Special Session 14: Mathematical Models in Biology and Medicine

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This special session emphasizes the dual roles of both theory and applications of dynamical systems and differential equations to mathematical models in biology and medicine. Recent advances within mathematical ecology (including competition between species, predator-prey and cooperative systems, and evolutionary theory) will be presented alongside those for mathematical models in various fields of medicine (including immunology, epidemiology, oncology, endocrinology, and neurobiology).

The dual oscillator model for pancreatic islets

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Insulin is a key hormone for glucose uptake and utilization in the body. It is known to be pulsatile, with a period of about 5 min, and this pulsatility is altered in type 2 diabetics and their nearest relatives. We describe a mathematical model that has been developed over the past decade for the electrical activity, calcium handling, and metabolism of insulin-secreting beta-cells within pancreatic islets. This Dual Oscillator Model consists of an oscillator involving ionic currents and calcium feedback, and a separate but coupled oscillator driven by oscillations in glycolysis. The model has been used successfully to make predictions that have been tested in the laboratory, as we discuss in this presentation.

Slow passage through a Hopf bifurcation in spatially extended excitable systems: some examples from neuroscience

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Hopf bifurcation is a common mechanism by which a dynamical system featuring a constant parameter $p$ exhibits steady-state seeking behavior if $p$ is less than some critical value $p_{\text{Hopf}}$, and sustained oscillations if $p > p_{\text{Hopf}}$. It is known that when $p$ is not constant in time, but rather, slowly ramped up through $p_{\text{Hopf}}$, sustained oscillations do not ensue as soon as $p$ exceeds $p_{\text{Hopf}}$. How delayed the onset of instability is depends on the exact time course of the ramp as well as its initial value $p_0$, and can be obtained from the WKB method of perturbation theory. In the current work, we have investigated the response of a spatially extended system to a slow parameter ramp. The particular system studied is one from neuroscience: a reaction-diffusion model of a dendrite studded with excitable spines, into one end of which we inject current $I$; here, $I$ is the bifurcation parameter. It is found that the WKB method also provides the location along the cable at which instability first shows itself. By manipulating the current ramp, we can choose the location along the cable at which the approach to sustained oscillations is first apparent.

A mathematical model of Imatinib and Interferon-alpha combined treatment of chronic myeloid leukemia

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We propose and analyze a mathematical model for the treatment of chronic myelogenous (or myeloid) leukemia (CML), a cancer of the blood. We introduce combined treatment of CML based on Imatinib therapy and Immunotherapy. Imatinib therapy is a molecular targeted therapy that inhibits the cell containing the oncogenic protein BCR-ABL, involved in the chronic CML pathogenesis. Immunotherapy based on interferon alfa-2a (IFN) affects on the cancer cells mortality and leads to improvement outcome of the combined therapy. We model the interaction between CML cancer cells in the body and effector cells of the immune system, using a system of differential equations. The proposed model belongs to a special class of nonlinear nonautonomous systems of ordinary differential equations (ODEs) with time-varying delays in the treatment. For this system the following results were obtained: existence of a unique global positive solution, existence of a unique nontrivial equilibrium, explicit local and global stability conditions for the nontrivial equilibrium.

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Interpretation of the IVGTT by means of a distributed-controller model of the endocrine pancreas

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Since the publication of the original model by Grodsky, a possible paradigm for the function of the endocrine pancreas has been that of a population of independent insulin-secreting controllers, coupled by the circulating levels of the controlled substrate, glucose. In 2009, an explicit non-reductionist stochastic-differential model of the 1 million independent human pancreatic islets was published, showing how the glucose threshold and recovery time distributions over the population of controllers could allow the model to simultaneously explain observed low- and high-frequency oscillations in the circulating levels of insulin. The present work shows how the model is able to replicate the observed morphology of glycemia and insulinemia time-courses after a standard perturbation experiment (Intra Venous Glucose Tolerance Test, IVGTT). The analysis of the model features necessary to faithfully reproduce observations links the present high-detail formulation with previous, much simpler delay-differential models for the same perturbation experiment, which were shown to achieve excellent predictive power in clinical research. Conclusions are drawn as to the likely essential components of the physiologic system under investigation.

