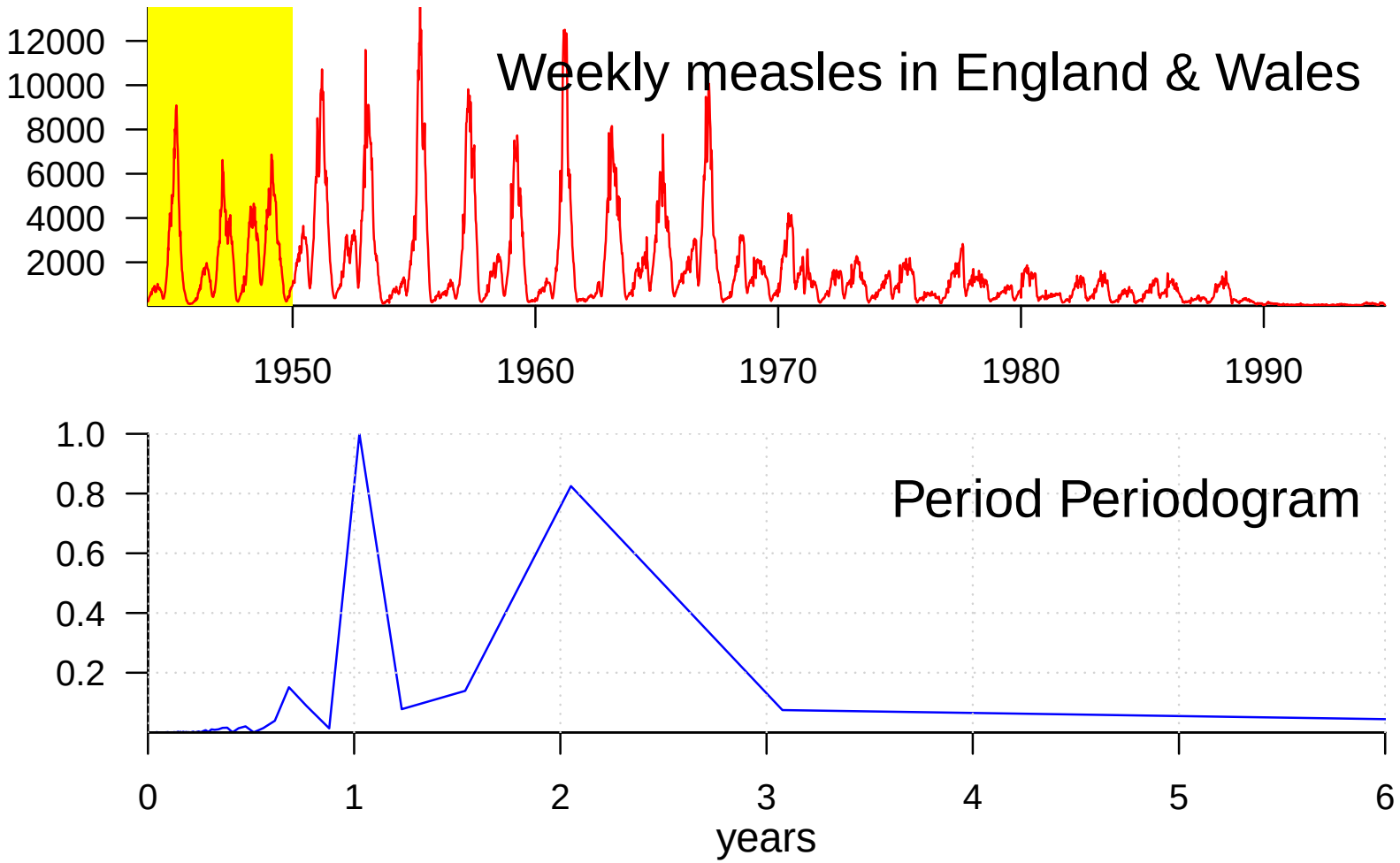
13 Mechanistic Modelling of Recurrent Epidemics

14 Mechanistic Modelling of Recurrent Epidemics II

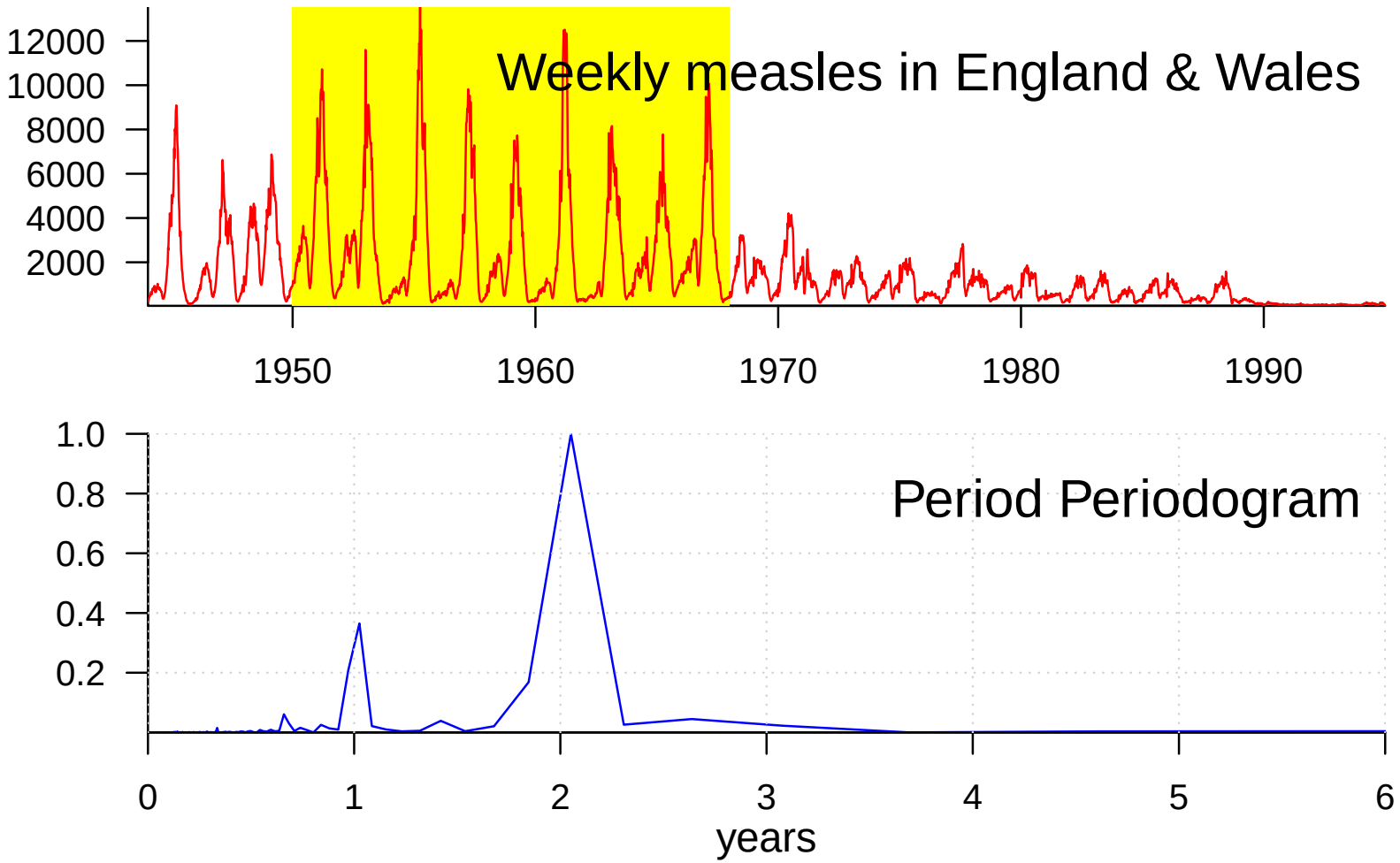
15 Mechanistic Modelling of Recurrent Epidemics III

