Perspectives on Epidemiological Models, their History and Analysis

Francesco Bullo

Center for Control,
Dynamical Systems & Computation
University of California at Santa Barbara
http://motion.me.ucsb.edu

Tutorial Session: Modeling, Estimation, and Control of COVID-19
Modeling, Estimation and Control Conference (MECC 2021)
Online, Oct 24-27, 2021

Acknowledgments

Terrible impact of the COVID pandemic

The complex, dangerous, critical work by healthcare professionals all over the world on the front line of this battle

All essential frontline workers, including first responders, grocery-store workers, and transit workers

We owe them all a great deal of gratitude

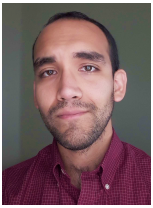
Acknowledgments

Wenjun Mei
Peking University

Shadi Mohagheghi
Aerospace Corp

Kevin D. Smith
UCSB

Sandro Zampieri
Univ Padova



Pedro Cisneros-Velarde
Univ illinois

- W. Mei, S. Mohagheghi, S. Zampieri, and F. Bullo. On the dynamics of deterministic epidemic propagation over networks. *Annual Reviews in Control*, 44:116–128, 2017. doi:10.1016/j.arcontrol.2017.09.002
- P. Cisneros-Velarde and F. Bullo. Multi-group SIS epidemics with simplicial and higher-order interactions. *IEEE Transactions on Control of Network Systems*, May 2020. Submitted. URL: https://arxiv.org/pdf/2005.11404.pdf
- K. D. Smith and F. Bullo. Convex optimization of the basic reproduction number. *IEEE Transactions on Automatic Control*, October 2021. URL: https://arxiv.org/abs/2109.07643

Outline

1. **historical notes**
2. mathematical models for epidemiology
3. analysis of determistic multigroup/network models

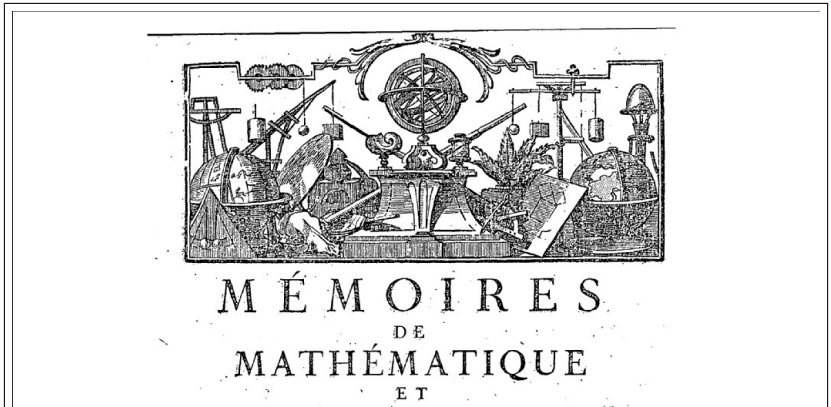
Daniel Bernoulli 1760: controversial smallpox variolation

- "the greatest killer in history"
- variolation, i.e., inoculation with a mild strain
- controversy: long-term benefit vs risk of immediate death

Daniel Bernoulli 1760: controversial smallpox variolation

- "the greatest killer in history"
- variolation, i.e., inoculation with a mild strain
- controversy: long-term benefit vs risk of immediate death

based on empirical data, Bernoulli proved that inoculation could increase life expectancy at birth up to three years



W. Hamer 1906: nonlinear incidence

- **compartments**: S, I and R
- incidence = number of new cases per unit time
  depends on the **product of the densities of S and I**

THE LANCET, MARCH 3, 1906.

The Milroy Lectures

ON

EPIDEMIC DISEASE IN ENGLAND—THE EVIDENCE OF VARIABILITY AND OF PERSISTENCY OF TYPE.

Delivered before the Royal College of Physicians of London,

BY W. H. HAMER, M.A., M.D. CANTAB., F.R.C.P. LOND.

LECTURE I.[1]

Delivered on March 1st.

