) or through indirect transmission. The possibility of indirect transmission is due to studies that have shown the capability of viral particles to survive in the environment outside of a host for a certain period of time (Breban et al, 2009; Roche et al, 2009; Brown et al, 2009). During an AI outbreak, most countries employ culling, or the killing and disposal of infected animals, as the primary response.

In this work, we have adapted a model for avian influenza among domestic farm birds that incorporates two transmission routes (Wang et al, 2012) and two culling mechanisms - selective culling and priority culling (Gulbudak & Martcheva, 2013). We look at its equilibria and derive the basic reproductive number. In addition, we perform parameter estimation for some key parameters on data acquired from the 2015 Highly Pathogenic AI H5N2 outbreak among domestic geese in Yunlin County, Taiwan.

Complex balanced equilibria of weakly reversible power law kinetic systems

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PL-RDK system is a class of power law kinetic systems whose kinetic order vectors (which we call "interactions") are reactant-determined (i.e. reactions with the same reactant complex have identical vectors). Our main result is the existence of complex balanced equilibria for zero kinetic reactant deficiency weakly reversible PL-RDK systems for any rate constant.

Sustainability of Consumption Strategies in Resource Dynamics Models with Allee and Crowding Effects

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Mathematical models of production and consumption of resources are useful in devising policies for sustainable management. We study minimal ordinary differential equation models which are compartmentalized to two functions: production and consumption. Classical models include a logistic production function with constant or with non-constant linear consumption functions. Here, we propose production functions considering Allee and crowding effects and nonlinear consumption functions that are hyperbolic and sigmoidal. We analyze the models to determine the conditions for sustainable consumption. We further analyze these models by incorporating delay and stochasticity. Our results can be used as an input in formulating strategies to properly manage renewable resources.

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