Epidemic Modeling

Henry Glick

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Outline

- Overview of epidemic models
  - Bernoulli and one of first epidemic models
  - Susceptible-Infected-Recovered (SIR) models
- Covid-19 models
  - The Institute for Health Metrics and Evaluation (IHME) COVID-19 hospital forecasting project at the University of Washington
  - The University of Pennsylvania's COVID-19 Hospital Impact Model for Epidemics (CHIME)
  - COVID-19 Acute and Intensive Care Resource Tool (CAIC-RT)

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Modeling of Infectious Disease

- Epidemic models used to assess mechanisms of disease spread, predict course of outbreak, and evaluate epidemic control strategies
- Typology of models includes compartmental equations, stochastic equations, agent-based simulations, etc.
- Required data/assumptions can include biological description of disease, mechanisms of pathogen transmission, target population social interactions and its spatial structure, etc.

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Bernoulli Smallpox Model

- An early version of disease modeling was carried out by Daniel Bernoulli in 1766
- Compared two states: one with and one without the presence of endemic smallpox
  - Smallpox elimination strategy: universal smallpox vaccination at birth
- Final conclusion based on maximizing life expectancy, which was calculated by use of derivatives

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Mechanism of Prediction

- Bernoulli model depended on 3 projections:
  - Survival curve that describes (current) population mortality over time
  - Survival curve that describes population mortality once smallpox is eradicated (i.e., all individual vaccinated)
  - Survival curve taking into account risk of dying from vaccination

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Bernoulli Assumptions

- Individuals infected with smallpox for the first time die with a probability p and survive with a probability 1 − p;
- Each individual has the probability q of being infected each year. In an infinitesimal interval of time dx, the probability of being infected between age x and age x + dx (with dx = 1 for the sake of simplicity) is qdx.
- Individuals who survive smallpox are immunized for the remainder of their lives.

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Bernoulli Results

- Life expectancy with smallpox ≈ 26.57 years
- Life expectancy with smallpox ≈ 29.65 years
- Net Gain: 3.08 years

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Including Both Susceptible and Infected Populations

- In 1908 Brownlee pointed out need to incorporate both host population and susceptibles in epidemic modeling
- Ross (1910) and Hamer (1928) applied law of mass action to explain epidemic behavior
  - Law of mass action: Proposition that rate of a chemical reaction is directly proportional to product of activities or concentrations of reactants.
    - If there are 2 reactants, activities of both affect rate of reaction
- This work formed basis of compartmental models of disease in mathematical epidemiology

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Compartmental Models

- Divide a population into categories, e.g., susceptible (S), infected (I), and recovered (immune/dead) (R) (SIR models)
- SIR (and related) models apply well to many disease systems and provide useful outcomes in many circumstances when Mass Action Principle applies

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Beyond Compartment Models

- Molecules in ideal solution, i.e., subjects of law of mass action, are considered to mix homogeneously
- Human and animal populations generally are considered not to
- When nonhomogeneous mixing is great enough, predictions from SIR model may be invalid
  - When there is substantial non-homogeneity, “more sophisticated” models may be useful

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Broad Categorization of Epidemic Models

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Static vs Dynamic Epidemic Models

- Static models: Risk/force of infection (probability per unit time) unrelated to proportion susceptible (e.g., risk/force remains constant whether there are 80% susceptible or 10% susceptible).
- Dynamic models: Risk/force of infection changes based on proportion of susceptible (e.g., herd immunity, in which risk/force decreases as number of susceptible diminishes)

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Deterministic Vs Stochastic Epidemic Models

- Deterministic models: individuals assigned to different subgroups (or compartments)
- Transition rates from one class to another are mathematically expressed as derivatives
  - i.e., model formulated using differential equations
- In building such models:
  - Assumed that population size in a compartment is differentiable with respect to time
  - Epidemic process typically (but not necessarily) deterministic
  - → Changes in population of a compartment can be calculated using only history used to develop model

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Deterministic Vs Stochastic Epidemic Models (2)