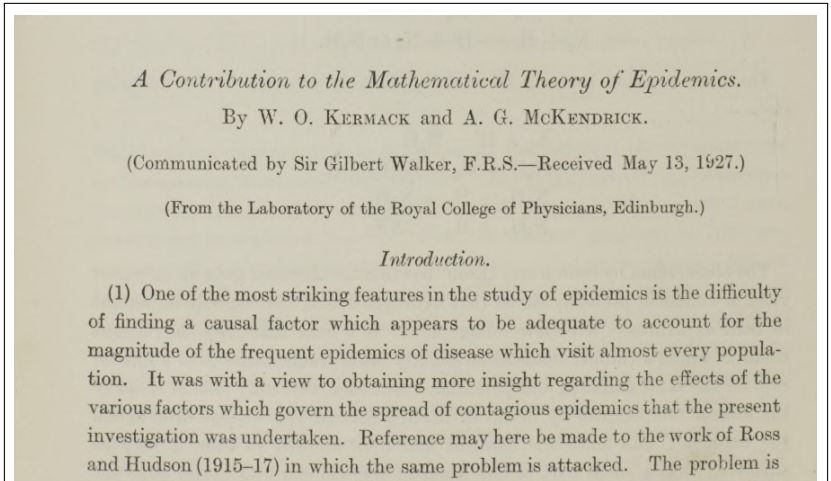
MR. PRESIDENT AND GENTLEMEN,—Changes of type in epidemic diseases was the subject chosen by Dr. B. A. Whitelegge for the Milroy lectures of 1893, to which the reader perforce returns again and again, as if increase of appetite had grown by what it fed on. The same topic has been variously approached and in recent years more particularly from the evolutionary standpoint. Already towards the close of the seventeenth century Sydenham had been accorded a Pisgah sight of the land to be explored, but prior to the Registrar-General and to Darwin no considerable advance into this new territory was possible. Even in the "fifties" there was

epidemiologist are unfortunately still of this primitive character; there is no standard case of typhus fever deposited at Kew and no one proposes to test strains of small-pox by their ability to kill unvaccinated vagrants of given weights in specified times.

Murchison has remarked that "in distinguishing the different forms of continued fever too much reliance has been placed on their symptoms and pathology, while there has been a want of sufficient investigation of their causes." With elaboration of the germ theory the pendulum has swung to the other extreme and it is now quite orthodox doctrine to hold that the presence of a particular germ spells specific disease; indeed, it may be questioned whether some modern bacteriologists, in the light of the demonstration of diphtheria, cholera, and enteric fever bacilli in persons presenting no symptoms of illness, would not feel that Murchison much exaggerated the difficulties inherent in a hypothesis requiring the co-existence of all pathogenic organisms in one individual. "The germ," Sir William Collins says, "has perhaps been too much with us, and the paramount importance of soil has been absurdly underrated." Or, to quote Dr. G. Newman, "The early school of preventive medicine declared for the health of the individual and laid the emphasis upon predisposition; the modern school have declared for the infecting agent and have laid emphasis upon the bacillus. The truth is to be found in a right perception of the action and interaction of the tissues and the bacillus." Or as Dr. F. G. Clemow expresses it, "Though constantly spoken of as if it were a material tangible entity disease is, in fact, no such thing. It is only a morbid phenomenon, or rather a group of morbid processes, in the tissues of a

Kermack and McKendrick 1927: epidemic thresholds and outbreaks

- **epidemic threshold**: the density of susceptibles must exceed a critical value in order for an **epidemic outbreak** to occur
- differential equations, calculus



A Contribution to the Mathematical Theory of Epidemics.

By W. O. Kermack and A. G. McKendrick.

(Communicated by Sir Gilbert Walker, F.R.S.—Received May 13, 1927.)

(From the Laboratory of the Royal College of Physicians, Edinburgh.)

Introduction.

