Applied Network Models for Infectious Disease Dynamics Motivating Examples

Network Modeling for Epidemics

Day 5

Models of Infectious Disease Agents Studies (MIDAS)

- NIH mechanism to understand and respond to infectious diseases
 - Started with focus on outbreaks and acute epidemics
 - Shifted towards addressing endemic diseases
- Our EpiModel 2.0 R01
 - Developing the next generation of methods and software tools for network-based modeling of infectious diseases
 - Primary focus on HIV/STI models, but methods useful broadly...

Odel Installation Getting Started Tutorials Workshops Other

EpiModel

Mathematical Modeling of Infectious Disease

EpiModel is an R package that provides tools for simulating and analyzing mathematical models of infectious disease. Supported epidemic model classes include deterministic compartmental models, stochastic individual contact models, and stochastic network models. Disease types include SI, SIR, and SIS epidemics with and without demography, with utilities available for expansion to epidemics of arbitrary complexity.

Installation

The current software version is EpiModel v1.1.3, which may be downloaded from CRAN and can be installed in R through:

install.packages("EpiModel")

The development version of EpiModel hosted on GitHub and may be installed via the devtools package by:

devtools::install_github("statnet/EpiModel")

The software source code is available at the <u>Github Repository</u>. Users should submit bug reports and feature requests as issues there. The <u>Releases Page</u>: on the repository lists all the changes to the software over time.

Getting Started

Software Manual

The EpiModel Software Manual provides a list of all the main functions within the package, with syntax and examples.

EpiModel Web

For beginning EpiModel users and those new to mathematical modeling generally, EpiModel includes two web-based applications for simulating epidemics, using the Shiny framework in R. These applications are included within EpiModel for deterministic compartmental models (DCMs) and stochastic individual contact models (ICMs). They are also hosted online CDCMs OLCMS

Tutorials

For each of the three model classes in EpiModel, the tutorials are organized into basic integrated models to guide new users in the features of the model class, and advanced extension models to build out the models to answer new research questions.

Basic Integrated Models

Basic DCMs with EpiModel This tutorial provides some mathematical background for deterministic compartmental models, with exploration of different model types and parameterizations within EpiModel.

Basic ICMs with EpiModel Stochastic individual contact models (ICMs) are the microsimulation analogs to DCMs. This tutorial explains the general differences between deterministic and stochastic modeling, with hands-on basic examples.

Advanced Extension Models

New DCMs with EpiModel Creating new deterministic compartmental models in EpiModel involves writing new model functions defining the mathematical transition processes, and then parameterizing and simulating those models. This tutorial shows examples of how to write model functions, including new parameters, and run new models.

Research Applications of EpiModel Across Diseases

Model recommendations meet management reality: implementation and evaluation of a network-informed vaccination effort for endangered Hawaiian monk seals

Stacie J. Robinson¹, Michelle M. Barbieri¹, Samantha Murphy², Jason D. Baker¹, Albert L. Harting³, Meggan E. Craft⁴ and Charles L. Littnan¹

movements and seaway distance betwe

Trude Marie Lyngstad^b, Tadaishi Yatabe^a, Edgar B

CA. USA

^b Norwegian Veterinary Institute, Oslo, Norway

between the physiological and behavioral s of pathogen transmission: host heterogeneity epidemic outcomes

James D. Forester and Meggan F. Craft mic Bayesian Markov model for health economic tions of interventions against infectious diseases

Katrin Haeussler, Ardo van den Hout, Gianluca Baio

September 5, 2018

A stochastic network-based model to sin A Network Model of Hand Hygiene: How Good Is Good Enough to Stop the Spread of MRSA? (PD) in the Norwegian salmon industry

Sara Amirpour Haredasht^a, Saraya Tavornpanich^b, Neal D. Goldstein, PhD, MBI;^{1,2} Stephen C. Eppes, MD;¹ Amy Mackley, MSN;¹ Deborah Tuttle, MD;¹ David A. Paul, MD^{1,2}

^a Center for Animal Disease Modeling and Surveillance (CADMS), Department of Medicine & Epidemiology, School Veterinary Medicin Host behaviour – parasite teedback: an ecceptial link between animal behaviour sease ecology

