Vaccination and Seasonality in Epidemic Models

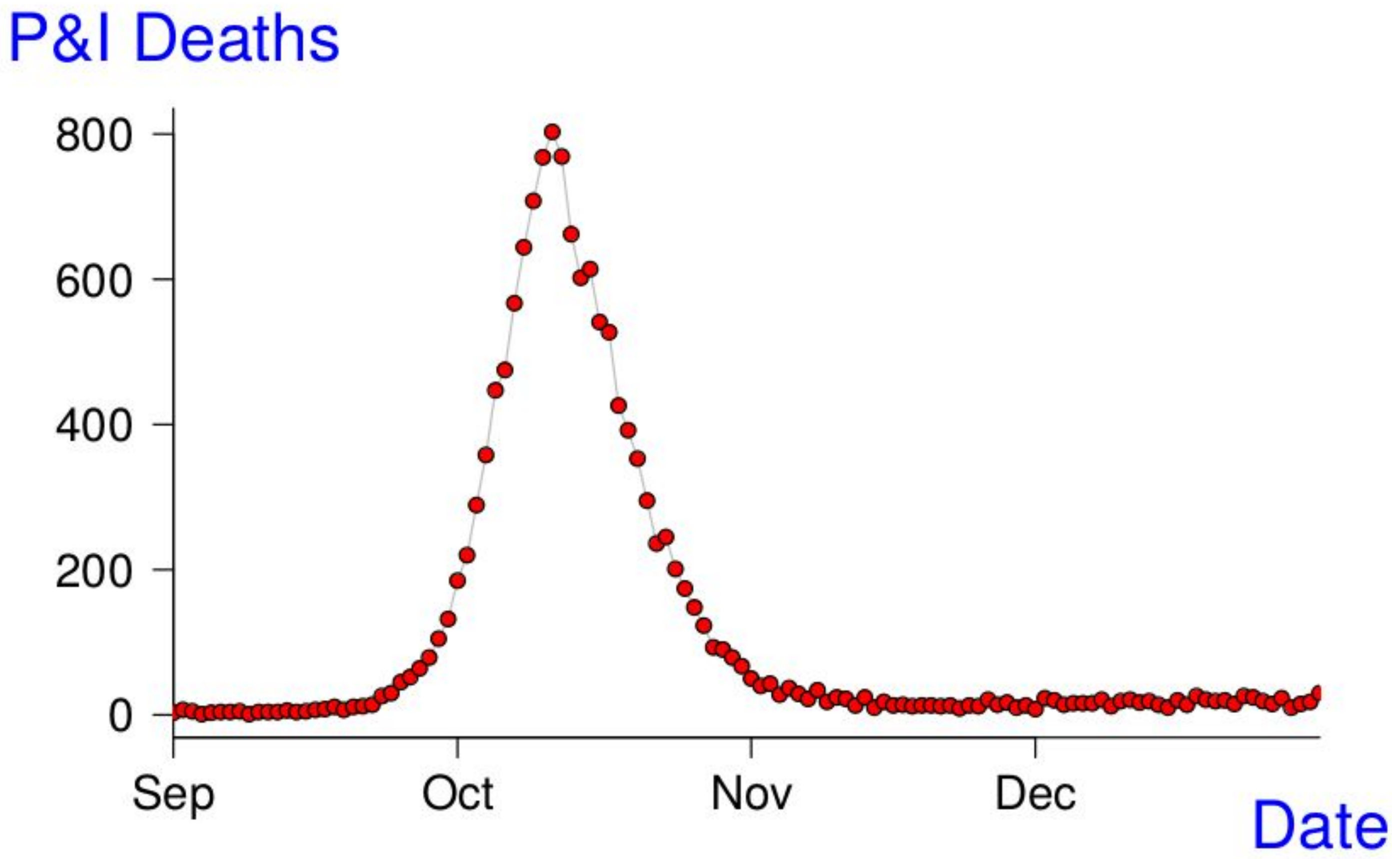
1.