- Stochastic: chance variation. Compartmental models possible, but more complicated for (closed-form?) analysis

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Common Epidemic Model Assumptions

- Stationary age distribution: all live to a constant age and same number of people at every age
- Homogeneous mixing: contacts are made between everyone at random (makes math tractable)
  - Disadvantage: Available data and simulations provide evidence that "disease spreading is largely affected by heterogeneity of contact network of population."
    - BUT may be reasonable for modelling pathogen transmission for airborne disease (not STDs)
    - AND some studies have shown that random-mixing can produce reliable predictions for both households and heterogeneous contact networks

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(Basic) Reproduction Number

- Basic reproduction number (R0, or R naught): A measure of how transferable a disease is
- Equals average number of people that a single infected (infectious) person will infect over the course of their infection (assuming a fully susceptible population)
- Can be computed as a ratio of known rates over time

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Implications of R0 for Epidemic Dynamics

- If R0 > 1, then each person on average infects more than one other person so disease will spread
- If R0 < 1, then each person infects fewer than one person on average so disease will die out
- If R0 = 1, then each person will infect exactly one other person, so disease will become endemic
  - i.e., will move throughout the population but not increase or decrease
- Value of intervention can be judged based on whether it changes R0 so that it is greater than 1, equal 1, or less than 1

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Calculating Basic Reproduction Number

- If an infected individual contacts β other people per unit time, and
- If all of contacts are assumed to contract the disease, and
- If disease has a mean infectious period of $1/\gamma$
- Then $R0 = \beta/\gamma$

- Liu et al.: "the classical concept of the basic reproduction number is untenable in realistic populations, and it does not provide any conceptual understanding of the epidemic evolution. This [finding]…can be simply explained by the (clustered) contact structure of the population."

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β (Beta)

- All susceptibles have an equal probability of contracting disease (β)
- β controls how often a susceptible-infected contact results in a new infection

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β (Beta) (cont.)

- Smith and Moore suggest there is no direct way to observe β. They instead suggest:
  - Define ratio of β to γ as β * 1/γ (i.e., R0 or contact number (C) which represents number of close contact days times number of days infected; also equals number of close contacts per infected individual)
  - R0/C, which represents relative contagiousness of disease, can be estimated after an epidemic has run its course
  - β can then be calculated as R0 γ or cγ

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Gamma (γ)

- All infected individuals have an equal probability of recovering from disease (γ)
- γ controls the rate at which an infected individual recovers and moves into the resistant phase
- Fraction γ of infected individuals recovering in a given time period can be estimated from observation of infected individuals
  - Specifically, γ is roughly the reciprocal of the number of days an individual is sick enough to infect others.

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SIR Epidemic Model (Kermack and McKendrick, 1927)

- One of simplest compartmental models
- "Reasonably predictive" for human to human transmission where recovery confers lasting resistance
- Assumes:
  - Every susceptible has equal probability of infection (β)
  - Every infected has equal probability of recovering (γ)
  - Rate of infection/recovery much faster than time scale of births and deaths, so latter are ignored

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SIR Epidemic Model (2)

- One distinction between this class of models and models we build in treeage is that they are expressed by a set of ordinary differential equations and have an "analytic solution in implicit form"
  - More recently an exact analytical solution has been proposed.

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SIR Model Fluctuations

- Fluctuates with time
  - During an epidemic, the number of susceptible individuals falls rapidly as more of them are infected and thus enter the infected and recovered compartments
    - Disease cannot break out again until number of susceptibles has built back up, e.g. as a result of offspring being born into susceptible compartment.
- Fluctuates within individual
  - Each member of population typically progresses from susceptible to infected to recovered

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Susceptible, Infected, and Recovered

- Susceptible S(t), number not yet infected at time t
- Infected I(t), number who have been infected and are capable of spreading the disease at time t
- Recovered R(t), number immunized or dead at time t
- At any point in time, S(t) + I(t) + R(t) = 1 (or 100, or 1000, etc.)
  - 1 if working with probabilities
  - 100 or 1000 if we assume a population of 100 or 1000