(1) One of the most striking features in the study of epidemics is the difficulty of finding a causal factor which appears to be adequate to account for the magnitude of the frequent epidemics of disease which visit almost every population. It was with a view to obtaining more insight regarding the effects of the various factors which govern the spread of contagious epidemics that the present investigation was undertaken. Reference may here be made to the work of Ross and Hudson (1915–17) in which the same problem is attacked. The problem is

Lajmanovic and Yorke 1976: multigroup models and network science

- multi-group models
- equilibrium theorem
- spectral radius of contact graph

A Deterministic Model for Gonorrhea in a Nonhomogeneous Population*

ANA LAJMANOVICH

AND

JAMES A. YORKE

Institute for Fluid Dynamics and Applied Mathematics, University of Maryland, College Park, Maryland 20742

Communicated by J. Hearon

ABSTRACT

The spread of gonorrhea in a population is highly nonuniform. The mathematical model discussed takes this into account, splitting the population into n groups. The

Hethcote's leading survey in 2000

motivated by a range of infectious diseases and outbreaks,
one thousand and one models have been analyzed mathematically

threshold theorems for **epidemic outbreaks**

SIAM REVIEW
Vol. 42, No. 4, pp. 599–653

The Mathematics of Infectious Diseases*

Herbert W. Hethcote†

Abstract. Many models for the spread of infectious diseases in populations have been analyzed mathematically and applied to specific diseases. Threshold theorems involving the basic reproduction number R_0, the contact number σ, and the replacement number R are reviewed for the classic SIR epidemic and endemic models. Similar results with new expressions for R_0 are obtained for MSEIR and SEIR endemic models with either continuous age or age groups. Values of R_0 and σ are estimated for various diseases including measles in Niger and pertussis in the United States. Previous models with age structure, heterogeneity, and spatial structure are surveyed.

Key words. thresholds, basic reproduction number, contact number, epidemiology, infectious diseases

Historical review of mathematical epidemiology

- Daniel Bernoulli. Essai d'une nouvelle analyse de la mortalité causée par la petite vérole, et des avantages de l'inoculation pour la prévenir. *Mémoires de Mathématiques et de Physique, Académie Royale des Sciences*, pages 1–45, 1760
- W. H. Hamer. On epidemic disease in England. *The Lancet*, 167(4305):569–574, 1906. doi:10.1016/S0140-6736(01)80187-2
- W. O. Kermack and A. G. McKendrick. A contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society A*, 115:700–721, 1927. doi:10.1098/rspa.1927.0118
- N. T. J. Bailey. *The Mathematical Theory of Infectious Diseases*. Griffin, 1957
- A. Lajmanovich and J. A. Yorke. A deterministic model for gonorrhea in a nonhomogeneous population. *Mathematical Biosciences*, 28(3):221–236, 1976. doi:10.1016/0025-5564(76)90125-5
- H. W. Hethcote. The mathematics of infectious diseases. *SIAM Review*, 42(4):599–653, 2000. doi:10.1137/S0036144500371907

Outline

1. historical notes
2. **mathematical models for epidemiology**
3. analysis of determistic multigroup/network models

Compartmental Models: SIR model #1

each individual is in one of multiple possible states:

Compartmental Models: SIR model #1

each individual is in one of multiple possible states:

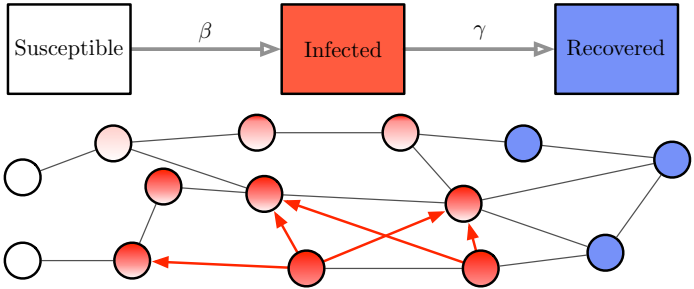
Two types of transitions:

1. $S \to I$: interaction between a susceptible and an infected
2. $I \to R$: spontaneous, independent of interactions

given infection rate β and recovery rate γ,
given initial values $s(0)$, $x(0)$, $r(0)$:

