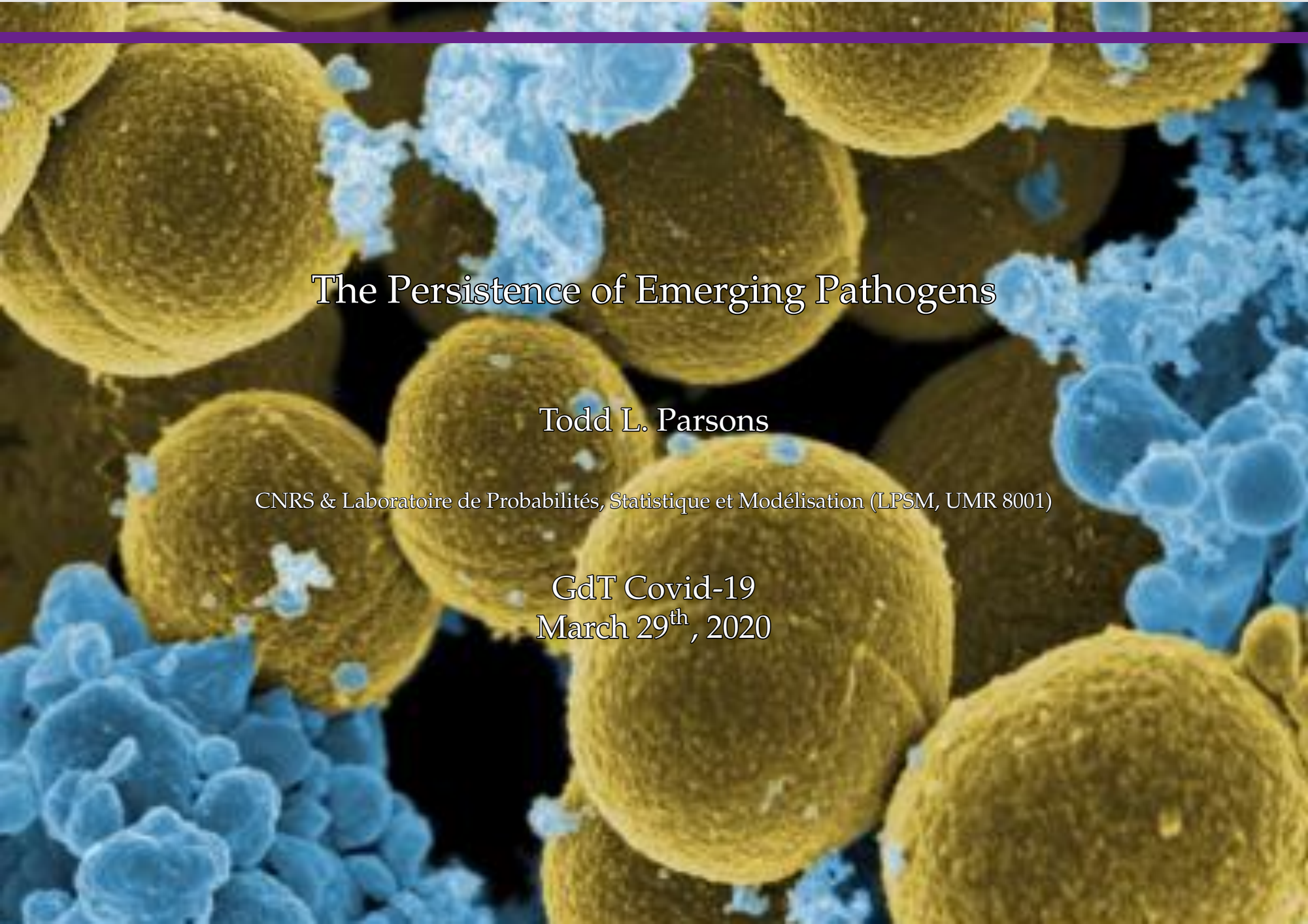

The Persistence of Emerging Pathogens

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GdT Covid-19
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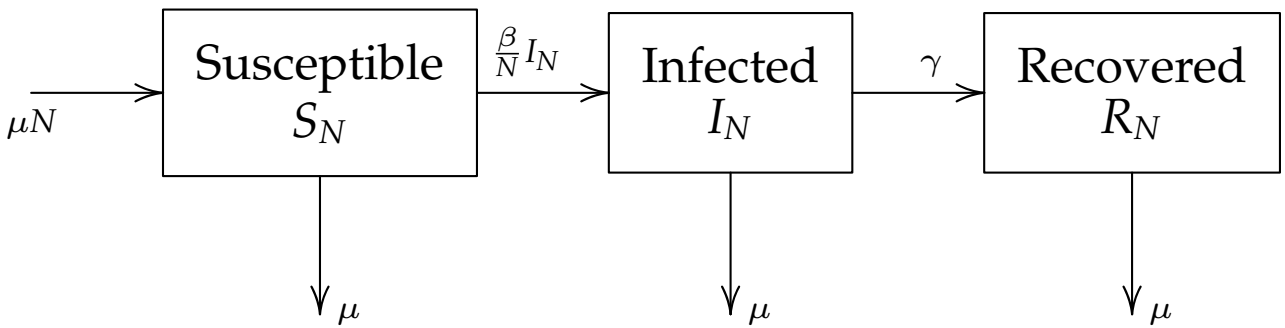
Outline

THE SIR EPIDEMIC MODEL (KERMACK & MCKENDRICK, 1927)



- $N = S + I + R$
- $\mu =$ birth/immigration and death rates
- $\beta =$ transmission rate
- $\gamma =$ recovery rate

THE SIR EPIDEMIC MODEL, DETERMINISTIC FORMULATION

We typically analyze this via a system of differential equations:

$$\begin{aligned}
\frac{dS_N}{dt} &= \mu N - \beta \frac{S_N I_N}{N} - \mu S_N \\
\frac{dI_N}{dt} &= \beta \frac{S_N I_N}{N} - \gamma I_N - \mu I_N \\
\frac{dR_N}{dt} &= \gamma I_N - \mu R_N
\end{aligned}$$

THE SIR EPIDEMIC MODEL, DENSITY FORMULATION

For reasons I'll elaborate upon, this is better expressed in terms of the *densities* $S = \frac{S_N}{N}$, $I = \frac{I_N}{N}$, $R = \frac{R_N}{N}$ ($S + I + R = 1$).

$$\begin{aligned} \frac{dS}{dt} &= \mu - \beta SI - \mu S \\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I \\ \frac{dR}{dt} &= \gamma I - \mu R \end{aligned}$$

ASIDE #1: IN PRAISE OF TOY MODELS

Attributed to John von Neumann by Enrico Fermi:

