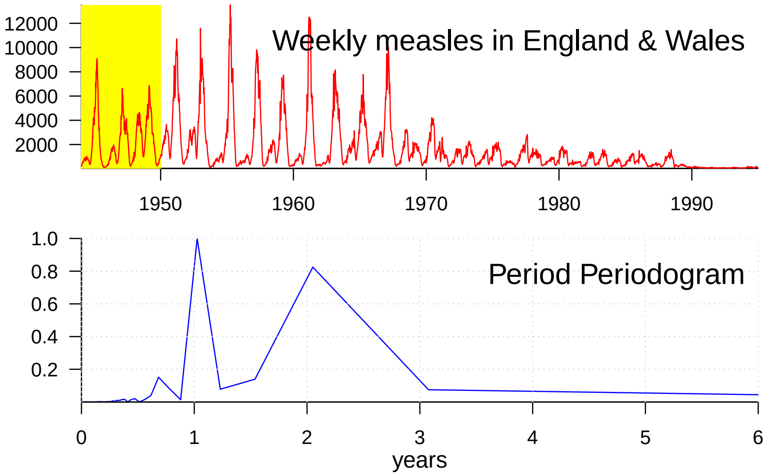
Mechanistic Modelling of Recurrent Epidemics

What causes changes in frequency content over time?



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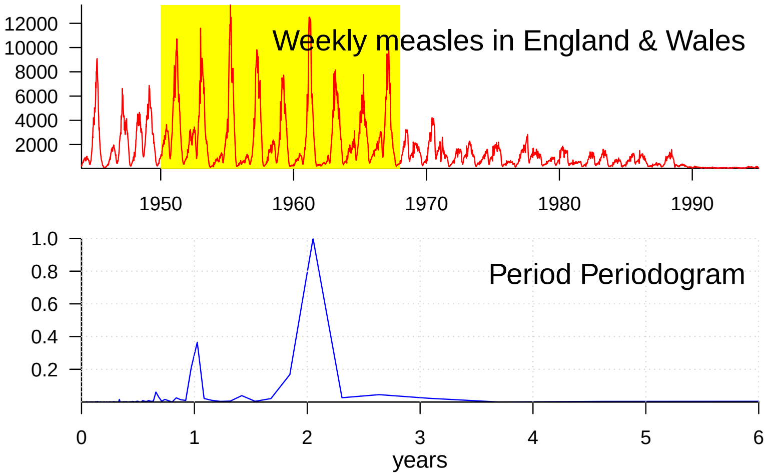
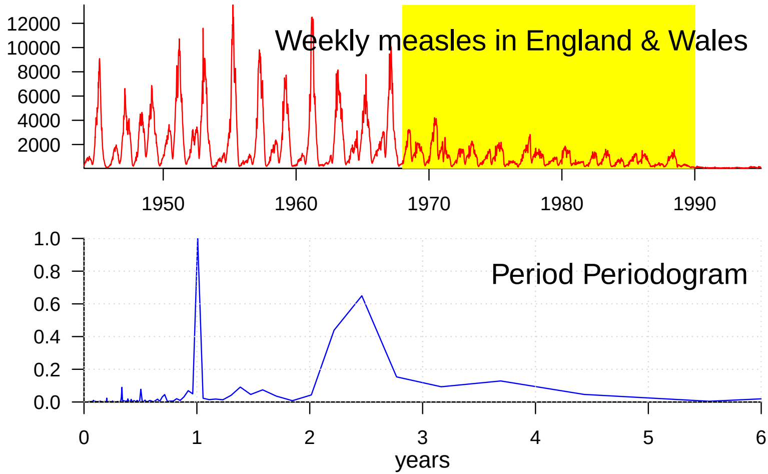
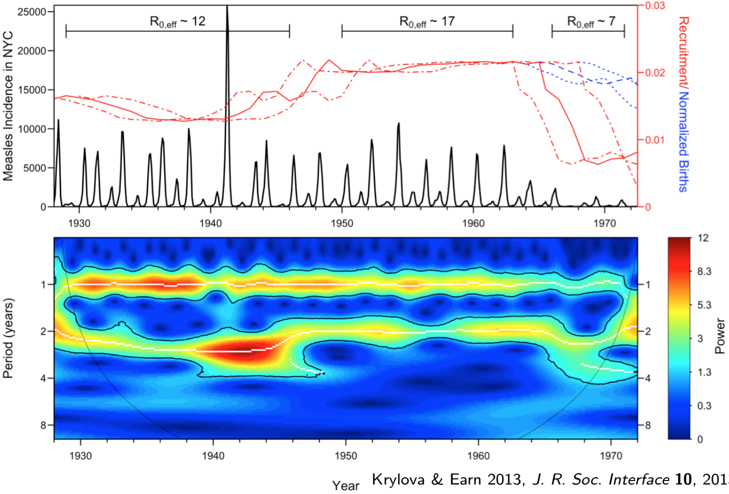