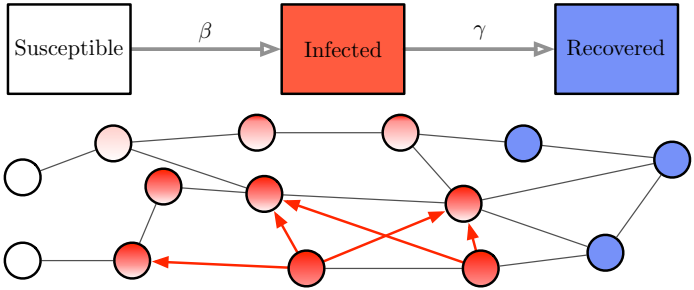
$$\dot{s} = -\beta s x$$
$$\dot{x} = \beta s x - \gamma x$$
$$\dot{r} = \gamma x$$

Multigroup model #2



$n = \#$ individuals OR # of homogeneous groups in heterogeneous population, based on spatial position, age, behavior, social degree

Multigroup model #2



$n = \#$ individuals OR # of homogeneous groups in heterogeneous population, based on spatial position, age, behavior, social degree

1. *contact rate* matrix A
2. *infection rate* $\beta > 0$: if susceptible i is in contact with infected j for Δt, then infection probability $a_{ij}\beta\Delta t$
3. each infected recovers with rate γ_i

An approximate deterministic model #2

infection rate β, contact rates A and recovery γ_i
define *infection variable* $X_i(t) \in \{1, 0\}$ and $x_i = \mathbb{E}[X_i(t)] = \mathbb{P}[X_i(t) = 1]$

1. The probabilities of infection satisfy

$$\frac{d}{dt}\mathbb{E}[X_i] = \beta \sum_{j=1}^{n} a_{ij}\,\mathbb{E}[(1 - X_i)X_j] - \gamma_i\,\mathbb{E}[X_i] \qquad \text{(No closure)}$$

An approximate deterministic model #2

infection rate β, contact rates A and recovery γ_i
define *infection variable* $X_i(t) \in \{1, 0\}$ and $x_i = \mathbb{E}[X_i(t)] = \mathbb{P}[X_i(t) = 1]$

1. The probabilities of infection satisfy

$$\frac{d}{dt}\mathbb{E}[X_i] = \beta \sum_{j=1}^{n} a_{ij}\,\mathbb{E}[(1 - X_i)X_j] - \gamma_i\,\mathbb{E}[X_i] \qquad \text{(No closure)}$$

2. independence assumption: $\mathbb{E}[X_i(t)X_j(t)] = \mathbb{E}[X_i(t)]\,\mathbb{E}[X_j(t)]$,
multigroup SIR model (contact based):

$$\dot{s} = -\beta\,\mathrm{diag}(s)Ax \tag{1a}$$
$$\dot{x} = \beta\,\mathrm{diag}(s)Ax - \gamma x \tag{1b}$$

F. D. Sahneh, C. Scoglio, and P. Van Mieghem. Generalized epidemic mean-field model for spreading processes over multilayer complex networks. *IEEE/ACM Transactions on Networking*, 21(5):1609–1620, 2013. doi:10.1109/TNET.2013.2239658

Equivalence with degree-based model

Let $\rho_i(t)$ fraction of infective nodes with degree i:

$$\dot{\rho}_i = -\gamma_i \rho_i + i(1-\rho_i)\lambda(i)\Theta(\rho), \qquad i \in \{1, \ldots, d_{\max}\}$$

where $\lambda(i)$ transmission rate,
$\Theta(\rho)$ probability that link points to infected

Lemma

Degree-based model = multi-group contact SIR model,
where parameters β and a_{ij} have specific form

R. Pastor-Satorras and A. Vespignani. Epidemic spreading in scale-free networks. *Physical Review Letters*, 86(14):3200–3203, 2001. doi:10.1103/PhysRevLett.86.3200

A. d'Onofrio. A note on the global behaviour of the network-based SIS epidemic model. *Nonlinear Analysis: Real World Applications*, 9(4):1567–1572, 2008. doi:10.1016/j.nonrwa.2007.04.001