Incidence rate estimation, periodic testing and the limitations of the mid-point imputation approach

Alain Vandormael,^{1,2}* Adrian Dobra,³ Till Bärnighausen,^{1,4,5,6} Tulio de Oliveira^{2,7} and Frank Tanser^{1,6,7,8}

zenwa¹, Elizabeth A. Archie², Meggan E. Craft³, Dana M. Hawley⁵, rtin⁶, Janice Moore⁷ and Lauren White⁴

Research Applications of EpiModel Across Diseases

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https://github.com/statnet/EpiModel/wiki

COVID University DCM with EpiModel



- Compartmental model for COVID on university campus led by Ben Lopman and Carol Liu, supported by Adrien Le Guillou and me
- Projects impact of testing & quarantine and screening & isolation strategies
- Model programmed and simulated in EpiModel

COVID University DCM with EpiModel



https://epimodel.shinyapps.io/covid-university/

A Network Model of Hand Hygiene: How Good Is Good Enough to Stop the Spread of MRSA?

Neal D. Goldstein, PhD, MBI;^{1,2} Stephen C. Eppes, MD;¹ Amy Mackley, MSN;¹ Deborah Tuttle, MD;¹ David A. Paul, MD^{1,2}



- Network model of MRSA infection within a NICU setting
- Networks defined as shared hospital worker contacts between infants

Network Model for Seal Influenza

PROCEEDINGS B

rspb.royalsocietypublishing.org

Research **a**

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Model recommendations meet management reality: implementation and evaluation of a network-informed vaccination effort for endangered Hawaiian monk seals

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Where disease threatens endangered wildlife populations, substantial resources are required for management actions such as vaccination. While network models provide a promising tool for identifying key spreaders and prioritizing efforts to maximize efficiency, population-scale vaccination remains rare, providing few opportunities to evaluate performance of model-informed strategies under realistic scenarios. Because the endangered Hawaiian monk seal could be heavily impacted by disease threats such as morbillivirus, we implemented a prophylactic vaccination programme. We used contact networks to prioritize vaccinating animals with high contact rates. We used dynamic network models to simulate morbillivirus outbreaks under real and idealized vaccination scenarios. We then evaluated the efficacy of model recommendations in this real-world vaccination project. We found that deviating from the model recommendations decreased the efficiency; requiring 44% more vaccinations to achieve a given decrease in outbreak size. However, we gained protection more quickly by vaccinating available animals rather than waiting to encounter priority seals. This work demonstrates the value of network models, but also makes trade-offs clear. If vaccines were limited but time was ample, vaccinating only priority animals would maximize herd protection. However, where time is the limiting factor, vaccinating additional lower-priority animals could more quickly protect the population.

1. Introduction

Infectious agents can negatively impact the demographics and fitness of wildlife populations, and disease outbreaks have the potential to threaten the persistence of small populations or endangered species [1,2]. Vaccination has become an important tool for managing disease to protect threatened populations [3]. Network models can help to characterize heterogeneous contact patterns, and are often suggested as useful means of optimizing disease control strategies [4,5]. Network models have demonstrated the potential to maximize vaccination efficiency by targeting those individuals or locations most connected in the network [6,7]. However, we do not know of instances where such model recommendations have been put into practice or evaluated under realistic field conditions encountered during wildlife vaccination efforts. This study provides

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- Allows you to easily add in any processes of interest into the ID system, and use the base EpiModel tools (estimation, simulation, analysis, plotting)
 - These are tools that we are invested in helping you master!
- It enforces you (the user) to think modularly: building a complex system in small, interconnected building blocks
- This facilitates efficient expansion once you have a starting codebase

HIV Preexposure Prophylaxis (PrEP)

- Anti-retroviral treatment provided to HIV-uninfected persons
- Decreases biological risk of infection when HIV-infected partner has uncontrolled viral replication
- Men who have sex with men (MSM) in the US are a high-priority population for PrEP
- 5% to 50% of MSM with indications with indications currently using it



Why is PrEP a Network Problem?

