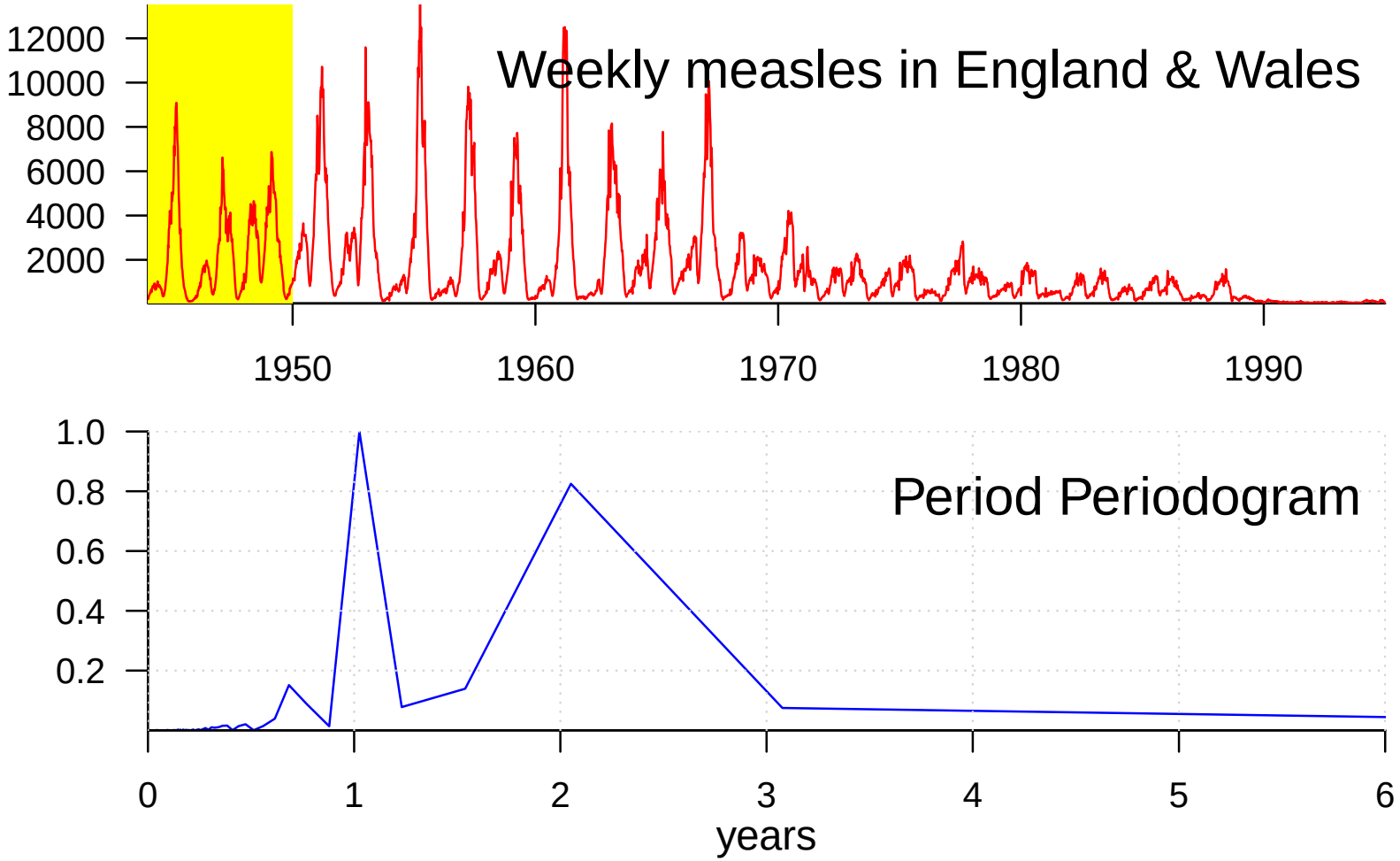
Mechanistic Modelling of Recurrent Epidemics

What causes changes in frequency content over time?



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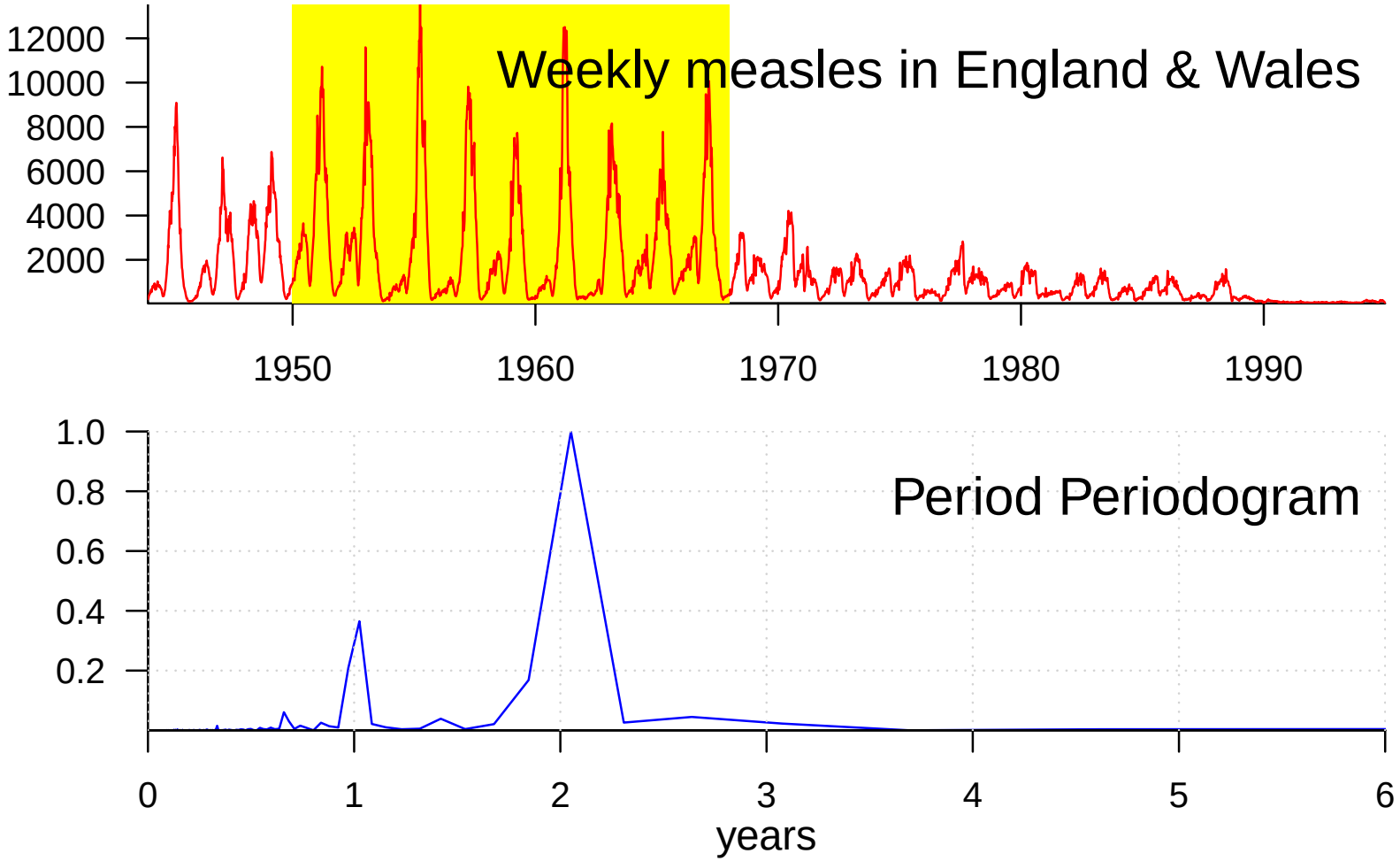

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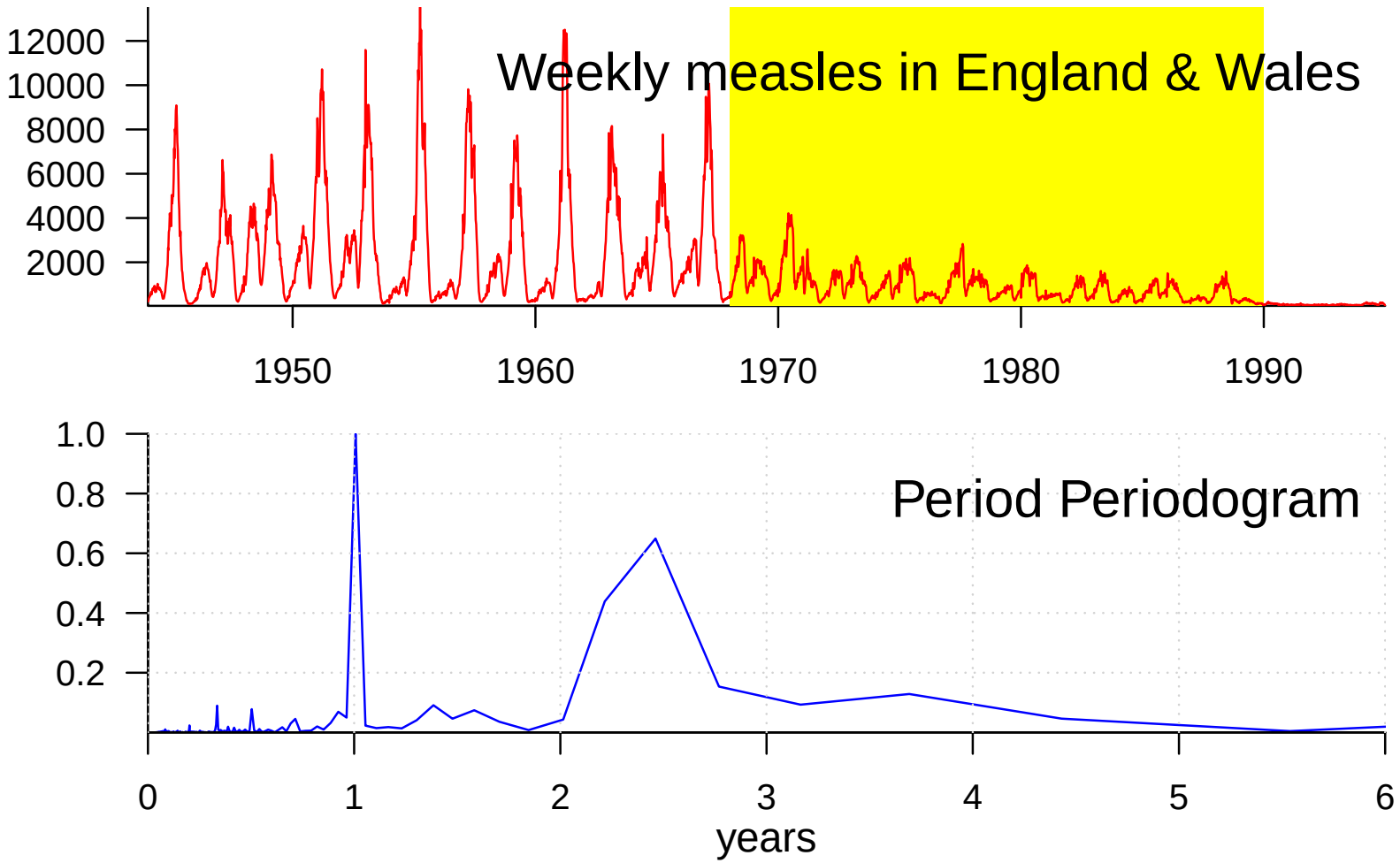
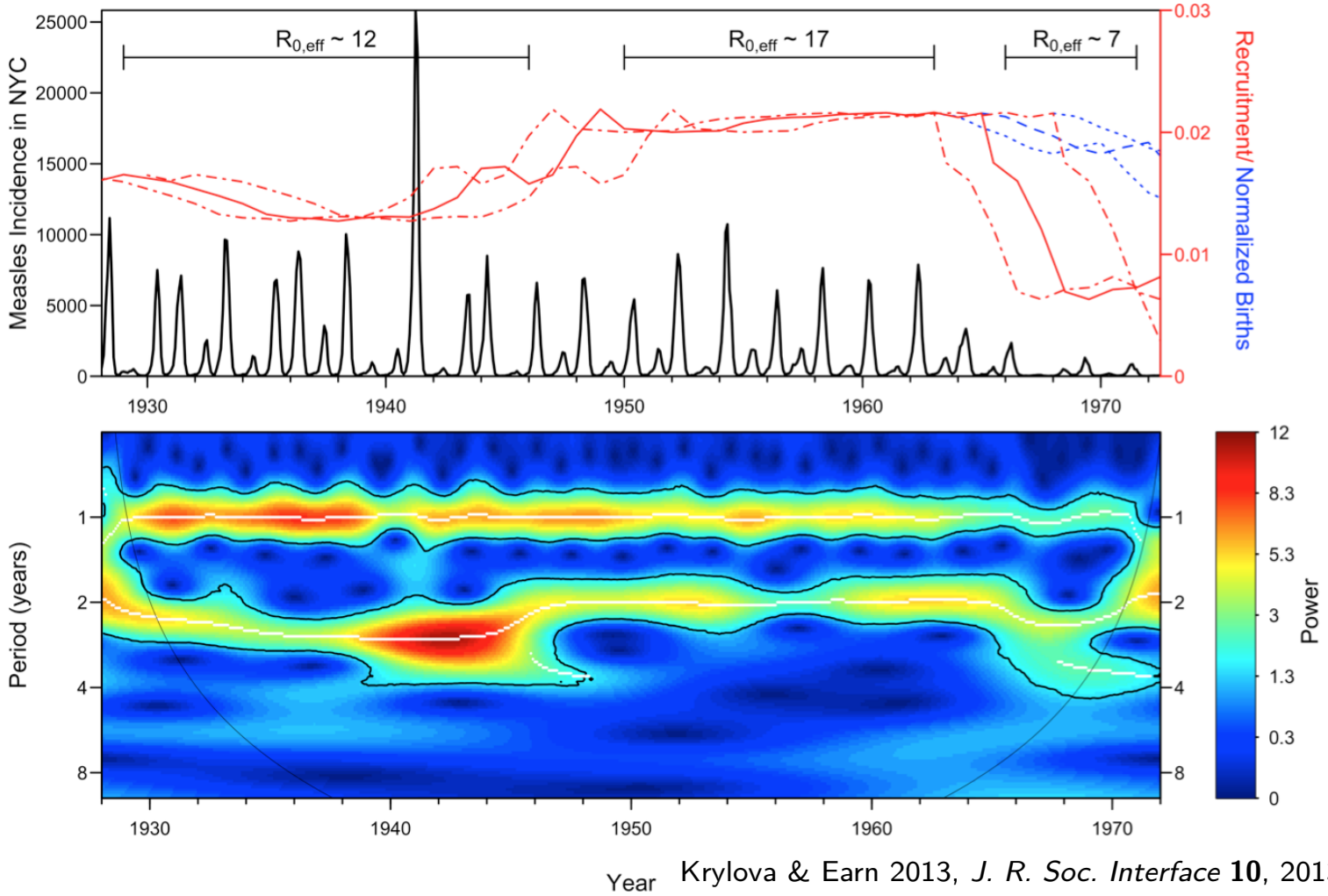


What causes changes in frequency content over time?