Patchy model with population dispersal/mobility #3

Individuals travel/disperse to other regions, according to Markov chain

- contact rate matrix A (often diagonal in dispersal models)
- mobility/transition rate matrix $Q = A_{\text{travel}}^{\top} - \text{diag}(A_{\text{travel}}^{\top} \mathbb{1}_n)$
- infection and recovery rates β and γ

Combination: **multigroup SIR model with contact and mobility**:

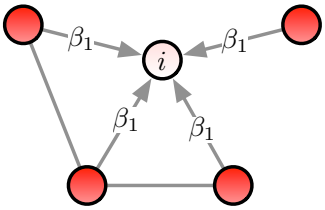
$$\dot{s} = -\beta \,\text{diag}(s) A x + Q s \tag{2a}$$

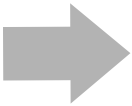
$$\dot{x} = \beta \,\text{diag}(s) A x - \gamma x + Q x \tag{2b}$$

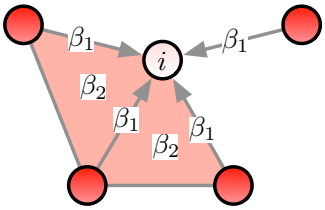
L. Sattenspiel and K. Dietz. A structured epidemic model incorporating geographic mobility among regions. *Mathematical Biosciences*, 128(1):71–91, 1995. doi:10.1016/0025-5564(94)00068-B

Simplicial and higher interactions, model #4

from pair-wise contagion models to
simplicial and higher-order graphical models to describe transmission events during large gatherings or other social aggregation phenomena







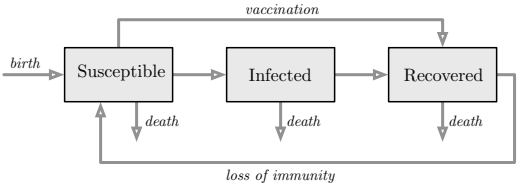
$$\dot{x}_i = -\gamma_i x_i + \beta_1(1 - x_i)\sum_{j=1}^{n} a_{ij}x_j$$

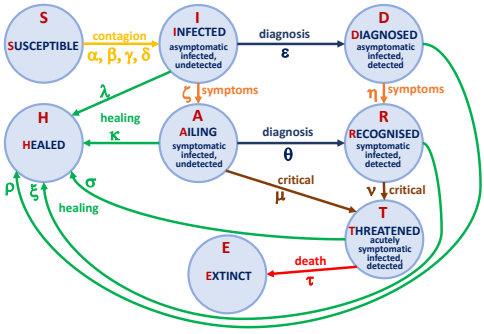
$$\dot{x}_i = -\gamma_i x_i + \beta_1(1 - x_i)\sum_{j=1}^{n} a_{ij}x_j + \beta_2(1 - x_i)\sum_{j,k=1}^{n} b_{ijk}x_j x_k,$$

P. Cisneros-Velarde and F. Bullo. Multi-group SIS epidemics with simplicial and higher-order interactions. *IEEE Transactions on Control of Network Systems*, May 2020. Submitted. URL: https://arxiv.org/pdf/2005.11404.pdf

Research directions on modeling

1. when do mean-field approximation leads to a guaranteed upper-bound
2. more accurate models
   - more realistic compartments
   - higher-order moment closure approximations
   - non-Markovian non-Poisson setting





G. Giordano, F. Blanchini, R. Bruno, P. Colaneri, A. Di Filippo, A. Di Matteo, and M. Colaneri. Modelling the covid-19 epidemic and implementation of population-wide interventions in Italy. *Nature Medicine*, 26:855–860, 2020. doi:10.1038/s41591-020-0883-7

Outline

1. historical notes
2. mathematical models for epidemiology
3. **analysis of determistic multigroup/network models**

Scalar and Multigroup SIR

$$\dot{s} = -\beta s x$$
$$\dot{x} = \beta s x - \gamma x$$
$$\dot{r} = \gamma x$$

$$\dot{s} = -\beta \,\mathrm{diag}(s) A x$$
$$\dot{x} = \beta \,\mathrm{diag}(s) A x - \gamma x$$
$$\dot{r} = \gamma x$$