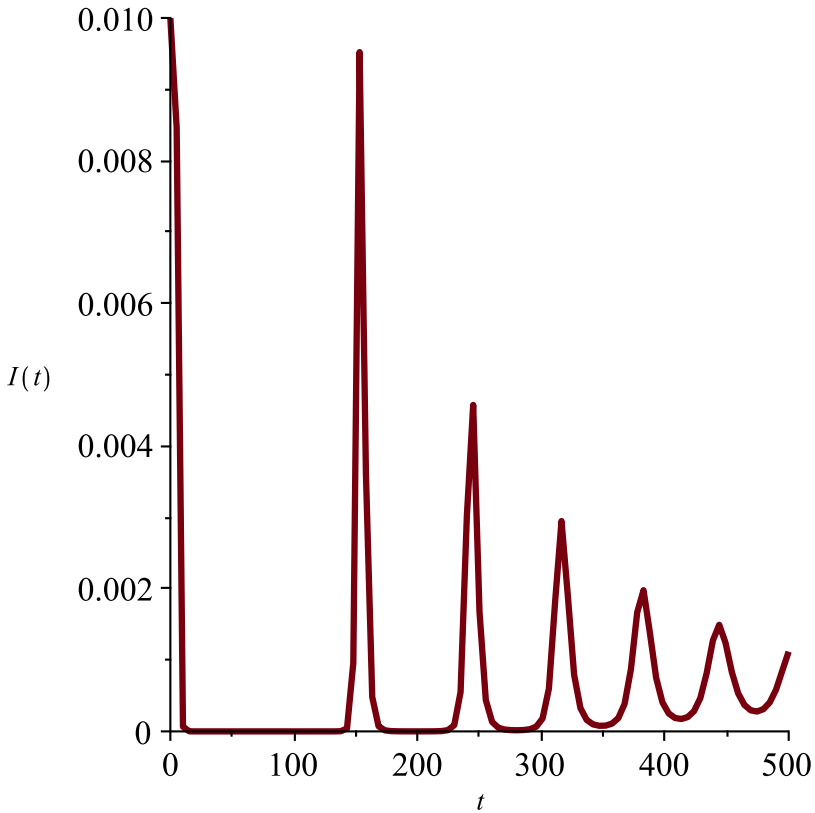
> *"With four parameters I can fit an elephant, and with five, I can make him wiggle his trunk"*
>
> *Dyson (2004) "A meeting with Enrico Fermi" Nature 427 p. 297*

Even fitting a single parameter, $\mathcal{R}_0$, at the early stages of an epidemic is a challenge:

Park *et al.* (2020) "Reconciling early-outbreak estimates of the basic reproductive number and its uncertainty: framework and applications to the novel coronavirus (SARS-CoV-2) outbreak" (doi:10.1101/2020.01.30.20019877)

RECURRING EPIDEMICS

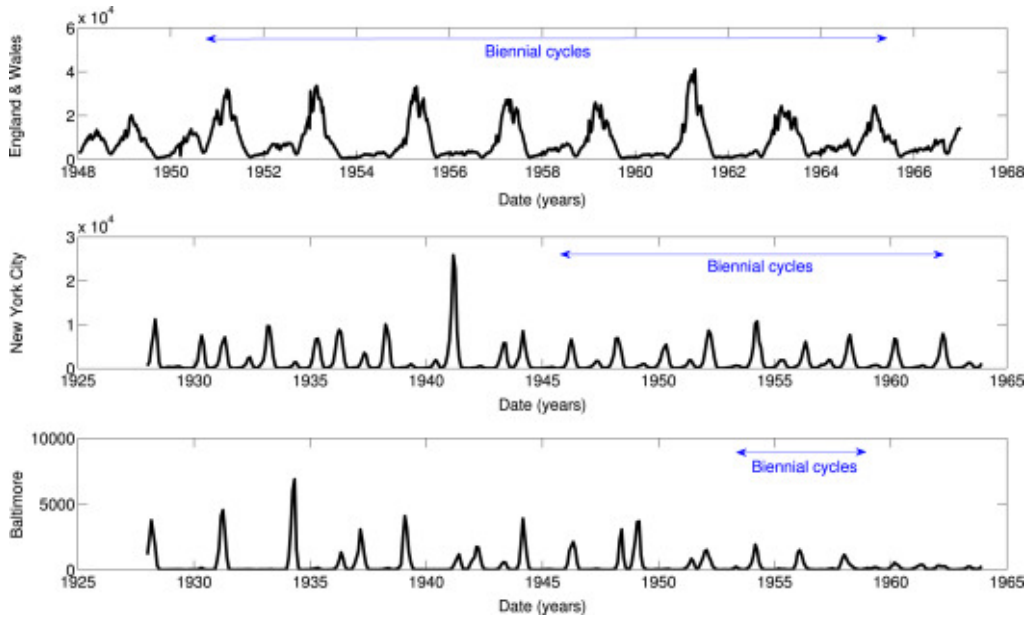
For a wide range of parameters, the SIR model predicts recurring epidemics as damped cycles



$$S(0) = 0.99, I(0) = 0.01.$$

$\mathcal{R}_0 = 17, \gamma^{-1} = 13$ days, $\mu = 0.002/\text{day}, N = 100.$

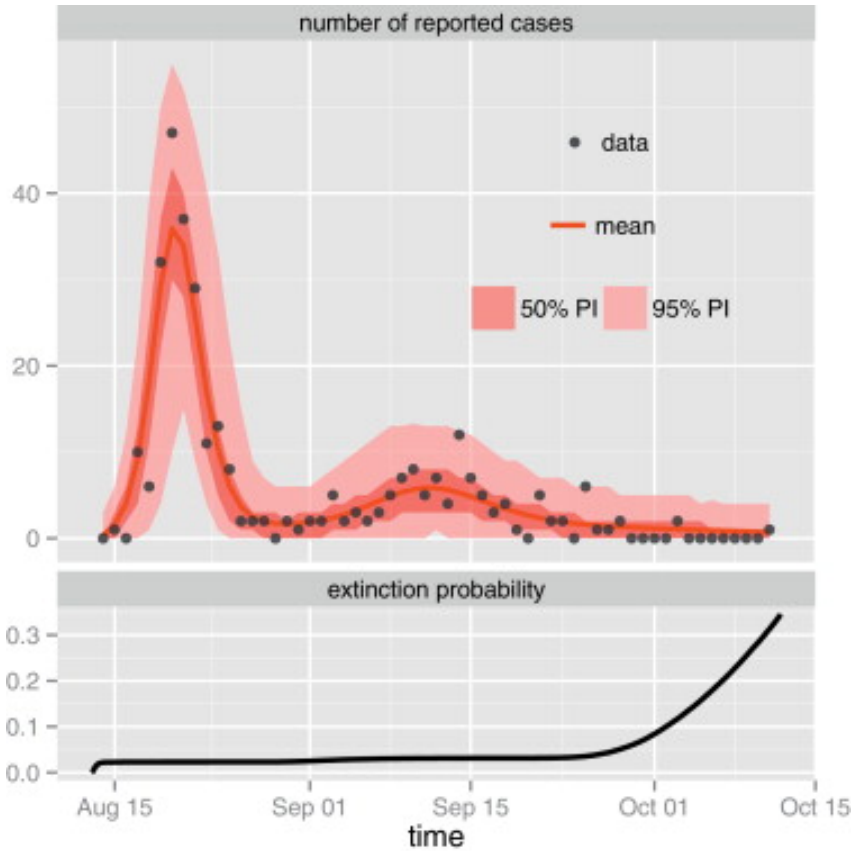
ASIDE # 2: MEASLES CYCLIC EPIDEMICS



(Chen & Epureanu, 2017)

Recurrent epidemic cycles in actual populations don't always show damping; the reasons are a topic of ongoing research: Dushoff *et. al.* (2004) "Dynamical resonance can account for seasonality of influenza epidemics" *PNAS* 101 (48) pp. 16915-16916.

FADE-OUT: INFLUENZA EPIDEMIC,TRISTAN DA CUNHA,1971



(Camacho & Cazelles 2013)

Other pathogens have a finite number of epidemics before stochasticity results in extinction of the pathogen. We wish to estimate the probability that this occurs.