A Brief Overview of SIR

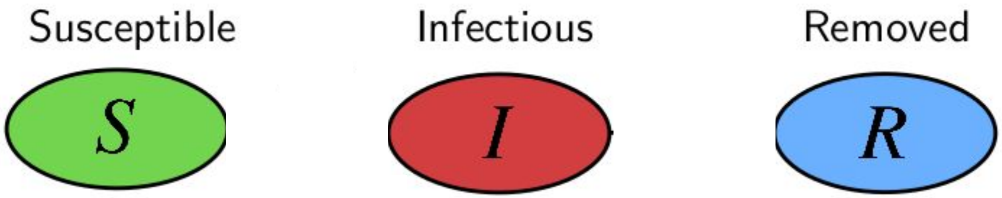
Epidemic Modelling

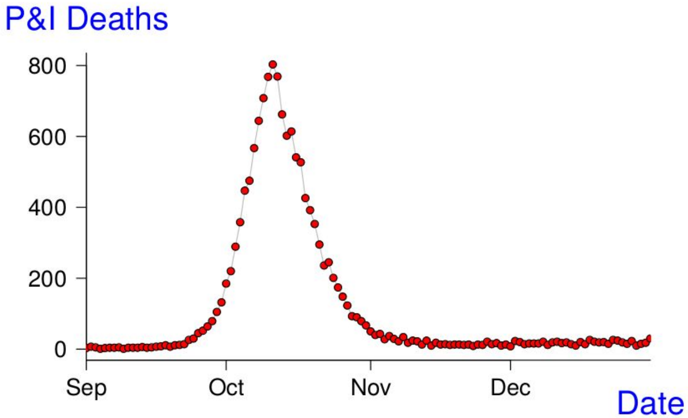
- Two main goals:
  - Historical
    - Explain P&I 1918 data, Measles data
  - Predictive
    - Develop tools for predictive results
    - 2003 SARS Outbreak
- Extra goals
  - Understanding the Mechanisms

1918 Spanish Flu (Philadelphia)

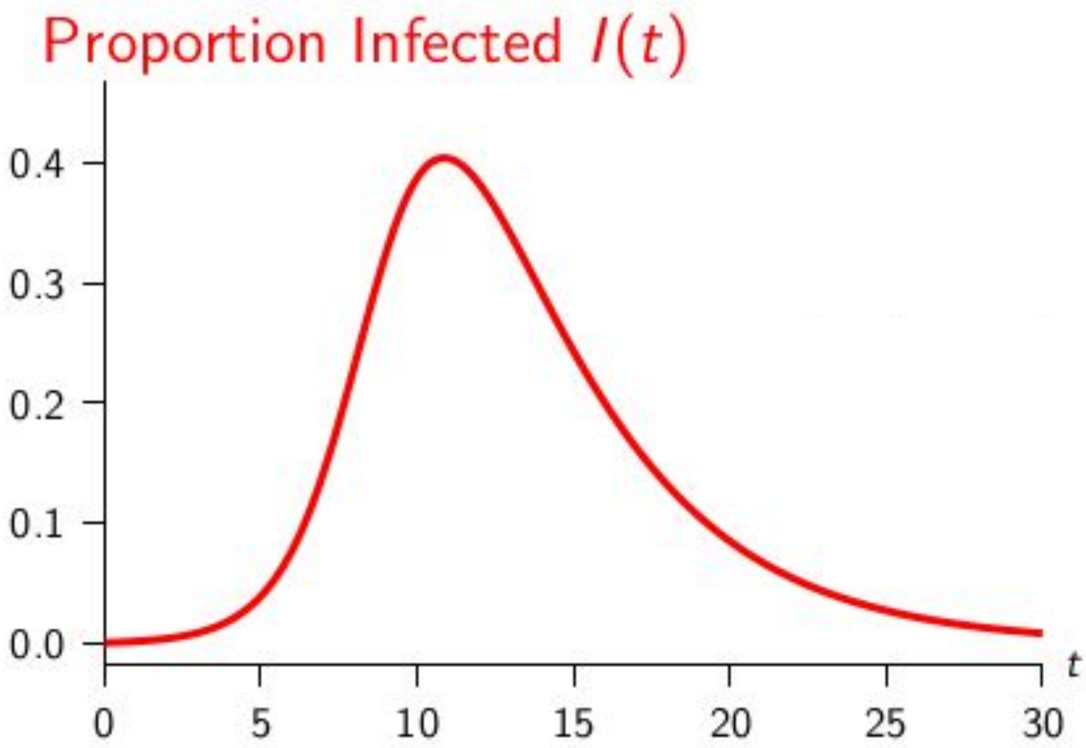


Deriving SIR Model





SIR Model Fitting



Basic Reproduction Number

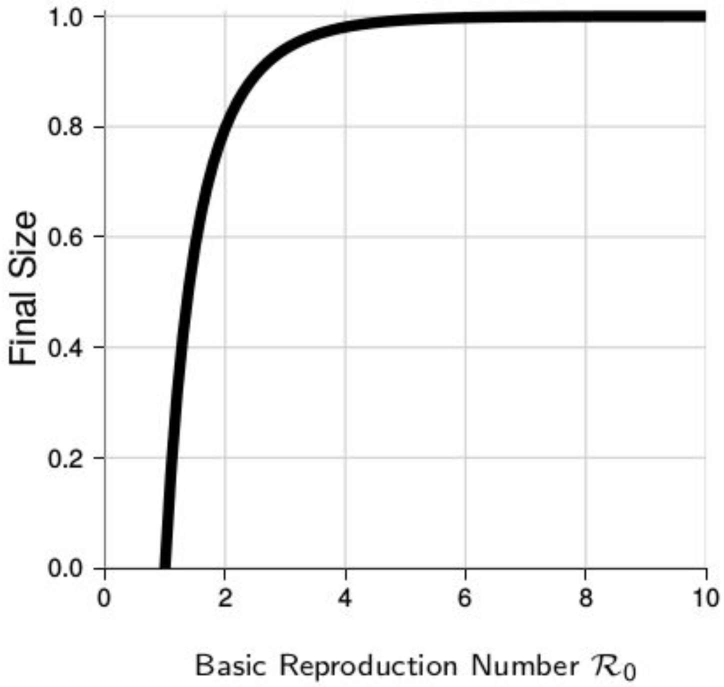
$$\mathcal{R}_0 = \beta \cdot \frac{1}{\gamma}$$