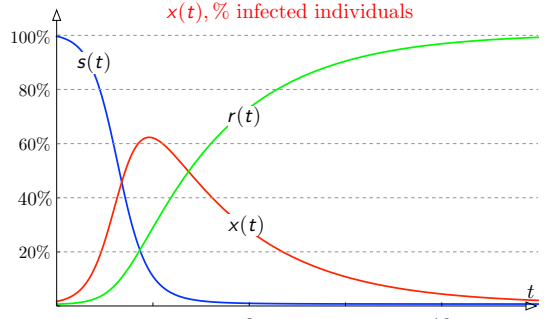
Analysis SIR model #1: Reproduction number & epidemic threshold

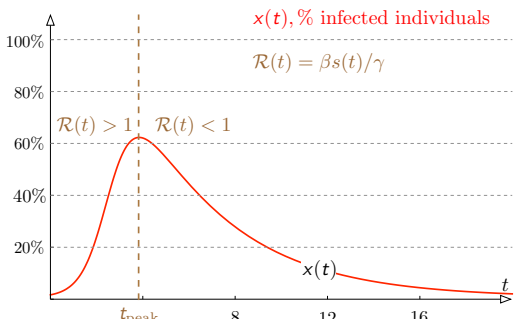
$\mathcal{R}_0 =$ expected # cases produced by typical infective at epidemic start

$= \beta \times 1/\gamma \times s(0)$

$\approx \Big((\text{contacts/day}) \times (\text{transmission}) \Big) \times (\text{infective days}) \times s(0)$

$\mathcal{R}_0 > 1 \quad \Longrightarrow \quad$ exponential growth





Analysis SIR model #1

from $s_0 > 0$, $x_0 > 0$ and $r_0 \geq 0$, define $\mathcal{R}_0 = \beta s_0/\gamma$

1. $\lim_{t\to\infty}(s(t), x(t), r(t)) = (s_\infty, 0, r_\infty)$, where r_∞ solves

$$1 - r_\infty = s_0\, \mathrm{e}^{-\frac{\beta}{\gamma}\left(r_\infty - r_0\right)} \tag{3}$$

2. if $\mathcal{R}_0 < 1$, then $x(t)$ monotonically/exponentially vanishes as $t \to \infty$
3. if $\mathcal{R}_0 > 1$, then $x(t)$ first increases to a peak and then vanishes as $t \to \infty$; the peak infection density and time:

$$\begin{aligned} x_{\max} &= x_0 + s_0 - \frac{\gamma}{\beta}\Big(\log(s_0) + 1 - \log\Big(\frac{\gamma}{\beta}\Big)\Big) \\ t_{\max} &= \int_{\gamma/\beta}^{s_0} \frac{1}{\beta s(x_0 + s_0 - s) + \gamma s \log(s/s_0)}\, ds \end{aligned} \tag{4}$$

Question 1: what are individual factors in $\mathcal{R}_0$? For thought experiments – without evidence – imagine

$$\underbrace{\mathcal{R}_0}_{\text{2.5 persons}} \approx \Big(\underbrace{(\text{contacts/day})}_{\text{2 persons/day}} \times \underbrace{(\text{transmission})}_{25\%} \Big) \times \underbrace{(\text{infective days})}_{\text{5 days}} \times \underbrace{s(0)}_{100\%}$$

Question 2: how to compute the doubling time? While $s \approx 1$,

$$t_{\text{doubling}} \approx \frac{\ln(2)}{(\beta - \gamma)} = \frac{\ln(2)}{1/2 - 1/5} \approx 2.3\text{days}$$

Question 3 (Herd Immunity): what percentage of the population x^* needs to have immunity in order for $\mathcal{R}(t) = 1$? Assume all population is susceptible $s(0) = 100\%$, then

$$1 = \mathcal{R}(t) = \mathcal{R}_0 s(t^*) \quad \Longrightarrow \quad x^* = 1 - s(t^*) = 1 - \frac{1}{\mathcal{R}_0} = 60\%$$