Mathematical models of the role of immune exhaustion in Hepatitis B and delta coinfection

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Hepatitis Delta Virus (HDV) is a dependent satellite virus of the more common Hepatitis B Virus. HDV encodes only one protein of its own, relying on HBV to supply the additional proteins needed for its replication cycle. Although it HDV is noncytotoxic and present few targets for immune reaction, the symptoms of patients with HBV-HDV coinfection are much worse than those infected with HBV alone. The cause of this negative outcome is not clear. This work presents o.d.e. models for the interaction of HBV, HDV and the specific immune responses to each, and analyzes the implication of these models for understanding patient outcomes. In particular, the role of T cell exhaustion in chronic HBV is explored, and how superinfection with HDV may actually strengthen the HBV specific immune response, indirectly leading to the observed symptoms. Additionally, the role of nonspecific immune responses is explored.

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In this talk, we study a class of parabolic systems which can be used as a dispersion model of biological populations. Under certain parametric conditions, we apply the center manifold method and Bendixon’s test to obtain the local behavior around a non-hyperbolic point of codimension one in the phase plane. Then we analyze the associated determining system through the linearized symmetry condition. Classical and non-classical symmetries are classified. Nontrivial infinitesimal generators are found, and exact solutions are established accordingly.

Effects of surgery and chemotherapy on growth of metastases in prostate cancer: evidence from the natural history of the disease reconstructed through mathematical modeling

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We present a comprehensive model of cancer progression accounting for primary tumor growth, shedding of metastases, their dormancy and growth at secondary sites. Model parameters were estimated from the volumes of the primary tumor and bone metastases collected from 12 prostate cancer patients. This enabled estimation of various unobservable characteristics of the individual natural history of cancer and the effects of treatment. We found that for all patients: (1) inception of the first metastasis occurred when the primary tumor was undetectable; (2) inception of all or most of the metastases occurred before the start of treatment; (3) the rate of metastasis shedding was essentially constant in time regardless of the size of the primary tumor and so it was only marginally affected by treatment; and, most importantly, (4) surgery and chemotherapy brought about a dramatic increase in the rate of growth of metastases. These conclusions agree with the findings of numerous clinical studies, animal experiments and epidemiological analyses conducted since the early
1900s. Our analysis supports the notion of metastasis dormancy and the existence of prostate cancer stem cells. This is a joint work with Dr. Marco Zaider from the Memorial Sloan-Kettering Cancer Center.

Mathematical models of immunological tolerance and immune activation following perinatal infection with hepatitis B virus

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Stanca Ciupu
We develop mathematical models for the role of hepatitis B e-antigen in creating immunological tolerance during hepatitis B virus infection and propose mechanisms for hepatitis B e-antigen clearance, subsequent emergence of a potent cellular immune response, and the effect of these on liver damage. We investigate the dynamics of virus-immune cells interactions, and derive parameter regimes that allow for viral persistence. We modify the model to account for mechanisms responsible for hepatitis B e-antigen loss, such as seroconversion and virus mutations that lead to emergence of potent cellular immune response to the mutant virus. Our models demonstrate that either seroconversion or mutations can induce immune activation and that instantaneous loss of e-antigen by either mechanism is associated with least liver damage and is therefore more beneficial for disease outcomes.

A refuge-mediated apparent competition model

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Lih-ing Wu Roeger
We analyze a competition model of two plant species for a single-limited resource while the competition is apparent: an indirect interaction where the invading plants provide a refuge for a shared consumer, subsequently increasing the consumer pressure on the resident plant species. When there is no refuge effect, the resident species is a superior species. As the refuge effect increases, the coexistence state appears as a saddle point with a two-dimensional stable manifold while the two extinction equilibria are locally stable. Thus the refuge-mediated apparent competition creates an Allee effect for both the invading and the resident species. A Lyapunov function is found to show the global stability of the equilibrium in which only the resident species survives.

Modeling the distribution of insulin in pancreas

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Jiaxu Li, James Johnson
Maintenance of adequate pancreatic β-cell mass, via suppression of programmed cell death and/or sustained proliferation is critical for the prevention or delay of diabetes mellitus. In this talk we report a novel mathematical model to investigate the distribution and concentration of insulin within pancreas using existing physiological data and islet imaging data. Our studies reveal that insulin concentration along pancreas, related to glucose level, increases nearly linearly in the fashion of increasing quicker in tail area but slower in head area. We also showed that the factor of small diffusion with blood is negligible since the convection of blood flux dominates. To the best of our knowledge, our model is the first attempt to estimate the glucose and insulin distributions in pancreas. Our model is simple, robust and thus can be easily adopted to study more sophisticated cases.