Final Size Formula

Final Size Formula:

$$Z = 1 - e^{-\mathcal{R}_0 Z}$$

- Final size is determined entirely by $\mathcal{R}_0$
- Final size is never the whole population ($Z < 1$)
- Formula is valid for much more realistic models (Ma & Earn, 2006)



- For 1918 flu: $1.5 \lesssim \mathcal{R}_0 \lesssim 2$
- Proportion of world population infected?
- $\sim$60–80%

Basic Reproductive Number

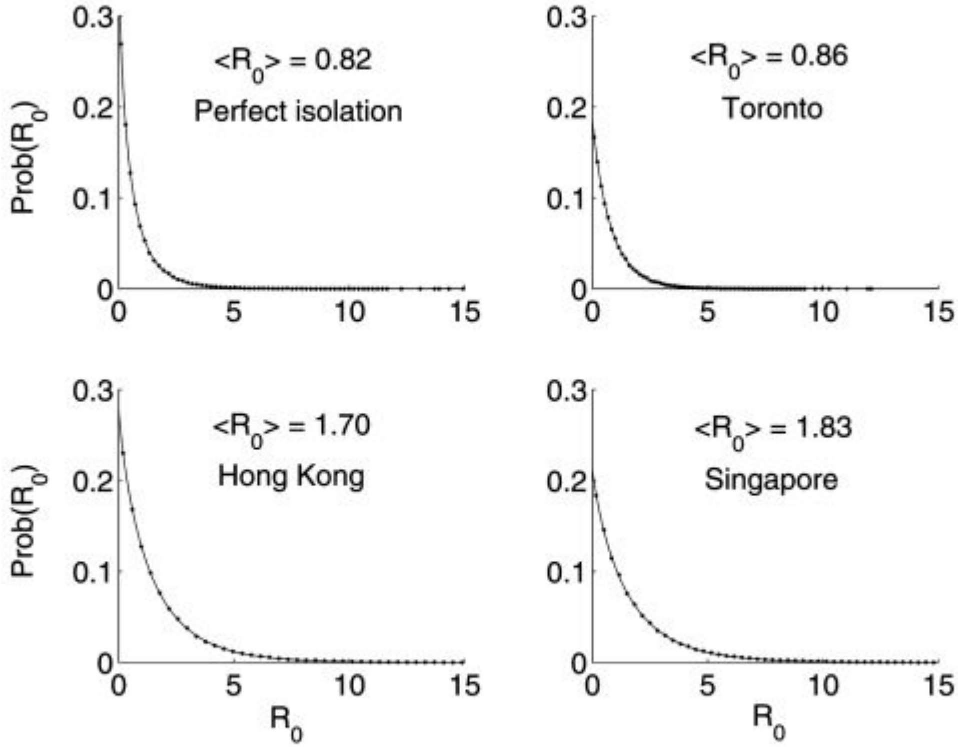


Fig 2. Chowell, Gerardo et al. “Model Parameters and Outbreak Control for SARS.” *Emerging Infectious Diseases* 10.7 (2004): 1258–1263. *PMC*. Web. 12 Apr. 2018.

2.

Vaccination

Vaccination

- Anything that reduces $\mathcal{R}_0$ reduces the final size of the epidemic
- What could they have done in 1918 to reduce this number?
- Masks? Quarantine? Isolation?
- Vaccination tech just wasn't there in 1918
  - Hard enough in modern times (H1N1)
- How do vaccines reduce the spread of a virus

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\mathcal{R}_0\,\gamma\,S\,I, \quad \frac{\mathrm{d}I}{\mathrm{d}t} = \mathcal{R}_0\,\gamma\,S\,I - \gamma\,I$$

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\beta\,S\,I, \quad \frac{\mathrm{d}I}{\mathrm{d}t} = \beta\,S\,I - \gamma\,I$$

- If we vaccinate everybody, then clearly no epidemic takes place
  - If we vaccinate everybody except for one person, no epidemic will take place
- What critical proportion of the population do we need to vaccinate in order to ensure herd immunity

Vaccination

- What critical proportion of the population do we need to vaccinate in order to ensure herd immunity

$$\left.\frac{\mathrm{d}I}{\mathrm{d}t}\right|_{t=0} = \left((\mathcal{R}_0\, S - 1)\,\gamma\, I\right)\big|_{t=0}$$

In conclusion, we need to vaccinate a proportion

$$p \geq p_{\text{crit}} = 1 - \frac{1}{\mathcal{R}_0}$$

Hence, knowing the reproduction number is important *again*.

The Model's Predictive Success (?)