US CDC PrEP Indications

- US PHS/CDC released clinical practice guidelines indicating PrEP for those at "substantial risk" in 2014, revised in 2017
- For MSM, prescription indications were:
 - Unprotected anal intercourse (UAI) in monogamous partnership with person not recently tested for HIV
 - UAI outside of a monogamous partnership
 - AI (including with condoms) in a known serodiscordant partnership
 - Any non-HIV STI diagnosis
- Clinicians recommended to screen for conditions in past 6 months, reevaluate risk every 12 months

- Many math models have represented HIV PrEP
- Compartmental models typically represent simple high/low risk groups
 - Loosely related to empirical data on partnership change rates

Model frameworks that do not realistically reflect underlying contact processes that drive transmission dynamics are limited in modeling primary prevention interventions

Our Models for HIV Preexposure Prophylaxis

Evaluating CDC Guidelines



- Jenness SM, Johnson JA, Hoover KW, Smith DK, Delaney K. Modeling an Integrated HIV Prevention and Care Continuum to Achieve the Ending the HIV Epidemic Goals. AIDS. 2020; 34(14): 2103–2113.
 - PDF of paper: http://samueljenness.org/pdf/Jenness-2020-AIDS.pdf
 - EpiModelHIV Code: https://github.com/statnet/EpiModelHIV
 - Model scripts for paper: https://github.com/epimodel/combprev

An Integrated Prevention & Care Continuum



• Ending the HIV Epidemic plan introduced in Feb 2019

- 75% incidence reduction by 2025
- 90% reduction by 2030
- Resources directed at high-burden counties and states
- Will it be enough for HIV?
 - Lowest levels of HIV viral suppression in the Southern states where Medicaid not expanded through ACA

Ending the HIV Epidemic: A Plan for America

HHS is proposing a once-in-a-generation opportunity to eliminate new HIV infections in our nation. The multi-year program will infuse 48 counties, Washington, D.C., San Juan, Puerto Rico, as well as 7 states that have a substantial rural HIV burden with the additional expertise, technology, and resources needed to end the HIV epidemic in the United States. Our four strategies – diagnose, treat, protect, and respond – will be implemented across the entire U.S. within 10 years.



The Initiative will target our resources to the 48 highest burden counties, Washington, D.C., San Juan, Puerto Rico, and 7 states with a substantial rural HIV burden.



*2016-2017 data

Geographical Selection:

Data on burden of HIV in the US shows areas where HIV transmission occurs more frequently. More than 50% of new HIV diagnoses* occurred in only 48 counties, Washington, D.C., and San Juan, Puerto Rico. In addition, 7 states have a substantial rural burden – with over 75 cases and 10% or more of their diagnoses in rural areas.

Ending the HIV Epidemic Using modeling to understand an integrated HIV prevention and care continuum to achieve EHE goals

- Primary Study Question
 - What combinations of improvements to HIV screening (alone or as a gateway to PrEP initiation), HIV care linkage, and HIV care retention could meet the 2030 EHE goal of a 90% reduction in HIV incidence?

- Stochastic network model for HIV transmission dynamics
- Target study population:
 - Men who have sex with men (MSM) in Atlanta metropolitan area
 - Aged 15 to 65, stratified by Black, Hispanic, White/Other race/ethnicity
- Model calibrated to recent estimates of HIV care continuum steps and PrEP utilization in population
- Intervention scenarios for improvements to:
 - HIV screening
 - With and without PrEP initiation linked to HIV screening events
 - HIV care linkage
 - HIV retention in care

Network Modeling Methods

- Temporal exponential random graph models (TERGMs) define partnership formation and dissolution
 - Sexual network types: main, casual, one-off
 - Men form partnerships according to model terms based on numbers of each partner type, differential activity and mixing on race and age, sexual role segregation
- HIV epidemiology
 - Natural history (disease stages, continuous VL, HIV-related mortality)

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- ART initiation and adherence
- HIV transmission dynamics within serodiscordant partnerships
- Demographic processes