Measles in New York City

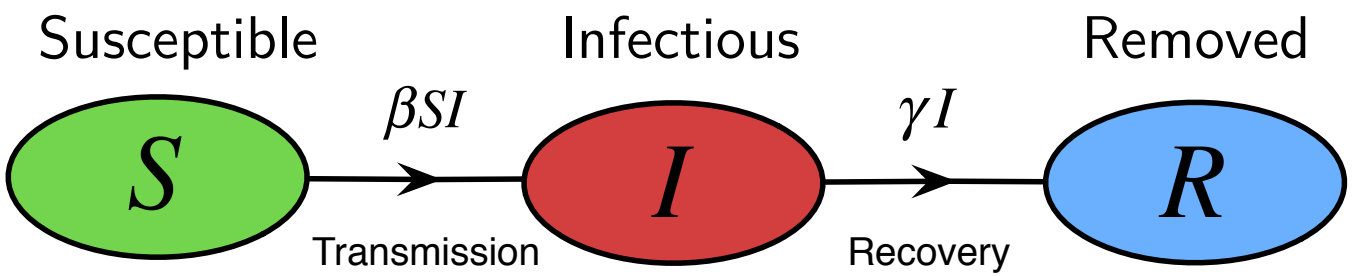


Krylova & Earn 2013, *J. R. Soc. Interface* **10**, 20130098

Mechanistic Epidemic Modelling: Principles

- Consider the biological mechanisms involved in disease transmission and spread
- Model mechanisms and infer their effects
- Start as simple as possible!
- Rule out simple models by comparing results with observed time series of incidence or mortality
- Add complexity one step at a time, so key mechanisms can be identified
- Ideally converge on simplest possible model that can explain observed patterns

The SIR model: Flow Chart and Parameters



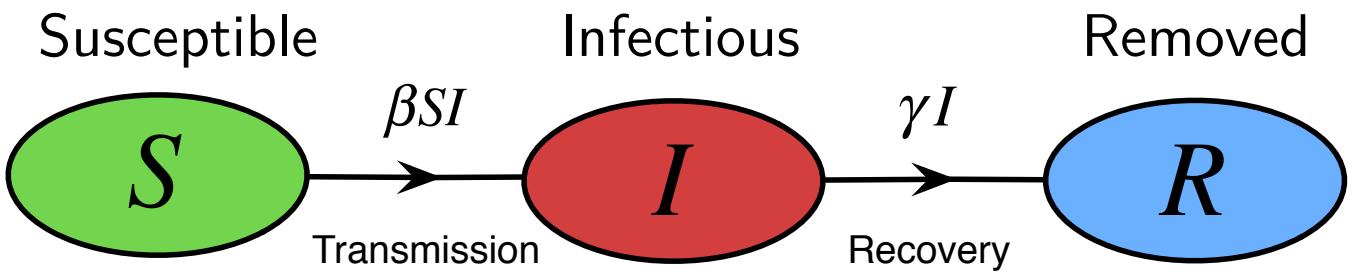
$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

- **Parameters:**
  - Transmission rate β
  - Recovery rate γ
    (or Removal rate)

The SIR model: Derived Parameters



$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

- **Derived Parameters:**
  - Initial growth rate $\beta - \gamma$
  - Mean infectious period $\frac{1}{\gamma}$
  - Basic Reproduction Number

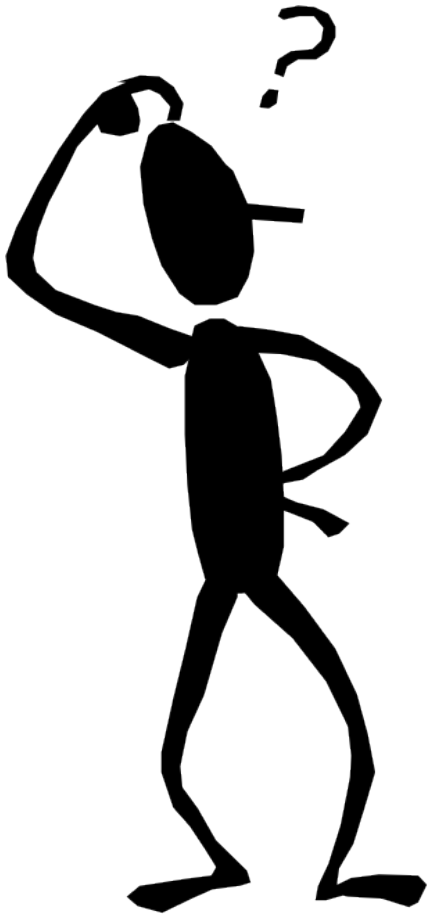
$$\mathcal{R}_0 = \frac{\beta}{\gamma}$$

Basic SIR Model: Important Results

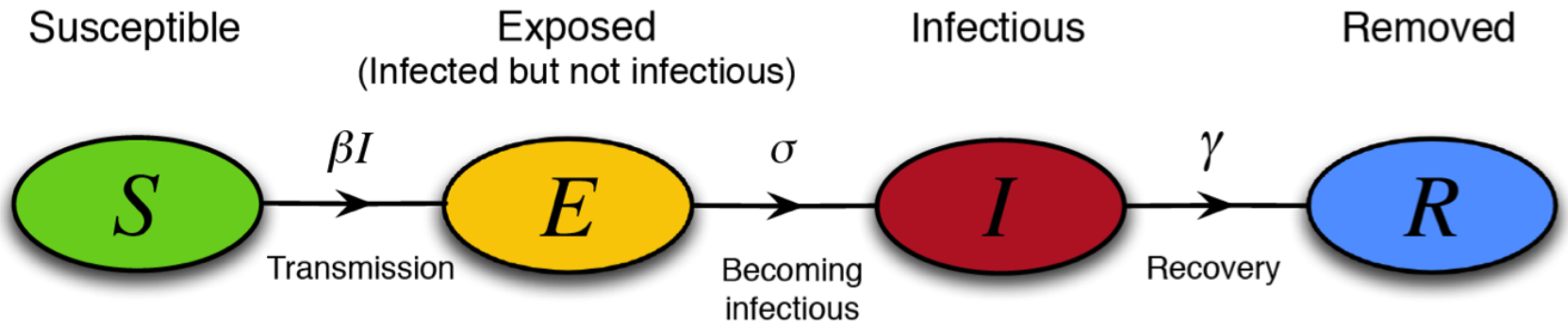
- Epidemic occurs if and only if $\mathcal{R}_0 > 1$
- Exact solution for phase portrait
- Single epidemic, then disease disappears
- Exact formula for final size as a function of $\mathcal{R}_0$

- Cannot explain diseases that persist
- Cannot explain recurrent cycles of epidemics

What are we missing?

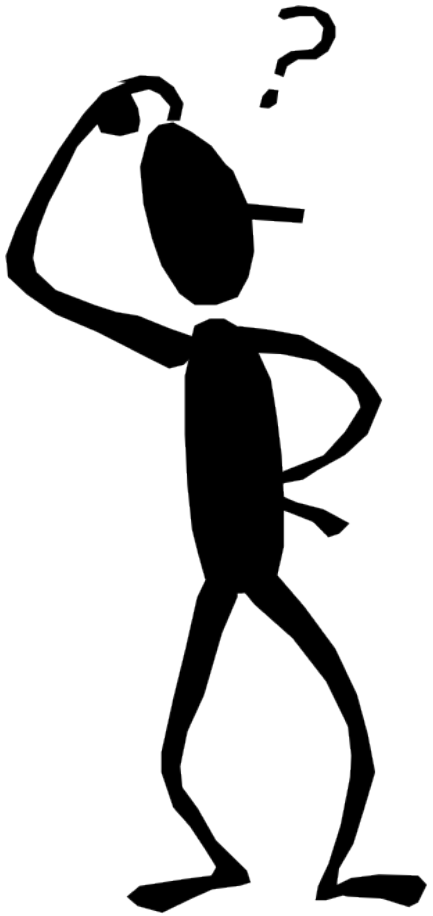


SEIR Model: flow chart

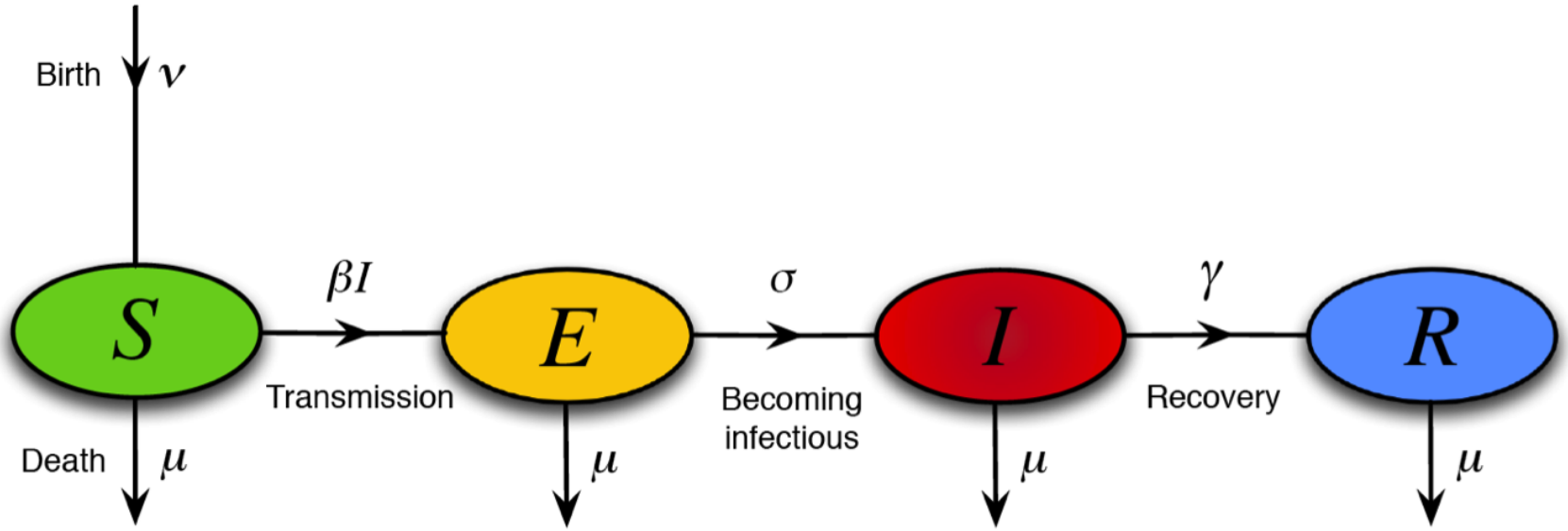


- Introduces only one new parameter (σ)
- Mean latent period ($1/\sigma$) can often be estimated
- But... effect of inclusion of exposed class usually small

What are we still missing?



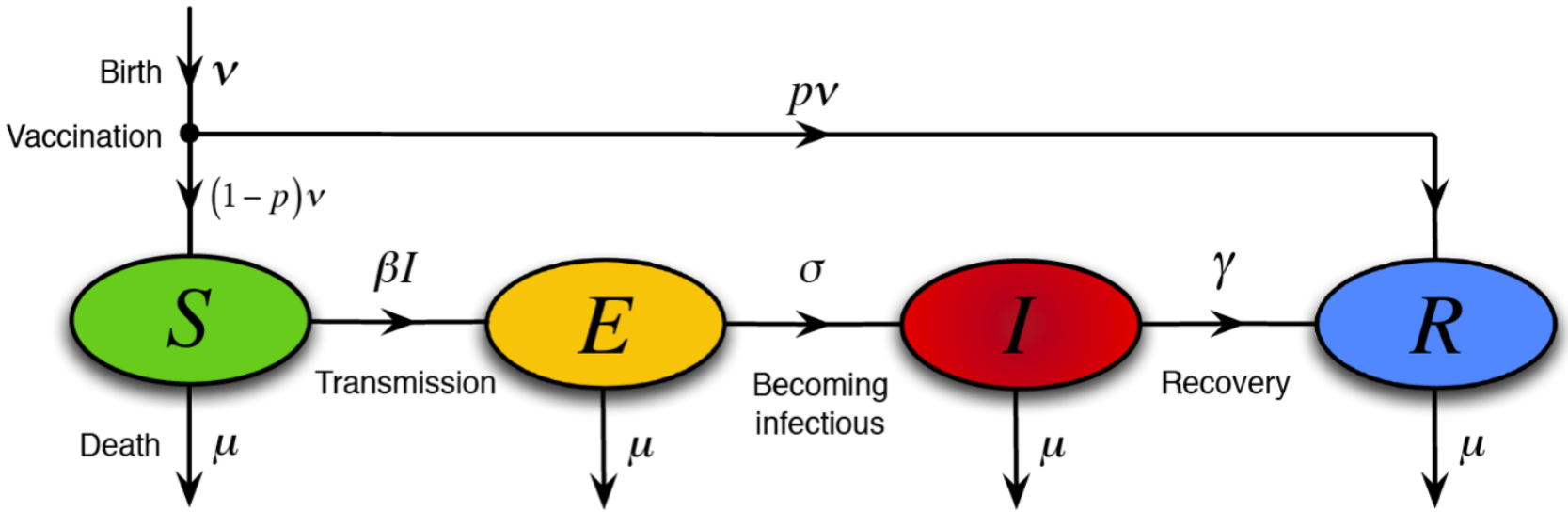
SEIR Model with vital dynamics: flow chart



New Parameters:

- Birth rate (ν for natality)
- Death rate (μ for mortality)
- Mean latent period ($1/\sigma$)

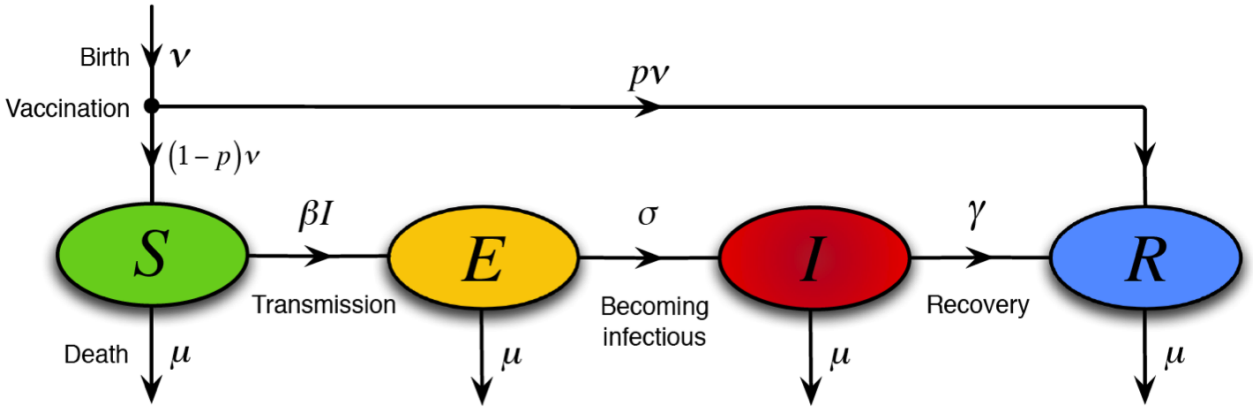
SEIR with vital dynamics and vaccination: flow chart



New Parameters:

- Birth rate (ν for natality)
- Death rate (μ for mortality)
- Mean latent period ($1/\sigma$)
- Proportion vaccinated (p)

SEIR with vital dynamics and vaccination: Equations



$$\frac{dS}{dt} = \nu(1-p) - \beta SI - \mu S$$

$$\frac{dE}{dt} = \beta SI - \sigma E - \mu E$$

$$\frac{dI}{dt} = \sigma E - \gamma I - \mu I$$

$$\frac{dR}{dt} = \nu p + \gamma I - \mu R$$

- Birth rate (ν for natality)
- Death rate (μ for mortality)
- Proportion vaccinated (p)
- Transmission rate (β)
- Mean latent period ($1/\sigma$)
- Mean infectious period ($1/\gamma$)

SEIR with vital dynamics and vaccination: Analysis

- $\mathcal{R}_0$?
  - Biological derivation: (assuming $\nu = \mu$ and $p = 0$)
    $\mathcal{R}_0 = \beta \times \frac{\sigma}{\sigma+\mu} \times \frac{1}{\gamma+\mu} \quad \simeq \frac{\beta}{\gamma} \quad \because \frac{1}{\mu} \gg \max\left(\frac{1}{\sigma}, \frac{1}{\gamma}\right)$
  - Mathematical derivation:
    $\mathcal{R}_0 = 1$ is stability boundary
- Final size ? Not well defined (because of continuous source of new susceptibles).
- Equilibria ?
  - Disease Free Equilibrium (DFE)
  - Endemic Equilibrium (EE)
  - That's all folks.
- Periodic solutions ? No.
- What else ? Chaos?