- So far we've seen that knowing $\mathcal{R}_0$ is <u>very</u> important!
- Epidemics occur if, and only if, $\mathcal{R}_0 > 1$
- Single epidemic -- disease disappears
  - Every non-equilibrium solution is a heteroclinic orbit
- Can prevent epidemics entirely with aggressive enough initial vaccination
- Can completely explain the dynamics of 1918 flu

Stability Analysis of Vaccination

- Flu done, we're looking at childhood diseases like measles next
- The way we just handled vaccination is dynamically equivalent to just changing initial conditions
- Most public health issues are on long time scales
- We've been focused on small time scales (*an* epidemic)
    - On small time scales, we can safely ignore births and deaths
    - Births and deaths are real
- Assume ν is the birth rate and μ is the death rate
- Assume we vaccinate our newborns at a rate p
- For convenience we consider four classes, *SIRV*
- It is dynamically equivalent to consider birth and death rates to be the same, so for simplicity we do

Stability Analysis of Vaccination

$$\frac{\mathrm{d}S}{\mathrm{d}t} = (1-p)\,\mu - \beta\,I\,S - \mu\,S$$
$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta\,I\,S - \gamma\,I - \mu\,I$$
$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma\,I - \mu\,R$$
$$\frac{\mathrm{d}V}{\mathrm{d}t} = p\,\mu - \mu\,V$$

If we solve the *S'(t)*=0 equation for *I* we get

$$I = \frac{(1-p)\,\mu}{\beta\,S} - \frac{\mu}{\beta}$$

Plugging this into the *I'(t)=0* equation to find the *S*-value at equilibrium and we see

$$I\,(\beta\,S - \gamma - \mu) = 0$$

...continued...

The discriminant of this equation is

$$\Delta = (1 - p + \tfrac{\gamma}{\beta} + \tfrac{\mu}{\beta})^2 - 4\left(\frac{(1-p)\,(\gamma+\mu)}{\beta}\right)$$

For real solutions, $$(1 - p + \tfrac{\gamma}{\beta} + \tfrac{\mu}{\beta})^2 \geq 4\left(\frac{(1-p)\,(\gamma+\mu)}{\beta}\right)$$

$$\left(\frac{\beta\,(1-p)+(\gamma+mu)}{\beta}\right)^2 \geq 4\left(\frac{(1-p)\,(\gamma+\mu)}{\beta}\right)$$

$$\left(\frac{\gamma+\mu}{\beta}\right)^2\left(1+\beta\frac{1-p}{\gamma+\mu}\right)^2 \geq 4\left(\frac{(1-p)\,(\gamma+\mu)}{\beta}\right)$$

$$\left(1+\beta\frac{1-p}{\gamma+\mu}\right)^2 \geq 4\left(\frac{(1-p)\,(\beta)}{\gamma+\mu}\right)$$

$$\left(\beta\frac{(1-p)}{\gamma+\mu} - 1\right)^2 \geq 0$$

Bifurcation Analysis

Hence a transcritical bifurcation occurs

$$\beta\frac{(1-p)}{\gamma+\mu}=1$$

Where two equilibria points co-exist. At equality, one solution for S exists.

When the value is bigger than 1, two solutions for S exist.

Sound familiar? This is the *effective* $\mathcal{R}_0$ value!

An equilibrium can only exist if the effective $\mathcal{R}_0$ value is greater than 1. Increasing the per-birth vaccination rate p, decreases our effective $\mathcal{R}_0$.

Linear Stability Analysis

Disease Free

$$\begin{vmatrix} -\mu-\lambda & -\beta(1-p) & 0 \\ 0 & \beta(1-p)-\gamma-\mu-\lambda & 0 \\ 0 & 0 & -\mu-\lambda \end{vmatrix} = 0$$

You can read the three eigenvalues off the diagonal.

Note the first and third are always negative.

For the second, recall

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

Hence the second eigenvalue is positive when $\mathcal{R}_0 > 1$ (and so the equilibrium is unstable) and negative when $\mathcal{R}_0 < 1$ (and so the equilibrium is stable)

Linear Stability Analysis

Endemic Equilibrium

$$\begin{vmatrix} -\frac{\mu\beta(1-p)}{\gamma+\mu}-\lambda & -(\gamma+\mu) & 0 \\ \frac{\mu[\beta(1-p)-\gamma-\mu]}{\gamma+\mu} & -\lambda & 0 \\ 0 & 0 & -\mu-\lambda \end{vmatrix} = 0$$

The eigenvalues are a little messier…

$$\lambda_1 = -\mu$$
$$\lambda_{2,3} = -\mu\,\mathcal{R}_0 \pm \sqrt{\mu^2\,\mathcal{R}_0^2 - 4\,\mu\,(\gamma+\mu)\,(\mathcal{R}_0 - 1)}$$

If $\mathcal{R}_0 > 1$, all three eigenvalues are have negative real part and the equilibrium is stable.

If $\mathcal{R}_0 < 1$, then the second eigenvalue has positive real part and the equilibrium is unstable

Global Stability Analysis

Can show that the equilibria are globally stable with the use of Lyapunov functions. For the Disease Free Equilibrium the Lyapunov function

$$L_1(S, I, V) = S(t) + I(t)$$

will suffice.