What causes changes in frequency content over time?



What causes changes in frequency content over time?

Measles in New York City

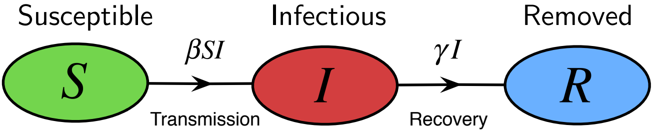


Krylova & Earn 2013, *J. R. Soc. Interface* **10**, 20130098

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



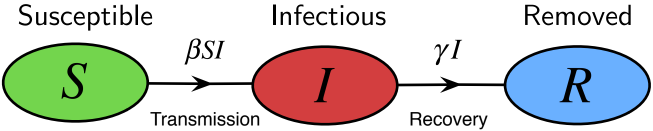
$$\frac{dS}{dt} = -\beta SI$$

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

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

- **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

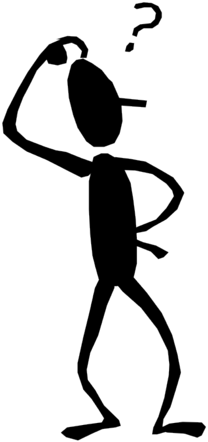
$$\mathcal{R}_0 = \frac{\beta}{\gamma}$$

Basic SIR Model: Important Results

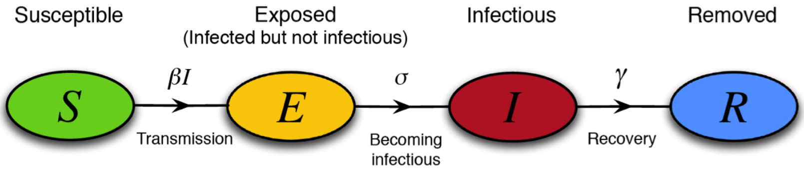
- Epidemic occurs if and only if $\mathcal{R}_0 > 1$
- Exact solution for phase portrait
- Single epidemic, then disease disappears
- Exact formula for final size as a function of $\mathcal{R}_0$

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

What are we missing?

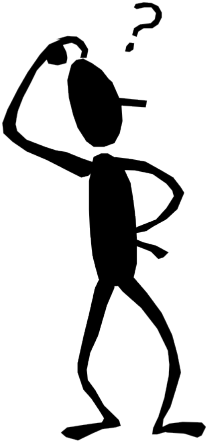


SEIR Model: flow chart

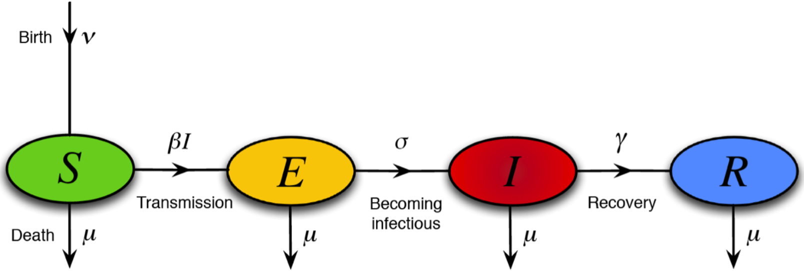


- Introduces only one new parameter (σ)
- Mean latent period ($1/\sigma$) can often be estimated
- But. . . effect of inclusion of exposed class usually small

What are we still missing?