Multi-Layer Networks for Sexual Partnerships

- Three partnership networks: main, casual, one-time
 - Same node set, different edge set
- Distinguished in both their formation and dissolution model components
 - Formation formula for main network differs from other two
 - Dissolution model varies (substantially) by average duration of partnerships
- Model code mechanics:
 - Estimation (netest): https://github.com/EpiModel/CombPrev/blob/ master/estimation/estimation.R
 - Simulation (module for netsim): https://github.com/statnet/ EpiModelHIV/blob/CombPrev/R/mod.simnet.R

Empirical Data -----> Network Model Parameters

- Recently completed **ARTnet Study** of MSM in the US (R21 MH112449)
 - 4904 MSM reporting on 16198 sexual partnerships
- **Primary innovation:** data-driven statistical models embedded within ID transmission models where primary data available
 - TERGMs for network structure www simulate
 - Poisson models for coital frequency www predict
 - Logit models for condom use www predict
- Allows for confounding adjustment and addressing parameter covariance, statistical interactions when necessary
- Secondary data for (more) universal parameters
 - PrEP/ART effectiveness, probability of HIV transmission per act, ...



STI and most HIV transmissions circulate. The pathogens are transmitted by sexual acts embedded within partnerships, and circulation through the population depends on how those partnerships form and dissolve — a highly structured and population-specific dynamic process (Morris et al., 2009; Goodreau et al., 2012; Jenness et al., 2016a). While sexual network structure can be measured and analyzed either cross-

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(Oster et al., 2015). Of the estimated 40,000 new HIV infections oc-

curring in 2017, two-thirds were among men who have sex with men

(MSM) (Centers for Disease Control and Prevention, 2019b). The large

disparities in HIV/STI cases by race and age have worsened, with in-

cidence increasing among younger non-white MSM while decreasing in

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https://pubmed.ncbi.nlm.nih.gov/32004795/
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Model Calibration for Reference Scenario

- Prevalence of diagnosed HIV Infection among MSM
 - Rosenberg, Ann Epidemiol, 2018
 - ▶ B/H/W targets: 33.3%, 12.7%, 8.4%
- Proportion of HIV+ MSM who are diagnosed
 - Singh, Ann Intern Med, 2018
 - ► B/H/W targets: 80.4%, 79.9%, 88.0%
- Proportion of diagnosed MSM linked to care within 1m
 - GA DPH surveillance
 - ▶ B/H/W targets: 62%, 65%, 76%
- Proportion of diagnosed MSM with HIV VL suppression
 - ► GA DPH surveillance
 - ▶ B/H/W targets: 55%, 60%, 72%
- Proportion of Indicated MSM Using PrEP
 - Triangulation of ARTnet and other local estimates
 - Estimates for MSM in the Atlanta area: 15%



Bayesian Approaches to Model Calibration

- When the model form becomes complicated (e.g, collinearity), or there are many parameters to estimate, Bayesian approaches are favorable
- General setup:
 - Define prior distributions for uncertain input parameters
 - Draw samples from those distributions
 - Simulate the model with that parameter sample
 - Compare outcome statistics (prevalence/incidence) to external target data points
 - Some method for iteratively selecting which parameters to keep
- Approximate Bayesian Computation
 - Toni et al: https://royalsocietypublishing.org/doi/10.1098/ rsif.2008.0172

Infections Averted Under Different Prevention Scenarios



How Long Will it Take to Achieve the EHE Goals?



- Jenness SM, Willebrand KS, Malik AA, Lopman BA, Omer SB. Modeling Dynamic Network Strategies for SARS-CoV-2 Control on a Cruise Ship.
 - Pre-Print: https://doi.org/10.1101/2020.08.26.20182766
 - EpiModelCOVID Code: https://github.com/epimodel/epimodelcovid
 - Model scripts for paper: https://github.com/EpiModel/COVID-CruiseShip

Cruise Ship Network Model Schematic





Multi-Layer Dynamic Contact Networks



- Three overlapping ERGMs to represent guest/guest, crew/guest, and crew/crew contacts
- Multi-level structure: guests within cabins, cabins within ship sectors, crew assigned to cabins within sectors
 - x2 ERGMs, for pre-lockdown and post-lockdown network structures
- ERGMs with ship structure allow for repeated contacts with deterministic dissolution
- Scenarios focused on timing of lockdown, design of sectorization, and degree and within-cabin and within-sector mixing constraints given lockdown
 - Control-based strategies: after outbreak has started
 - Prevention-based strategies: informing future ship design