Multiple attractors in intraguild predation models with generalist/specialist predator

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Lauren Wedekin
Intraguild predation (IGP) is a combination of competition and predation which is the most basic system in food webs that contains three species where two species that are involved in a predator/prey relationship are also competing for a shared resource or prey. We formulate two intraguild predation (IGP: resource, IG prey and IG predator) models: one has a predator who is a generalist while the other one is a specialist. Both models have Holling-Type I functional response between resource-IG prey, resource-IG predator and Holling-Type III functional response between IG prey and IG predator. We prove sufficient conditions of the persistence and extinction of all possible scenarios for these two models, which give us a complete picture on their global dynamics. These analytical results indicate that IGP model with generalist predator has “top down” regulation while IGP model with specialist predator has “bottom up” regulation. In addition, we show that both IGP models can have multiple interior equilibria. Our analysis and numerical simulations suggest that 1. Both IGP models can have multiple attractors with complicated dynamical pattern; 2. Only IGP model with specialist predator can have both boundary attractor and interior attractor: i.e., whether the system has the extinction of one species or the...
coexistence of three species dependent on initial conditions; 3. IGP model with generalist predator is prone to have stable dynamics.

Age structured population model with state dependent time delay

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In this talk we consider an age structured population model in which the age to maturity at a given time depends on whether or not the food consumed by the immature population within that time span reaches a prescribed threshold value. This introduces a state dependent delay into the model. In contrast with other works on this problem, we consider it from the point of view of a hyperbolic partial differential equation with a state dependent time delay.

Designing optimal combined chemotherapy and immunotherapy protocols for a model of tumor immune interactions under drug pharmacokinetics

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In the design of protocols for cancer treatment various questions need to be addressed related to dosage, frequency and in the case of more than one drug also their sequencing. In answering, from a more theoretical point of view tools of optimal control can be of use. In this talk we present such an analysis of a mathematical model for cancer combination therapy as an optimal control problem. Since the treatment involves combination of classical chemotherapy with an immune boost, the adequate model for consideration is the one that describes dynamics of the interactions between the tumor cells and the immune system. Within this framework we introduce into the dynamics the controls representing the action of each therapeutic agent. There exist various approaches for choosing the objective, but based on the dynamical behavior of the uncontrolled and fully controlled system, we choose the one to minimize the size of the tumor at the end of treatment while at the same time maximizing the immune-competent cell-densities and keeping side effects of both treatments low. This leads to a multi-input optimal control problem with many challenging features. The complexity of the models becomes even higher if we also take into account the pharmacokinetics of both therapeutic agents. Analytical and numerical results about the structures of optimal controls will be presented. Particularly the effect of the inclusion of pharmacokinetics of both drugs on the qualitative structure of solutions will be discussed. Overall the presented research is expected to provide insights into how to optimally design protocols for the combination of these two drugs in the sense of the scheduling the dosages and sequencing.

Global bifurcation branch of a spatially heterogeneous cooperative system with cross-diffusion

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In this paper, we will consider the strongly coupled cooperative system in a spatially heterogeneous environment with Neumann boundary condition. We show that the positive solution curve to form an unbounded fish-hook shaped continuum. Our results deduce that the spatial heterogeneity of environments can produce multiple coexistence states.

Modeling impulsive injections of insulin analogues: towards artificial pancreas

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We propose two novel mathematical models with impulsive injection of insulin or its analogues for type 1 and type 2 diabetes mellitus. One model incorporates with periodic impulsive injection of insulin. We analytically showed the existence and uniqueness of a positive globally asymptotically stable periodic solution for type 1 diabetes, which implies that the perturbation due to insulin injection will not disturb the homeostasis of plasma glucose concentration. We also showed that the system is uniformly permanent for type 2 diabetes, that is, the glucose concentration level is uniformly bounded above and below. The other model has the feature that determines the insulin injection by closely monitoring the glucose level when the glucose level reaches or passes a predefined but adjustable threshold value. We analytically proved the existence and stability of the order one periodic solution, which ensures that the perturbation by the injection in such an automated way can make the blood glucose concentration under control. Our numerical analyses confirm and further enhance the usefulness and robustness of our models. The first model has implications in clinic that the glucose level of a diabetic can be controlled within...
desired level by adjusting the values of two model parameters, injection period and injection dose. The second model is probably the first attempt to conquer some critical issues in the design of artificial pancreas with closed-loop approach. For both cases, our numerical analysis reveal that smaller but shorter insulin delivery therapy is more efficient and effective. This can be significant in design and development of insulin pump and artificial pancreas.