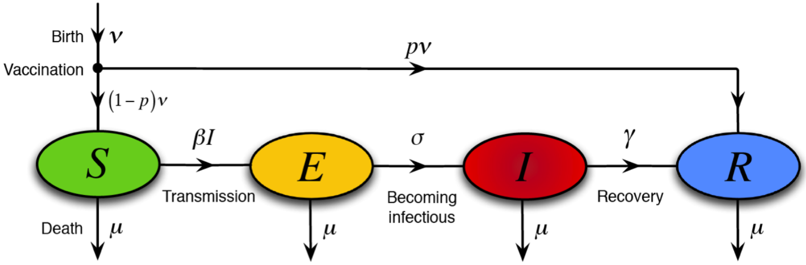
SEIR Model with vital dynamics: flow chart



New Parameters:

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

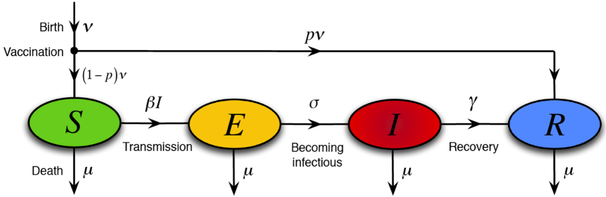
SEIR with vital dynamics and vaccination: flow chart



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 ($1/\gamma$)

McMaster University

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 5 February 2018

Announcements

- **Assignment 2:** Due TODAY!
  Do the Group contribution survey TODAY.
- **Assignment 3:** Will be posted tonight or tomorrow.
  Due Wednesday 28 February 2018, 11:30am.
- **Midterm test:**
  - *Date:* Thursday 8 March 2018
  - *Time:* 7:00pm to 9:00pm
  - *Location:* BSB-B154

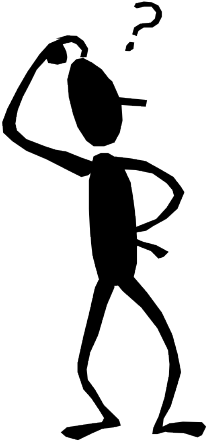
SEIR with vital dynamics and vaccination: Analysis

- $\mathcal{R}_0$?
  - 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?

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: $\mathcal{R}_0 \sim 4 \implies p_{\rm crit} \sim 75\%$
  - Measles: $\mathcal{R}_0 \sim 20 \implies p_{\rm crit} \sim 95\%$
- 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

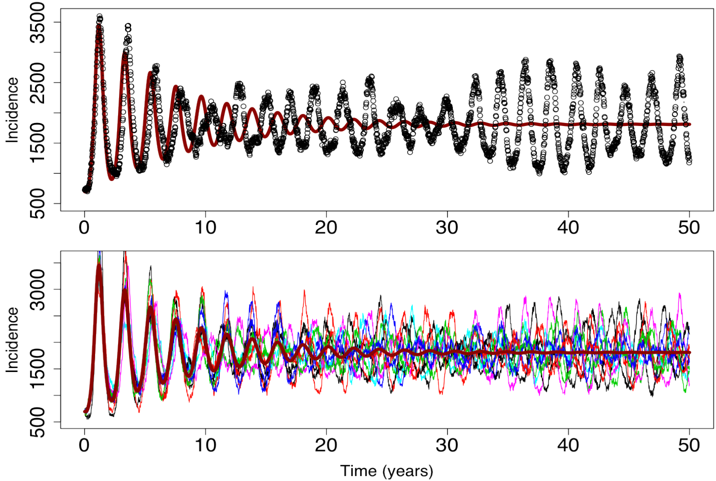
- We now know the time t of the next event, but we must still determine what type of event occurs at time t.
- Probability of event of type i is $\frac{a_i}{a_0}$
- $\therefore$ Can easily determine type of event by sampling a point from a uniform distribution on $[0, a_0]$:
  - Event is type i if the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