Mechanistic Modelling of Recurrent Epidemics

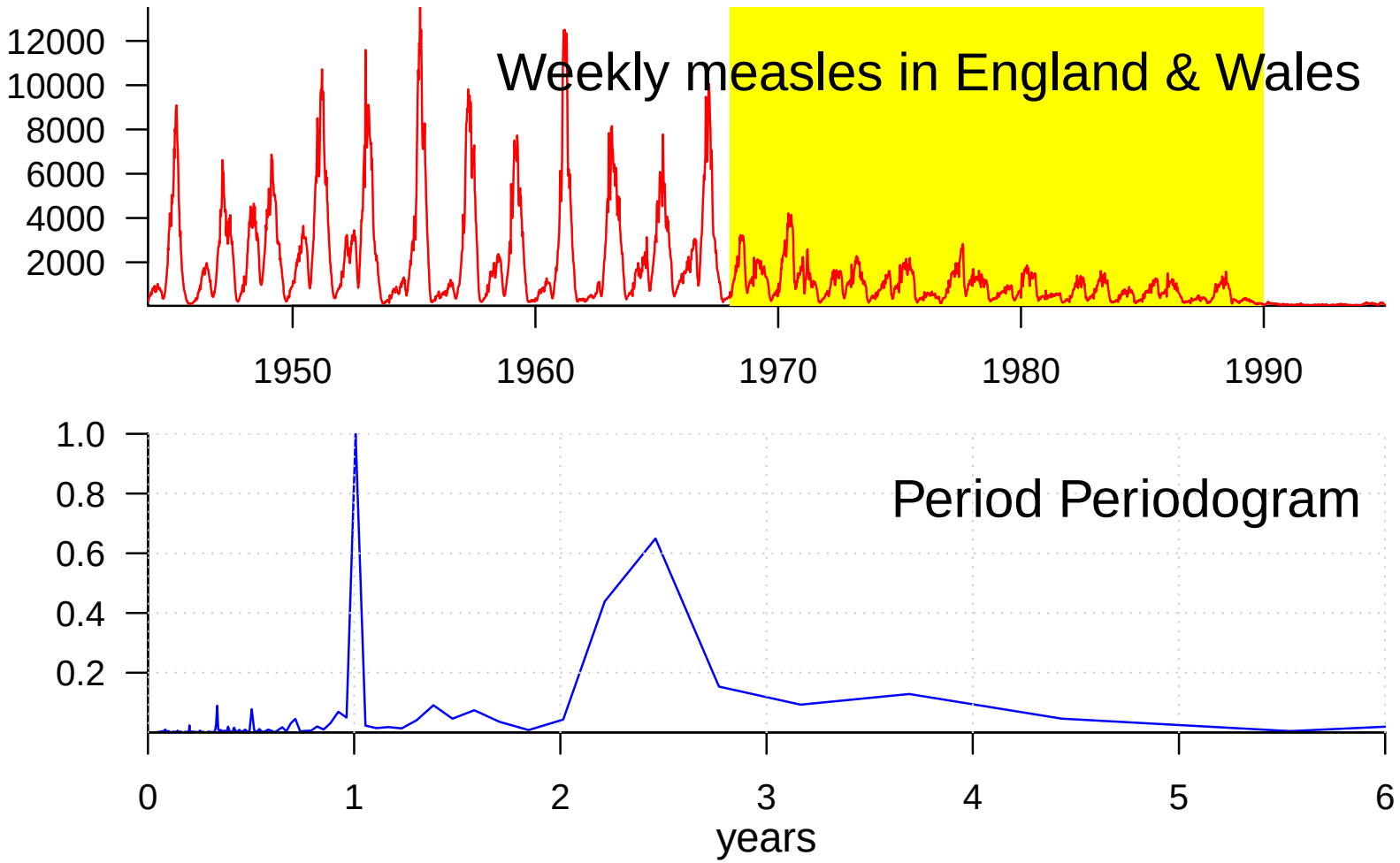
What causes changes in frequency content over time?



What causes changes in frequency content over time?

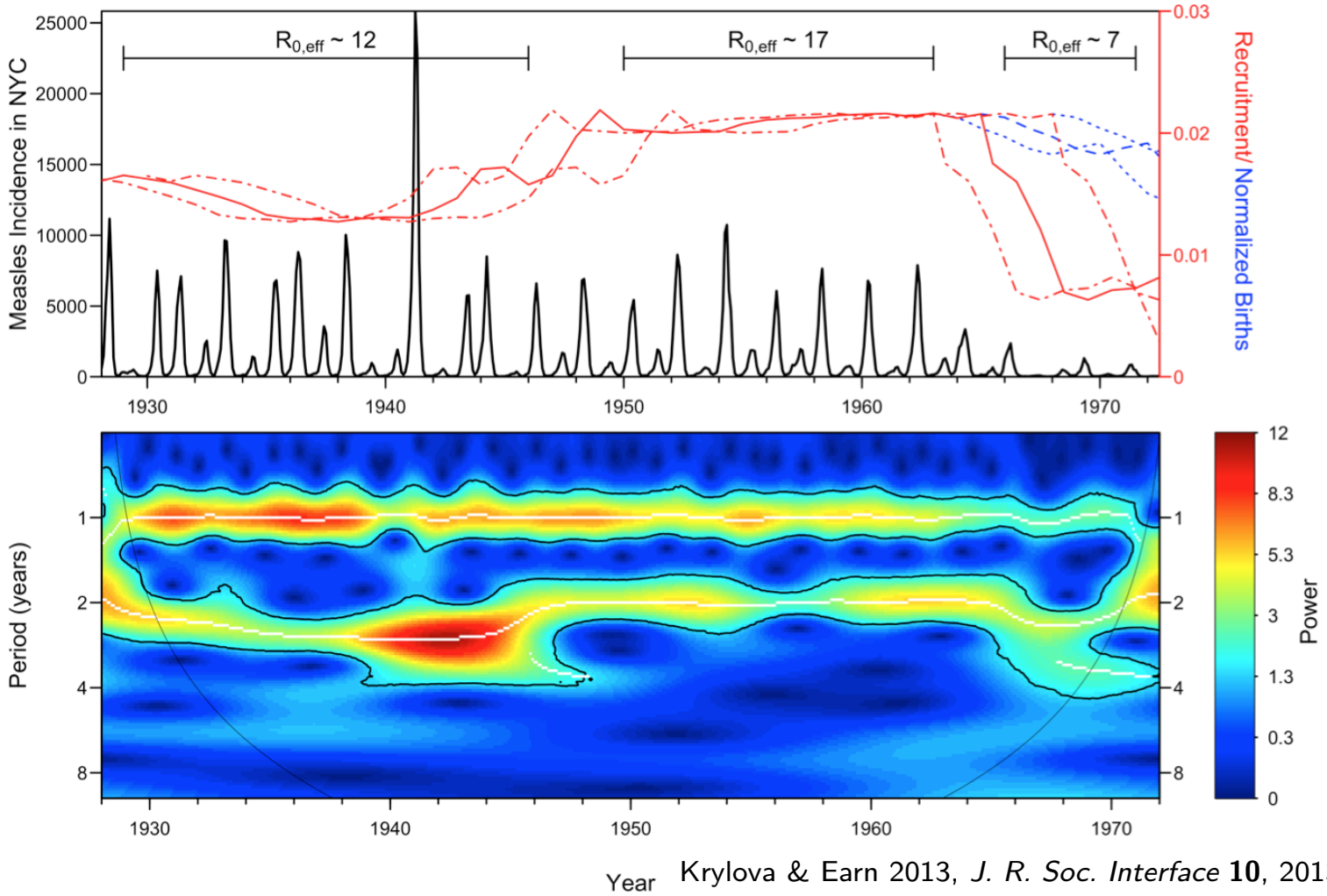


What causes changes in frequency content over time?



What causes changes in frequency content over time?

Measles in New York City

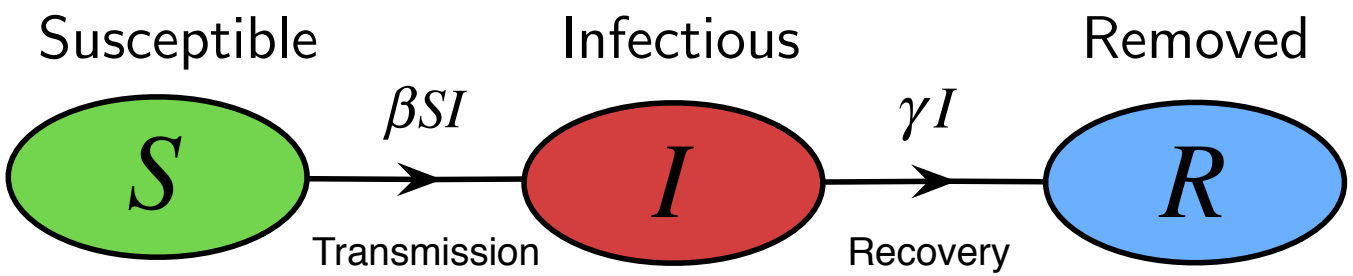


Krylova & Earn 2013, *J. R. Soc. Interface* **10**, 20130098

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



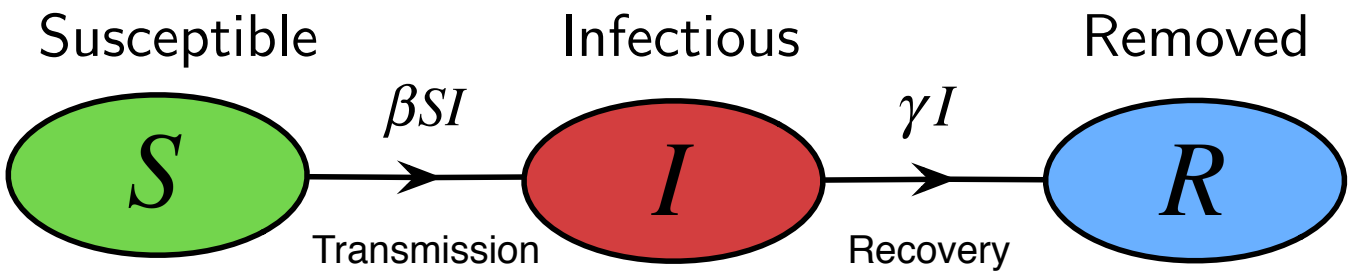
$$\frac{dS}{dt} = -\beta SI$$

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

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

- **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

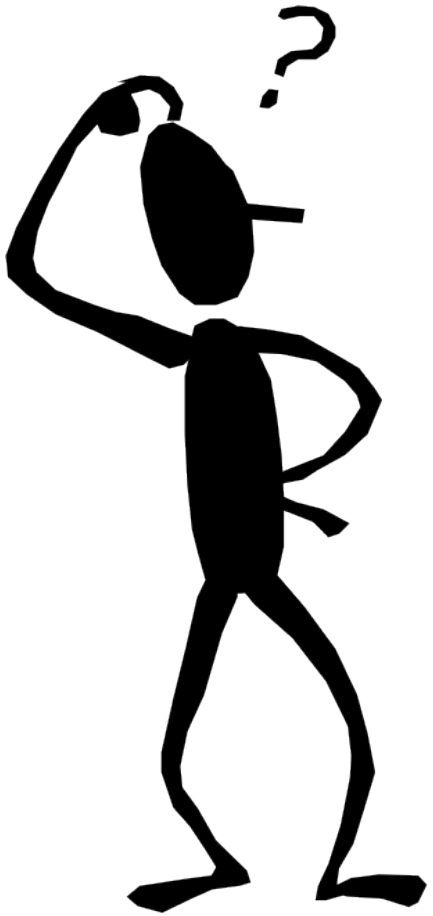
$$\mathcal{R}_0 = \frac{\beta}{\gamma}$$