McMaster University

Mathematics and Statistics

$$\int_M d\omega = \int_{\partial M} \omega$$

Mathematics 4MB3/6MB3 Mathematical Biology

Instructor: David Earn

Lecture 5
Mechanistic Modelling of Recurrent Epidemics
Monday 7 October 2019

Announcements

- **Assignment 2:** Due TODAY by e-mail before class.
  Do the Group contribution survey for Assignment 2 TODAY.
  Read my solutions and ask if you don't understand them.

- **Assignment 3** is posted.
  Due Monday 21 October 2019 before class

- **Midterm test:**
  - *Date:* Monday 4 November 2019
  - *Time:* 11:30am–1:30pm
  - *Location:* in class, ETB-237

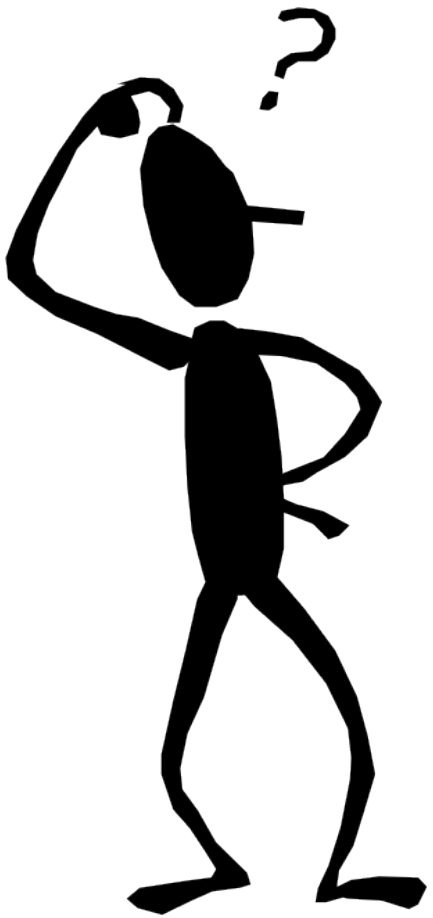
Attendance

Who is here?

SEIR with vital dynamics and vaccination: Results

- $\exists$ Endemic Equilibrium $\iff \mathcal{R}_0(1-p) > 1$
  - EE is GAS in this case.
  - DFE is GAS otherwise.
- Eradication $\iff p > 1 - \frac{1}{\mathcal{R}_0}$ (herd immunity)
  - Smallpox: $\mathcal{R}_0 \sim 4 \implies p_{\text{crit}} \sim 75\%$
  - Measles: $\mathcal{R}_0 \sim 20 \implies p_{\text{crit}} \sim 95\%$
- Explains persistence of diseases (via births)
- No periodic solutions $\overset{?}{\implies}$ no recurrent epidemics
- GAS equilibrium $\implies$ no periodic solutions and no chaos
- Equilibrium approached by *damped oscillations* $\implies$ recurrent epidemics
- But observed epidemic patterns show *undamped* oscillations. . .

What are we STILL missing?



Demographic Stochasticity

- Differential equations describe the expected behaviour in the limit that the population size goes to infinity
- How do dynamics differ in finite populations?
- Re-cast the SEIR model as a stochastic process (Continuous time Markov process)
- Proving anything about stochastic epidemic models is difficult, but we can easily simulate them and learn a lot
- Standard algorithm for creating realizations of a stochastic epidemic model attributed to Daniel T. Gillespie

Gillespie 1976, *J. Comp. Phys.* **22**, 403–434

  - Rather than rates of change of compartment sizes consider event rates for transitions between disease states
  - Finite number of individuals
  - Assume event rates depend only on current state of population

Gillespie Algorithm

- Let a_1, a_2, ..., be the rates at which the various processes occur, *e.g.*,
  - a_1 = birth rate,
  - a_2 = rate of going from susceptible to exposed,
  - a_3 = the rate of going from infectious to removed (recovering),
  - *etc.*
- Let a_0 be the overall event rate, *i.e.*, $a_0 = \sum_i a_i$ (so average time between events $= 1/a_0$).
- Assume time spent in any state is exponentially distributed (transitions between states are "Poisson processes")
- $\therefore$ Probability next event occurs in $(t, t+dt)$ is $a_0 e^{-a_0 t} dt$
- Let $u = 1 - e^{-a_0 t}$. Then $u \in [0,1]$ and $du = a_0 e^{-a_0 t} dt$ $\implies$ u is uniformly distributed in $[0,1]$.
- $\therefore$ Get time t to next event by sampling u from uniform distribution in $[0,1]$ and setting $t = \frac{1}{a_0} \ln \frac{1}{1-u}$.

Gillespie Algorithm continued

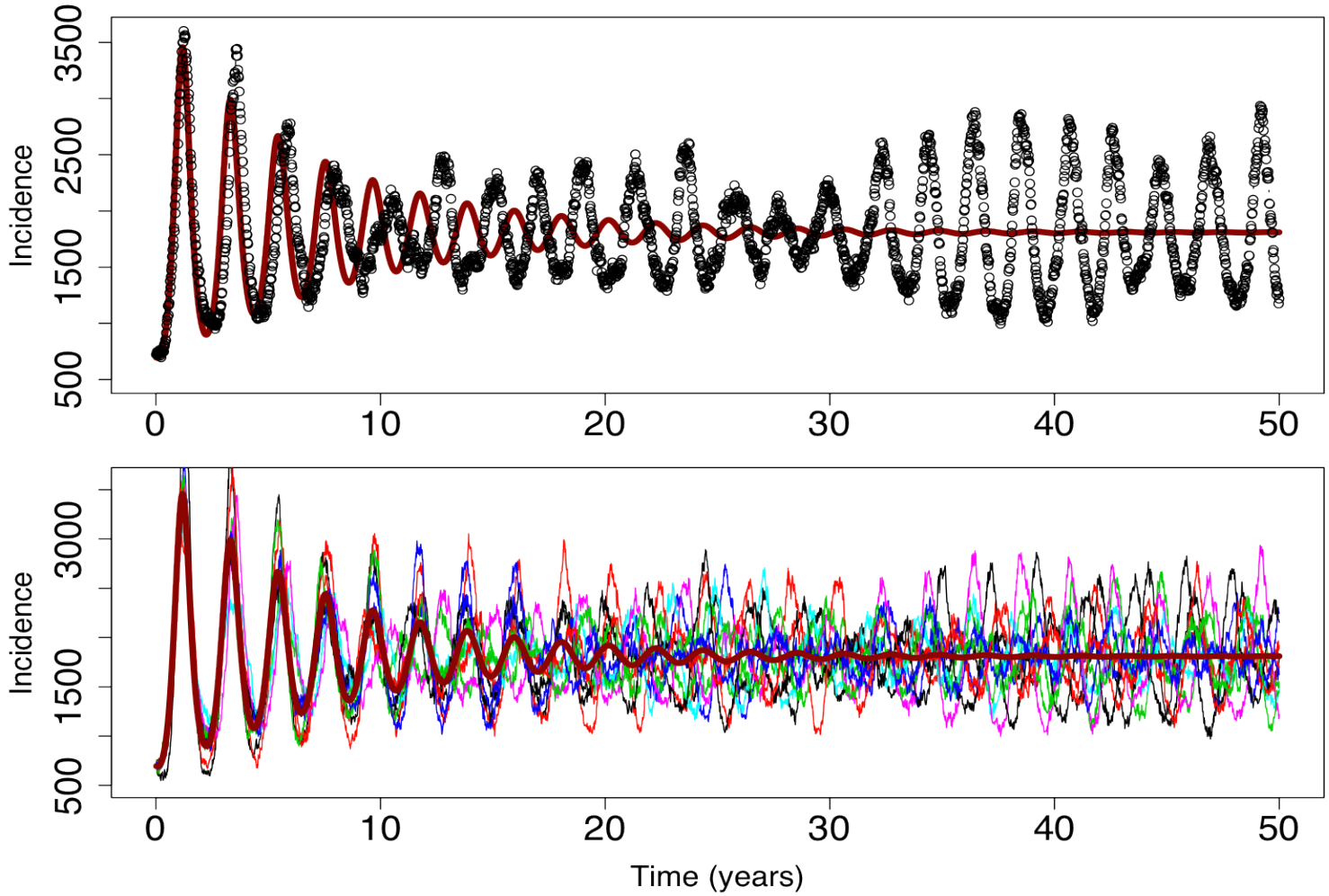
- We now know the time t of the next event, but we must still determine what type of event occurs at time t.
- Probability of event of type i is $\dfrac{a_i}{a_0}$
- $\therefore$ Can easily determine type of event by sampling a point from a uniform distribution on $[0, a_0]$:
  - Event is type i if the uniform deviate lies in the ith interval in the following list:

$$[0, a_1),\ [a_1, a_1 + a_2),\ \ldots,\ [a_1 + \cdots + a_{i-1}, a_1 + \cdots + a_i),\ \ldots$$

- How do realizations of this process differ from the solution of the deterministic (differential equation) model?

Gillespie Simulations: Results for Measles Parameters

$\mathcal{R}_0 = 17$, $T_{\rm lat} = 8$ days, $T_{\rm inf} = 5$ days, $\nu = \mu = 0.02$/year, $N = 5,000,000$

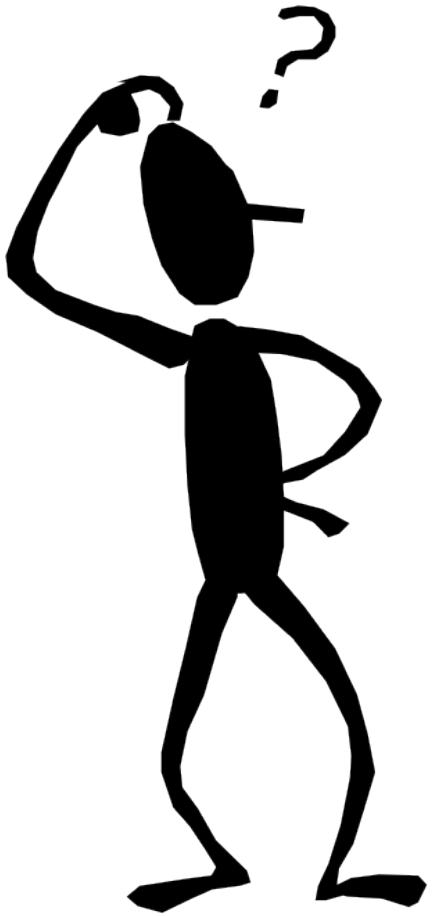


Earn 2009, *IAS/Park City Mathematics Series* **14**, 151–186

Effects of Demographic Stochasticity

- Sustains transient behaviour (oscillations do not damp out) (Bartlett 1950's)
- Explains undamped oscillations at a single period
- But, unable to explain changes in interepidemic period, or irregularity

What are we **STILL** missing?



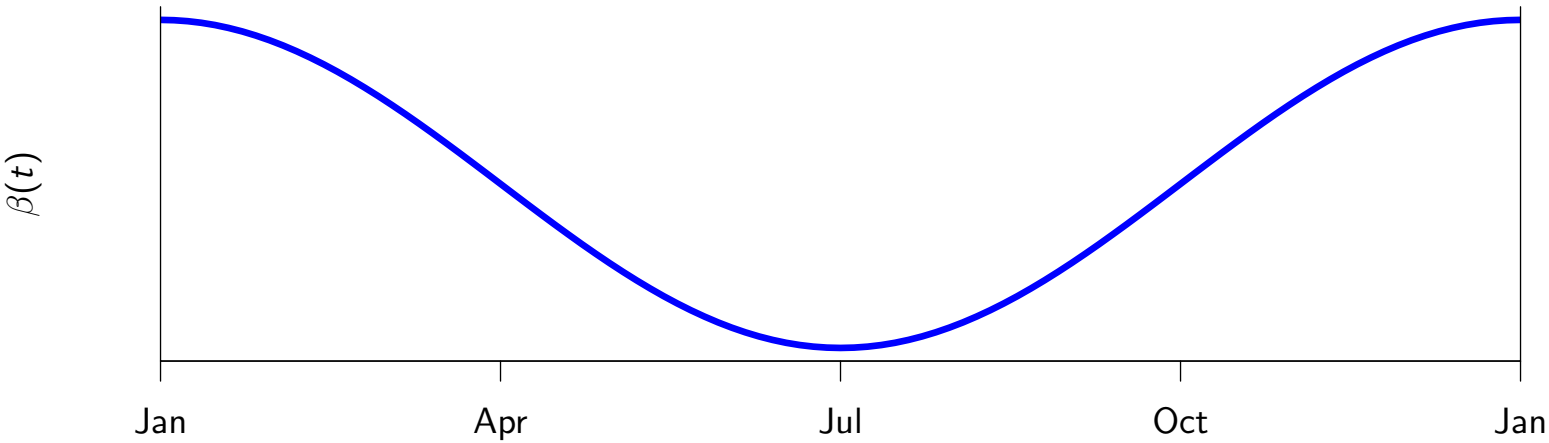
Contact rates are higher during school terms!

Sinusoidal SEIR Model

- Transmission rate β is not constant:
  high during school terms, low in summer
- For simplicity, model as a sine wave:

$$\beta(t) = \langle\beta\rangle\,(1 + \alpha\cos 2\pi t)$$

  - $\langle\beta\rangle$ = mean transmission rate
  - α = amplitude of seasonal variation in contact rate



Is this change significant?

- We now have a forced nonlinear system
- Forcing frequency can resonate with the natural timescales of the disease (*e.g.*, damping period)
- Very rich dynamical system. . .
  (analogy: forced pendulum)

Sinusoidal SEIR Model: Numerical Results

- Stable cycles of various lengths (annual, biennial, 3-year, . . .)
- Multiple co-existing stable cycles
- Chaotic dynamics
- Lots of work on this model in 1980s and 1990s

Smith HL, 1983, *J. Math. Biol.* **17**, 163–177

Schwartz IB, Smith HL, 1983, *J. Math. Biol.* **18**, 233–253

Aron JL, Schwartz IB, 1984, *J. theor. Biol.* **110**, 665-679

Olsen LF, Schaffer WM, 1990, *Science* **249**, 499–504

. . .