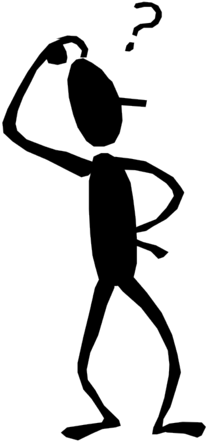


Earn 2009, *IAS/Park City Mathematics Series* **14**, 151–186

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?



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

Wednesday 7 February 2018

Announcements

- **Assignment 3:** Will be posted tonight or tomorrow.
  Due Wednesday 28 February 2018, 11:30am.
- **Midterm test:**
  - *Date:* Thursday 8 March 2018
  - *Time:* 7:00pm to 9:00pm
  - *Location:* BSB-B154

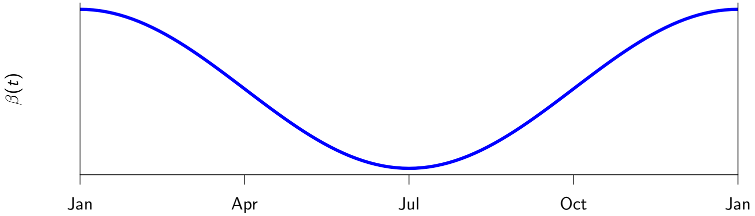
Contact rates are higher during school terms!

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

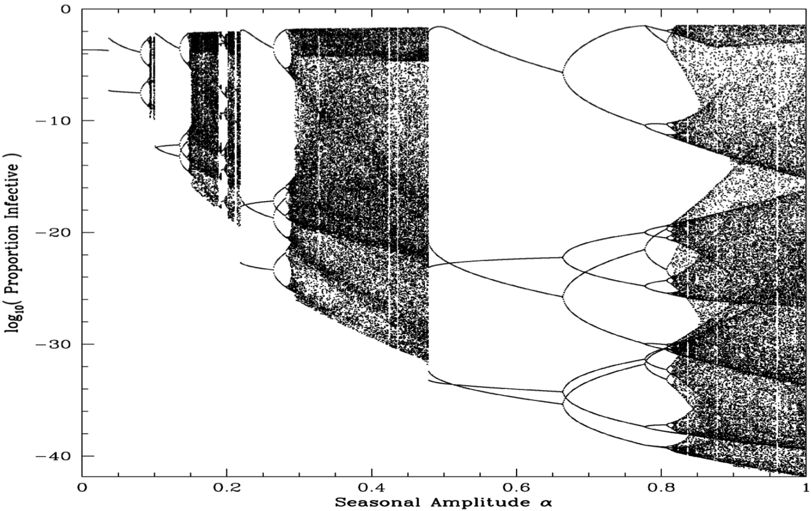
- There exist parameter values such that infinitely many stable cycles co-exist

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)



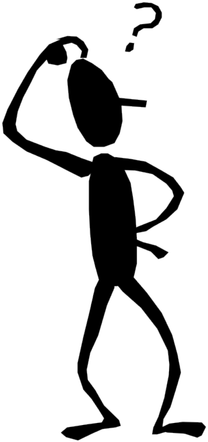
Earn (2009) *IAS/Park City Mathematics Series* **14**, 151–186