Analysis of multigroup SIR model #2

corresponding analysis of multigroup SIR model is incomplete

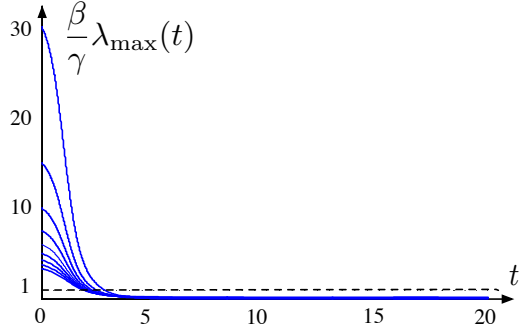
W. Mei, S. Mohagheghi, S. Zampieri, and F. Bullo. On the dynamics of deterministic epidemic propagation over networks. *Annual Reviews in Control*, 44:116–128, 2017. doi:10.1016/j.arcontrol.2017.09.002

Analysis of multigroup SIR model #2

take A irreducible, and
define $(\lambda_{\max}(t), v_{\max}(t) :=$ Perron left eigenpair of matrix $\operatorname{diag}(s(t))A$

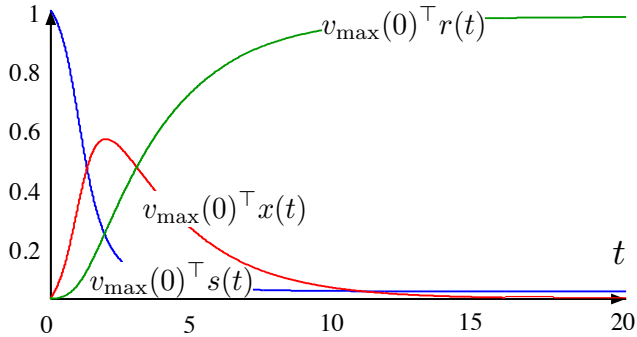
$$\mathcal{R}(\tau) := \beta\lambda_{\max}(\tau)/\gamma \text{ and, specifically, } \mathcal{R}_0 := \beta\lambda_{\max}(0)/\gamma$$

1. $t \mapsto \lambda_{\max}(t)$ and $t \mapsto \mathcal{R}(t)$ are monotonically decreasing
2. there exists $\tau > 0$ such that $\mathcal{R}(\tau) < 1$



2. **(behavior above the threshold = epidemic outbreak)** if $\mathcal{R}_0 > 1$ and $x_0 > 0$, then for small time, $t \mapsto v_{\max}(0)^\top x(t)$ grows exponentially fast with rate $\gamma(\mathcal{R}_0 - 1)$
3. **(behavior below the threshold)** pick $\tau \geq 0$ satisfying $\mathcal{R}(\tau) < 1$. For $t \geq \tau$, $t \mapsto v_{\max}(\tau)^\top x(t)$ is monotonically/exponentially vanishing

4. $\lim_{t \mapsto \infty} x(t) = 0$ so that epidemic asymptotically disappears



Existence, uniqueness, & computation of asymptotic recovered fraction

5. Given initial conditions $\big(s_0, x_0, r_0\big)$, final state $\big(s_\infty, 0, r_\infty\big)$ satisfies

$$\frac{\gamma}{\beta}\big(\ln s_\infty - \ln s_0\big) = A\big(s_\infty - \mathbb{1}_n + r_0\big)$$

6. $s_\infty = \lim_{t\to\infty} y(k)$ where $y(k+1) = H(y(k))$ with

$$H(y) := \exp\left(\frac{\beta}{\gamma}\operatorname{diag}\big(A(y - \mathbb{1}_n + r_0)\big)\right)s_0$$

$$\mathbb{0}_n \le y(0) \le \mathbb{1}_n - r_0$$

Conclusions

Today's outline

1. historical notes
2. mathematical models for epidemiology
3. analysis of determistic multigroup/network models

Future work

- peak time and value for multigroup SIR
- multigroup SIR with contact and mobility
- corresponding analysis of degree-based models