THE BASIC REPRODUCTION RATIO

The basic reproduction number is

$$\mathcal{R}_0 := \underbrace{\beta}_{\text{transmission rate}} \times \underbrace{\frac{1}{\mu+\gamma}}_{\text{duration of infection}} \times \underbrace{S_0(=1)}_{\text{inital proportion of susceptbles}}$$

Disease is endemic (persists indefinitely) if $\mathcal{R}_0 > 1$.

Disease	$\mathcal{R}_0$	*Herd immunity*
Mumps	4-7	75-86 %
Polio	5-7	80-86 %
Small pops	5-7	80-85 %
Diphteria	6-7	85 %
Rubella	6-7	83-85 %
Pertussis	12-17	92-94 %
Measles	12-18	83-94 %

(Doherty *et al., 2016*)

Outline

JOINT WITH

Ben Bolker

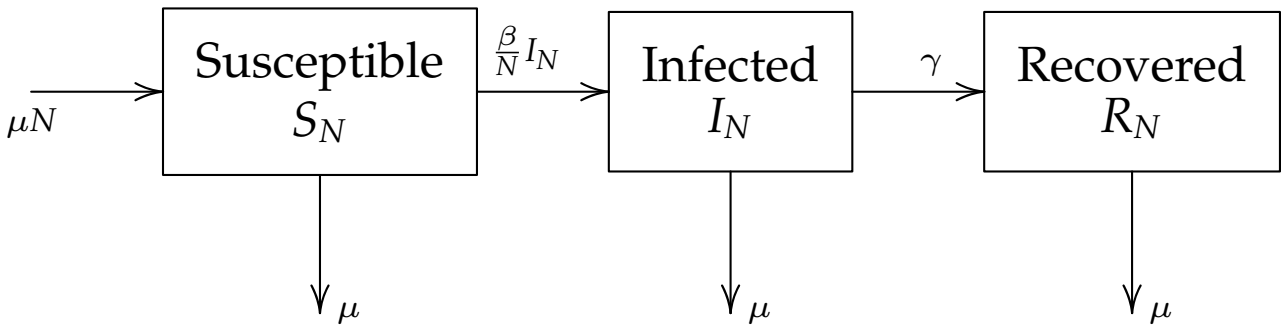
Jonathan Dushoff

David Earn

A PERSISTENCE PUZZLE

- Provided that $\mu \ll 1$, approximately $e^{-\mathcal{R}_0}$ susceptible at the end of the epidemic.
- *e.g.* for measles, less than 1 in a billion remain susceptible at the end of the first outbreak $\Rightarrow$ suggests it should not persist.
- Larger $\mathcal{R}_0 \Rightarrow$ larger, faster first epidemic $\Rightarrow$ persistence seems *less* likely.
- Yet, many diseases have large values of $\mathcal{R}_0$: measles (12–18), pertussis (12–17), malaria (32–48)
- How can a disease with very high $\mathcal{R}_0$ persist after initial invasion?

THE SIR EPIDEMIC MODEL (KERMACK & MCKENDRICK, 1927), *Redux*



- To properly analyze persistence and extinction, we need to return to our original, discrete and stochastic formulation.
- $N = S + I + R$
- $\mu =$ birth/immigration and death rates
- $\beta =$ transmission rate
- $\gamma =$ recovery rate

ASIDE # 3: CONTINUOUS-TIME MARKOV CHAINS (CTMCS)

- A Markov process is a 'memoryless' stochastic process: loosely speaking, a process satisfies the Markov property if one can make predictions for the future of the process based solely on its present state just as well as one could knowing the process's full history.
- *i.e.,* conditional on the present state of the system, its future and past are independent
- A Markov process $\boldsymbol{X}(t)$ is described by it's initial state $\boldsymbol{X}(0)$ (which may be a random variable) and it's jump (or transiition) rates $q_{\boldsymbol{x},\boldsymbol{y}}$:

$$\mathbb{P}\left(\Delta\boldsymbol{X}(t+\Delta t) = \boldsymbol{y} | \boldsymbol{X}(t) = \boldsymbol{x}\right) = q_{\boldsymbol{x},\boldsymbol{y}}\Delta t + o(\Delta t).$$

- $\boldsymbol{j} = \boldsymbol{y} - \boldsymbol{x}$ is a jump; sometimes, I'll use $\mathcal{J}$ for the set of allowable jumps, *i.e.,* those $\boldsymbol{j}$ for which $q_{\boldsymbol{x},\boldsymbol{x}+\boldsymbol{j}} \neq 0$.

AN INDIVIDUAL-BASED STOCHASTIC FORMULATION

- We work with a continuous-time Markov chain with transitions

Jump	Rate
$(S_N, I_N) \to (S_N + 1, I_N)$	μN
$(S_N, I_N) \to (S_N - 1, I_N)$	μS_N
$(S_N, I_N) \to (S_N - 1, I_N + 1)$	$\frac{\beta}{N} S_N I_N$
$(S_N, I_N) \to (S_N, I_N - 1)$	$(\gamma + \mu) I_N$

- The corresponding master equation is, unfortunately, analytically intractable.

ASIDE #4: DENSITY DEPENDENT POPULATION PROCESSES (KURTZ, 1970)

- The SIR model is included in a broad class of models, that includes chemical reaction equations and many models of biological interest.
- Let $\{\lambda_j(\boldsymbol{x})\}_{j\in\mathcal{J}}$ be a collection of non-negative functions defined on a subset $E \subseteq \mathbb{R}^d_+$. Let $E^{(n)}$ be the set of (rescaled) lattice points in E:

$$E^{(n)} := E \cap \frac{1}{n}\mathbb{Z}^d,$$

  and assume that $\boldsymbol{x} \in E^{(n)}$ and $\lambda_j(\boldsymbol{x}) > 0$ imply $\boldsymbol{x} + n^{-1}\boldsymbol{j} \in E^{(n)}$.
- The *density dependent family* corresponding to the $\lambda_j(\boldsymbol{x})$ is a sequence $\{\bar{\boldsymbol{X}}^{(n)}\}$ of jump Markov processes such that $\bar{\boldsymbol{X}}^{(n)}$ has state space $E^{(n)}$ and intensities

$$q^{(n)}_{\boldsymbol{x},\boldsymbol{y}} = n\lambda_{n(\boldsymbol{y}-\boldsymbol{x})}(\boldsymbol{x}), \qquad \boldsymbol{x}, \boldsymbol{y} \in E^{(n)}.$$

- Can also allow rates that depend on n, $\lambda^{(n)}_{n(\boldsymbol{y}-\boldsymbol{x})}(\boldsymbol{x})$, provided $\lambda^{(n)}_{n(\boldsymbol{y}-\boldsymbol{x})}(\boldsymbol{x}) \to \lambda_{n(\boldsymbol{y}-\boldsymbol{x})}(\boldsymbol{x})$ as $n \to \infty$.