Model Results 1: Calibration



- Fit the model transmission parameters to daily screening rates and diagnoses on ship
 - True incidence > diagnosed incidence
- Empirical lockdown occurred Day 15 of the cruise

Model Results 2: Timing of Network Lockdown



- Distribution of cumulative incidence across 1000 simulations in each scenario
- Earlier (counterfactual) lockdown associated with major reduction in cumulative incidence compared to empirical (actual) lockdown on Day
 - Little impact of PPE in these settings: high-intensity contact and directionality of transmission...

Model Results 3: Directionality of Transmission

 Table 2. Directionality of Transmission and Contact Intensity Reductions, with Day 15 Network Lockdown and PPE, on COVID Incidence at 1

 Month

	Total	Passenger to Passenge	Passenger to Crew Cuml. Incid.	Crew to Passenger Cuml. Incid.	Crew to Crew Cuml. Incid.
Scenario	Cuml. Incid.	Cuml. Incid.			
	Median (95% SI)	Median (95% SI)	Median (95% SI)	Median (95% SI)	Median (95% SI)
With Contact Intensity Re	eductions, Network Lock	down, and PPE at Day 1	5		
Base Scenario					
No Intensity Reduction	933.5 (366.0, 1556.2)	551.0 (213.9, 941.0)	163.0 (66.0, 265.0)	124.0 (46.0, 211.0)	93.0 (33.0, 175.0)
Varying Passenger-Passer	ger Contact Intensity				
50% Reduction	862.5 (353.9, 1454.0)	488.0 (203.9, 843.0)	155.0 (67.0, 257.0)	124.5 (47.0, 216.0)	93.5 (29.0, 174.0)
90% Reduction	765.5 (316.9, 1348.0)	401.0 (164.9, 727.0)	145.5 (63.0, 248.0)	122.0 (44.0, 214.0)	90.0 (31.0, 173.0)
100% Reduction	749.0 (297.9, 1255.1)	381.0 (155.9, 677.0)	147.5 (61.0, 241.0)	126.0 (44.0, 208.0)	93.0 (32.0, 168.0)
Varying Passenger-Crew C	Contact Intensity				
50% Reduction	849.0 (352.9, 1379.1)	545.0 (230.0, 868.0)	125.5 (54.0, 203.0)	87.0 (31.0, 158.1)	90.0 (31.0, 168.0)
90% Reduction	787.0 (332.9, 1346.1)	535.5 (227.0, 899.0)	96.0 (41.0, 173.0)	62.0 (17.0, 130.0)	87.0 (30.0, 170.0)
100% Reduction	744.0 (325.0, 1274.1)	519.5 (225.9, 865.0)	86.0 (37.0, 152.0)	55.0 (17.0, 117.0)	84.0 (29.0, 167.0)
Varying Crew-Crew Contac	t Intensity				
50% Reduction	897.0 (379.9, 1471.2)	542.0 (220.8, 904.0)	161.0 (70.0, 254.0)	120.0 (48.0, 203.1)	74.0 (23.0, 142.0)
90% Reduction	899.0 (404.0, 1529.2)	558.0 (255.0, 943.2)	165.0 (78.0, 274.0)	118.0 (47.0, 206.0)	61.0 (17.0, 132.0)
100% Reduction	895.5 (362.9, 1459.1)	558.0 (218.0, 909.1)	162.0 (68.0, 263.0)	115.0 (44.0, 200.0)	55.0 (15.0, 119.0)

- In base model, most transmissions were passenger to passenger
 - No/limited PPE was used within cabins
- Reducing the contact intensity could avert hundreds of infections

Model Results 4: Prevention with Mass Screening

Table 4. Impact of Timing of Mass Asymptomatic Screening and Diagnosis-Based Case Isolation, with No Network Lockdown and Stratified by PPE Use, on COVID Incidence and Mortality at 1 Month