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SIR "Transition" Rates

- Between S and I: $S \times I \times \beta / N$
  - Where S = number/proportion of population who are susceptible; I = number of proportion who are infected; β is how often a susceptible-infected contact results in a new infection; and N = the total number in the sample (or for proportions, 1)
- Between I and R: γ
  - If the duration of the infective period is denoted D, then $\gamma = 1/D$, since an individual experiences one recovery in D units of time
- Typically assumed estimates of permanence of individuals in "states" are random variables with exponential distribution, although more realistic distributions can be used

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$S \times I \times \beta / N$

- Number of patients susceptible and number of patients infected equally important to rate of new cases
- IF S+I is fixed (e.g., 1.0), highest infection rate occurs when S = I

S		I		Rate
0.1	x	0.9	=	0.09
0.2	x	0.8	=	0.16
0.3	x	0.7	=	0.21
0.4	x	0.6	=	0.24
0.5	x	0.5	=	0.25
0.6	x	0.4	=	0.24
0.7	x	0.3	=	0.21
0.8	x	0.2	=	0.16
0.9	x	0.1	=	0.09

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Approximate Numbers/Probabilities per Period

- Simple math
  - ~Numbers in:
    - S this period = $S_{i-1} – (S_{i-1} * I_{i-1} * β) / N$
    - I this period = $(I_{i-1} * (1-γ)) + (S_{i-1} * I_{i-1} * β) / N$
    - R this period = $R_{i-1} + (I_{i-1} * γ)$
- Would be able to build in Treeage if can access probability of being in a state in prior period
  - But not sure these probabilities are accessible
- More appropriate to base estimates on integrals
  - One web-based SIR application uses fourth-order Runge-Kutta algorithm for numeric solutions

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Approximate Calculations, Period 2 *

Period	Suscept	Infect	Recover
1	997	3	0
2	996.1693	3.49745	0.3333
3			
4			
5			
6			
7			
8			
9			

- # new cases: 997*3*0.27775 / 1000 = 0.83075025
- # recovered cases: 3*0.1111 = 0.33333
- New distribution
- Susp: 997 – 0.83075 = 996.1693
- Infect: 3+0.83075-0.3333 = 3.49745
- Recover: 0.3333

* Assumptions: R0 = 2.5; γ = 1/9 days; β = R0 ˣ γ = 0.27775. Initial distribution 997, 3, 0

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Approximate Calculations, Period 3

Period	Suscept	Infect	Recover
1	997	3	0
2	996.1693	3.49745	0.3333
3	995.2015	4.07658	0.72187
4			
5			
6			
7			
8			
9			

- # new cases: 996.17*3.5*0.27775 / 1000 = 0.83006
- # recovered cases: 3.5*0.1111 = 0.38857
- New distribution
- Susp: 996.1693 - 0.83006 = 995.2015
- Infect: 3.49745+0.83006-0.38857 = 4.07658
- Recovered: 0.72187

Assumptions: R0 = 2.5; γ = 1/9 days; β = R0 ˣ γ = 0.27775. Initial distribution 997, 3, 0

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Approximate Calculations, Periods 4-9

Period	Suscept	Infect	Recover
1	997	3	0
2	996.1693	3.49745	0.3333
3	995.2015	4.07658	0.72187
4	994.0704	4.750508	1.174775
5	992.7631	5.534362	1.702556
6	991.237	6.445539	2.317424
7	989.4625	7.504	3.033523
8	987.4002	8.732579	3.867218
9	985.053	10.1573	4.837407

Assumptions: R0 = 2.5; γ = 1/9 days; β = R0 × γ = 0.27775. Initial distribution 997, 3, 0

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"Transition" Probabilities

Period	S→ S	S→ I	I→ I	I→ R
1 to 2	0.99917	0.00083	0.88889	0.11111
2 to 3	0.99903	0.00097	0.88889	0.11111
3 to 4	0.99887	0.00113	0.88889	0.11111
4 to 5	0.99868	0.00132	0.88889	0.11111