Sinusoidal SEIR Model: Rigorous Results

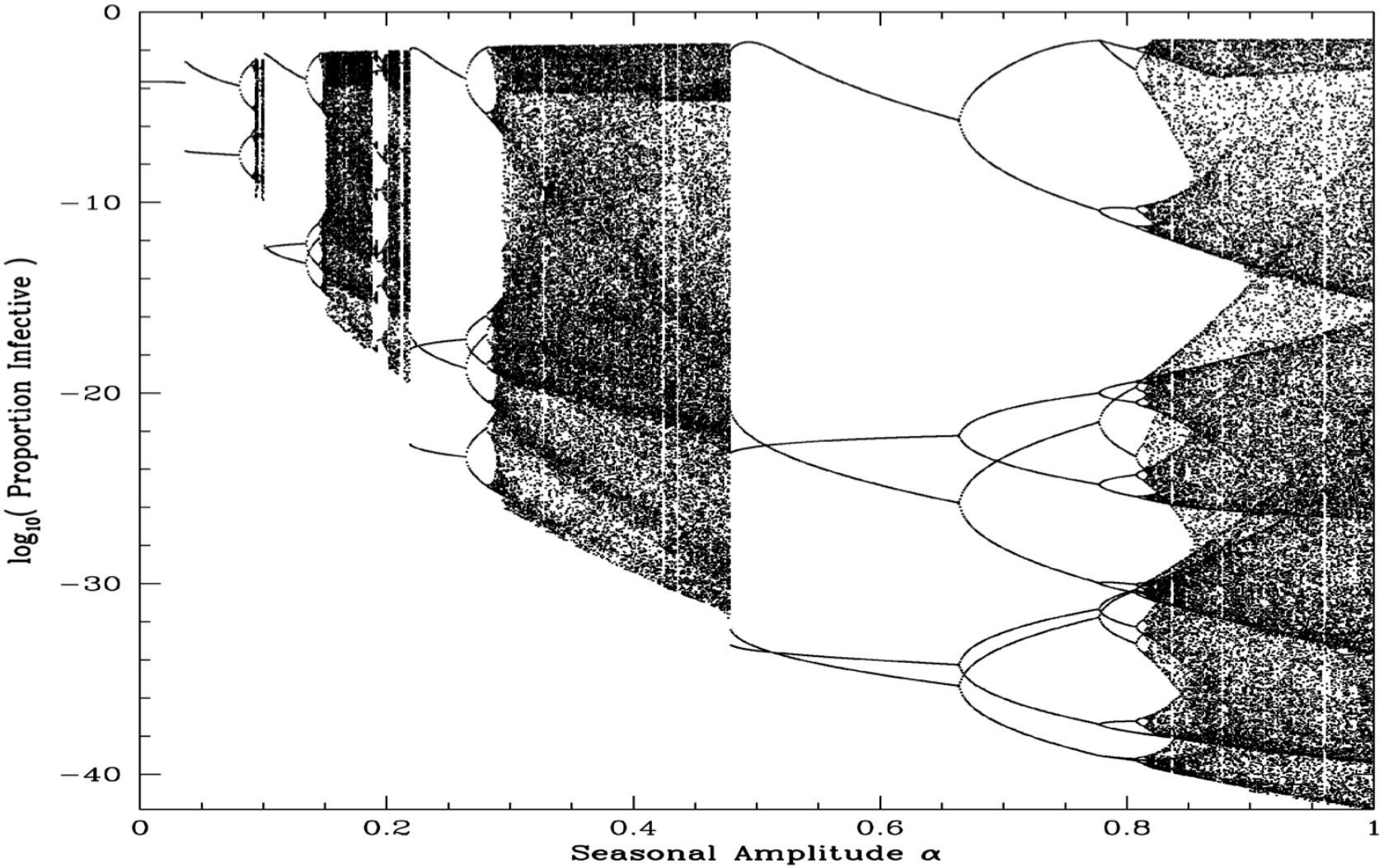
- There exist parameter values such that infinitely many stable cycles co-exist

Schwartz IB, Smith HL, 1983, *J. Math. Biol.* **18**, 233–253

- There exist chaotic repellors (in a modified SEIR model)

Glendinning P, Perry LP, 1997, *J. Math. Biol.* **35**, 359–373

Measles Bifurcation Diagram (Sinusoidal SEIR model)



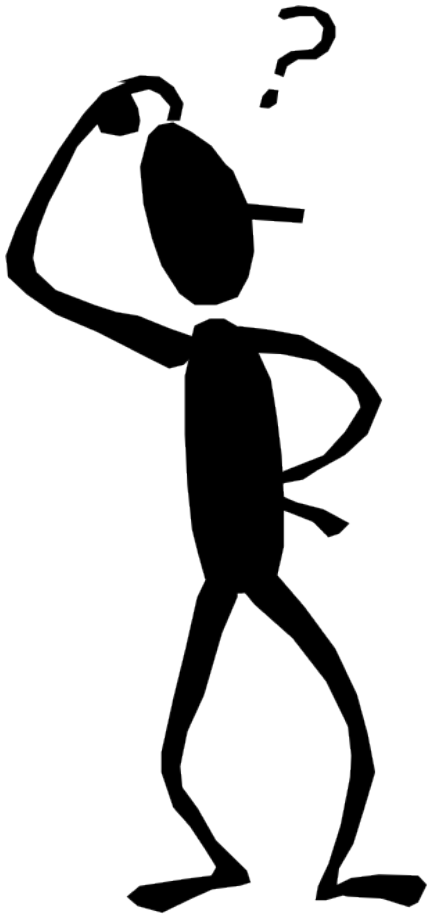
Earn (2009) *IAS/Park City Mathematics Series* **14**, 151–186

Does Sinusoidal SEIR Model Explain Measles Dynamics?

SEIR model with sinusoidal forcing:

- Produces recurrent undamped epidemics of all frequencies observed in measles time series.
- Produces chaos, which can explain irregular behaviour and transitions from one type of cycle to another
  - If correct, this implies these transitions are *unpredictable*.
- BUT... the model also predicts rapid extinction of the virus (not persistence).

What are we **STILL** missing?



Is Age Structure Important?

- Real system is not homogeneously mixed
- Contact structure is age-dependent

- Schenzle (1984) argued for creating a Realistically Age-Structured (RAS) SEIR model
  - 21 age classes (0–1, 1–2, . . . , 19–20, > 20)
  - SEIR compartments for each age class
  - Different contact rates between all these age classes

$$\beta(t) \quad \longrightarrow \quad \begin{pmatrix} \beta_{1,1}(t) & \beta_{1,2}(t) & \cdots & \beta_{1,21}(t) \\ \beta_{2,1}(t) & \beta_{2,2}(t) & \cdots & \beta_{2,21}(t) \\ \vdots & \vdots & \ddots & \vdots \\ \beta_{21,1}(t) & \beta_{21,2}(t) & \cdots & \beta_{21,21}(t) \end{pmatrix}$$

Schenzle D (1984) *IMA Journal of Mathematics Applied in Medicine and Biology* **1**, 169–191

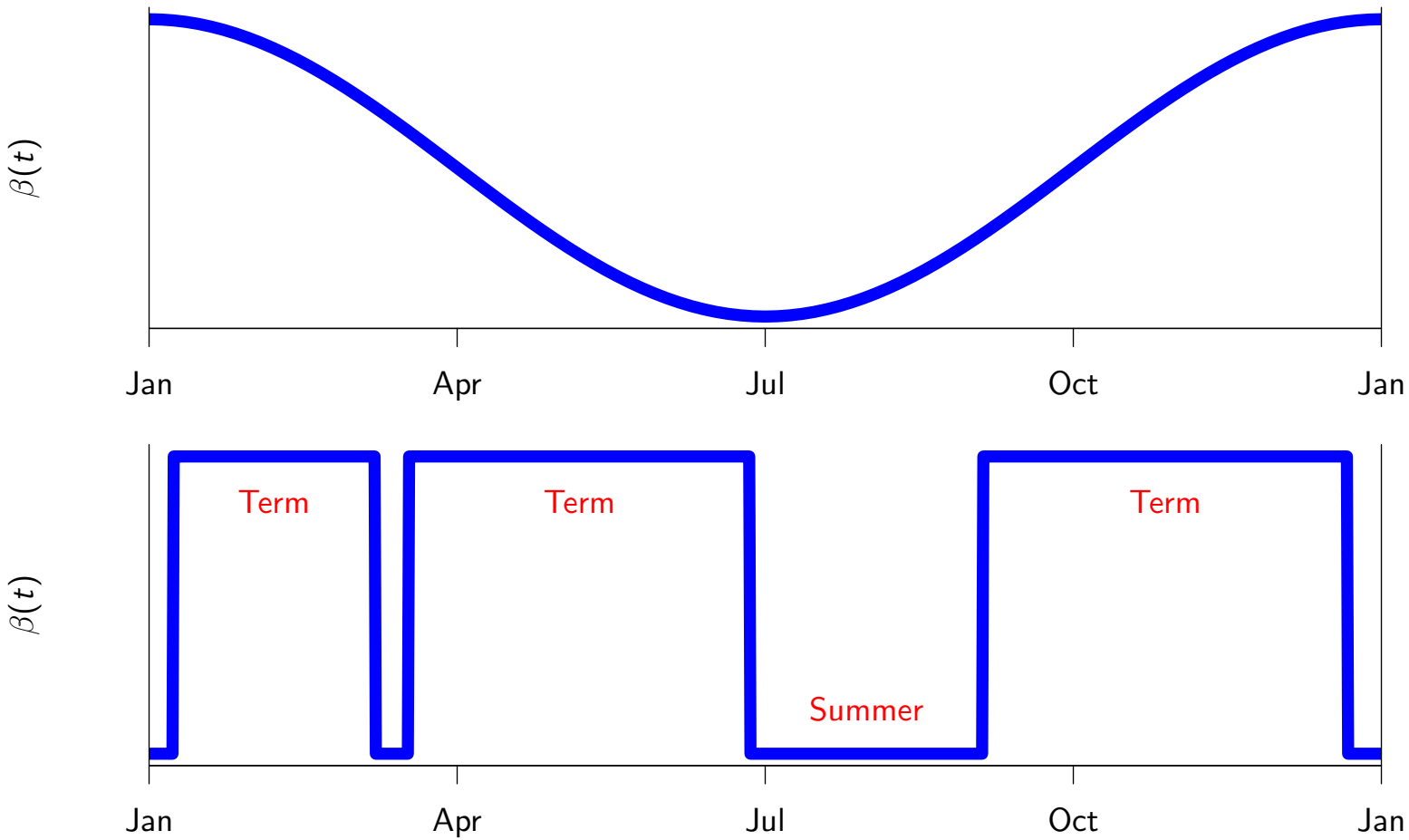
- Lots of work on RAS models since Schenzle (1984)

RAS SEIR model: Results for Measles

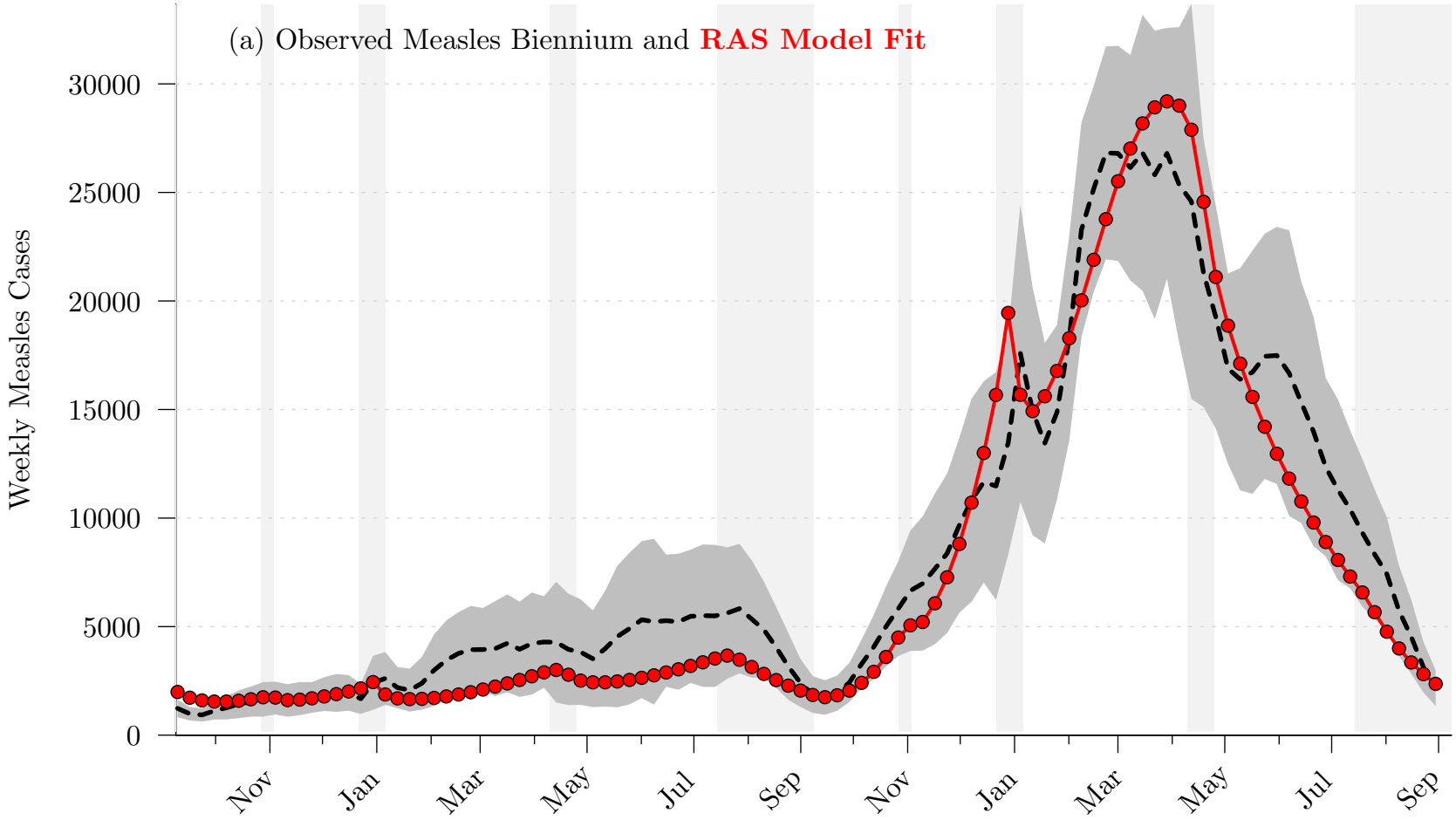
- Persistent biennial cycle
- Matches biennial cycle in data extremely well
- And we need only 84 ODEs
  and fewer than 500 new parameters!
- Can get an even better fit by adding spatial structure
  with 6000 ODEs and only 1500 new parameters!
- ***Woohoo!*** Time to celebrate.
- hmmm. . . maybe not. . .
- In fact, age structure is a **RED HERRING!**
- Critical ingredient of RAS model is. . .