Scenario	Cumulative Incidence			Cumulative Mortality					
	Total	NIA ¹	PIA ²	Total	NDA ³	PDA ⁴			
	Median (95% SI)	Median (95% SI)	Median (95% SI)	Median (95% SI)	Median (95% SI)	Median (95% SI)			
Varying Timing of Mass Screening (Never PPE)									
Day 1	2286.0 (0.0, 3421.0)	1403.5 (1396.0, 1409.0)	38.0 (37.9, 38.1)	7.0 (0.0, 24.0)	29.0 (28.0, 29.0)	81.2 (80.6, 81.8)			
Day 5	2621.5 (16.0, 3353.1)	1070.5 (1067.0, 1074.0)	29.0 (28.9, 29.1)	9.0 (0.0, 23.0)	27.0 (27.0, 27.0)	75.6 (75.0, 76.0)			
Day 10	2917.0 (1787.8, 3310.1)	775.0 (772.5, 777.5)	21.0 (20.9, 21.1)	13.0 (4.0, 25.0)	23.0 (22.0, 23.0)	63.6 (62.9, 64.1)			
Day 15	2944.5 (2256.8, 3176.1)	746.0 (744.0, 748.0)	20.2 (20.2, 20.3)	18.0 (8.0, 32.0)	18.0 (17.0, 18.0)	50.0 (48.6, 50.0)			
Day 20	3102.5 (2588.8, 3360.1)	590.0 (588.0, 591.5)	16.0 (15.9, 16.0)	30.0 (16.0, 45.0)	6.0 (6.0, 7.0)	17.1 (16.1, 18.4)			
Day 25	3607.0 (3360.9, 3668.0)	85.0 (84.0, 86.0)	2.3 (2.3, 2.3)	36.0 (24.0, 50.0)	0.0 (-1.0, 0.0)	0.0 (-2.5, 0.0)			
Never (Reference)	3692.0 (3679.0, 3699.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	36.0 (25.0, 49.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)			
Varying Timing of Mass Screening (Always PPE)									
Day 1	1629.5 (0.0, 3013.0)	2012.0 (1998.0, 2023.0)	55.3 (55.0, 55.4)	5.0 (0.0, 20.0)	27.0 (27.0, 28.0)	85.2 (84.5, 85.7)			
Day 5	1856.5 (12.0, 2837.4)	1776.0 (1766.0, 1784.5)	48.8 (48.6, 49.0)	6.0 (0.0, 19.0)	26.0 (26.0, 27.0)	81.0 (80.5, 81.5)			
Day 10	2240.5 (1058.0, 2815.1)	1395.0 (1387.0, 1402.0)	38.3 (38.2, 38.5)	10.0 (2.0, 20.0)	23.0 (23.0, 23.0)	70.6 (70.0, 71.1)			
Day 15	2372.0 (1585.6, 2755.0)	1267.5 (1262.0, 1273.0)	34.8 (34.7, 34.9)	15.0 (5.0, 27.0)	18.0 (17.0, 18.0)	54.3 (53.5, 55.0)			
Day 20	2656.0 (1980.9, 3033.0)	983.5 (977.5, 988.5)	27.0 (26.9, 27.2)	26.0 (12.0, 40.0)	7.0 (7.0, 8.0)	22.2 (20.9, 23.3)			
Day 25	3354.0 (2831.8, 3537.1)	285.5 (282.0, 290.0)	7.8 (7.8, 7.9)	33.0 (20.0, 47.0)	0.0 (0.0, 1.0)	0.0 (0.0, 2.5)			
Never (Reference)	3643.0 (3563.0, 3669.0)	0.0 (-1.0, 1.0)	0.0 (-0.0, 0.0)	33.0 (20.0, 45.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)			

- In absence of behavioral change, screening and diagnosis-based case isolation could avert a substantial number of infections but not 100%
 - Here, PPE has an impact!
 - Why does Day 1 screening not prevent an outbreak?

Model Results 5: Sensitivity Analysis for Screening Interventions



- Base model assumed 100% reduction in contacts after case isolation, 80% PCR test sensitivity, and a Day 1 screening strategy
- Only when PCR sensitivity reaches 100% is an outbreak averted in the absence of behavioral change