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(One of many) Online SIR Models With Modifiable Inputs

- http://www.public.asu.edu/~hnesse/classes/sir.html

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Extensions of SIR models

- SIRD model: Susceptible-Infected-Recovered-Deceased (distinguishes between recovered and now immune vs deceased)
- MSIR model: Begin immune (e.g., infants) and then become susceptible
- SIS: No immunity (cycle between susceptible and infectious)
- SIRS: Time immune/time recovered limited
- SEIS and SEIR: latent period when person is exposed (E) but not infectious (I)
- SICR: Susceptible-Infected-Either Carrier (C) or Recovered (R)

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Three US Covid-19 Models

(Relies heavily on / steals from)

Wong J. Pandemic surge models in time of severe acute respiratory syndrome coronaviras-2: Wrong or useful? Ann Intern Med. 16 April 2020

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The Models

- The Institute for Health Metrics and Evaluation (IHME) COVID-19 hospital forecasting project at the University of Washington
- The University of Pennsylvania's COVID-19 Hospital Impact Model for Epidemics (CHIME)
- COVID-19 Acute and Intensive Care Resource Tool (CAIC-RT)

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Model Goals

- At least initially: Forecast demand for hospital such as acute and critical care beds and mechanical ventilators and determine when peak demand will occur
- At least some have added on goals
  - e.g., IHME model
    - Evaluates effect of interventions
    - Provides input for state-by-state dates when restrictions can be eased
    - Quantifies where COVID-19 daily deaths have peaked and how long peaks last

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Fit for Purpose

- Rapidly developed to be fit for purpose and user friendly
- At least some regularly updated with new data and new capabilities

DIFFER IN METHODOLOGICAL APPROACH AND DEGREE TO WHICH PROJECTIONS CAN BE CUSTOMIZED TO LOCAL CONTEXT

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IHME COVID-19 hospital forecasting project

Preprint of paper:

http://www.healthdata.org/sites/default/files/files/Projects/COVID/RA_COVID-forecasting-USA-EEA_042120.pdf

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Mortality Prediction

- Entire model derives from mortality prediction
- Uses observed mortality curves in cities that have already reached their peak during the pandemic to predict deaths in other areas that have not yet had their peaks
  - Mortality predictions initially based on observed mortality in Wuhan City
  - Mortality data augmented to include Italy, Spain, France, and Korea (and more?)
- Mortality curve fitting assumes shape of curve (with adjustments for timing of policy interventions) and incorporates infectious disease transmission

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Predicting Mortality Peak

- “When a given location reaches its peak, the natural log of the daily death curve should either essentially reach or pass where the curve’s tangent line is horizontal. We fit a spline to the natural log of the daily death rate and identify the peak where the slope of the spline is 0.”

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Epidemiologic Roots

- Mortality prediction has roots in work by William Farr in mid-1800s
- Farr fit curves through epidemic mortality data in 1840 and found epidemics could be described as bell-shaped curves (approximate normal distributions)
- “[The curve] ascends first rapidly and then slowly, until at last it attains a maximum, makes a turn, and falls down more rapidly than it mounted” (i.e., asymmetric, but approximately normal)

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Farr's "Law", English Cattle Plague of 1865/1866

Date	Total Cases
October 7, 1865	11,300
November 4	20,897
December 2	39,714
December 30	73,549
January 27, 1866	120,740

- Mr. Lowe's speech to Parliament: "If we do not get the disease under control by the middle of April, prepare yourself for calamity….[Y]ou will see the averages, which have been thousands, grow to tens of thousands, for there is no reason why the same terrible law of increase which has prevailed hitherto should not prevail henceforth."

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Farr's Observation

Date	Total Cases	New Cases	% Increase
October 7, 1865	11,300	--	--
November 4	20,897	9597	--
December 2	39,714	18,817	96
December 30	73,549	33,835	80
January 27, 1866	120,740	47,191	40

- "[A]lthough the attacks in the second period…were nearly double those in the first period, that rate of increase did not continue….The real law implies that the ratio of increase goes on rapidly decreasing….

