RESEARCH STATEMENT

Daniel Wood

My research interest is broadly in mathematical biology, and specifically in epidemic and population modeling alongside the construction and analysis of numerical methods to accurately compute biological models. During my time at the University of Texas at Arlington, I constructed numerical methods which preserve key dynamical properties of the underlying system they simulate and began work on analyzing population models involving HIV. At the Fred Hutchinson Cancer Research Center (FHCRC) I am a part of a multi-disciplinary team working on HIV prevention research. My current interest is the development and analysis of HIV models for evaluation of interventions.

Mathematical Analysis of Dynamical Systems

Within my first research projects on HIV transmission, I explored how different demographic mechanisms influence the outcomes of dynamical systems used to evaluate the effectiveness of HIV prevention interventions [29]. This topic is of importance because many models that have appeared in the scientific literature use specific mechanisms that are not fully justified. For instance, modelers use either constant recruitment, assuming that a fixed number of individuals are joining the population per unit time [28, 20, 19, 16, 11, 2] or proportional recruitment, in which the number of "newcomers" is proportional to the population size [26, 15, 3, 5, 13]. In addition to these two mechanisms, we have explored logistic recruitment, assuming that the number of people who join the population increases with population size but saturates at specific level driven by resource limitations. Our bifurcation analysis reveals differing qualitative behavior based on the recruitment mechanisms. Constant recruitment allows for only a disease free and an endemic equilibrium, whereas both proportional and logistic recruitment support four long-term outcomes including a disease free equilibrium, an endemic equilibrium, an equilibrium corresponding to population extinction under the pressure of HIV and an equilibrium corresponding to population extinction in absence of HIV. Somewhat unexpected, the model equipped with constant and the logistic recruitment share an endemic fractional equilibrium (asymptotic HIV prevalence) which is different from the proportional model. Furthermore, given that the endemic equilibrium is reached, the recruitment rate has no influence on the asymptotic HIV prevalence under the constant and the logistic mechanisms while being of importance if the proportional mechanism is employed. Simulations of pre-exposure prophylaxis (PrEP) interventions show that the recruitment mechanism has no substantial impact on the effectiveness indicators over the initial period, but significant differences are observed over fifty years and dramatically by two hundred years.

Modeling the Impact of Biomedical Interventions

Estimating efficacy observed in clinical trials. I have been involved in two projects estimating the true efficacy of biomedical prevention interventions in randomized controlled trials (RCTs) which can be difficult due to confounding factors such as varying sexual behavior and non-adherence to medication among the participants. Clinical trials can be lengthy, costly, and can raise ethical concerns. Mathematical modeling can help alleviate some of the risks involved and give insight into the process before actual studies are performed. In my role at the FHCRC, I have helped construct various models to test strategies to better predict the true efficacy of biomedical interventions.

In the first project we considered the effect of enrolling female sex workers (FSW) in a RCT on the trial duration and observed efficacy via a stochastic individual-based model [25]. Previous modeling analyses suggest that most women enrolled in HIV prevention trials in places with high HIV prevelance are not exposed to HIV since their partners are uninfected [7], which leads to heterogeneity of HIV risk among the participants and drives efficacy estimates downwards. Intentionally enrolling female sex workers may reduce this heterogeneity of HIV risk and give better efficacy estimates. In the model, we stratified participants by sexual behavior and partnership status, and used data from the literature to inform parameters relating to the infectivity of HIV and parameters governing sexual behavior of

participants. We calibrated the model to best fit the reported HIV incidence close to the desired HIV incidence among general population and FSW in Sub-Saharan epidemic settings. Preliminary results show that enrolling commercial sex workers will give better efficacy estimates and reduce trial durations (see Figure 1).

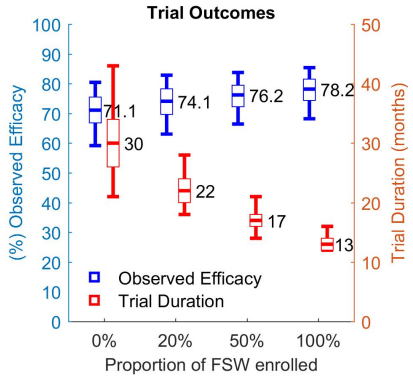


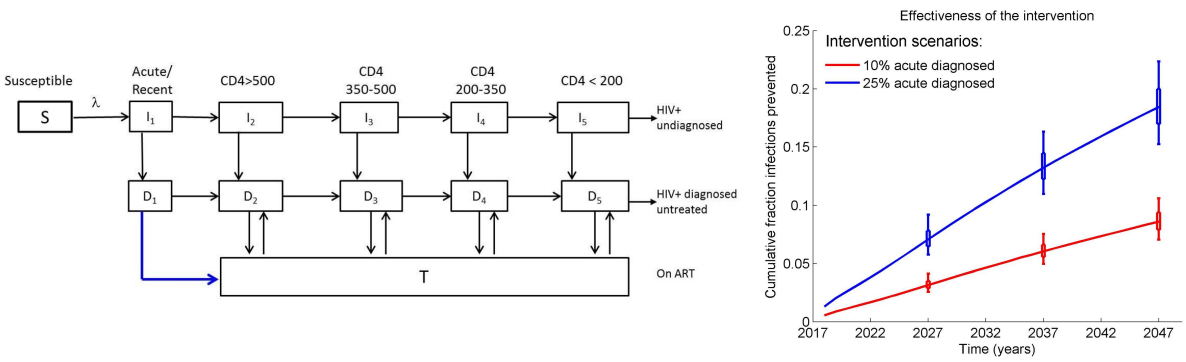
Figure 1: **Impact of female sex worker (FSW) enrollment on RCT outcomes**: trial duration and observed efficacy of the biomedical intervention. Fixed efficacy of 80% in reducing HIV susceptibility per act and 5% annual dropout rate are assumed over the course of the trials. Box plots (5th, 25th, 50th, 75th, and 95th percentiles) reflect variation over 1000 trials simulated.