ASIDE #4: LAW OF LARGE NUMBERS (KURTZ, 1970)

- Let $\{\lambda_j^{(n)}(\boldsymbol{x})\}_{j\in\mathcal{J}}$ be as above and let $\{\bar{\boldsymbol{X}}^{(n)}\}$ be the corresponding density-dependent family.
- Assume that there exist functions $\{\lambda_j(\boldsymbol{x})\}_{j\in\mathcal{J}}$ such that

$$\lim_{n\to\infty}\sum_{\boldsymbol{j}\in\mathbb{Z}^K}\|\boldsymbol{j}\|\sup_{\boldsymbol{x}\in K}|\lambda_j^{(n)}(\boldsymbol{x})-\lambda_j(\boldsymbol{x})|=0 \quad\text{and}\quad \sum_{\boldsymbol{j}\in\mathcal{J}}\|\boldsymbol{j}\|\sup_{\boldsymbol{x}\in K}\lambda_j(\boldsymbol{x})<\infty$$

  for all compact sets $K\subset E$.
- Let $\mathbf{F}(\boldsymbol{x})=\sum_{j\in\mathcal{J}}\boldsymbol{j}\lambda_j(\boldsymbol{x})$. Suppose $\bar{\boldsymbol{X}}^{(n)}(0)\to\boldsymbol{x}_0$ and let $\bar{\boldsymbol{X}}(t,\boldsymbol{x}_0)$ satisfy

$$\frac{d}{dt}\bar{\boldsymbol{X}}=\mathbf{F}(\bar{\boldsymbol{X}}).$$

  with $\bar{\boldsymbol{X}}(0,\boldsymbol{x}_0)=\boldsymbol{x}_0$
- Then, for any fixed $T>0$,

$$\lim_{n\to\infty}\sup_{t\le T}|\bar{\boldsymbol{X}}^{(n)}(t)-\bar{\boldsymbol{X}}(t,\boldsymbol{x}_0)|=0 \quad \text{a.s.}$$

ASIDE #4: CENTRAL LIMIT THEOREM (KURTZ, 1971)

- Assume in addition that

$$\lim_{n\to\infty} \sqrt{n} \sum_{j\in\mathcal{J}} \|\boldsymbol{j}\| \sup_{x\in K} |\lambda_j^{(n)}(\boldsymbol{x}) - \lambda_j(\boldsymbol{x})| = 0 \quad \text{and} \quad \sum_{j\in\mathcal{J}} \|\boldsymbol{j}\|^2 \sup_{x\in K} \lambda_j(\boldsymbol{x}) < \infty.$$

- Let $\boldsymbol{V}^{(n)} = \sqrt{n}(\bar{\boldsymbol{X}}^{(n)} - \bar{\boldsymbol{X}})$ and suppose that $V^{(n)}(0) \to V(0)$.
- Then, $\boldsymbol{V}^{(n)} \Rightarrow \boldsymbol{V}$ in $\mathbb{D}_E[0,\infty)$, where $\boldsymbol{V}$ is an Ornstein-Uhlenbeck process with (Itô) SDE:

$$d\boldsymbol{V}(t) = \boldsymbol{J}(\bar{\boldsymbol{X}}(t,\boldsymbol{x}_0))\boldsymbol{V}(t)\,dt + \sum_{j\in\mathcal{J}} \boldsymbol{j}\sqrt{\lambda_j(\bar{\boldsymbol{X}}(t,\boldsymbol{x}_0))}\,dB_j(t)$$

  where $\boldsymbol{J}$ is the Jacobian of $\boldsymbol{F}$ (previous slide) and the B_j are independent Brownian motions.
- Intuitively: $\bar{\boldsymbol{X}}^{(n)} = \bar{\boldsymbol{X}}(t,\boldsymbol{x}_0) + \frac{1}{\sqrt{n}}\boldsymbol{V}(t) +$ lower order terms.

LAW OF LARGE NUMBERS FOR THE SIR MODEL

- On **finite** time intervals, the **densities** for the *Markov chain* $\frac{S_N(t)}{N}$, $\frac{I_N(t)}{N}$ converge to the solution of the Kermack-McKendrick ordinary differential equations:

$$\begin{aligned} \frac{dS}{dt} &= \mu - \beta SI - \mu S \\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I \end{aligned}$$

  almost surely as $N \to \infty$.
- Initial conditions

$$S(0) = \lim_{N\to\infty} \frac{S_N(t)}{N} \quad \text{and} \quad I(0) = \lim_{N\to\infty} \frac{I_N(t)}{N}.$$

MULTI-SCALE ANALYSIS

- However, if we assume that $I_N(t) \ll N$, then

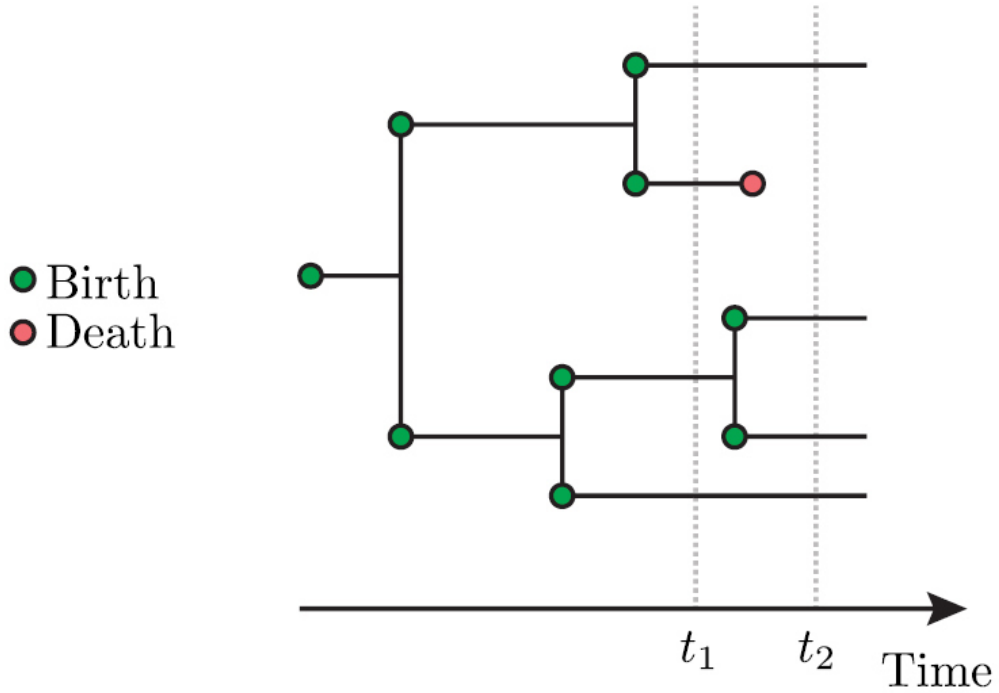
$$\lim_{N\to\infty} \frac{I_N(0)}{N} = 0.$$

- The law of large numbers doesn't "see" the infected individuals.
- If $S_N(0) = \Theta(N)$, then $S(0) > 0$, and we get a much simpler approximation for the *density* of susceptibles

$$\frac{dS}{dt} = \mu(1 - S),$$

- This has solution $S(t) = 1 + e^{-\mu t}(S(0) - 1)$.
- We need to characterize the **number** infected.

(BRANCHING) BIRTH AND DEATH PROCESSES



- Time-dependent individual infection rate $\beta \frac{S_N(t)}{N} \approx \beta S(t)$.
- Recovery and/or death rate $\gamma + \mu$.
- The number of infecteds is approximately birth (infections) and death (or recovery) process.
- This approximation holds exactly when the pathogen can go extinct: when first appearing, and at the end of a major outbreak.