Basic SIR Model: Important Results

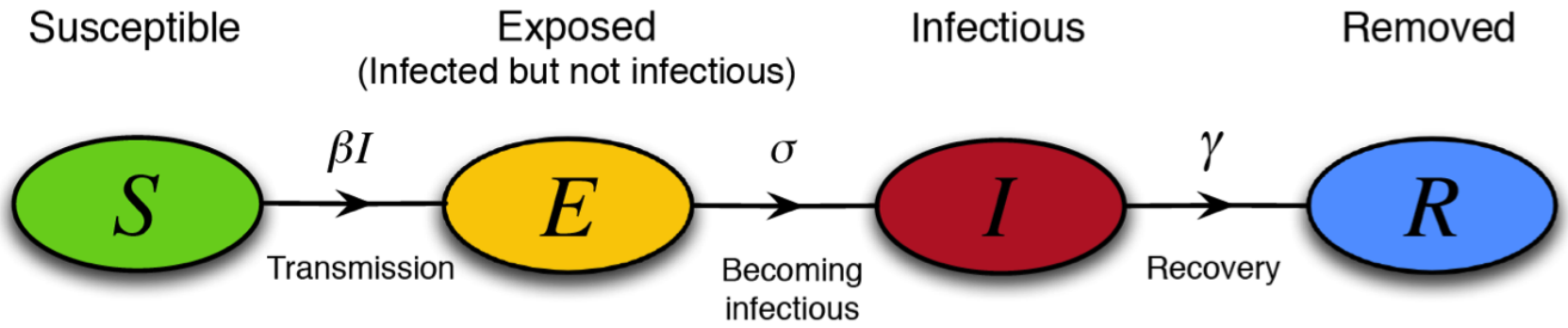
- Epidemic occurs if and only if $\mathcal{R}_0 > 1$
- Exact solution for phase portrait
- Single epidemic, then disease disappears
- Exact formula for final size as a function of $\mathcal{R}_0$

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

What are we missing?

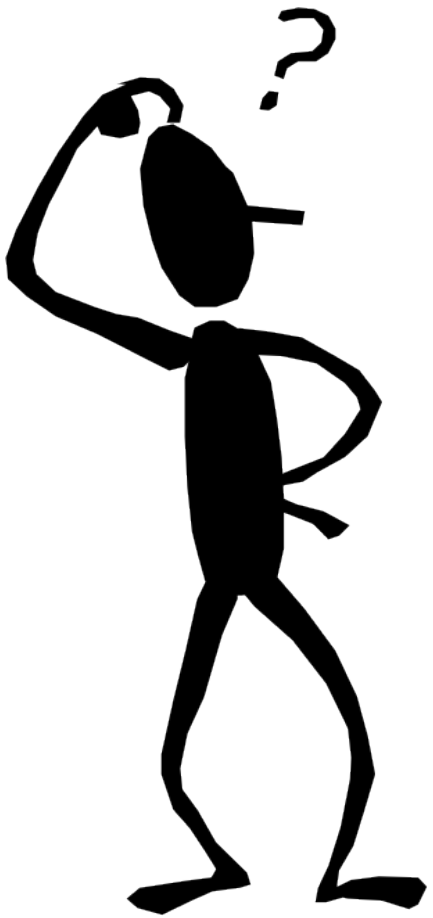


SEIR Model: flow chart

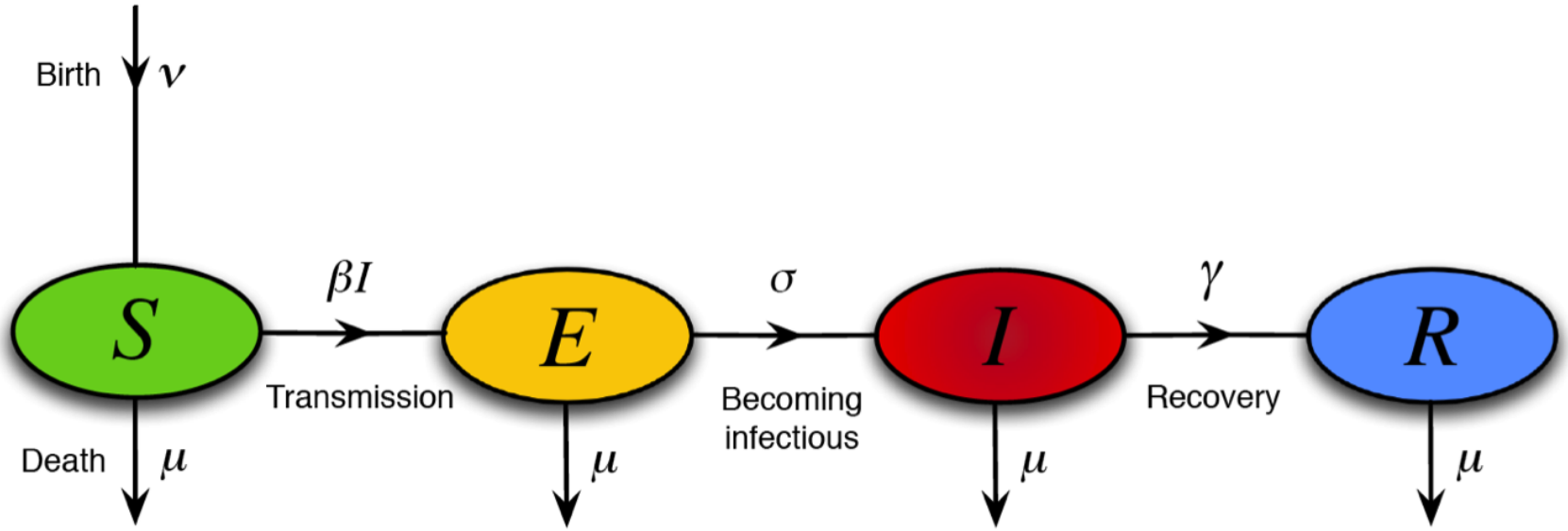


- Introduces only one new parameter (σ)
- Mean latent period ($1/\sigma$) can often be estimated
- But... effect of inclusion of exposed class usually small

What are we still missing?



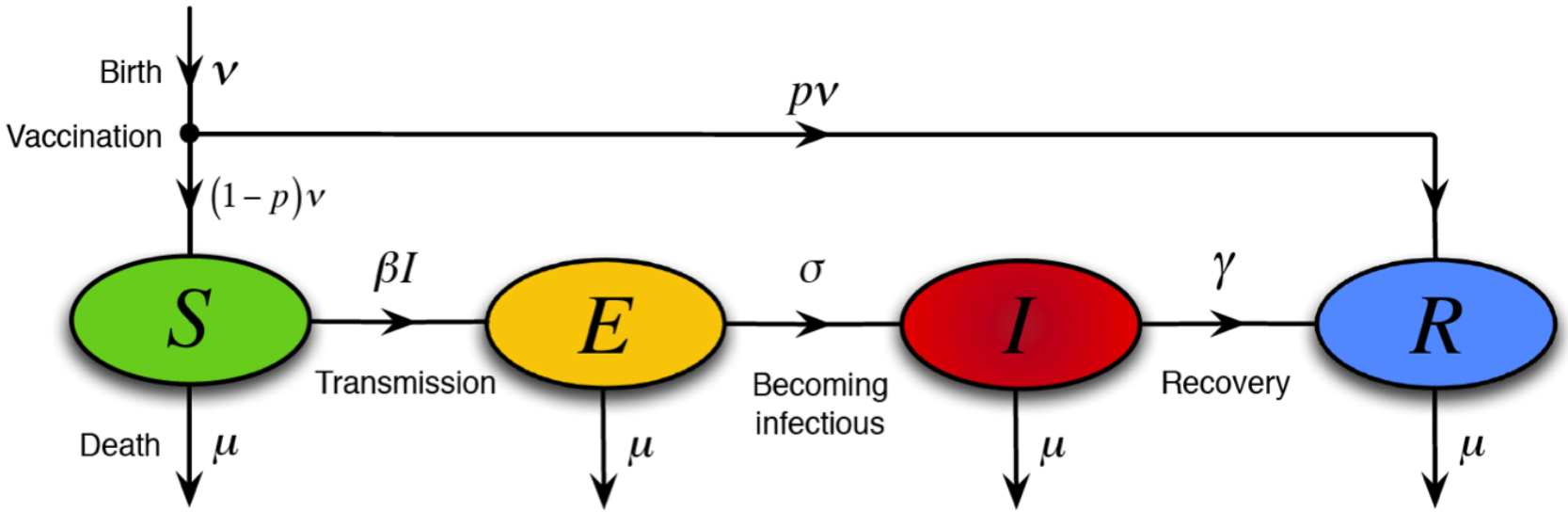
SEIR Model with vital dynamics: flow chart