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

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

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

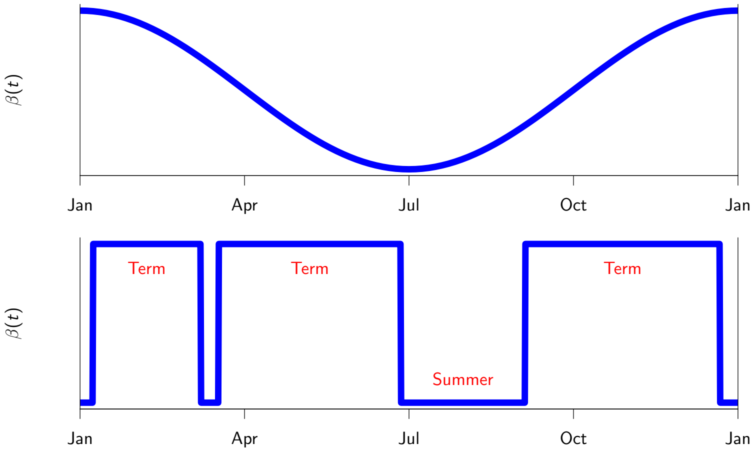
- Lots of work on RAS models since Schenzle (1984)

RAS SEIR model: Results for Measles

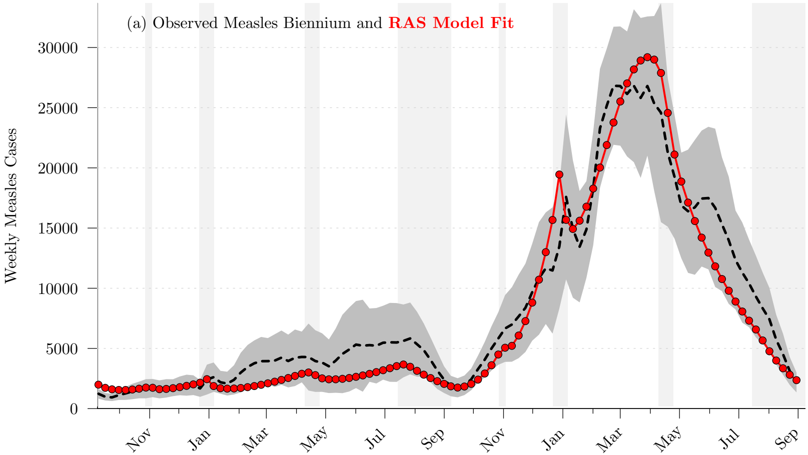
- Persistent biennial cycle
- Matches biennial cycle in data extremely well
- And we need only 84 ODEs
  and fewer than 500 new parameters!
- Can get an even better fit by adding spatial structure
  with 6000 ODEs and only 1500 new parameters!
- **Woohoo!** Time to celebrate.
- hmmm. . . maybe not. .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

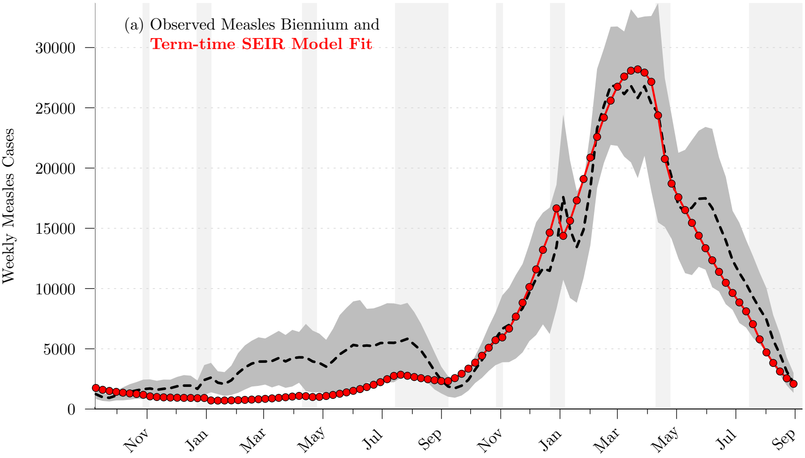


RAS model fit to measles in England and Wales



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

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



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