Aside # 5: Monotone Coupling

Lemma

For $\varepsilon > 0$ sufficiently small, we can simultaneously construct $S_N(t)$, $I_N(t)$, and and supercritical time-inhomogeneous Markov birth-and-death processes $Z_{\pm\varepsilon}(t)$ with transition rates

$$\mathbb{P}\left\{Z_{\pm\varepsilon}(t+\Delta t) = Z_{\pm\varepsilon}(t) + 1\right\} = \beta\left(S(t) \pm \varepsilon\right) Z_{\pm\varepsilon}(t)\Delta t + o(\Delta t)$$
$$\mathbb{P}\left\{Z_{\pm\varepsilon}(t+\Delta t) = Z_{\pm\varepsilon}(t) - 1\right\} = (\mu+\gamma) Z_{\pm\varepsilon}(t)\Delta t + o(\Delta t)$$

such that

$$Z_{-\varepsilon}(t) \leq I_N(t) \leq Z_{+\varepsilon}(t)$$

for all t such that $I_N(t) \leq \varepsilon N$. Thus,

$$\mathbb{P}\left\{\sup_t I_N(t) \geq \varepsilon N\right\} \geq \mathbb{P}\left\{\sup_t Z_{-\varepsilon}(t) \geq \varepsilon N\right\}$$
$$\mathbb{P}\{I_N(t) = 0\} \geq \mathbb{P}\{Z_{+\varepsilon}(t) = 0\}$$

ASIDE # 5: MONOTONE COUPLING (SKETCH PROOF)

- Order individuals so that $Z_{-\varepsilon}(t) \subseteq I_N(t) \subseteq Z_{+\varepsilon}(t)$.
- Generate potential births and deaths at the fastest possible rate for all processes:
$$\beta(S(t)+\varepsilon)Z_{+\varepsilon}(t) \quad \text{and} \quad (\gamma+\mu)Z_{+\varepsilon}(t)$$
- Each potential birth is always a birth for $Z_{+\varepsilon}(t)$, and is a birth for $I_N(t)$ and $Z_{-\varepsilon}(t)$ with probabilities
$$\frac{S_N(t)I_N(t)}{N(S(t)+\varepsilon)Z_{+\varepsilon}(t)} \quad \text{and} \quad \frac{(S(t)-\varepsilon)Z_{-\varepsilon}(t)}{(S(t)+\varepsilon)Z_{+\varepsilon}(t)}$$
Add a "phantom individual" for each birth not occurring in $I_N(t)$.
- Each potential death is always a death for $Z_{+\varepsilon}(t)$, and is a birth for $I_N(t)$ and $Z_{-\varepsilon}(t)$ with probabilities
$$\frac{I_N(t)}{Z_{+\varepsilon}(t)} \quad \text{and} \quad \frac{Z_{-\varepsilon}(t)}{Z_{+\varepsilon}(t)}$$
Kill an individual in $Z_{-\varepsilon}(t)$, $I_N(t) \setminus Z_{-\varepsilon}(t)$ or $Z_{+\varepsilon}(t) \setminus I_N(t)$ accordingly.
- Refine Kurtz to show that either $Z_{-\varepsilon}(t) > \varepsilon N$ or $Z_{+\varepsilon}(t) = 0$ before $S_N(t) \notin [N(S(t)+\varepsilon), N(S(t)+\varepsilon)]$ with high probability.

Birth and Death Processes: Extinction Probabilities

Theorem (Kendall, 1948)

Let $Z(t)$ be a continuous time Markov birth-and-death process with transitions and rates given by

$$\mathbb{P}\{Z(t+\Delta t) = Z(t)+1\} = b(t)Z_t\Delta t + o(\Delta t)$$
$$\mathbb{P}\{Z(t+\Delta t) = Z(t)-1\} = d(t)Z_t\Delta t + o(\Delta t)$$

Then, the probability of extinction in finite time, q, is

$$\frac{\int_0^\infty e^{\int_0^s d(u)-b(u)\,du} d(s)\,ds}{1+\int_0^\infty e^{\int_0^s d(u)-b(u)\,du} d(s)\,ds},$$

which is equal to 1 if and only if the integral $\int_0^\infty e^{\int_0^s d(u)-b(u)\,du} d(s)\,ds$ diverges. If the process does not go extinct, it grows indefinitely.

OUTBREAK AND PERSISTENCE PROBABILITIES

- In particular, the probability of persistence starting from $(S(0) = S_0, I_N(0) = I_0)$ is asymptotically

$$\begin{aligned} \mathbb{P}\{I_N(t) = 0\} &= \left(\frac{\int_0^t e^{-\int_0^\tau \beta S(u) - \gamma - \mu \, du} (\gamma + \mu) \, d\tau}{1 + \int_0^t e^{-\int_0^\tau \beta S(u) - \gamma - \mu \, du} (\gamma + \mu) \, d\tau} \right)^{I_0} \\ S(t) &= 1 + e^{-\mu t}(S_0 - 1) \end{aligned}$$

- At the beginning of the outbreak $S(t) \approx S_0 \approx 1$ and one infected.
- Simplifies to give outbreak probability $\approx 1 - \frac{1}{\mathcal{R}_0}$.

EXACT EXPRESSIONS

In particular, setting $\kappa = \frac{\beta}{\mu}(1 - S_0)$ and $\theta = \frac{\beta-\gamma}{\mu} - 1$, the probability of burnout is

$$\left(\frac{(\gamma + \mu)e^{\kappa}\kappa^{-\theta}\gamma(\theta, \kappa)}{1 + (\gamma + \mu)e^{\kappa}\kappa^{-\theta}\gamma(\theta, \kappa)} \right)^{I_0}.$$

Where $\gamma(\theta, \kappa)$ is the incomplete γ-function:

$$\begin{aligned} \gamma(\theta, \kappa) &= \int_0^{\theta} e^{-x} x^{\kappa - 1}\, dx \\ &= e^{-\kappa}\kappa^{\theta} \sum_{n=0}^{\infty} \frac{\kappa^n}{\theta^{(n+1)}}, \end{aligned}$$

where $\theta^{(n)} = \theta(\theta + 1) \cdots (\theta + n - 1)$ is the Pochhammer symbol and the sum converges for all $\kappa > 0$.

PERSISTENCE PROBABILITIES

- To apply this to the probability of post-epidemic burnout, we need to choose an initial condition (S_0, I_0) that reflect the **end** of the initial epidemic.
- The law of large numbers tells us that the Kermack-McKendrick ODEs describe the process up to corrections of $o(N)$:

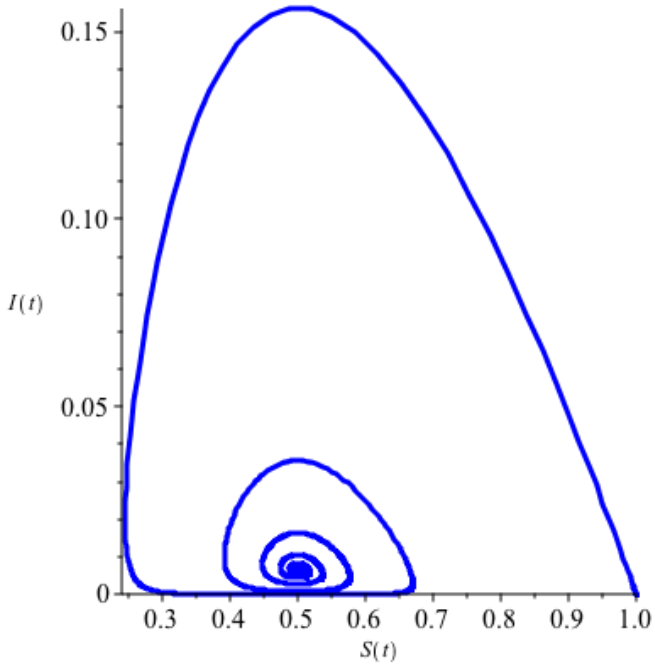
$$S_N(t) = NS(t) + o(N) \quad I_N(t) = NI(t) + o(N).$$

- If I_{min} is the minimum value attained by the ODE, and $1 \gg \delta \geq I_{min}$, take $I_0 = \lfloor \delta N \rfloor$.
- There is then a t_δ and S_δ such that $(S(t_\delta), I(t_\delta)) = (S_\delta, \delta)$.
- By the Law of Large Numbers, $\left(\frac{S_N(t_\delta)}{N}, \frac{I_N(t_\delta)}{N} \right) \to (S_0, \delta)$ a.s. as $N \to \infty$.
- Take $(S_0, I_0) = (S_\delta, \delta)$.