For the Endemic Equilibrium, the classic Lyapunov function

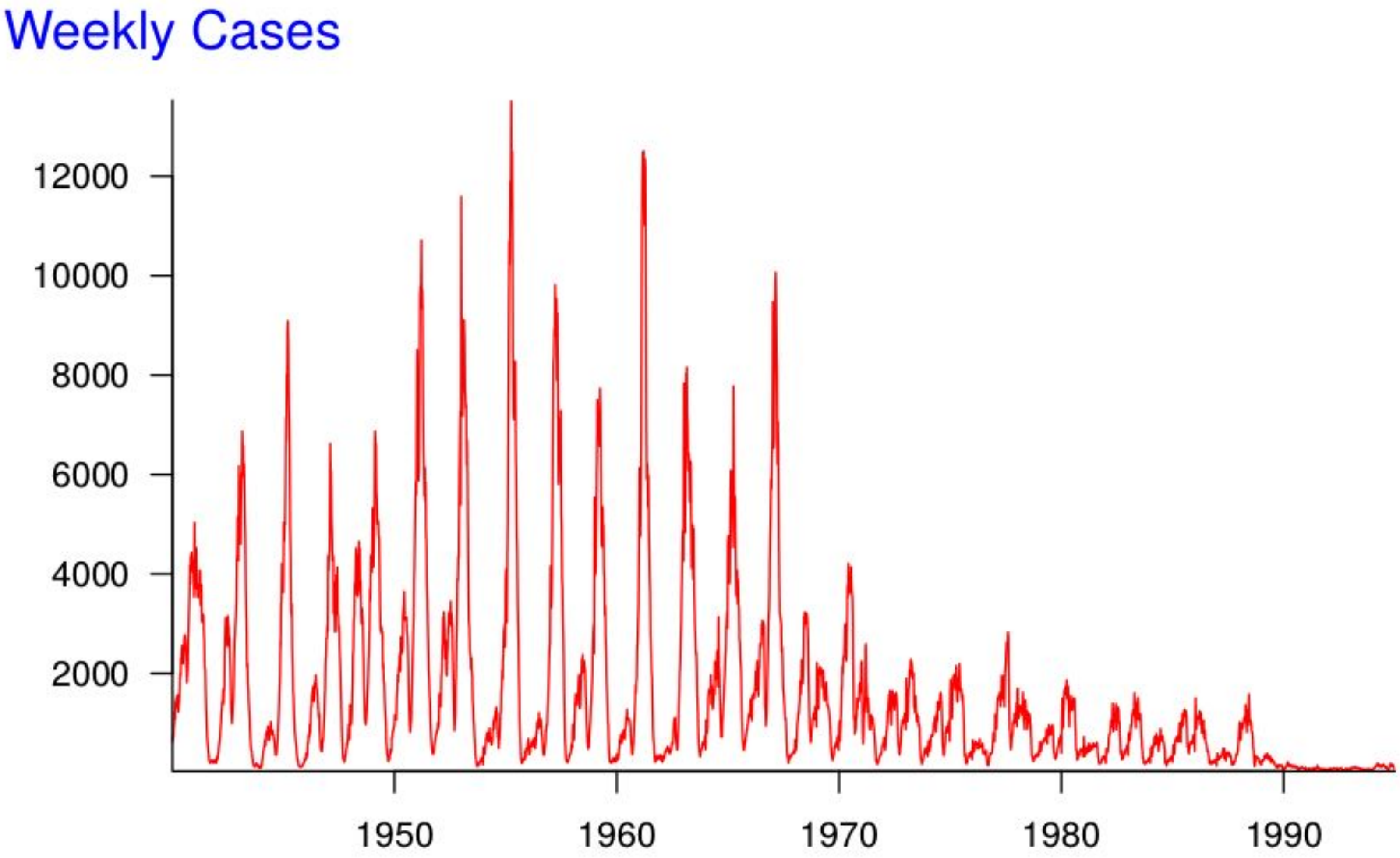
$$L_2(S,I,V) = S - S^* \log\left(\frac{S}{S^*}\right) + I - I^* \log\left(\frac{I}{I^*}\right) + V - V^* \log\left(\frac{V}{V^*}\right)$$

works.

Take Away

- This SIRV model with birth/death dynamics behaves exactly like the regular SIR model in terms of its *qualitative* dynamics
- Saw how $\mathscr{R}_0$ can be affected by including new things in the model
- Vaccination can affect the dynamics in multiple ways (blanket vaccination, ongoing vaccination)
- Both strategies in use commonly
- Can consider all different kinds of vaccination schedules
- Ongoing research in epidemic models with vaccination