New Parameters:

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

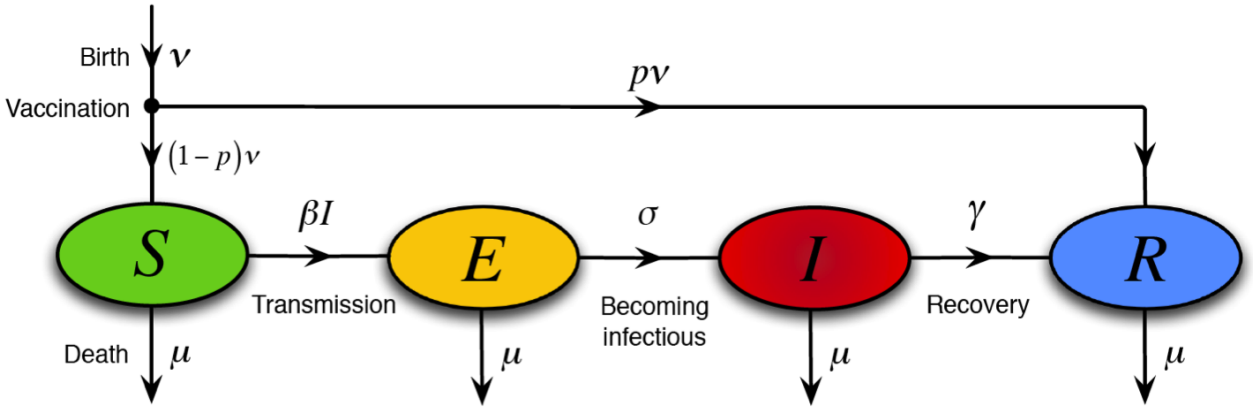
SEIR with vital dynamics and vaccination: flow chart



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 ($1/\gamma$)

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Mathematics and Statistics

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

Mathematics 4MB3/6MB3 Mathematical Biology

Instructor: David Earn

Lecture 13
Mechanistic Modelling of Recurrent Epidemics
Monday 4 February 2019

Announcements

- **Assignment 2:** Due TODAY!
- Do the Group contribution survey for Assignment 2 TODAY.
- **Assignment 3** is posted.
  Due Monday 25 February 2019 at 9:30am
- **Midterm test:**
  - *Date:* Monday 11 March 2019
  - *Time:* 9:30am–11:20am
  - *Location:* Hamilton Hall 410

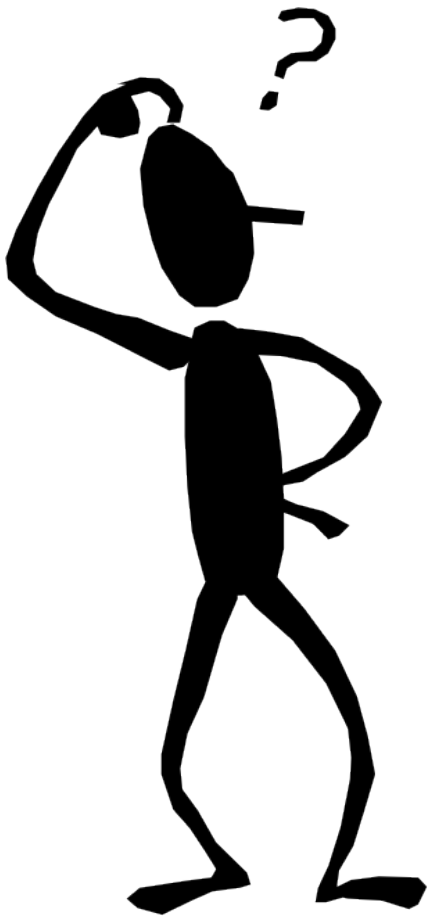
SEIR with vital dynamics and vaccination: Analysis

- $\mathcal{R}_0$?
  - Biological derivation: (assuming $\nu = \mu$ and $p = 0$)
    $\mathcal{R}_0 = \beta \times \frac{\sigma}{\sigma+\mu} \times \frac{1}{\gamma+\mu} \simeq \frac{\beta}{\gamma} \quad \because \frac{1}{\mu} \gg \max\left(\frac{1}{\sigma}, \frac{1}{\gamma}\right)$
  - 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?

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

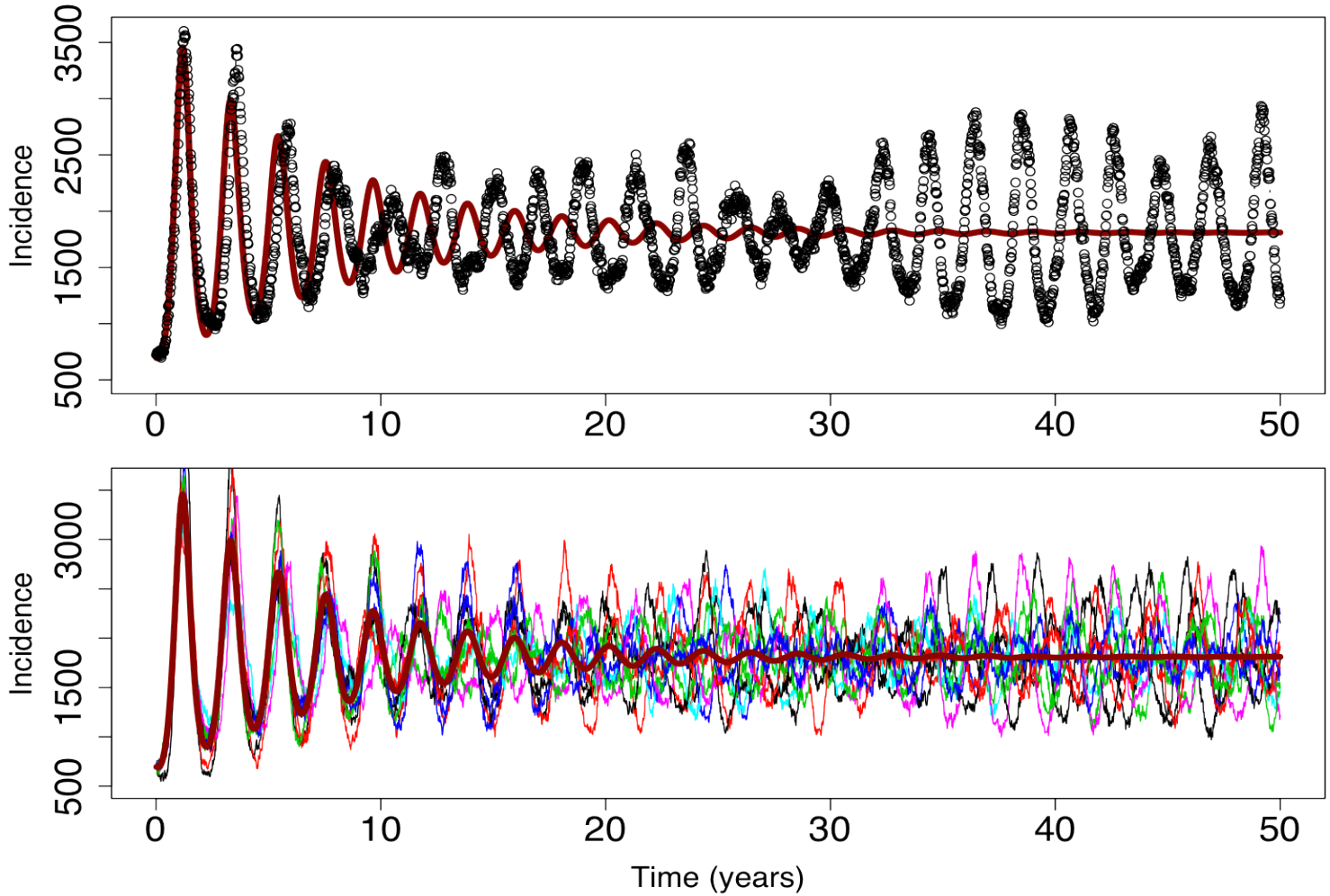
- We now know the time t of the next event, but we must still determine what type of event occurs at time t.
- Probability of event of type i is $\dfrac{a_i}{a_0}$
- $\therefore$ Can easily determine type of event by sampling a point from a uniform distribution on $[0, a_0]$:
  - Event is type i if the 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, $N = 5,000,000$