Outline

SIR PHASE PORTRAIT

$$\mathcal{R}_0 \approx 2, \gamma^{-1} = 13 \text{ days}, \mu = 0.001/\text{day}, N = 10^6.$$



$$S(0) = 1 - \tfrac{1}{N}, I(0) = \tfrac{1}{N}.$$

- Unfortunately, if $\mu > 0$, the SIR ODEs are analytically intractable, so we need to either numerically evaluate or approximate (t_δ, S_δ).
- Use the host mortality rate μ (*e.g.* $\approx 5 \times 10^{-5}$/day for humans) as a small parameter for asymptotic expansions.

OUTER APPROXIMATION

- For $\mu \ll 1$, we have

$$\frac{dI}{dS} = \frac{\beta SI - \gamma I - \mu I}{\mu(1-S) - \beta SI} \approx -1 + \frac{\gamma}{\beta}\frac{1}{S},$$

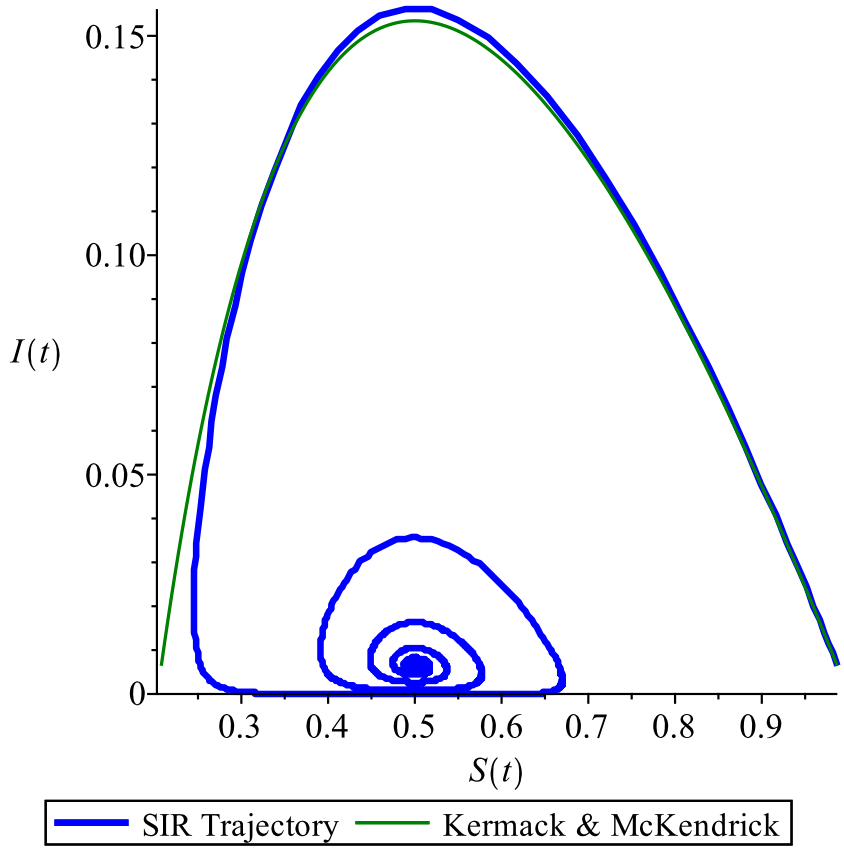
  which may be solved (Kermack & McKendrick, 1927) to yield

$$I = I_0 + (S_0 - S) + \frac{1}{\mathcal{R}_0} \ln\left(\frac{S}{S_0}\right).$$

- For large values of N, we can approximate $(S_0, I_0) = (1, 0)$.
- This gives a good approximation of the true trajectory where $\frac{dS}{dt} < 0$;
- Recognizing that maxima and minima of $I(t)$ occur when $S(t) = \frac{1}{\mathcal{R}_0}$, we see that $I_{max} \approx \left(1 - \frac{1}{\mathcal{R}_0}\right) + \frac{1}{\mathcal{R}_0} \ln\left(\frac{1}{\mathcal{R}_0}\right)$.

Outer Approximation

$\mathcal{R}_0 \approx 2, \gamma^{-1} = 13$ days, $\mu = 0.001/\text{day}, N = 10^6$.



$S(0) = 1 - \frac{1}{N}, I(0) = \frac{1}{N}$.

BOUNDARY LAYER APPROXIMATION

- To obtain the behaviour near the boundary, we assume $I(t) = \mu\iota(t)$.

$$\frac{d\iota}{dS} = \frac{1}{\mu}\frac{(\beta S - \gamma - \mu)\iota}{(1 - S - \beta S\iota)} \approx \frac{1}{\mu}\frac{(\beta S - \gamma)\iota}{(1 - S)}.$$

- Solve this to obtain "boundary-layer" solution

$$I(S) \approx \sqrt{\varepsilon} I_b \left(1 - \frac{1}{\mathcal{R}_0}\right) \left(\frac{1 - S_b}{1 - S}\right)^{\frac{\mathcal{R}_0 - 1}{\varepsilon}} e^{\frac{\mathcal{R}_0 (S_b - S)}{\varepsilon}}.$$

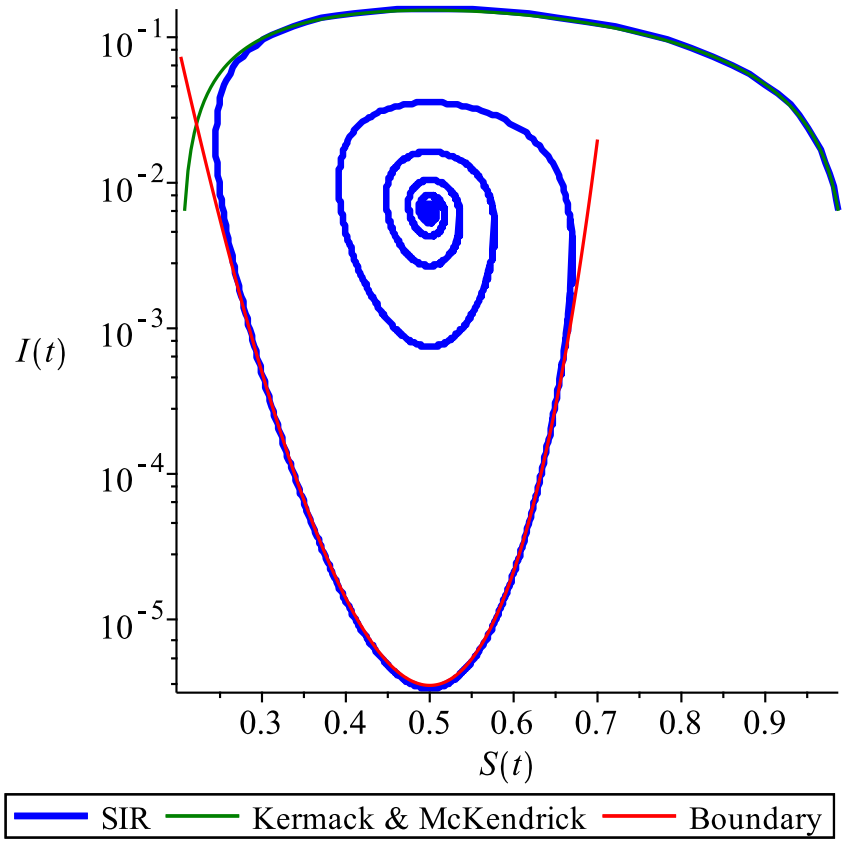
  for $\varepsilon = \frac{\mu}{\gamma + \mu}$, where (S_b, I_b) are the point of entry into the boundary (somewhat arbitrary).
- In practice, we take $I_b = \frac{\mu}{\beta}(\mathcal{R}_0 - 1)$ (the proportion at the endemic equilibrium), while to first approximation S_b solves

$$(1 - S_b) + \frac{1}{\mathcal{R}_0} \ln(S_b) = \frac{\mu}{\beta}(\mathcal{R}_0 - 1)$$

- Obtain analytical expressions for S_δ and the minimum infected, I_{min}.