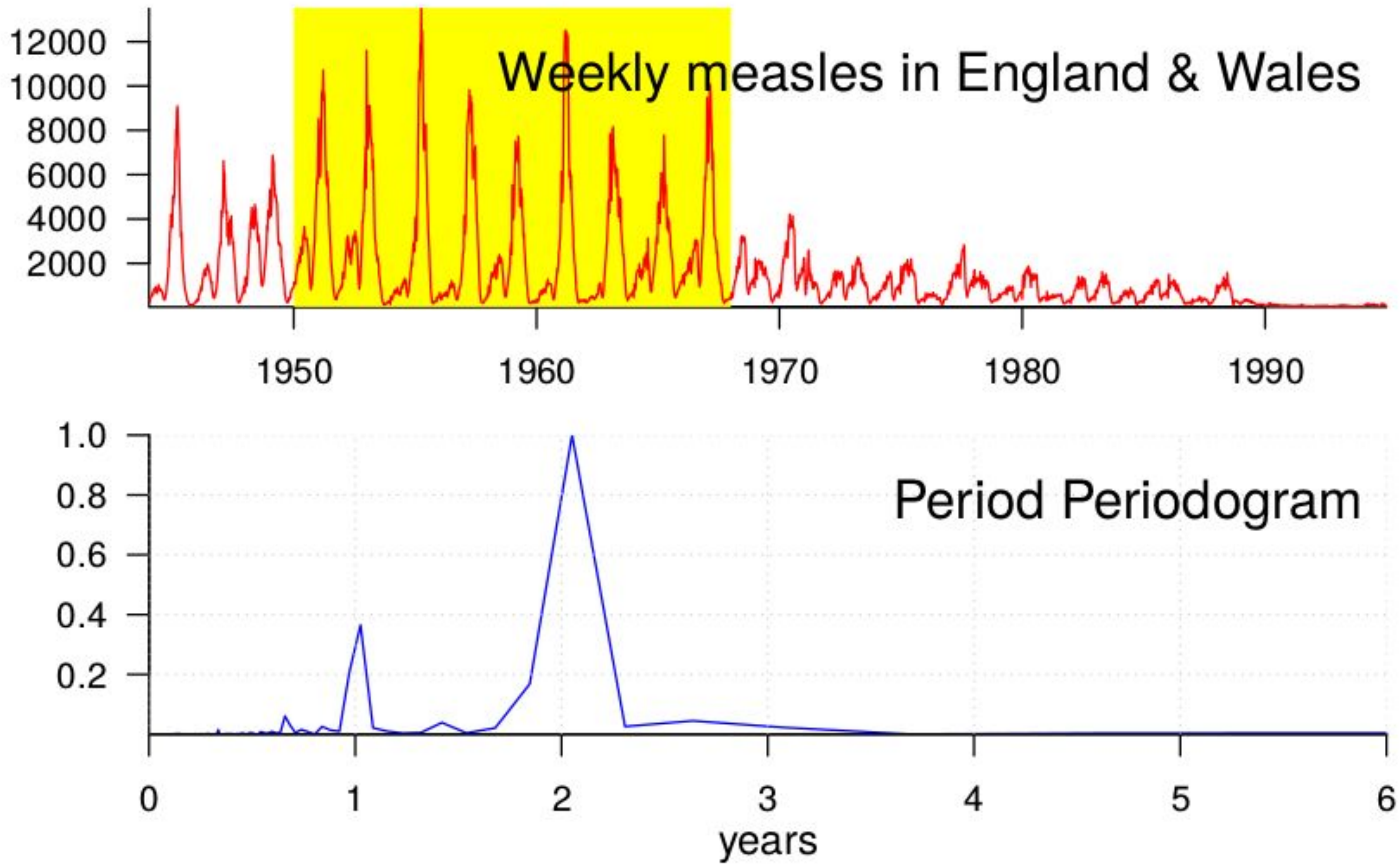
Measles in England and Wales



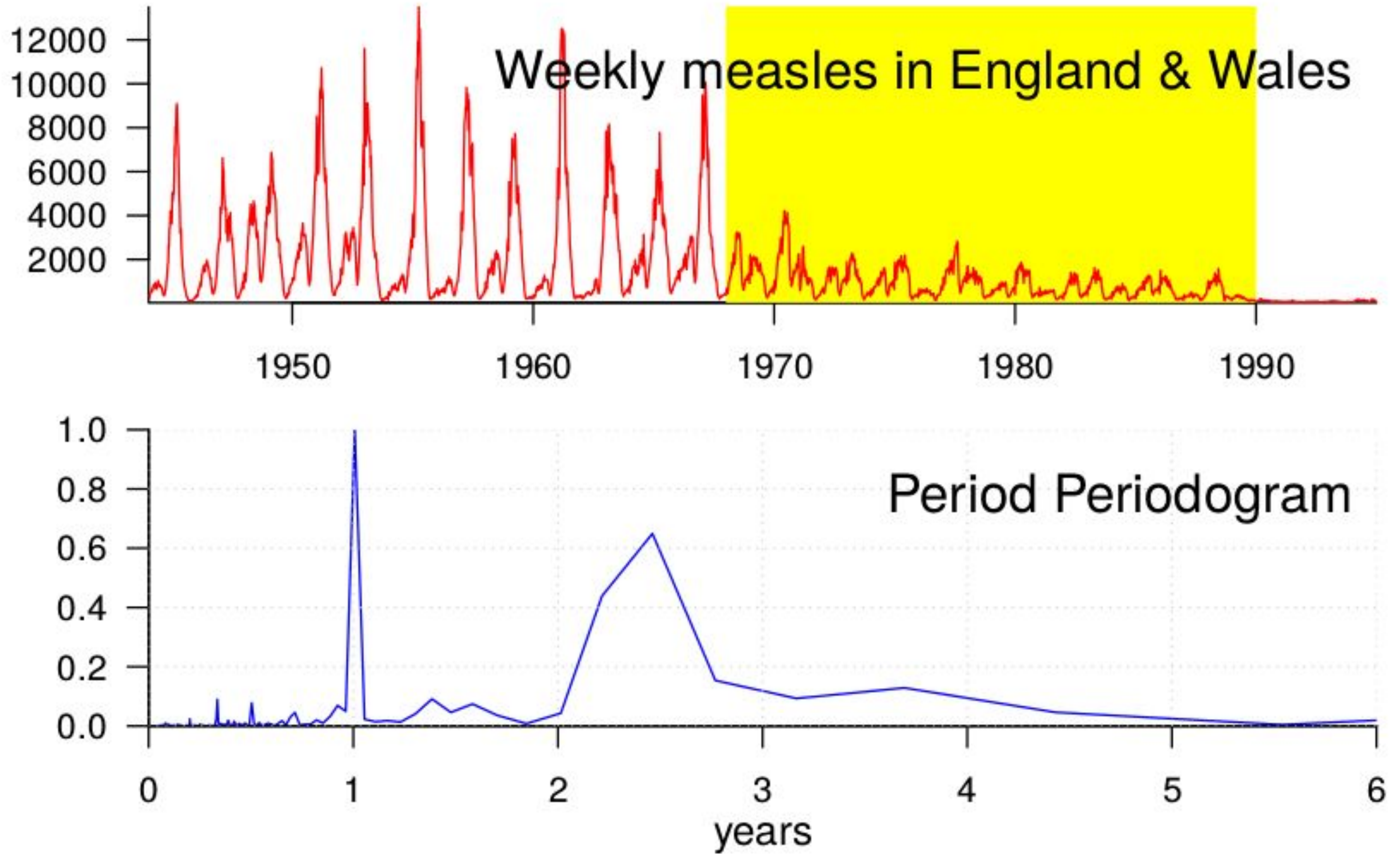
Measles in England and Wales

- Over 100,000 children a year still die from measles
- Recurrent Epidemics
- No* immune decay with measles
- Epidemics are still recurrent after the introduction of the MMR vaccine
- Our SIR with Vaccination can't explain this
- What is wrong??

Oscillatory Period