Contact rates are higher during **school terms!**

Sinusoidal forcing vs Term-time forcing

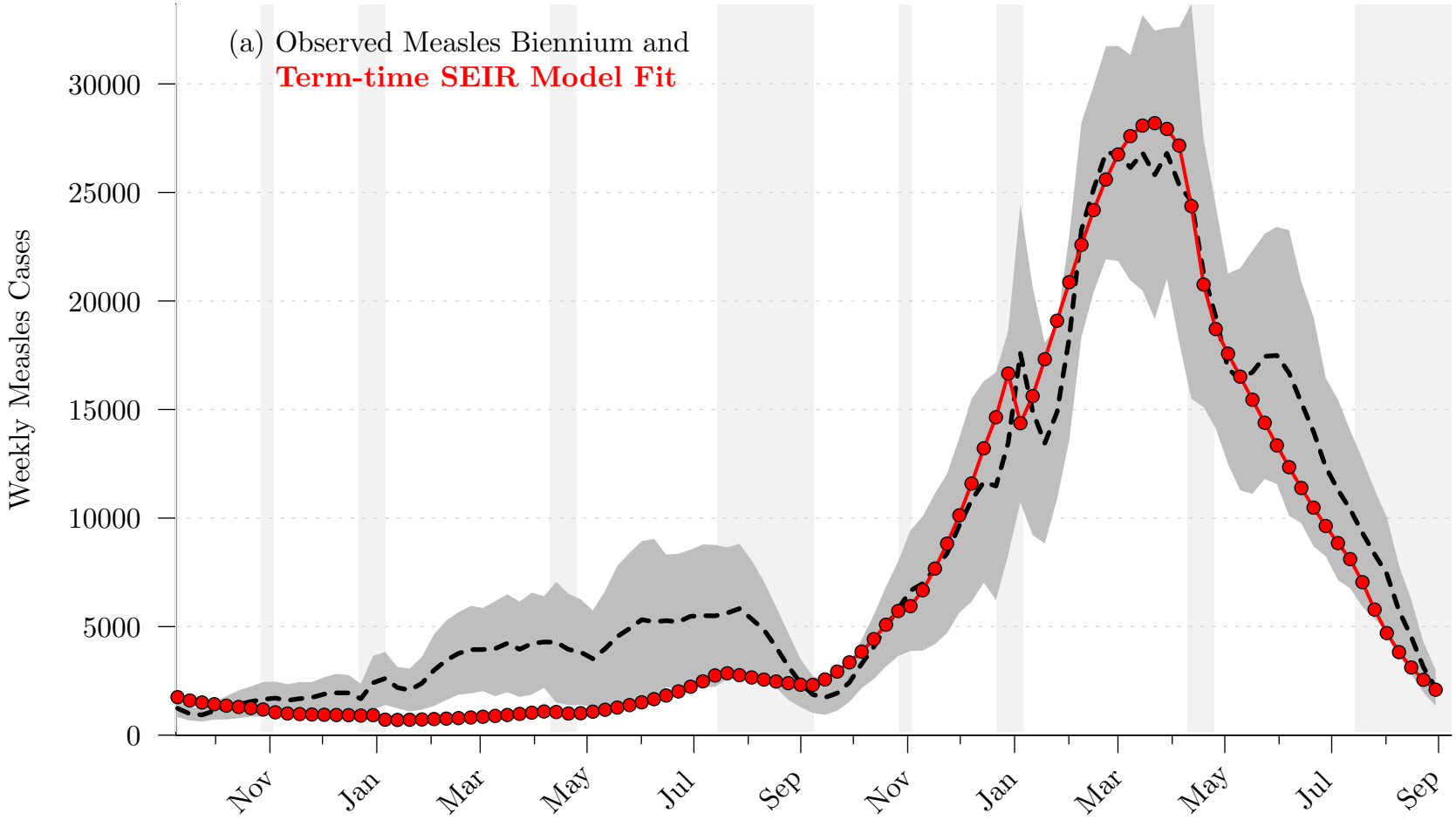


RAS model fit to measles in England and Wales



He & Earn (2016) *J. R. Soc. Interface* **13**, 20160156

Term-time SEIR model fit to measles in England and Wales



He & Earn (2016) *J. R. Soc. Interface* **13**, 20160156

Term-time SEIR model: Results for Measles

- **Fits** measles time-series just as well as full RAS model (RAS fit versus Term-time SEIR fit)
  - No need for hundreds of new parameters!!

- **Conclude:** explicit age structure is unnecessary
  - To understand aggregate measles time series
    - In particular, unnecessary for disease persistence

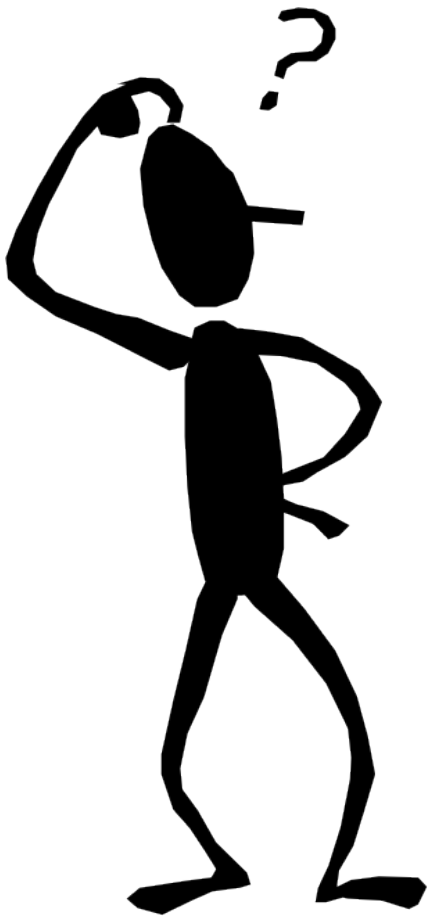
    Earn, Rohani, Bolker, Grenfell (2000) *Science* **287**, 667–670

  - But age-structured models do have their place
    - To investigate age-structured data
    - To explore effects of age-structured control strategies

Term-time SEIR model: Does it explain measles dynamics?

- **Can we explain the many different patterns of measles epidemics with the same model?**
  - The sinusoidal SEIR model could do that via chaos.
  - Term-time SEIR model predicts a strictly biennial cycle of measles epidemics, at all times and places.
  - Is superb agreement with post-war measles dynamics in London and New York *coincidental???*

What **ELSE** might we be missing?



Let's review what we've learned so far

What helps us explain temporal measles dynamics?

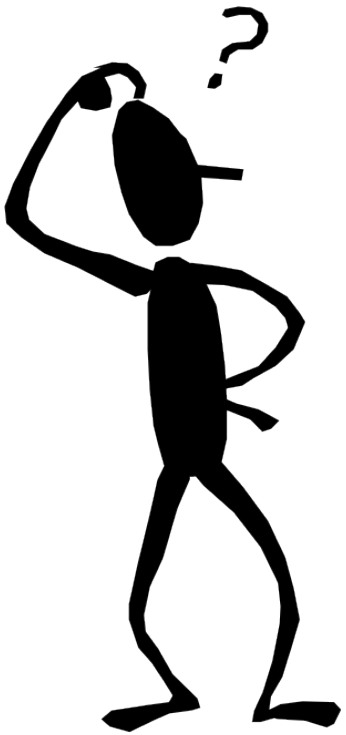
- Some key, biologically meaningful parameters
  - Basic reproductive ratio ($\mathcal{R}_0$)
    - Transmissibility.
    - Can an epidemic occur? If so, how big?
  - Amplitude of seasonal forcing (α)
    - Magnitude of seasonal variation in contact rate.
    - Stable, sustained oscillations or chaos.

- Some parameters are *less important* than previously thought
  - Age-structured mixing rates
    - Whew! Hard to estimate all those parameters anyway...
  - Spatially-structured mixing rates
    - Whew! Hard to estimate all those parameters anyway...

Let's review how our analysis has proceeded

- Considered a sequence of mechanistic mathematical models of measles transmission dynamics
- **Ruled out:**
  - Simple SIR and SEIR models, even with vital dynamics and vaccination (*oscillations damp out*)
  - Stochastic SEIR model (*undamped oscillations at only one frequency*)
  - Sinusoidally forced SEIR model (*pathogen goes extinct*)
- **Best model so far:**
  - **Term-time forced SEIR model**
    - Excellent description of post-war biennial measles dynamics in New York and London
    - **BUT:** appears unable to explain changes in pattern of epidemics over long time scales
    - Humph.

Hmmm...



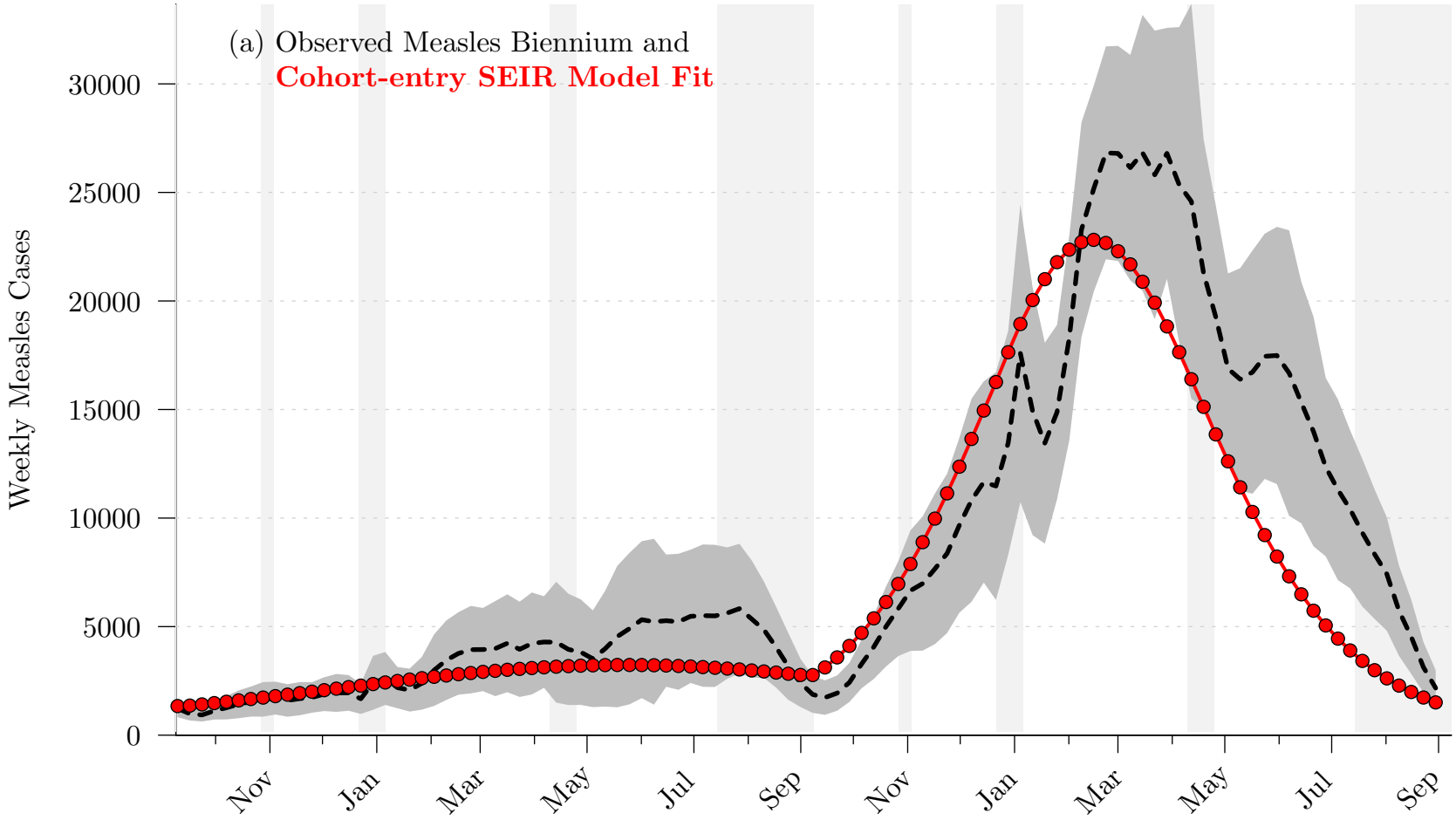
- What should we try next?
- Do we need more model structure?
- We changed $\beta \to \beta(t)$. Do other parameters vary significantly with time?
  - Birth rate?
  - Death rate?
  - Vaccination rate?
  - Other parameters?

Cohorts

- The RAS model fit was based on simplifying assumptions about the transmission matrix $(\beta_{ij}(t))$ in order to reduce the number of parameters.
- Perhaps we can do better—still without age-structure—but including the ***cohort effect***:
  - In the RAS model, everyone moves up one cohort at the start of each school year.
  - Consequently, it is *as if* most births occur on the first day of school each year ("impulsive births").
  - What is the dynamical influence of the cohort effect?

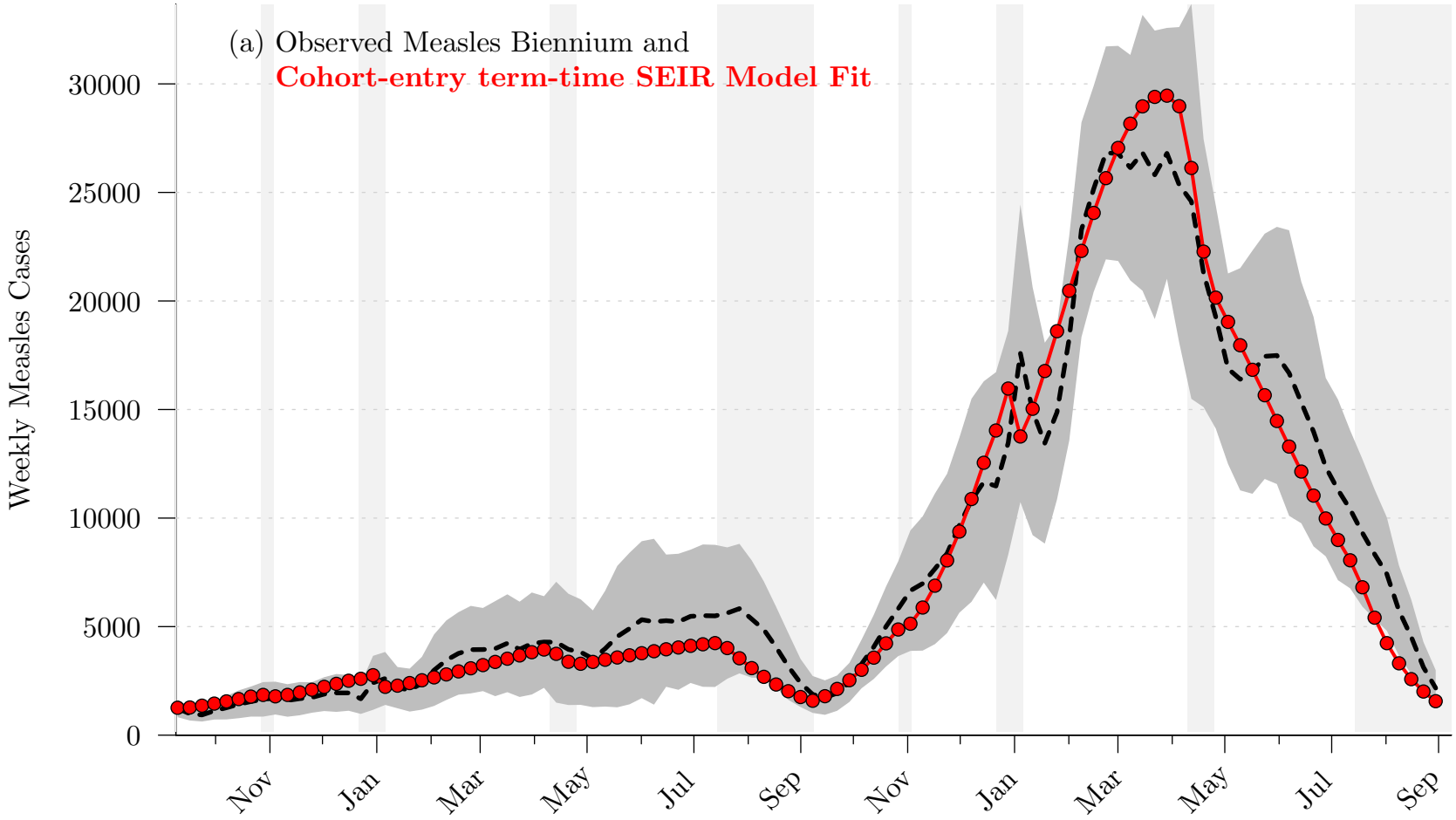
    He & Earn (2016) *J. R. Soc. Interface* **13**, 20160156
  - Compare fits of measles biennium in England and Wales with: (i) RAS, (ii) term-time, (iii) cohort, (iv) term-time and cohort.