Boundary Layer Approximation

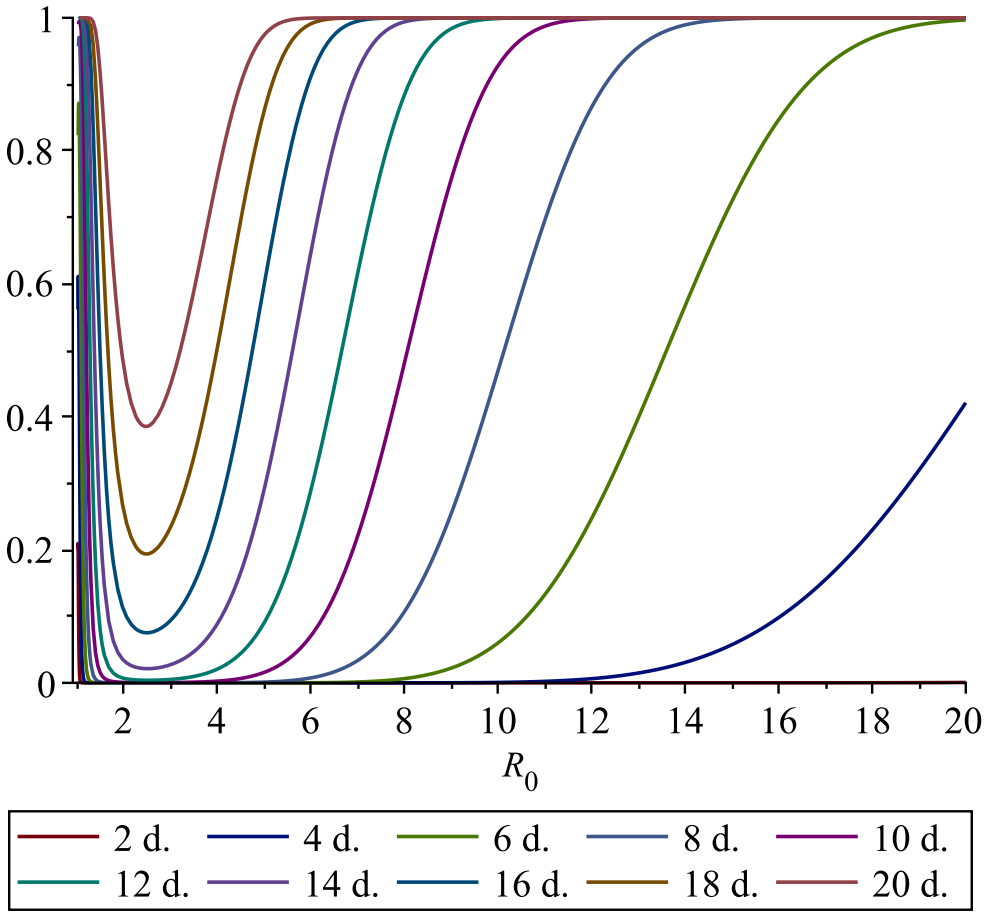
$\mathcal{R}_0 \approx 2$, $\gamma^{-1} = 13$ days, $\mu = 0.001/\text{day}$, $N = 10^6$.



$S(0) = 1 - \frac{1}{N}, I(0) = \frac{1}{N}$.

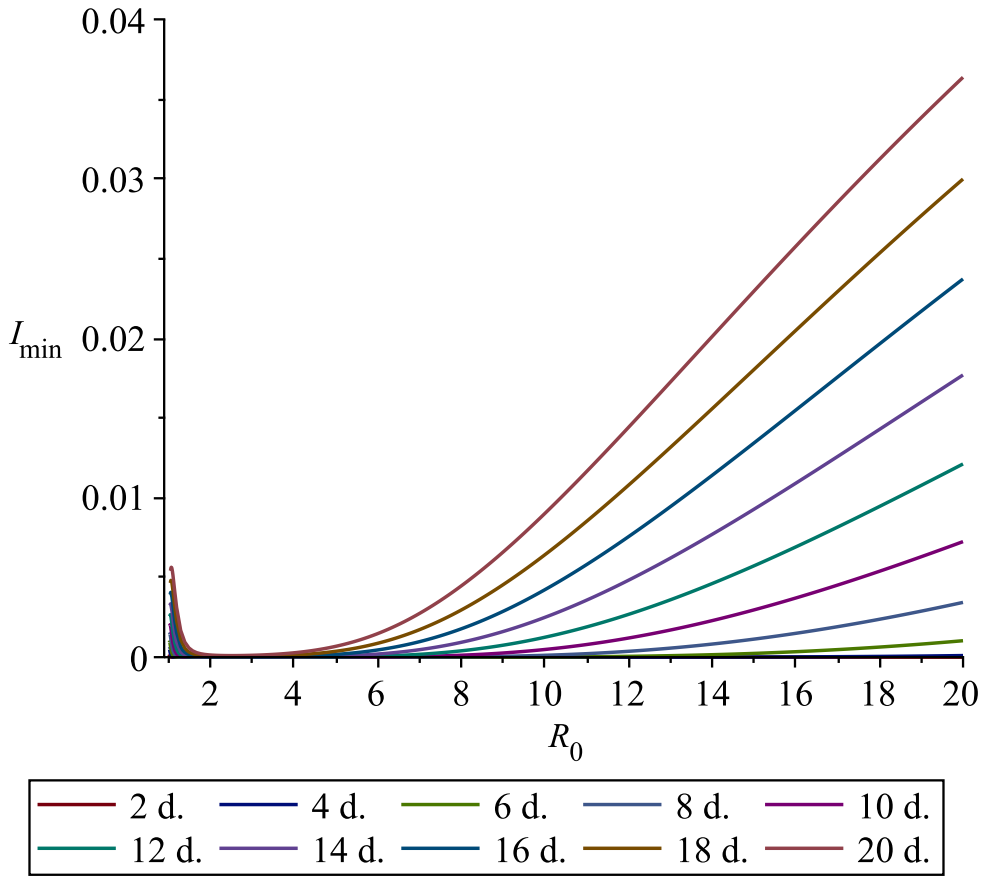
Outline

PROBABIILTY OF PERSISTENCE ($\mu \approx 0.001$/DAY)



Curves correspond to mean infectious period in days.
The probability of surviving the initial epidemic is maximized at $\mathcal{R}_0 \approx 1$ and at large values of $\mathcal{R}_0$, and for longer infectious periods.