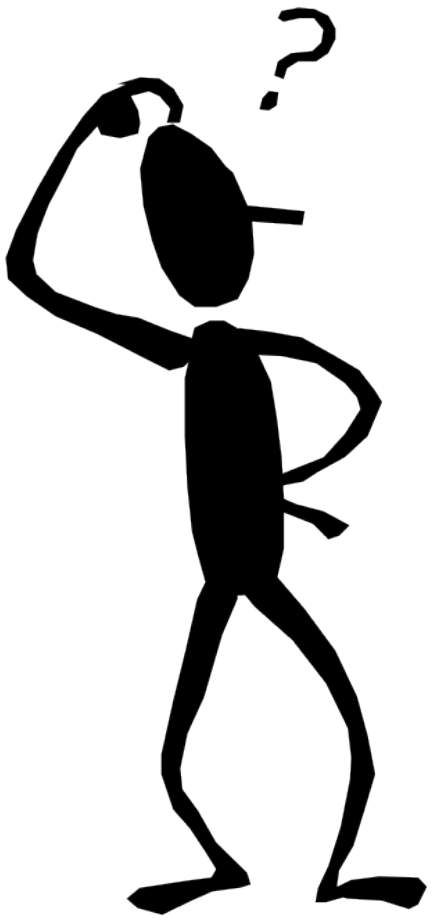


Earn 2009, *IAS/Park City Mathematics Series* **14**, 151–186

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?



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Mathematics and Statistics

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

Mathematics 4MB3/6MB3 Mathematical Biology

Instructor: David Earn

Lecture 14
Mechanistic Modelling of Recurrent Epidemics II
Monday 11 February 2019

Announcements

- **Assignment 3** is posted.
  Due Monday 25 February 2019 at 9:30am
- **Midterm test:**
  - *Date:* Monday 11 March 2019
  - *Time:* 9:30am–11:20am
  - *Location:* Hamilton Hall 410

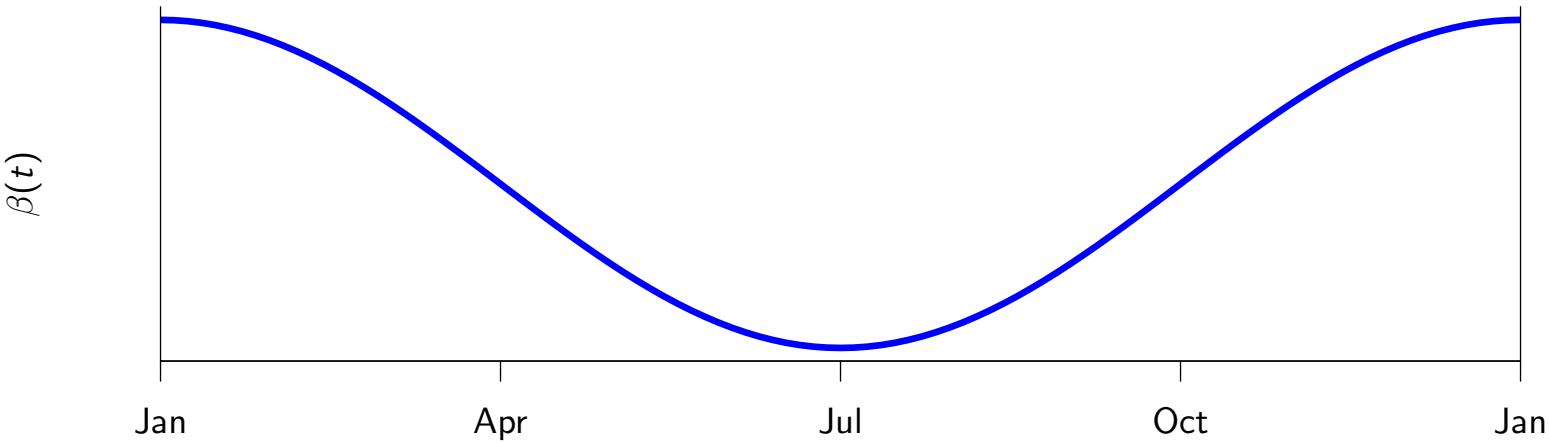
Contact rates are higher during school terms!

Sinusoidal SEIR Model

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

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

  - $\langle\beta\rangle$ = 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

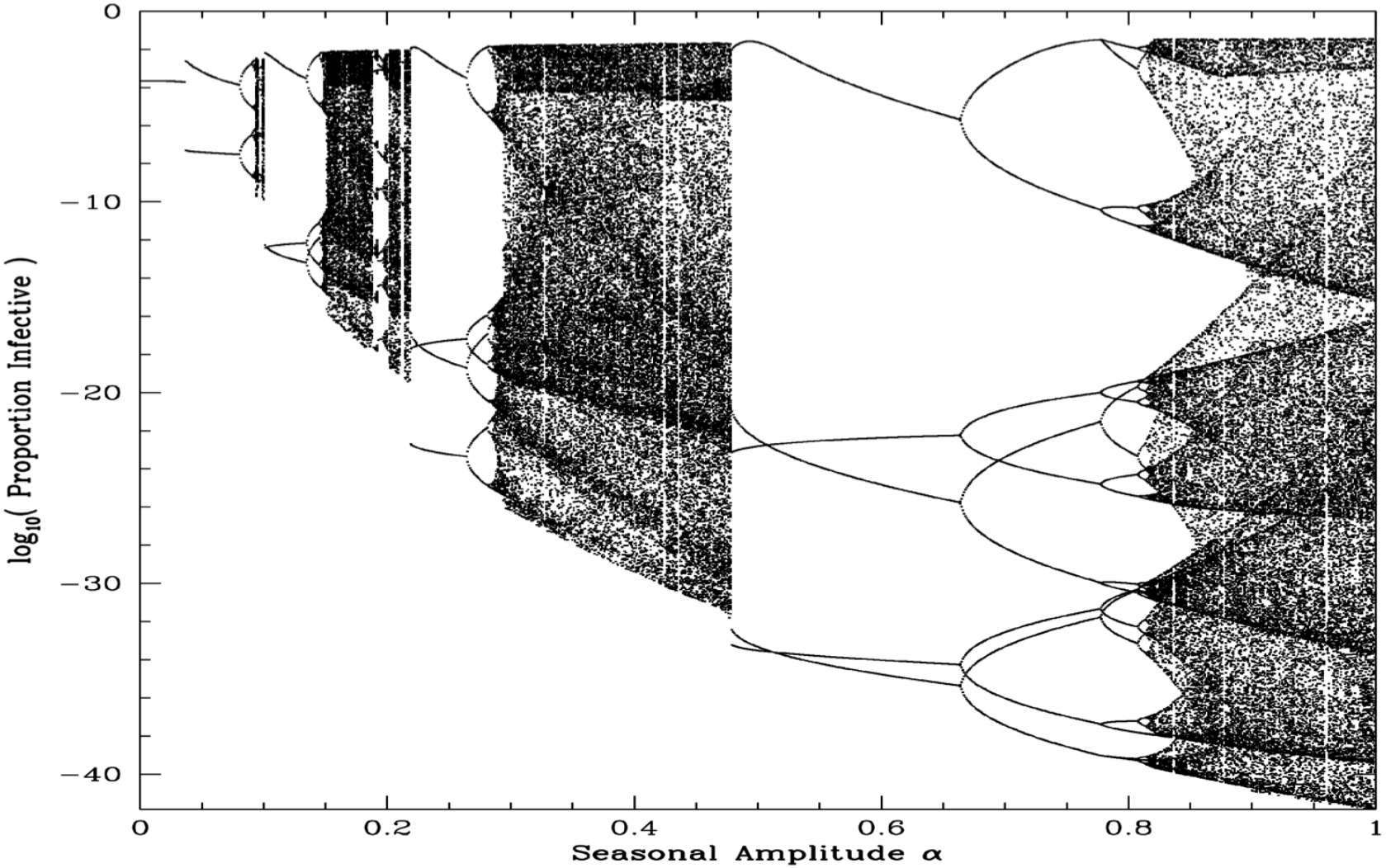
- There exist parameter values such that infinitely many stable cycles co-exist

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)



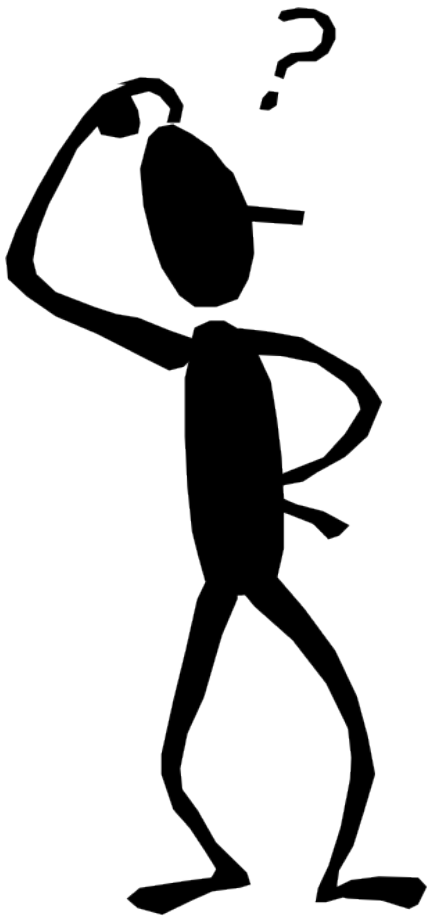
Earn (2009) *IAS/Park City Mathematics Series* **14**, 151–186