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**Traveling wave solutions in delayed cooperative systems**

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**Liang Zhang**

We discuss the existence of traveling wave solutions for delayed cooperative recursions that are allowed to have more than two equilibria. We define an important extended real number that is used to determine the speed of traveling wave solutions. The results can be applied to a large class of delayed cooperative reaction-diffusion models. We show that for a delayed Lotka-Volterra reaction-diffusion competition model, there exists a finite positive number that can be characterized as the slowest speed of traveling wave solutions connecting two mono-culture equilibria or connecting a mono-culture with the coexistence equilibrium.

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**The relative biologic effectiveness versus linear energy transfer curve as a phenotype**

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The magnitude of biological response varies with different radiation types. Using Linear Energy Transfer (LET) to differentiate types of incident radiation beam, the Relative Biologic Effectiveness (RBE) as a function of LET (RBE-LET) was found to have a peak around LET values 100-200 keV/nm. This general feature is believed to be a property of the incident beam. Our systems engineering model, however, suggests that the shape of the RBE-LET curve is a property of the cells. Here, we continue systems engineering analysis to show that the RBE-LET curve is a phenotype. Elementary state-space block diagram of the differential equation model suggests a genetic network and cellular context for this phenotype. Analogy to man-made analog computers suggests cell uses mathematical computations in its decision-making when faced with an external stress. The MRN protein complex, in particular, may perform addition to count the degree of DNA twisting for the homeostatic regulation of DNA supercoiling. The ATM protein may act as a feedback amplifier.

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**Theoretical and numerical analysis of a class of dynamics models describing eutrophication of Lake Guishui**

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**Zhanhui Wang, Wanbiao Ma, Hai Yan**

Firstly, two classes of dynamic models describing the growth of Microcystins (MCs) in lake are proposed. Secondly, locally asymptotic stability (LAS) of the equilibria and Hopf bifurcations of the models are analyzed by using theory of delay differential equations. Thirdly, the models are applied to the experimental data on eutrophication of Lake Guishui in Beijing, and the parameters in the models are determined. The numerical simulations suggest that the trajectories of the model fit the experimental data well.

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**Evolution of uncontrolled proliferation and the angiogenic switch in cancer**

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**Dieter Armbruster**

The major goal of evolutionary oncology is to explain how malignant traits evolve to become cancer “hallmarks.” One such hallmark—the angiogenic switch—is difficult to explain for the same reason altruism is difficult to explain. An angiogenic clone is vulnerable to “cheater” lineages that shunt energy from angiogenesis to proliferation, allowing the cheater to outcompete cooperative phenotypes in the environment built by the cooperators. Here we show that cell- or clone-level selection explain the angiogenic switch, but not because of direct selection on angiogenesis factor secretion. We study a multiscale mathematical model that includes an energy management system in an evolving angiogenic tumor. The energy management model makes the counterintuitive prediction that ATP concentration in resting cells increases with increasing ATP hydrolysis, as seen in other theoretical and empirical studies. As a result, increasing ATP hydrolysis for angiogenesis can increase proliferative potential, which is the trait directly under selection. Intriguingly, this energy dynamic allows an evolutionary stable angiogenesis strategy, but this strategy is an evolutionary repeller, leading to runaway selection for extreme vascular hypo- or hyperplasia. The former case yields a tumor-on-a-tumor, or hypertumor,
as predicted in other studies, and the latter case may explain vascular hyperplasia in certain tumor types.

A PDE model for predator-prey dynamics with a resource subsidy

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Junping Shi

The influence of a resource subsidy on predator-prey interactions is examined using a system of partial differential equations. The model arises from study of a biological system involving arctic foxes (predator), lemmings (prey), and seal carcasses (subsidy). The prey occurs in the interior of the habitat and the subsidy occurs near the edge. Criteria for feasibility and stability of the different equilibrium states are studied. At small subsidy input rates, there is a minimum prey carrying capacity needed to support both predator and prey. At intermediate subsidy input rates, the predator and prey can always coexist. At high subsidy input rates, prey persistence depends on a variety of factors. As the predator movement rate increases, the dynamic stability of the predator-prey-subsidy interactions also increases.