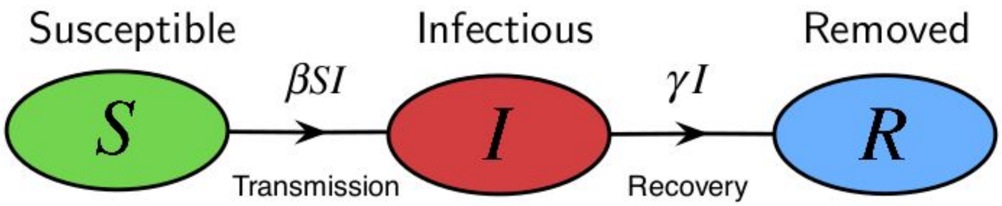
Oscillatory Period



Stochasticity

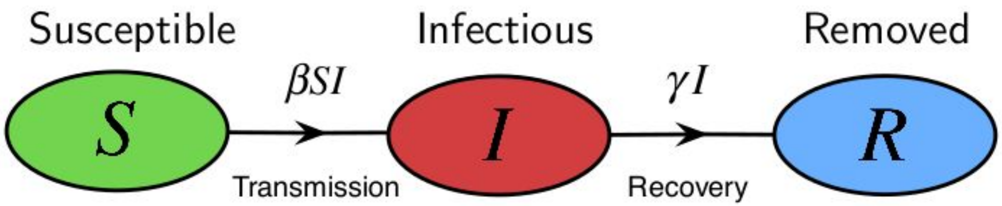
- In real life, random (stochastic) effects take place
- We have integer people in real life, not proportions
- There are tools to deal with Stochastic Differential Equations analytically
- There are also tools to deal with them numerically

- Gillespie's Algorithm
- We have two events occuring
  - Transmission & Recovery