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

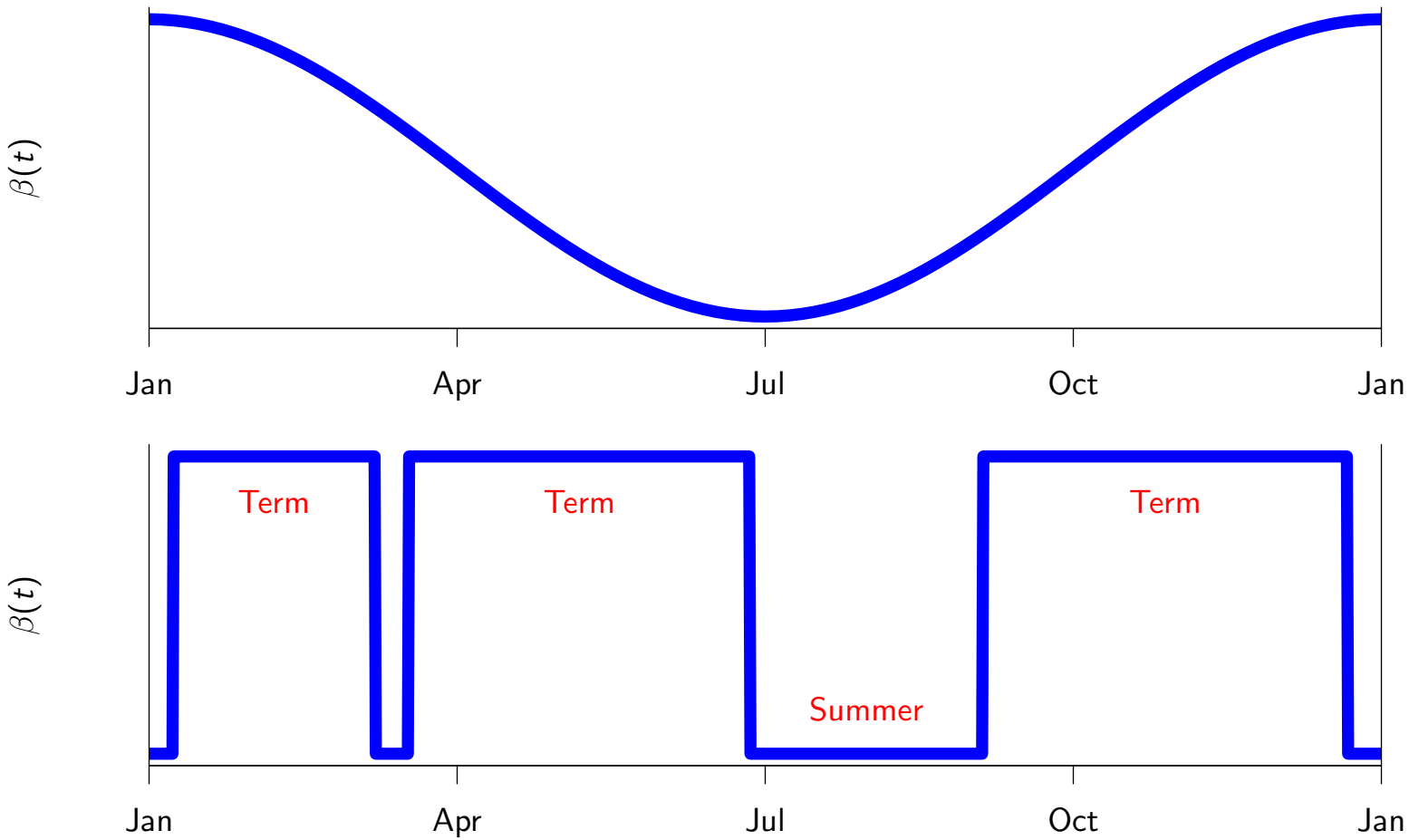
- Lots of work on RAS models since Schenzle (1984)

RAS SEIR model: Results for Measles

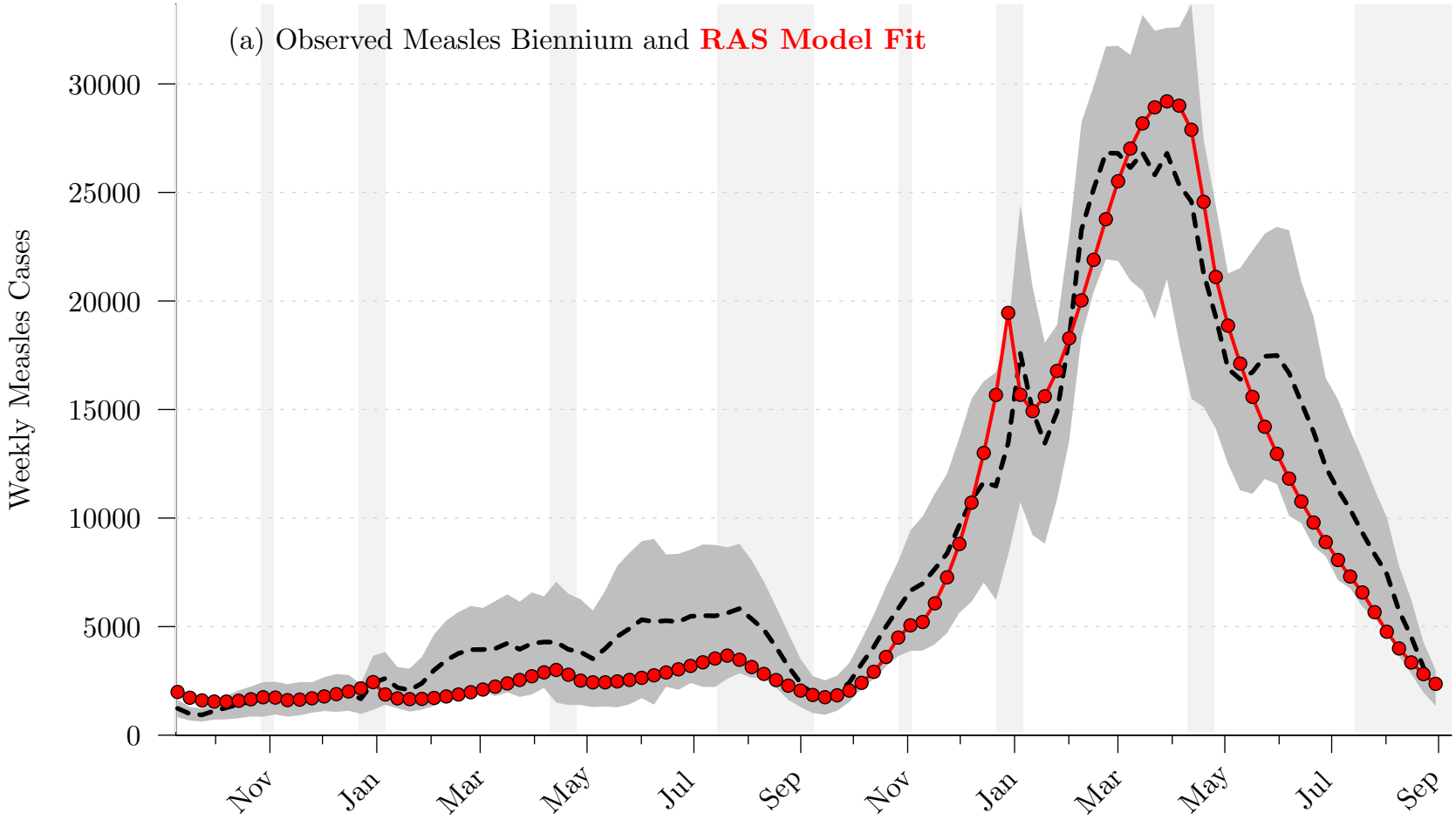
- Persistent biennial cycle
- Matches biennial cycle in data extremely well
- And we need only 84 ODEs
  and fewer than 500 new parameters!
- Can get an even better fit by adding spatial structure
  with 6000 ODEs and only 1500 new parameters!
- **Woohoo!** Time to celebrate.
- hmmm. . . maybe not. . .
- 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