Dynamically consistent discrete-time SI, SIS, and SIR epidemic models

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We construct discrete-time or difference equation SI, SIS, and SIR epidemic models such that they are dynamically consistent with their analog continuous-time models. The discrete-time models are constructed using the nonstandard finite difference discretization (NSFD) methods. All three basic standard incidence SI, SIS, and SIR models without births and deaths, with births and deaths, and with immigrations, are considered. The continuous models possess either the conservation law that the total population \( N \) is a constant or the total population \( N \) satisfies \( N'(t) = \lambda - \mu N \) and so that \( N \) approaches a constant \( \lambda/\mu \). The difference equation systems via NSFD schemes preserve all properties including the positivity of solutions, the conservation law, and the local and some of the global stability of the equilibria. Hence they are said to be dynamically consistent with the continuous models. We show that the a simple criterion for choosing certain NSFD scheme such that the positivity solutions are preserved is usually an indication of an appropriate NSFD scheme for an epidemic model.

Periodic solutions of a predator-prey system with nonmonotonic response function and impulsive harvesting

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Mingzhao Huang, Lansun Chen

In this talk, we propose a predator-prey model with state dependent impulsive harvesting which use a nonmonotonic response function to model the phenomenon of group defense. We mainly discuss the existence, uniqueness and stability of the order \( k \) periodic solution by differential equation geometry theory and the method of successor functions. Moreover, we give the parametric conditions that the system exhibits the phenomenon of homoclinic bifurcation. We also explain the ecological applications of these results at last.

Optimization of P. falciparum gametocyte sex ratios via competitive and non-competitive strategies: the evolutionary implications

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Thomas Yuster, Ha Nguyen, Ryan Warrier

We analyze two distinct fitness optimization strategies for sex ratio determination for P. falciparum with varying fecundity. Initial results indicate that no polymorphic population containing both strategies is stable. The pure strategy that is the final evolutionary state depends heavily on the composition of the initial polymorphic population.

Epidemic model as controlled switched system

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The aim of this work is to study a SIR model controlled by impulsive vaccination and isolation control. The goal is to determine an optimal impulsive controls to minimize the total outbreak size over the course of the epidemic and using necessary condition of optimality, our goal is to draw conclusions about the effect of the shortage of the drug treatment on the management of strategies of control policy. In other words, we are going to answer two questions: What if the treatment runs out during the epidemic? If this happens, could we still control the spread of the disease?
Integro-differential age-structured system for the SAIQR influenza model

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In this work, we present an Integro-Differential System to study the dynamics of an age-structured SAIQR influenza model. The population in consideration is divided into five age-dependent epidemiological classes: \(S(a,t)\), susceptible; \(A(a,t)\), asymptomatic; \(I(a,t)\), infectious; \(Q(a,t)\), isolated (quarantined) and \(R(a,t)\), recovered individuals. It is assumed that \(A(a,t)\)-individuals may be less infectious than those in the \(I(a,t)\)-class. We assume the “proportional mixing” property between age-groups. Existence of equilibria and the basic reproduction number are discussed. Furthermore, a multi age-group model and numerical simulations with influenza parameters are presented.

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Coexistence of the unstirred chemostat model

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In this talk, the coexistence of the unstirred chemostat model is given, and the related result is also surveyed if possible. The main ingredients include global bifurcation theory, fixed point index theory, perturbation method and simulations.

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On latencies in malaria infections and their impact on the disease dynamics

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We modify the classic Ross-Macdonald model for malaria disease dynamics by incorporating latencies for both human beings and female mosquitoes. Two general probability functions \((P_1(t)\) and \(P_2(t)\)) are introduced to reflect the fact that the latencies differ from individuals to individuals. We justify the well-posedness of the new model, identify the basic reproduction number \(R_0\) for the model and analyze the dynamics of the model. When \(R_0 < 1\), \(E_0\) becomes unstable. When \(R_0 > 1\), we consider two specific forms for \(P_1(t)\) and \(P_2(t)\): (i) \(P_1(t)\) and \(P_2(t)\) are both exponential functions; (ii) \(P_1(t)\) and \(P_2(t)\) are both step functions. For (i), the model reduces to an ODE system, and for (ii), the long term disease dynamics are governed by a DDE system. In both cases, we are able to show that when \(R_0 > 1\) then the disease will persist; moreover if there is no recovery \((\gamma_1 = 0)\), then all admissible positive solutions will converge to the unique endemic equilibrium. A significant impact of the latencies is that they reduce the basic reproduction number, regardless of the forms of the distributions.

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Infectious diseases and demographic allel effect

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Avner Friedman

If a healthy stable host population at the disease-free equilibrium is subject to the Allee effect, can a small number of infected individuals with a fatal disease cause the host population to go extinct? That is, does the Allee effect matter at high densities? In this talk, we use an SI epidemic model to answer these questions.

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