In the second project we used a similar method to predict PrEP efficacy based on pill-taking regimens informed by data from the recently concluded ADAPT trial of the HIV Prevention Trial Network. This study evaluated the feasibility of three PrEP regimens: daily dosing, time-driven dosing (two pills per week and one pill within two hours after sex) and event-driven dosing (one pill within two days before and one pill within two hours after sex) among men who have sex with men (MSM) in Bangkok and Harlem and heterosexual women in Cape Town, South Africa [21]. We inform the distribution of protected acts in our model by sexual activity and PrEP coverage data from the trial. Our model suggests non-daily PrEP dosing strategies to be inferior to daily dosing with respect to reduction in HIV incidence and that PrEP will be most effective among MSM in Thailand and least effective among women in South Africa. Our results still warrant further investigation into non-daily PrEP regimens to provide more reliable estimates of effectiveness.

Estimating population effectiveness. We used a compartmental transmission model to predict the efficacy of a treatment as prevention (TasP) strategy which targets acute HIV infections among the MSM population in Peru. Our analysis is based on data from SABES ('Do you know?' in Spanish) [9], an ongoing study which tests the hypothesis that intervening early will markedly reduce onward HIV transmission. We stratified the infected population by CD4 count as a surrogate for the progression of HIV, and also stratified the infected population by current treatment status as undiagnosed, diagnosed or on treatment to reflect the lag time between between diagnosis, being linked to care and taking antiretroviral therapy (ART) as per the HIV treatment cascade. We used a separate compartment for individuals who are recently infected (in the acute HIV stage), because without a targeted intervention it is unlikely for an individual to be diagnosed and put on ART within the short window of acute infection. Our simulated intervention assumes that proportion of acutely infected are diagnosed, linked to care and initiated on ART within 1 month. Initial results show a significant number of infections prevented (see Figure 2).

Numerical Methods to Approximate Dynamical Systems

I am interested in the construction and analysis of numerical methods to approximate dynamical systems used to model biological interactions. Many methods have been constructed for specific systems, usually in 2-4 dimensions (e.g. [17, 10, 14, 18, 4, 6, 12, 27]). The majority of these studies focus on preserving equilibria and their local stability as well as the positivity of the solutions which are among the critical properties of particular biological systems. However, most of these approaches are not easily generalizable to other systems of practical interest. I have constructed numerical methods to solve n-dimensional productive-destructive systems (PDS) [22] and general autonomous dynamical systems with a finite number of hyperbolic equilibria [23]. PDS are a wide class of systems used to model biological interactions. Previous work was done for 2- and 3-dimensional PDS [8], but required the



(a) (b)

Figure 2: **The compartmental transmission model of MSM in Peru**. (a) diagram of the model (b) projected effectiveness in terms of cumulative fraction of infections prevented. Box plots (5th, 25th, 75th, and 95th percentiles) reflect estimated variation over 1000 epidemic simulations, while the solid lines represent the median effectiveness estimates.

use of analyzing dimension specific equations to establish dynamical consistency. Instead of focusing on specific equations, I used a matrix encoding along with bilinear transformations in the complex plane in order to establish the corresponding stability between the PDS and the numerical scheme. I also compared several of these methods when applied to a two-sex HIV epidemic model [24].

Future Research

Further research directions include exploring the impact of a broader group of modeling assumptions on the outcomes of dynamical systems used to evaluate the effectiveness of HIV prevention interventions, developing data-driven model comparison tools based on a Bayesian framework, and designing numerical methods that preserve dynamical properties of systems with nonhyperbolic equilibria alongside those with higher orders of accuracy. I also believe that mathematical modeling can inform more effective future public-health strategies of HIV prevention. For example, recent efforts by UNAIDS aim to curb the HIV epidemic with their ambitious 90-90-90 treatment target: "By 2020, 90% of all people living with HIV will know their HIV status. By 2020, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy. By 2020, 90% of all people receiving antiretroviral therapy will have viral suppression" (UNAIDS [1]). The impact of achieving this target deserves exploration via mathematical modeling because how the 90% of people on care is distributed across HIV epidemic stages and risk groups could potentially have meaningful effects on the epidemic. This hypothesis seems plausible due to our results from the Peru model, where targeting acutely infected individuals has a significant impact on the projected effictiveness of the intervention. I also wish to use my knowledge of population modeling to explore more diverse mathematical biology questions, including the modeling of other diseases.

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