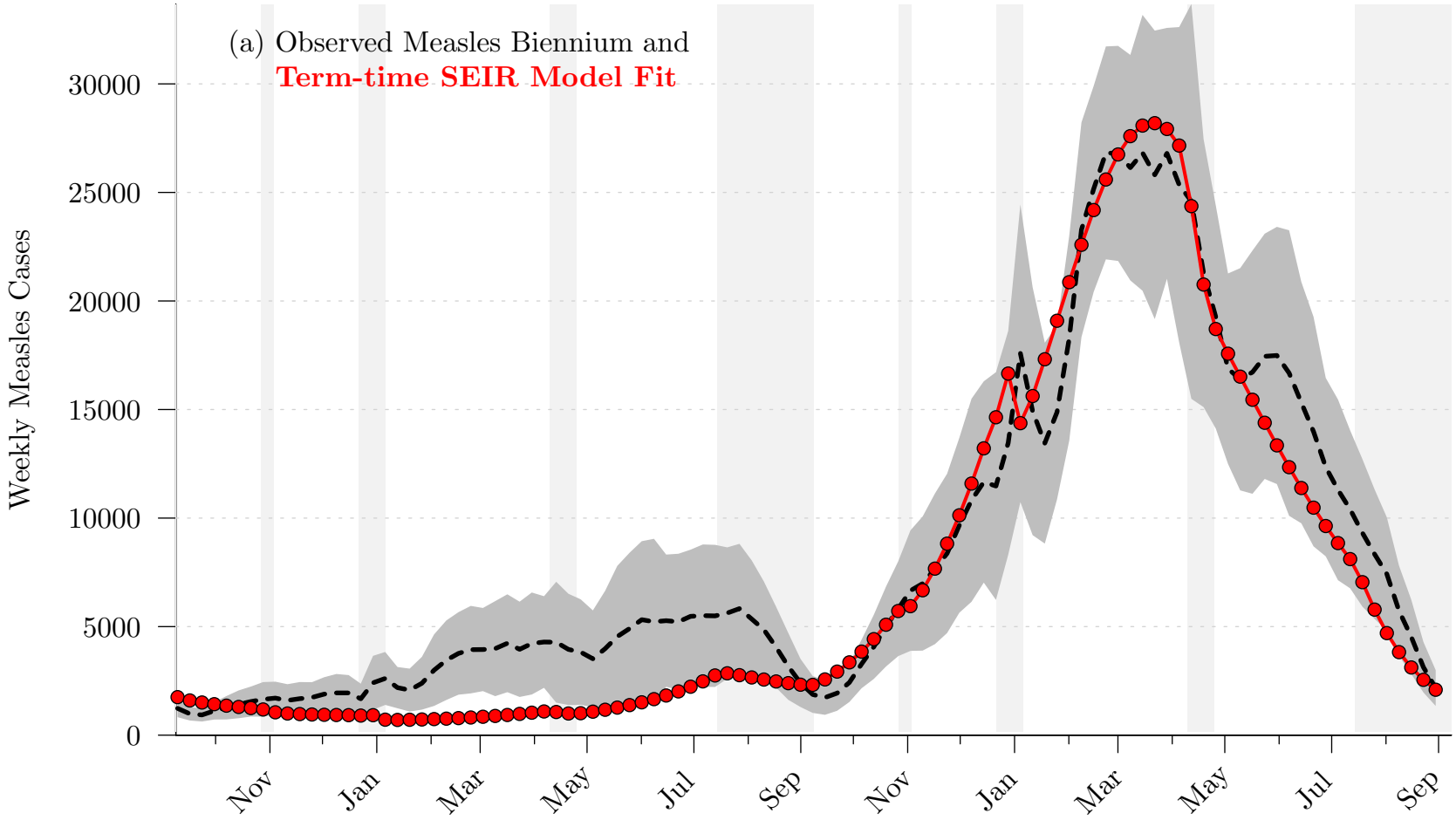


RAS model fit to measles in England and Wales



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

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Mathematics and Statistics

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

Mathematics 4MB3/6MB3 Mathematical Biology

Instructor: David Earn

Lecture 15
Mechanistic Modelling of Recurrent Epidemics III
Monday 11 February 2019

Announcements

- **Assignment 3** is posted.
  Due Monday 25 February 2019 at 9:30am
- **Midterm test:**
  - *Date:* Monday 11 March 2019
  - *Time:* 9:30am–11:20am
  - *Location:* Hamilton Hall 410

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

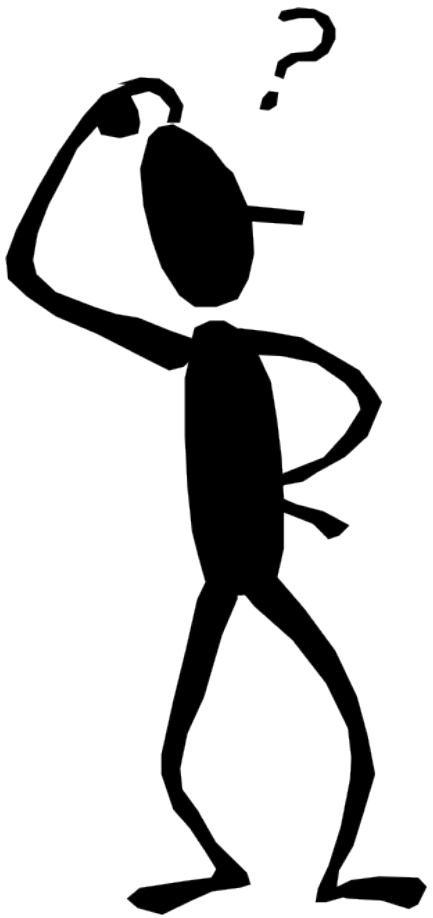
    Earn, Rohani, Bolker, Grenfell (2000) *Science* **287**, 667–670

  - 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?

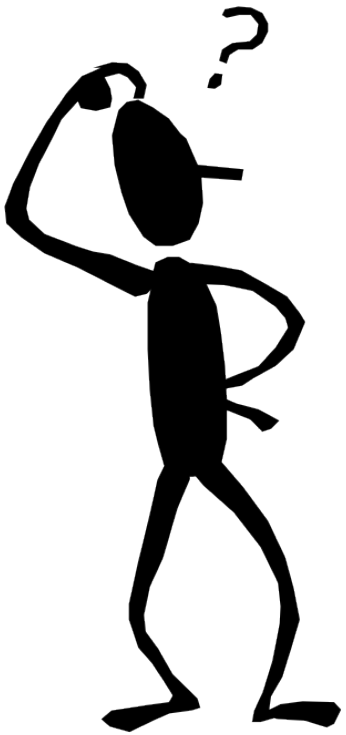
- Some key, biologically meaningful parameters
  - Basic reproductive ratio ($\mathcal{R}_0$)
    - Transmissibility.
    - Can an epidemic occur? If so, how big?
  - Amplitude of seasonal forcing (α)
    - Magnitude of seasonal variation in contact rate.
    - Stable, sustained oscillations or chaos.

- 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...



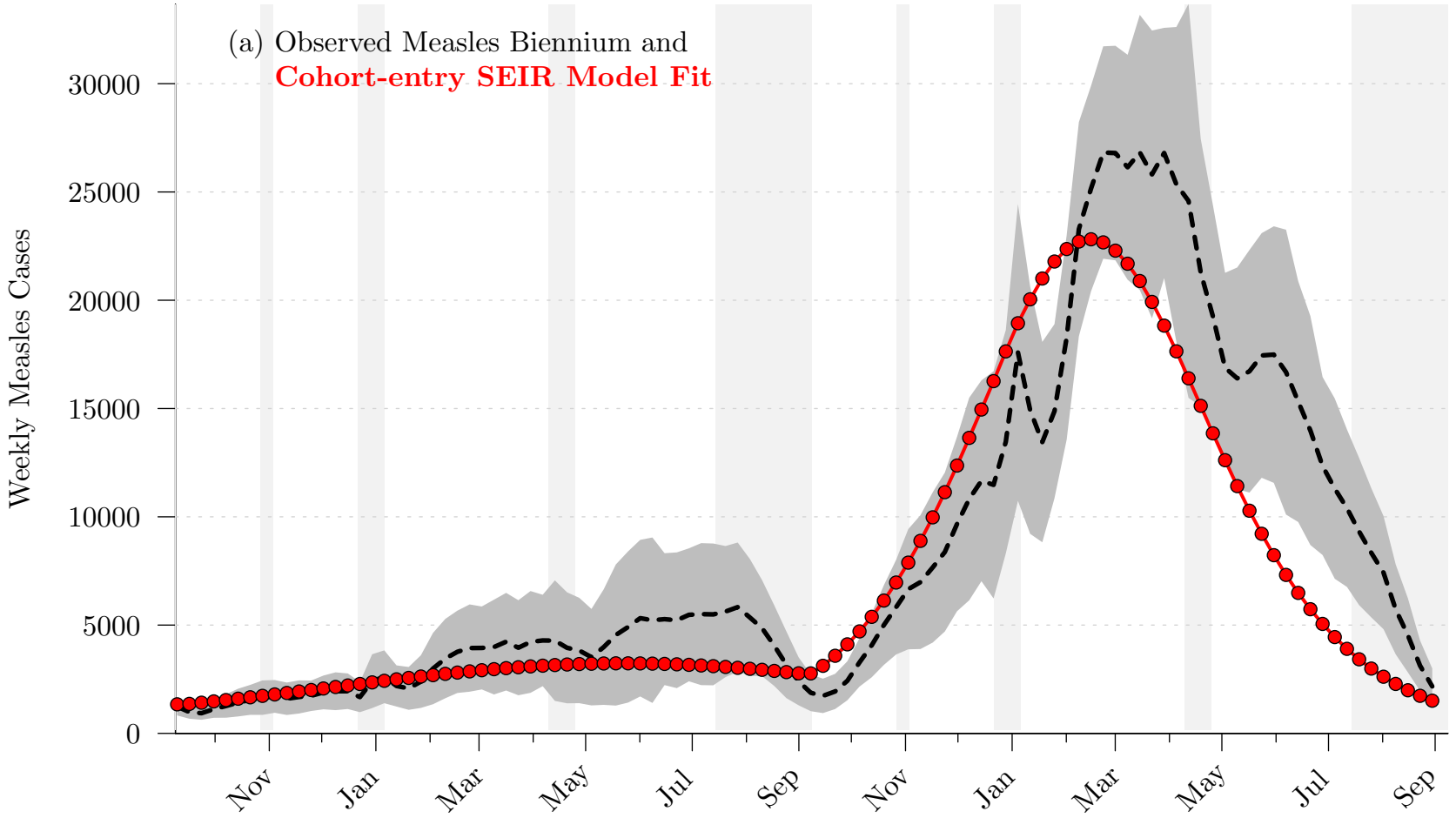
- What should we try next?
- Do we need more model structure?
- We changed $\beta \to \beta(t)$. Do other parameters vary significantly with time?
  - Birth rate?
  - Death rate?
  - Vaccination rate?
  - Other parameters?