Cohort SEIR model fit to measles in England and Wales



He & Earn (2016) *J. R. Soc. Interface* **13**, 20160156

Term-time cohort SEIR model fit to measles in E&W



He & Earn (2016) *J. R. Soc. Interface* **13**, 20160156

Cohort effect: summary

- Cohort effect alone (without transmission rate forcing) is sufficient to generate all the types of dynamics observed in models with seasonal forcing of the transmission rate (different dynamics obtained from different proportions of "births" occurring at start of school year).
- The source of seasonal forcing affects the detailed shape of the time series, but not the potential for complex dynamics.
- The best fit to the England and Wales measles biennium is obtained with term-time forcing together with the cohort effect.
  - Nevertheless, we will ignore the cohort effect because it complicates the model without helping us get to the bottom of the *changes* in dynamical structure over time.
- This does not address the issue of dynamical structure changing over time. . .

Effects of slow changes in birth rate

Consider SIR model with B births per unit time ($B \neq \mu N$):

$$\frac{dS}{dt} = B - \beta SI - \mu S$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

Suppose birth rate changes from B to $\tilde{B}$:

$$\frac{dS}{dt} = \tilde{B} - \beta SI - \mu S$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

- How are dynamics affected by the change from B to $\tilde{B}$?

Effects of slow changes in birth rate

Consider change of variables in second system with birth rate $\tilde{B}$:

$$S \to \tilde{S}\frac{\tilde{B}}{B}, \qquad I \to \tilde{I}\frac{\tilde{B}}{B}, \qquad R \to \tilde{R}\frac{\tilde{B}}{B}$$

Birth rate B:

$$\frac{dS}{dt} = B - \beta SI - \mu S$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

Birth rate $\tilde{B}$:

$$\frac{d\tilde{S}}{dt} = B - \frac{\beta\tilde{B}}{B}\tilde{S}\tilde{I} - \mu\tilde{S}$$

$$\frac{d\tilde{I}}{dt} = \frac{\beta\tilde{B}}{B}\tilde{S}\tilde{I} - \gamma\tilde{I} - \mu\tilde{I}$$

$$\frac{d\tilde{R}}{dt} = \gamma\tilde{I} - \mu\tilde{R}$$

- System with birth rate $\tilde{B}$ is identical (up to scaling) to system with birth rate B with transmission rate $\beta\tilde{B}/B$.

Key Insight

- Suppose $\mathcal{R}_0$ is estimated during a period when the birth rate is B
- If the birth rate changes to $\tilde{B}$ then the dynamical effect is identical to changing $\mathcal{R}_0$ instead:

$$\mathcal{R}_0 \quad \longrightarrow \quad \mathcal{R}_0 \frac{\tilde{B}}{B}$$

- Similarly, if the birth rate is B and a vaccination programme is initiated (vaccinating a proportion p of newborns) then the dynamical effect is identical to

$$\mathcal{R}_0 \quad \longrightarrow \quad \mathcal{R}_0(1-p)$$

- More generally, any change in susceptible recruitment rate is equivalent dynamically to a change in $\mathcal{R}_0$.

Predicting Epidemic Transitions

- Changes in
  - Birth rate (ν)
  - Vaccination proportion (p)
  - Transmission rate (β or $\mathcal{R}_0$)

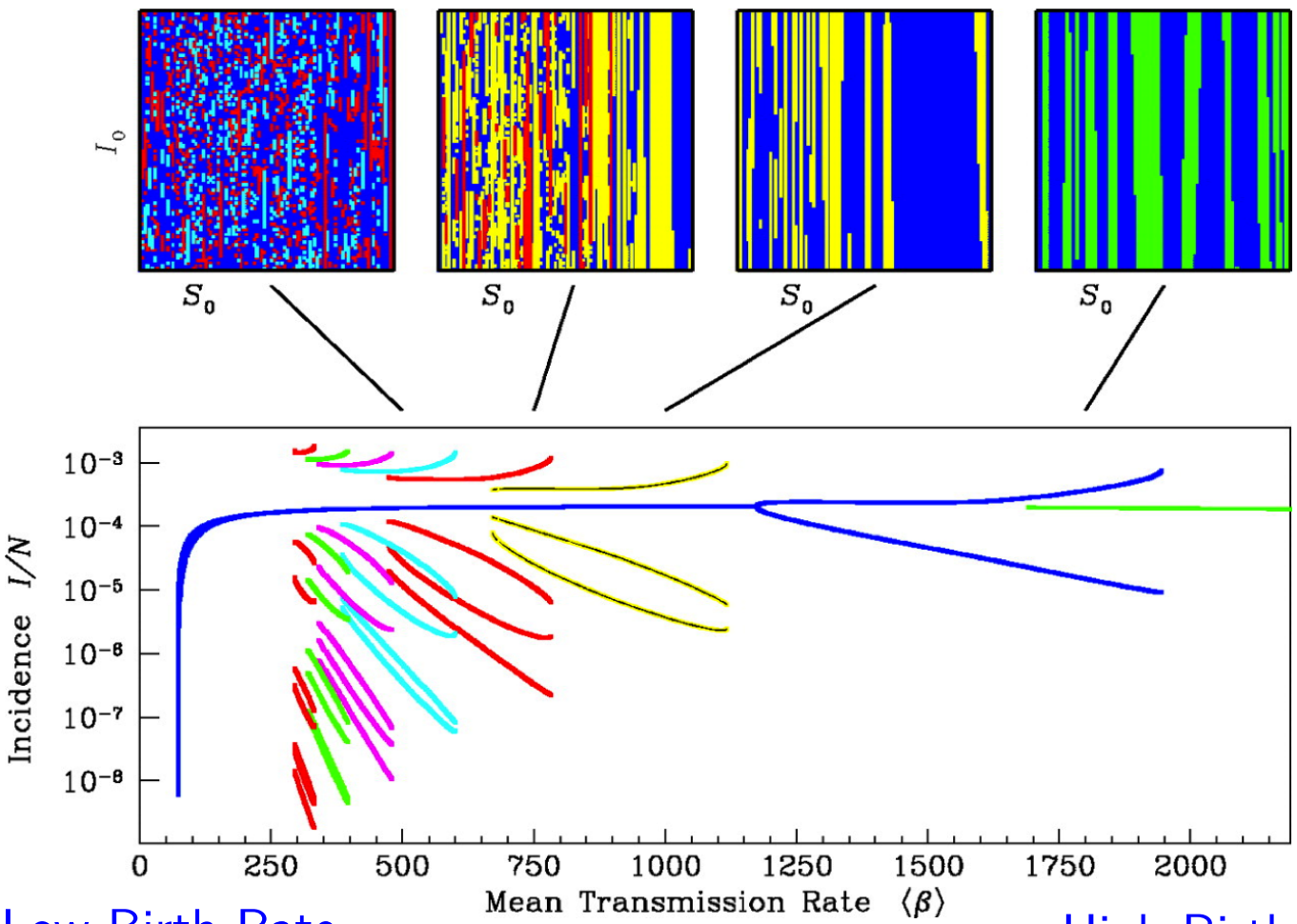
  all map onto the same parameter axis.

- $\therefore$ We can summarize possible dynamical changes induced by demographic/behavioural changes with a one-parameter bifurcation diagram.

- $\therefore$ We can predict epidemic transitions by mapping observed changes in ν, p or $\mathcal{R}_0$ onto this diagram.

- So let's try to do that for measles!

Measles Bifurcation Diagram (wrt $\langle\beta\rangle \simeq \gamma\mathcal{R}_0$)

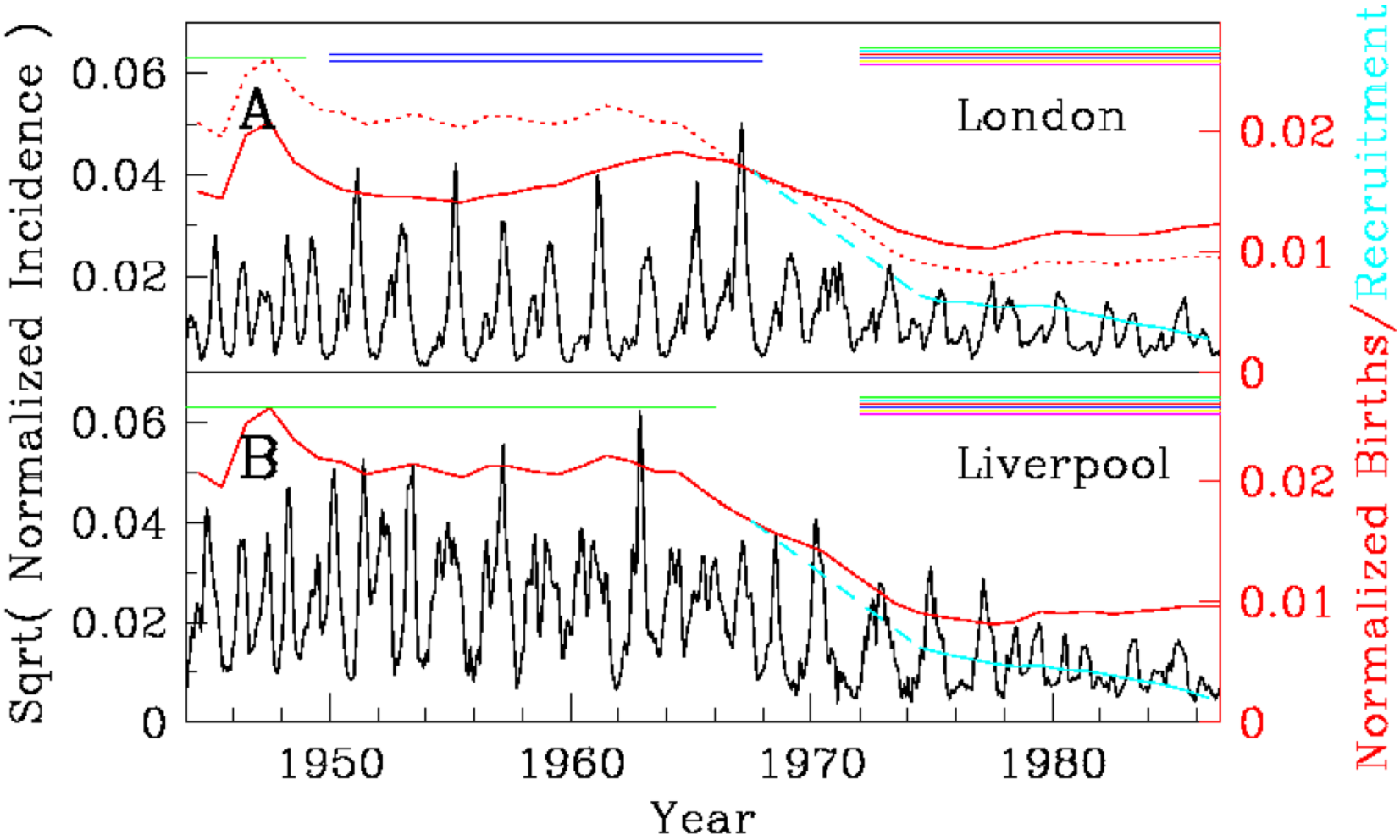


Low Birth Rate
High Vaccination

High Birth Rate
Low Vaccination

Earn, Rohani, Bolker, Grenfell (2000) *Science* **287**, 667–670

Measles in England



Earn, Rohani, Bolker, Grenfell (2000) *Science* **287**, 667–670

McMaster University

Mathematics and Statistics

$$\int_M d\omega = \int_{\partial M} \omega$$

Mathematics 4MB3/6MB3 Mathematical Biology

Instructor: David Earn

Lecture 6

Mechanistic Modelling of Recurrent Epidemics II; $\mathcal{R}_0$

Monday 21 October 2019

Announcements

- **Assignment 3** was due TODAY before class.
- **Midterm test:**
  - *Date:* Monday 4 November 2019
  - *Time:* 11:30am–1:30pm
  - *Location:* in class, ETB-237
- **Assignment 4** is posted; due before class on Monday 4 November 2019.
- Draft Project Description Document is posted.
  - The project is to be submitted as a paper in the style of a research article for publication. It is *not* just a big assignment.
  - The project descriptions ask you questions and suggest directions for investigation, but you must construct the final document as a coherent single manuscript, not answers to a bunch of questions.

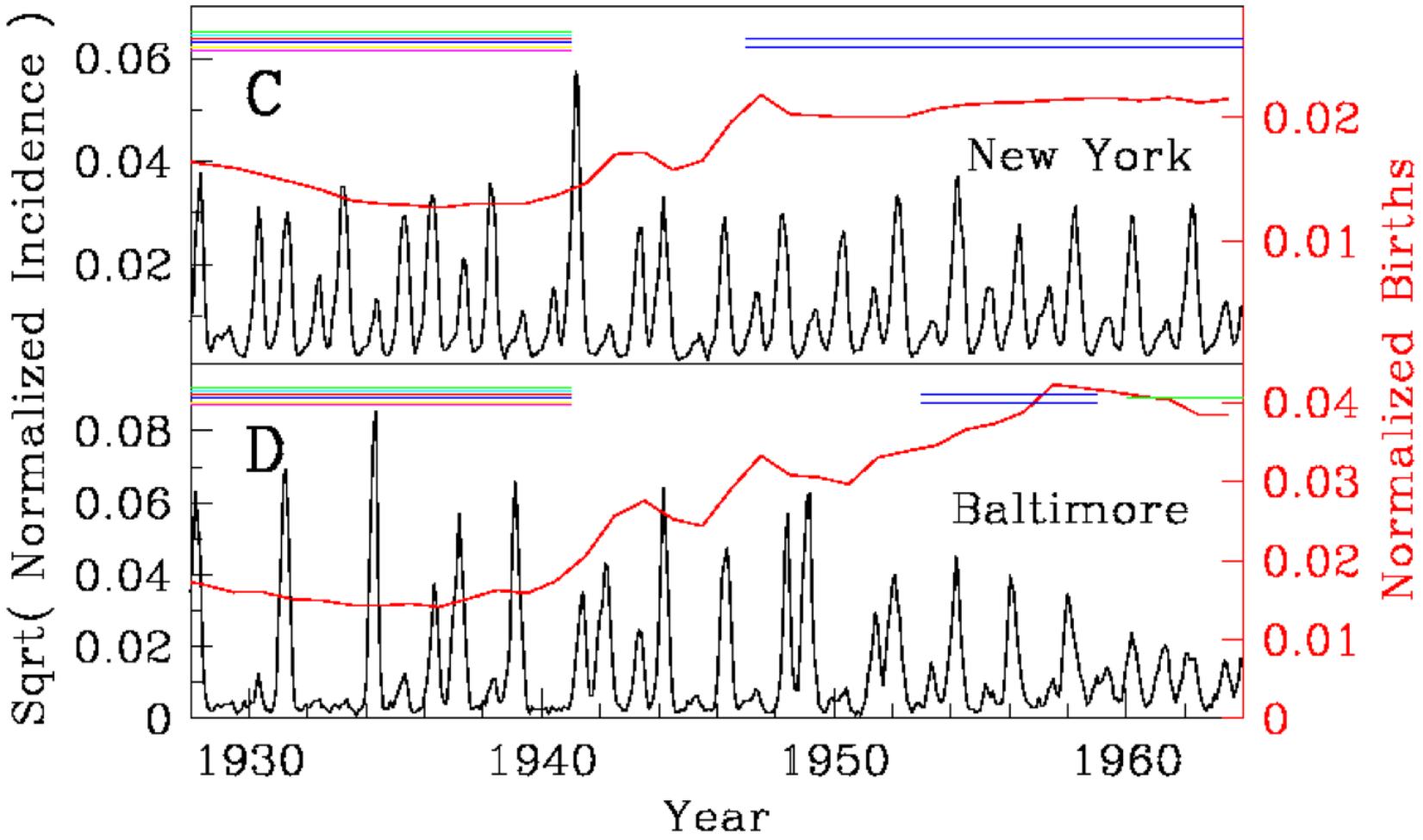
Attendance

Who is here?