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Farr's Predictions (and Later Observed Numbers)

Date	New Cases Through 1/27	Predicted Cases, "Law"	Observed
November 4	9597		
December 2	18,817	(96%)	(96%)
December 30	33,835	(80%)	(80%)
January 27, 1866	47,191	(40%)	(40%)
February 24		43,182 (-8%)	57,004 (20%)
March 24		21,927 (-49%)	27,958 (-51%)
April 21		5,225 (-76%)	15,856 (-32%)
May 19		494 (-90%)	14,734 (-7%)
June 16		16 (-96%)	5,000(-66%)

- Epidemic ended 2 weeks after Farr predicted it would

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Other Covid-19 Outcomes

- Predicted Total Cases
  - Derived using predicted deaths and infection fatality ratios (IFR)
- Predicted Hospitalizations
  - Derived using hospitalization-to-death ratios, from which it predicts intensive care unit (ICU) and mechanical ventilator use

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Interventions

- As of April 17, model includes the effects of a number interventions including 6 categories of social distancing measures
- Predictions reflect effect of social distancing policies enacted and people's behavioral response to these policies
- Uses 3 different models (short-term day 5, long-term day 20, and a time-dependent weighting of these predictions) to incorporate these effects

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The University of Pennsylvania's COVID-19 Hospital Impact Model for Epidemics (CHIME)

Weissman GE, Crane-Droesch A, Chivers C, et al. Locally informed simulation to predict hospital capacity needs during the COVID-19 pandemic. Ann Intern Med. 2020. [PMID: 32259197] doi:10.7326/M20-1260

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CHIME Model

- Dynamic transmission or mechanistic model
- Simplifies SIR disease inputs into:
  - Regional population at risk, where the number infected depends on the regional population size
  - Hospital market share
  - Hospitalized census
- Assumes uniform or homogeneous susceptibility to infection risk, regardless of population density, contact location, or heterogeneity in infectivity

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Other Assumptions/Inputs

- Severity impact of infection includes the proportion of acute and ICU hospitalization and mechanical ventilation and the average length of stay (LOS) in hospital and ICU with or without a ventilator
- Calculates basic reproductive number (R0) from inputs for doubling time and recovery (infectiousness) in days with a constant mitigation reduction from social distancing at date of implementation
- Can incorporate asymptomatic or mild infections by accounting for such persons when estimating proportions of need for hospitalization, ICU care, and mechanical ventilation

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COVID-19 Acute and Intensive Care Resource Tool (CAIC-RT)

Giannakeas V, Bhatia D, Warkentin MT, et al. Estimating the maximum capacity of COVID-19 cases manageable per day given a health care system's constrained resources. Ann Intern Med. 16 April 2020. [Epub ahead of print].

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CAIC-RT

- Hospital planning tool originating from models used in operations research
- Seeks to maximize outputs given constraints and identify queues and bottlenecks that may benefit from additional resources
- Ignores epidemic and focuses on capacity imposed by resource limitations
- Examines steady-state consequences of constrained hospital resources on patient throughput

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Model Flexibility

- Can be tailored to:
  - Local age distribution of patients with SARS–CoV-2 infection presenting to a health care system or hospital
  - Age-stratified proportion requiring hospitalization, critical care, and mechanical ventilation
- At beginning of epidemic, system considered to have sufficient resource capacity to care for all patients with SARS–CoV-2 infection
  - Eventually, with full use, steady-state assumption becomes necessary

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The COVID-19 Acute and Intensive Care Resource Tool (CAIC-RT) is open access and available at:

https://caic-rt.shinyapps.io/CAIC-RT

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Are the Models Good Enough?

- We've previously said strength of models depends on strength of assumptions and strength of data
- No model is "right," but can be useful
- Don't KNOW the outcome of Covid pandemic
- But models might improve our guesses about the policies we should adopt to address it

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