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?

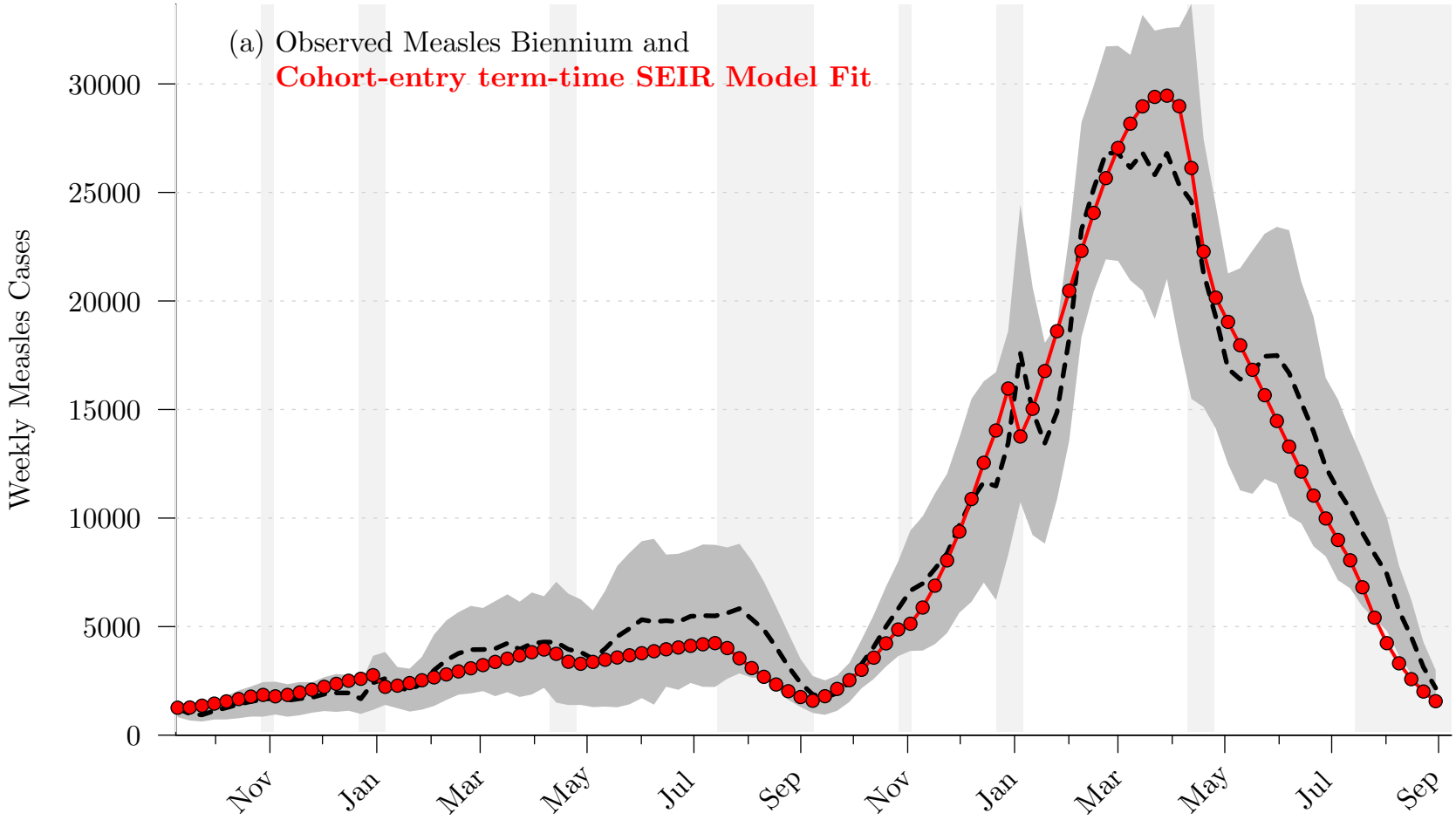
    He & Earn (2016) *J. R. Soc. Interface* **13**, 20160156
  - Compare fits of measles biennium in England and Wales with: (i) RAS, (ii) term-time, (iii) cohort, (iv) term-time and cohort.

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 $\mathcal{R}_0$)

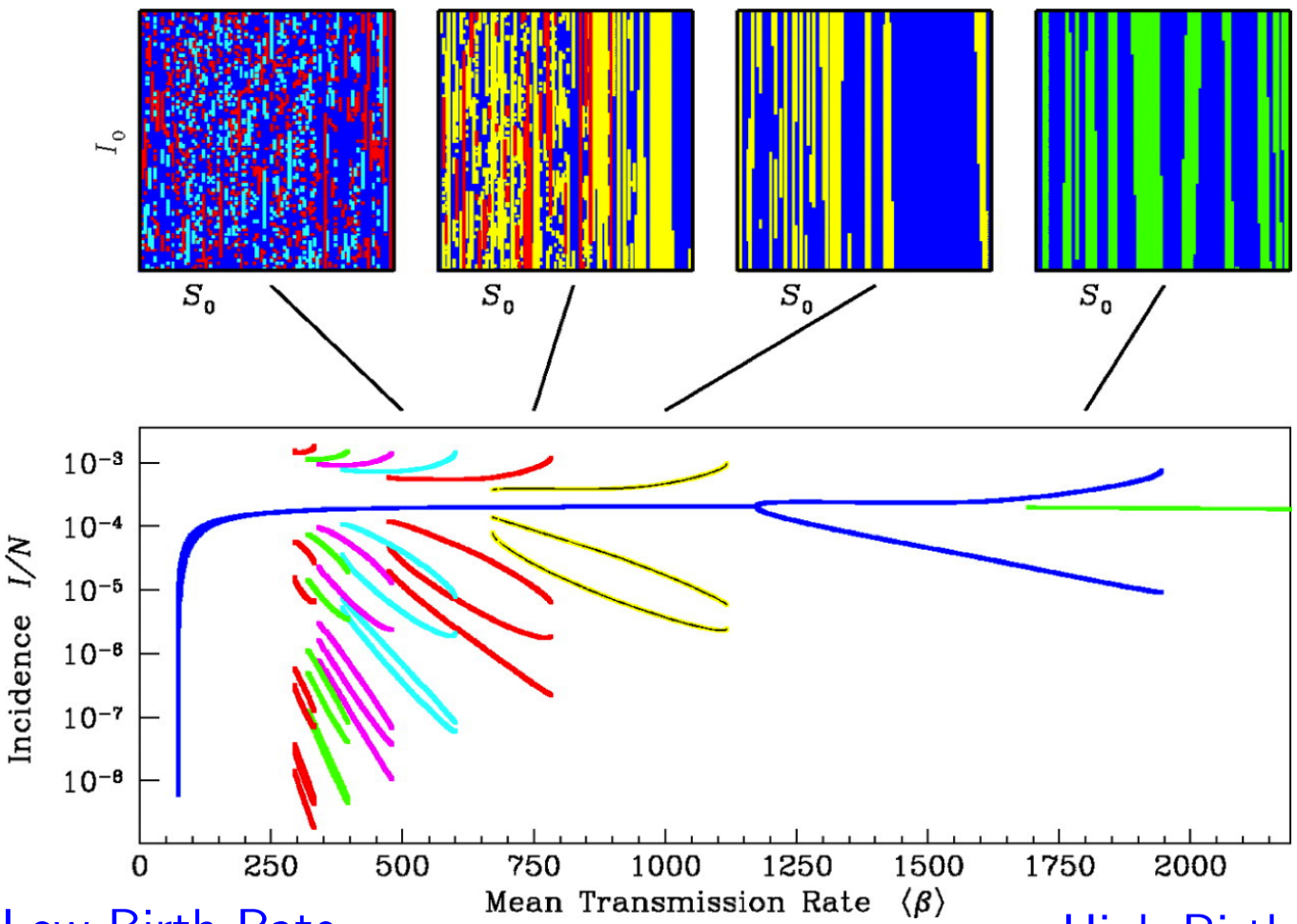
  all map onto the same parameter axis.

- $\therefore$ 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