Last time...

- Cohort effect: important for within-year structure of incidence patterns, not for long-term changes in frequency structure.
- Effects of slow changes in birth rate, vaccination proportion or $\mathcal{R}_0$ all map onto $\mathcal{R}_0$ axis.
- Can we explain measles time series with such an $\mathcal{R}_0$ bifurcation diagram?

Measles in the United States



Earn, Rohani, Bolker, Grenfell (2000) *Science* **287**, 667–670

What about other notifiable childhood infectious diseases?

- Rubella?
- Chicken pox?
- Whooping cough?

- Does same analysis explain patterns of recurrent epidemics for these and other diseases?

Does it work more generally?

Alas!

No!

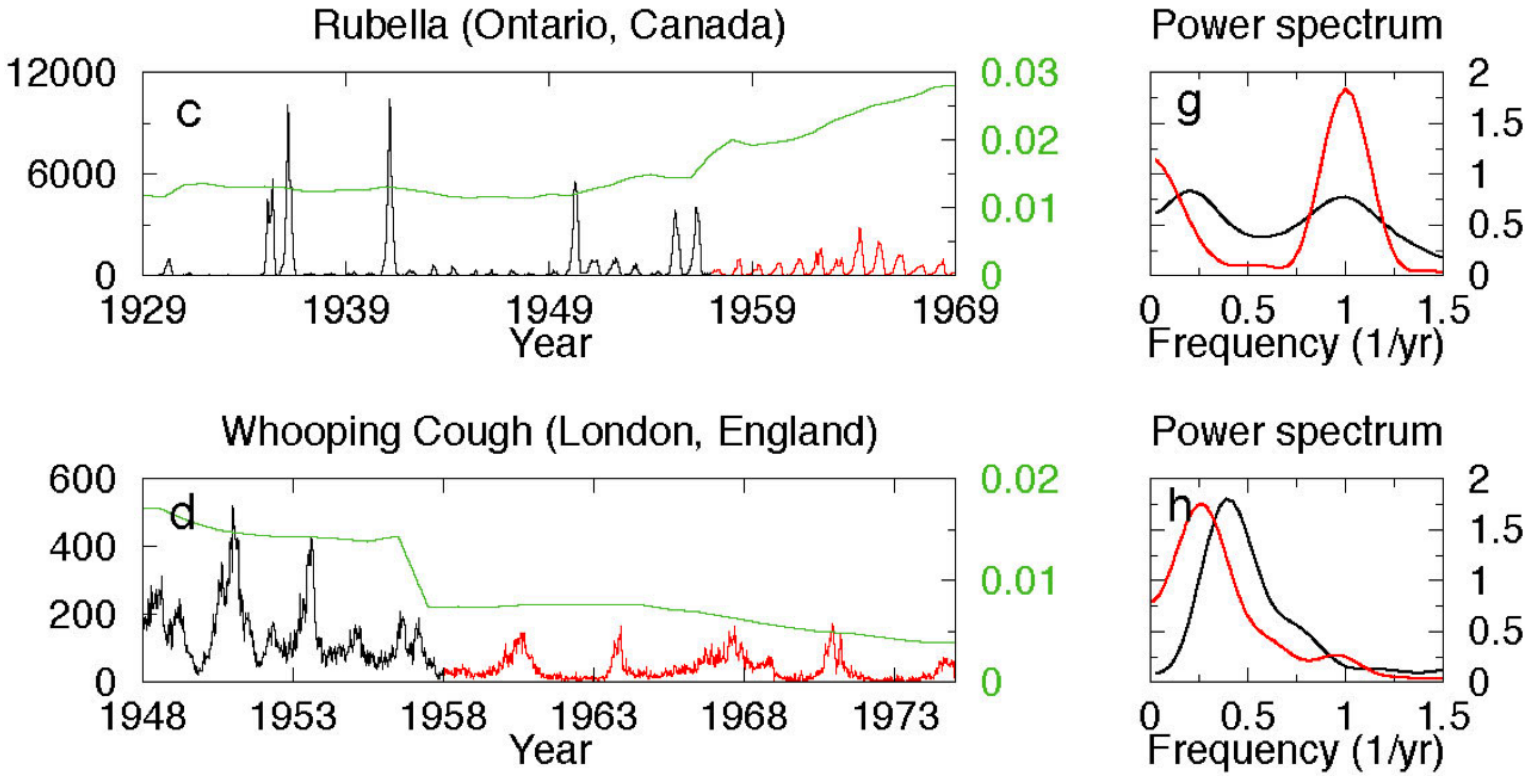
How can this be?!?

Prediction for other diseases

- For
  - Rubella
  - Whooping Cough
  - Chicken Pox

  only attractor of term-time SEIR model is annual cycle.
- Yet data for these diseases show much more complex dynamics!

Other Childhood Infections

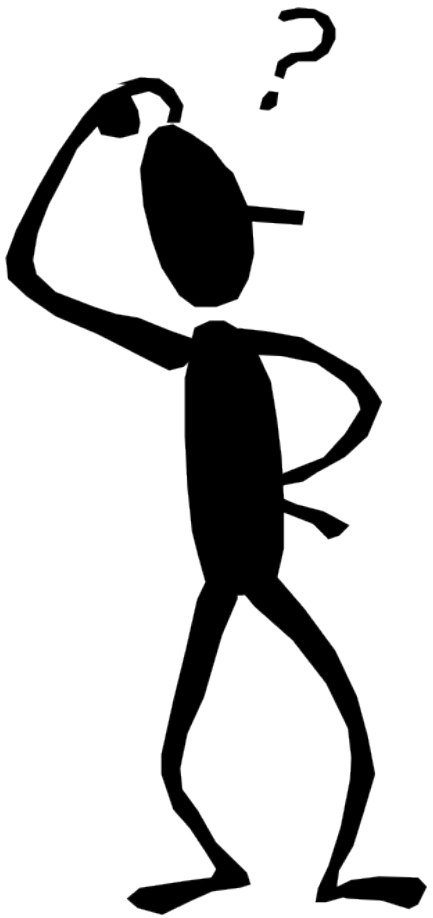


Incidence time series of these diseases show strong spectral peaks at frequencies not predicted by asymptotic analysis
(*i.e.*, **not** displayed by attractors of term-time SEIR model)

Bauch & Earn (2003) *Proc. R. Soc. Lond.* B **270**, 1573–1578

Argh!

What are we **STILL** missing?



Demographic Stochasticity Comes to the Rescue (Again!)

- Sustains transient behaviour
- Linear perturbation theory applied to the attractors of the model explains other spectral peaks in data
- *Whew!*

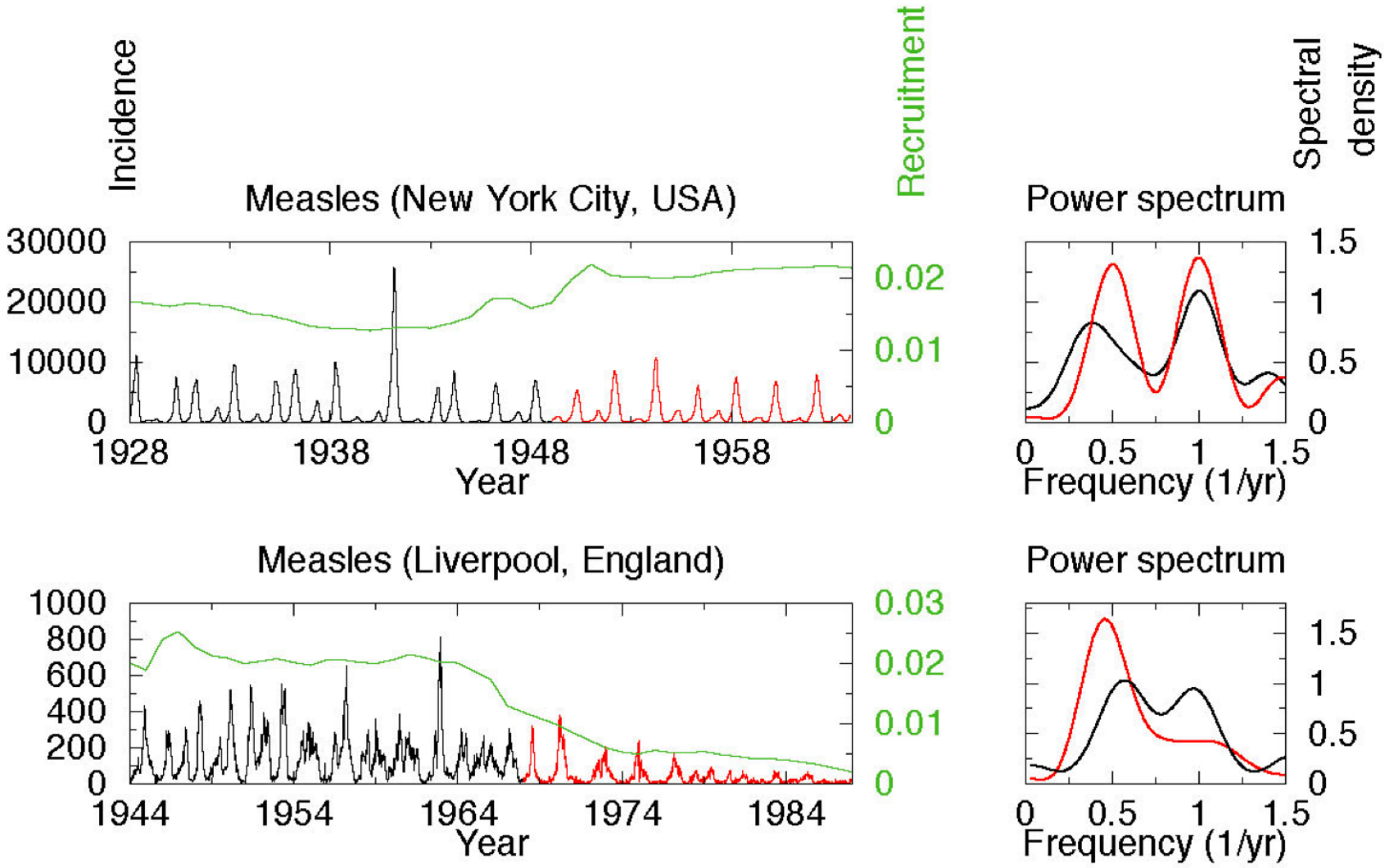
Get More Ambitious!

- Aim to predict all spectral peaks in the data
- Predict Resonant peaks from asymptotic analysis
- Predict Non-resonant peaks from perturbation analysis
- Predictions are accurate for rubella and whooping cough

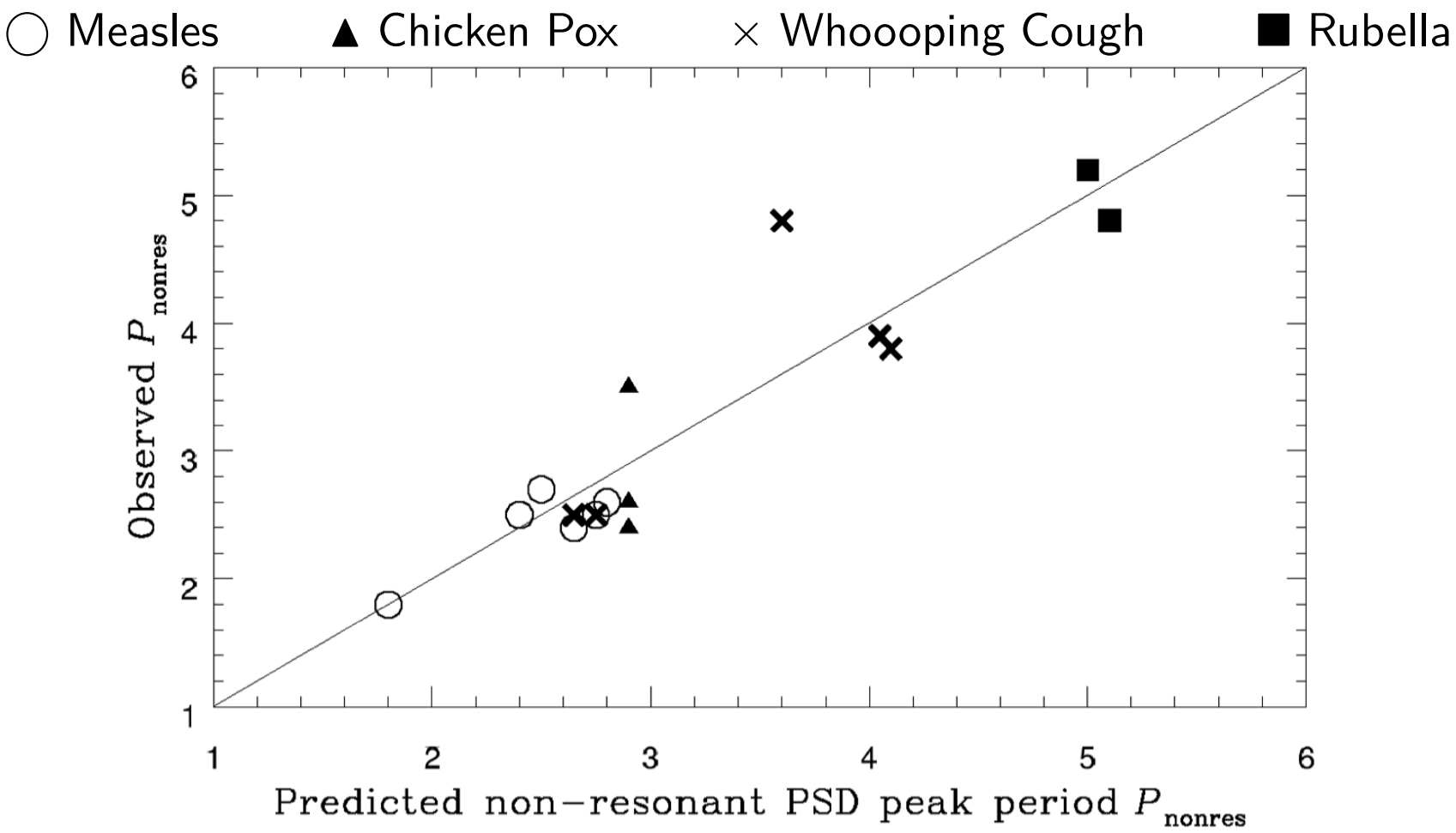
Bauch & Earn (2003) *Proc. R. Soc. Lond.* B **270**, 1573–1578

- Can we explain more details of measles dynamics?