$\mathcal{R}_0$ *vs.* I_{min} ($\mu \approx 0.001/\text{DAY}$)



I_{min} is minimized when $2 \leq \mathcal{R}_0 \leq 4$.

PIECING TOGETHER THE PUZZLE

Recall our approximation to the fade-out probability:

$$\mathbb{P}\{I_N(t) = 0\} = \left(\frac{\int_0^t e^{-\int_0^\tau \beta S(u) - \gamma - \mu \, du} (\gamma + \mu) \, d\tau}{1 + \int_0^t e^{-\int_0^\tau \beta S(u) - \gamma - \mu \, du} (\gamma + \mu) \, d\tau} \right)^{I_0}$$

- It depends not on the *current* density of susceptibles, but on the *future* density.
  - With demography, the susceptibles recover exponentially fast.
- It strongly depends on the number of infected individuals
  - Small or large values of $\mathcal{R}_0$ maximize the number of susceptibles remaining at the end of the first epidemic.
- **Caveat:** this is still insufficient to explain the persistence of *e.g.* measles. Other (extrinsic) mechanisms have been suggested:
  - Multiple introductions into the host population.
  - Spatial spread among cities promoting global persistence in spite of local fadeouts.
  - Invasion with low $\mathcal{R}_0$ followed by evolution to higher $\mathcal{R}_0$.

Outline

Joint With

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- Day *et al.* (2020) "The Price equation and evolutionary epidemiology" *Philos. Trans. Royal Soc. B.* 375 (1797) 20190357
- Parsons *et. al* (2018) "Pathogen evolution in finite populations: slow and steady spreads the best" *J. Royal Soc. Interface* 15 (47) 20180135

VIRULENCE

- The term virulence appears hazily throughout the epidemiological literature, often used to describe distinct aspects of a pathogen's disease-producing capacity:
  - infectivity: the ability to colonise and to invade a host, and
  - the severity of the disease produced.
- This is in part because there is evidence that these two quantities are positively associated: avenues of increasing transmission often involve more severe effects in hosts.
- We distinguish between transmissibility (β) from the virulence (α), which we define as the increase in the mortality rate in infected over non-infected hosts.

Attenuation of Virulence

Ongoing evidence that new host-pathogen associations tend to be more virulent (Read, 1994):

- As early as 1881, Pasteur observed the attenuation of anthrax bascillus.
- Myxomatosis, introduced into Australia in 1950 to control exploding rabbit populations initially had mortality rates of 99.8%, killing 85% of rabbits within 6–10 days of infection.
  - By 1957, mortality rates had declined to 50%, with those dying surviving 3–4 weeks after infection.
  - By infecting Australian and European rabbits with both current and originally introduced strains, Fenner & Marshall (1957) showed that this was due to both evolving resistance in rabbits and reduction in myxomatosis virulence.
- SIV (ancient) is less virulent than HIV (1970's)
- SARS-CoV-2 appears to be less virulent than SARS-CoV-1

The "Conventional Wisdom"

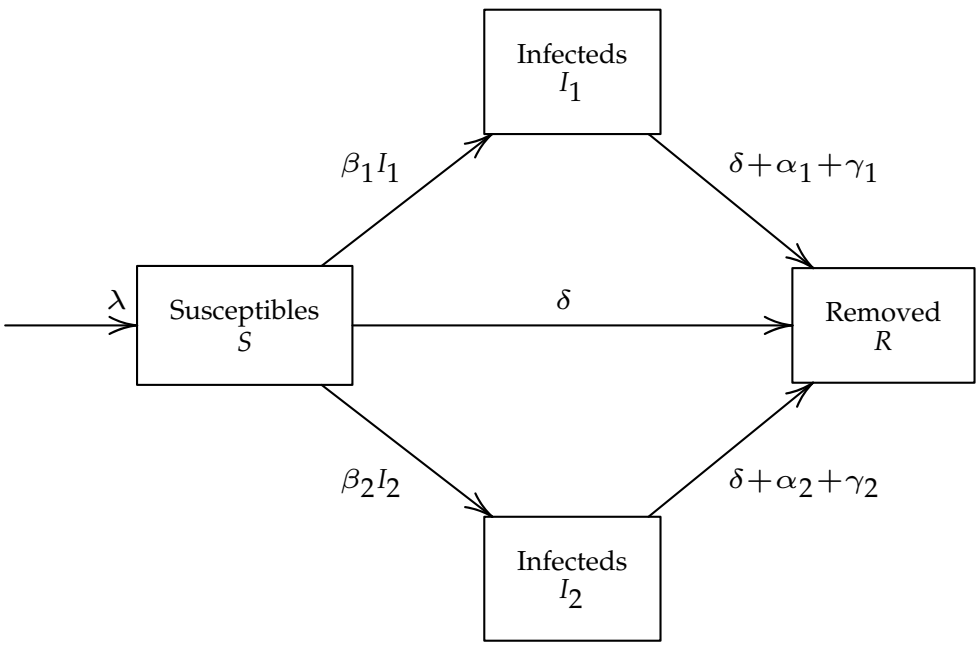
"[without] the early appearance and dominance of strains of virus which caused a lower mortality [...] rabbits would have been eradicated or greatly reduced in numbers, and the rabbit itself would have disappeared from such localities"

Fenner & Ratcliffe. Myxomatosis. Cambridge University Press, 1965.

"The 'conventional wisdom' that successful parasites have to become benign is not based on exact evolutionary thinking. Rather than minimizing virulence, selection will work to increase a parasite's reproductive rate."

Nowak & May (1994) Proc. R. Soc. Lond. B 255 (4): 81–89

SIR MODEL WITH DEMOGRAPHY



λ	immigration rate
δ	base mortality rate
β_i	infectivity, strain i
α_i	virulence, strain i
γ_i	recovery rate, strain i

Equilibrium Invasion

If strain one is already at its endemic steady state when strain two arrives, then it's probability of invading is

$$\begin{cases} 1 - \frac{\mathcal{R}_{(0,1)}}{\mathcal{R}_{(0,2)}} & \text{if } \mathcal{R}_{(0,2)} > \mathcal{R}_{(0,1)}, \text{ and} \\ 0 & \text{otherwise,} \end{cases}$$

This is consistent with $\mathcal{R}_0$ optimization.

Out-of-Equilibrium Invasion

If we start away from equilibrium, however, virulence matters:

- Let $I_1^\star$ be the endemic density of strain one.
- Suppose due to some (small) perturbation, it is instead at density $I_1 \neq I_1^\star$ when strain two appears.
- Strain two now has invasion probability

$$\left(1 - \frac{\mathcal{R}_{(0,1)}}{\mathcal{R}_{(0,2)}}\right)\left(1 - \frac{\mathcal{R}_{(0,1)}(\delta + \alpha_2 + \gamma_2)}{\lambda\mathcal{R}_{(0,1)} - \delta}(I_1 - I_1^\star)\right) + \mathcal{O}\left(\left(1 - \frac{\mathcal{R}_{(0,1)}}{\mathcal{R}_{(0,2)}}\right)^3\right)$$

- Recall $\mathcal{R}_{(0,2)} = \frac{\beta_2}{\delta+\alpha_2+\gamma_2}$. Any given value of $\mathcal{R}_{(0,2)}$ can be achieved infinitely many ways.
  - If $I_1 > I_1^\star$, among all those ways, those with the *lowest* virulence have the greatest invasion probability.
  - If $I_1 < I_1^\star$, those with the *highest* virulence have the greatest invasion probability.
- So, not only the ratio matters, but *how it is achieved*.
- Work in progress confirms that less virulent strains are more likely to escape fade-out.