Another Look at Measles



Predicted vs Observed Non-Resonant Spectral Peaks



$r^2 = 0.83,\ p < 10^{-6}$

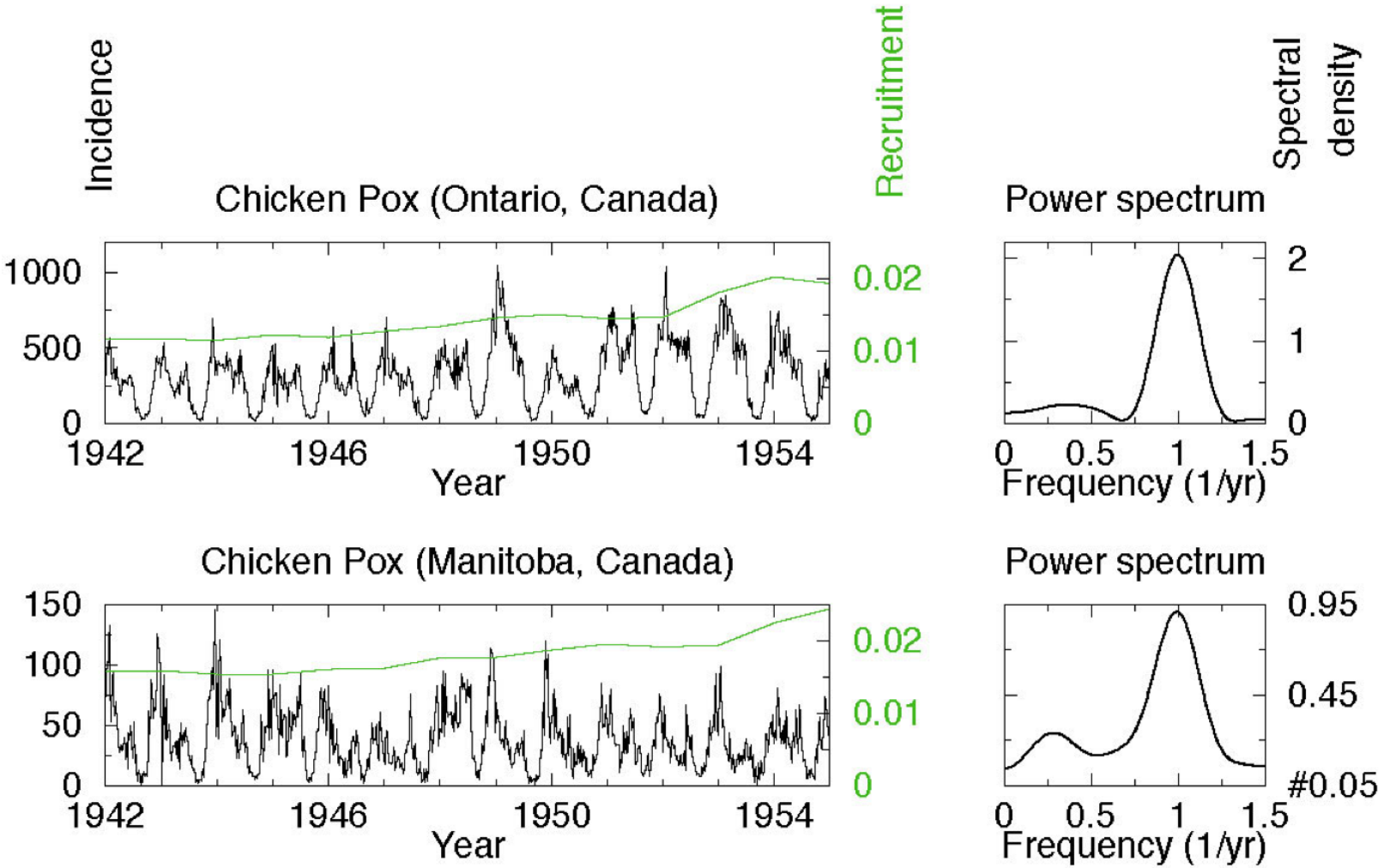
Bauch & Earn (2003) *Proc. R. Soc. Lond.* B **270**, 1573–1578

Summary so far

- Perfect prediction of resonant peaks
- Excellent prediction of non-resonant peaks ($p < 10^{-6}$)
- **Yippee!**
- Get even more ambitious...
- Can we predict magnitudes of spectral peaks?

Can we predict magnitudes of spectral peaks?

Example: Chicken Pox in Ontario vs Manitoba



Demographic Stochasticity

- Sustains transient behaviour

  Bartlett 1950s

- Greater stochasticity in smaller populations
  $\Longrightarrow$ larger non-resonant peaks

- Confirmed with stochastic simulations

  Bauch & Earn (2003) *Proc. R. Soc. Lond.* B **270**, 1573–1578

Summary: Modelling recurrent epidemics

- We now understand recurrent epidemic patterns of many infectious diseases
  (*e.g.*, measles, chicken pox, whooping cough, rubella, . . .)
- Perfect prediction of resonant spectral peaks
- Excellent prediction of non-resonant spectral peaks
- Population size is key determinant of relative magnitude of resonant vs non-resonant peaks
  (can only get at this with simulations at present)

Summary: Key Parameters

- Basic reproductive ratio: $\mathcal{R}_0$
  - Threshold for an epidemic to occur
- Amplitude of seasonal forcing: α
  - Sustained oscillations of different frequencies
- Effective reproductive ratio: $\mathcal{R}_0(1-p)\nu'/\nu$
  - Transitions in epidemic frequency/pattern
- Population size: N
  - Relative magnitude of spectral peaks

Can We Estimate the Key Parameters?

- Basic reproductive ratio: $\mathcal{R}_0$
  - Yes, *e.g.*, via mean age at infection
- Amplitude of seasonal forcing: α
  - Difficult: must use the disease time series itself
  - If possible, estimate from time series for several different diseases in same place and same time period
- Effective reproductive ratio: $\mathcal{R}_0(1-p)\nu'/\nu$
  - Yes, vaccination and birth rates are documented
- Population size: N
  - Yes, well known.

Advice to Take Home

- Start simple!!!
  - Don't add more structure and more parameters unless you're sure that the simpler model with fewer parameters is not adequate to explain the phenomena of interest.
- Increase complexity in steps
  - Rule out simpler models first
  - Try to add one parameter at a time, and if possible then do this independently for different parameters before trying to analyze a model with several new parameters.
- Beware of parameters that cannot be estimated
  - Results are only as reliable as your parameter guesses
  - Useful only to examine potential influences of mechanisms

6 Mechanistic Modelling of Recurrent Epidemics II; $\mathcal{R}_0$

Mathematics and Statistics

$$\int_M d\omega = \int_{\partial M} \omega$$

Mathematics 4MB3/6MB3 Mathematical Biology

Instructor: David Earn

Lecture 6
Mechanistic Modelling of Recurrent Epidemics II; $\mathcal{R}_0$
Monday 21 October 2019

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  - The project is to be submitted as a paper in the style of a research article for publication. It is *not* just a big assignment.
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  - *Date:* Monday 4 November 2019
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  - *Location:* in class, ETB-237

- **Assignment 4** is due the day of the midterm.
  Due Monday 4 November 2019 before class.
  - Make sure *you personally* can do the question on calculating $\mathcal{R}_0$ on this assignment *before* the midterm test.

$\mathcal{R}_0$: biological definition

The ***basic reproduction number*** $\mathcal{R}_0$ is:

> *the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual*

e.g., Anderson and May (1991) "Infectious Diseases of Humans"

$\mathcal{R}_0$: more mathematical definition

The ***basic reproduction number*** $\mathcal{R}_0$ is:

> *the number of new infections produced by a typical infective individual in a population at a disease free equilibrium (DFE)*

van den Driessche and Watmough (2002) *Mathematical Biosciences* **180**, 29–48

$\mathcal{R}_0$: most mathematical definition

The ***basic reproduction number*** $\mathcal{R}_0$ is:

> *the spectral radius of the next generation operator at a disease free equilibrium (DFE)*

Diekmann, Heesterbeek & Metz (1990) *J. Math. Biol.* **28**, 365–382

Definitions from matrix analysis

Definition (Spectrum of a matrix)

Let M be an $n \times n$ real (or complex) matrix. The ***spectrum of*** M is

$$\sigma(M) = \{\lambda : Mv = \lambda v \text{ for some non-zero } v \in \mathbb{C}^n\},$$

i.e., $\sigma(M)$ is the set of eigenvalues of M.

Definition (Spectral radius of a matrix)

Let M be an $n \times n$ real (or complex) matrix. The ***spectral radius of*** M is

$$\rho(M) = \max\{|\lambda| : \lambda \in \sigma(M)\},$$

i.e., $\rho(M)$ is the maximum modulus of the eigenvalues of M.

Computing $\mathcal{R}_0$

- In very simple models, $\mathcal{R}_0$ is the product of the transmission rate and the mean time in the infectious class. *e.g.*, In the SIR model with vital dynamics,

$$\mathcal{R}_0 = \beta \cdot \frac{1}{\gamma + \mu} .$$

- When there are multiple infected classes, it is more complicated to compute $\mathcal{R}_0$.
- In the SEIR model, we found (based on a biological argument) that

$$\mathcal{R}_0 = \beta \cdot \frac{\sigma}{\sigma + \mu} \cdot \frac{1}{\gamma + \mu} .$$

- Mathematically, the spectral radius of the next generation operator at the DFE is exactly this quantity. With this definition, it is also true that the disease persists if $\mathcal{R}_0 > 1$ and goes extinct if $\mathcal{R}_0 < 1$.

SEIR model (with vital dynamics)

$$\frac{dS}{dt} = \mu N - \frac{\beta SI}{N} - \mu S$$

$$\frac{dE}{dt} = \frac{\beta SI}{N} - \sigma E - \mu E$$

$$\frac{dI}{dt} = \sigma E - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

- Birth and death rate (μ)
- Transmission rate (β)
- Mean latent period ($1/\sigma$)
- Mean infectious period ($1/\gamma$)

Next generation matrix for the SEIR model

- Consider flows in and out of the infected compartments, and highlight flows that correspond to new infections:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} E \\ I \end{pmatrix} = \begin{pmatrix} \beta SI - \sigma E - \mu E \\ \sigma E - \gamma I - \mu I \end{pmatrix}$$

- $\mathcal{F} =$ inflow of new infecteds to infected compartments $= \begin{pmatrix} \beta SI \\ 0 \end{pmatrix}$
- $\mathcal{V} =$ outflow from infected compartments minus inflow of *non-new* infecteds $= \begin{pmatrix} \sigma E + \mu E \\ -\sigma E + \gamma I + \mu I \end{pmatrix}$
- Let $F =$ linearization of $\mathcal{F}$ at DFE
- Let $V =$ linearization of $\mathcal{V}$ at DFE
- Then the ***next generation matrix*** is FV^{-1}
- Analogous to $\beta\gamma^{-1}$ in simple case.

Interpretation of FV^{-1} as next generation matrix

Almost verbatim from p. 33 of van den Driessche and Watmough (2002) *Mathematical Biosciences* **180**, 29–48

- To interpret the entries of FV^{-1} and develop a meaningful definition of $\mathcal{R}_0$, consider the fate of an infected individual introduced into compartment k of a disease free population.
- The (j,k) entry of V^{-1} is the average length of time this individual spends in compartment j during its lifetime, assuming that the population remains near the DFE and barring reinfection.
- The (i,j) entry of F is the rate at which infected individuals in compartment j produce new infections in compartment i.
- Hence, the (i,k) entry of the product FV^{-1} is the expected number of new infections in compartment i produced by the infected individual originally introduced into compartment k.
- Following Diekmann et al. (1990), we call FV^{-1} the next generation matrix for the model and set

$$\mathcal{R}_0 = \rho(FV^{-1}),$$

where $\rho(A)$ denotes the spectral radius of a matrix A.

$\mathcal{R}_0$ via FV^{-1} for the SEIR model

$$\mathcal{F} = \begin{pmatrix} \beta SI \\ 0 \end{pmatrix} \qquad \mathcal{V} = \begin{pmatrix} \sigma E + \mu E \\ -\sigma E + \gamma I + \mu I \end{pmatrix}$$

$$F = \begin{pmatrix} 0 & \beta \\ 0 & 0 \end{pmatrix} \qquad V = \begin{pmatrix} (\sigma+\mu) & 0 \\ -\sigma & (\gamma+\mu) \end{pmatrix}$$

$$V^{-1} = \begin{pmatrix} \frac{1}{\sigma+\mu} & 0 \\ \frac{\sigma}{(\sigma+\mu)(\gamma+\mu)} & \frac{1}{\gamma+\mu} \end{pmatrix} \implies FV^{-1} = \begin{pmatrix} \frac{\beta\sigma}{(\sigma+\mu)(\gamma+\mu)} & \frac{\beta}{\gamma+\mu} \\ 0 & 0 \end{pmatrix}$$

$$\mathcal{R}_0 = \rho(FV^{-1}) = \beta\sigma/(\sigma+\mu)(\gamma+\mu)$$

- Note wrt previous slide that the $(2,1)$ entry of V^{-1} is the average time an individual who enters the E compartment spends in the I compartment: only a proportion $\sigma/(\sigma+\mu)$ of such individuals make it to the I compartment, where the average time spent—by individuals who get there—is $1/(\gamma+\mu)$.

Computing $\mathcal{R}_0$ for other compartmental ODE models

- The method applied in the previous slides to obtain $\mathcal{R}_0$ for the SEIR model works more generally for a very large class of "reasonable" infectious disease ODE models. "Reasonable" means:
  1. The vector field can be written $\mathcal{F} - \mathcal{V}$, where $\mathcal{F} \geq 0$ corresponds to *new infections* and $\mathcal{V}$ can be written $\mathcal{V} = \mathcal{V}^+ - \mathcal{V}^-$, where $\mathcal{V}^+ \geq 0$ corresponds to *outflow* and $\mathcal{V}^- \geq 0$ corresponds to *inflow of infectives that are not new*.
  2. The biologically relevant part of the state space is forward-invariant. In particular, if a compartment is empty, then there can be no transfer of individuals out of the compartment by death, infection, nor any other means.
  3. The DFE is stable in the absence of new infection (if there is more than one DFE, $\mathcal{R}_0$ may depend on which one we focus on).
  4. The population size N is constant (or the model is expressed in terms of proportions in each compartment).

Computing $\mathcal{R}_0$ for other compartmental ODE models

Theorem (van den Driessche and Watmough (2002))

If the vector field associated with an ODE infectious disease model satisfies the conditions specified on the previous slide, then

1. *$\mathcal{R}_0$ can be computed as $\rho(FV^{-1})$;*
2. *if $\mathcal{R}_0 < 1$ then the disease-free equilibrium (DFE) is locally asymptotically stable (LAS), whereas if $\mathcal{R}_0 > 1$ then there is a LAS endemic equilibrium (EE).*

$\mathcal{R}_0$ calculation: summary

- The biological method of deriving $\mathcal{R}_0$ is generally more informative in terms of what is going on. But it can be challenging to apply to complex models.
- The formal approach, *i.e.*, $\mathcal{R}_0 = \rho(FV^{-1})$, works in almost any situation you will encounter, even very complicated models with many compartments.
- If possible, it is best to use both methods to find an expression for $\mathcal{R}_0$, and make sure they agree.
- A completely different challenge is to estimate $\mathcal{R}_0$ for a real epidemic from data...

Estimating $\mathcal{R}_0$ based on the SEIR model

- If the SEIR model captures the natural history of some disease well, how can you *estimate* $\mathcal{R}_0 = \dfrac{\beta\sigma}{(\sigma+\mu)(\gamma+\mu)}$?
  - Mean latent period $1/\sigma$
  - Mean infectious period $1/\gamma$
  - Birth rate μ
  - Estimate β via initial growth rate r:
    - For the simplest SIR model, $r = \beta - \gamma$ so $\beta = r + \gamma$.
    - More generally, r is the largest positive (or least negative) real part of the eigenvalues of $F - V$.
    - For SEIR model we find:

$$r = \frac{1}{2}\left(\sqrt{4\beta\sigma + (\gamma-\sigma)^2} - (\gamma+\sigma+2\mu)\right)$$

    - Solving this for β we obtain: $\beta = \dfrac{(r+\sigma+\mu)(r+\gamma+\mu)}{\sigma}$