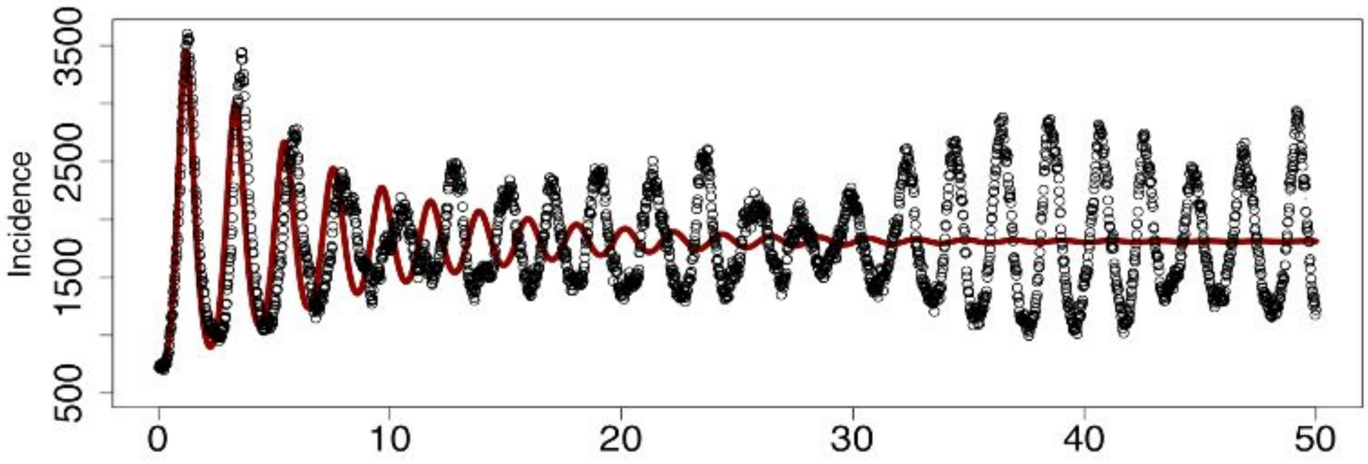


Gillespie's Algorithm

- Deals with integer population sizes.
- Initialise S,I,R to be S_0, I_0, R_0 and t to t_0 *(usually 0?)*
  - Generate a random number $0 < r < (\beta SI + \gamma I)$
  - If $r < \beta SI$, then transmission occurs
    - Change $S = S - 1$
      $I = I + 1$
  - Otherwise, recovery occurs
    - Change $I = I - 1$
      $R = R + 1$
  - Update time variable by an exponential random number
- The rate of reactions determines the probability they occur
- But even low probability reactions still have a chance
- Each *particular* realisation is different than the continuous case
- On *average* it recovers the continuous solution



Gillespie Simulations



Success

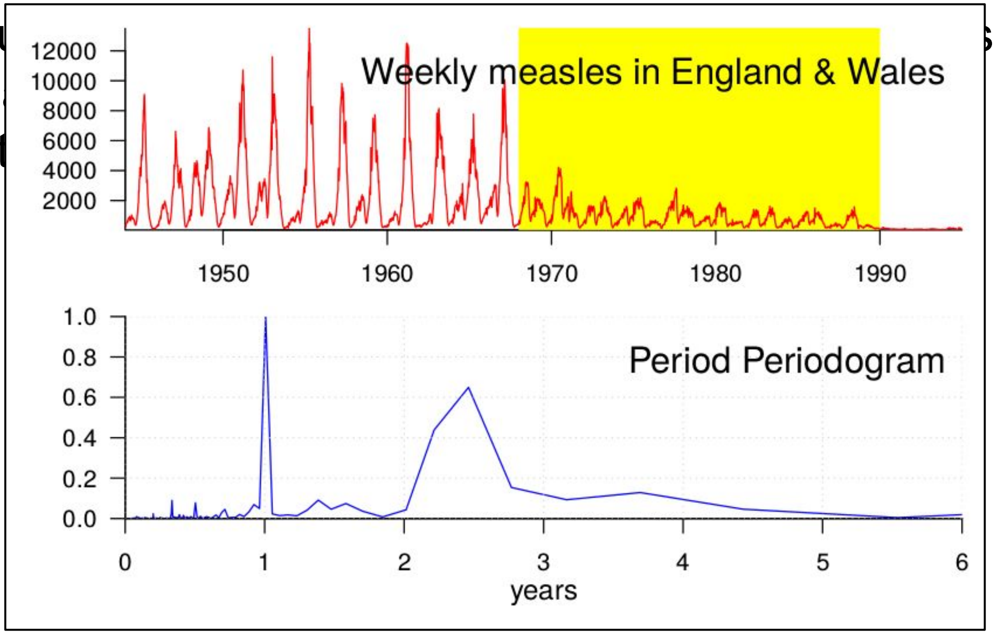
- We have explained the recurrent epidemic problem in Measles
  - Nothing wrong with the continuous model, just need stochastic effects!
  - Gillespie simulations recover oscillatory behaviour at a fixed period
  - Including vaccination and the oscillations just get smaller (smaller S_0 effectively)
  - Just like in the data set

Thanks!

Any questions?

~~Success~~ More to the Story...

- We have explained the recurrent epidemic problem in Measles
  - Nothing wrong with the continuous model, just need stochastic effects!
  - Gillespie simulations recover oscillatory behaviour at a ***fixed*** period
  - Incl smaller (sm
  - Just



3.

Seasonality

Seasonal Forcing

- In our simplest model we really only have two parameters β and γ which we sweep together in $\mathcal{R}_0$

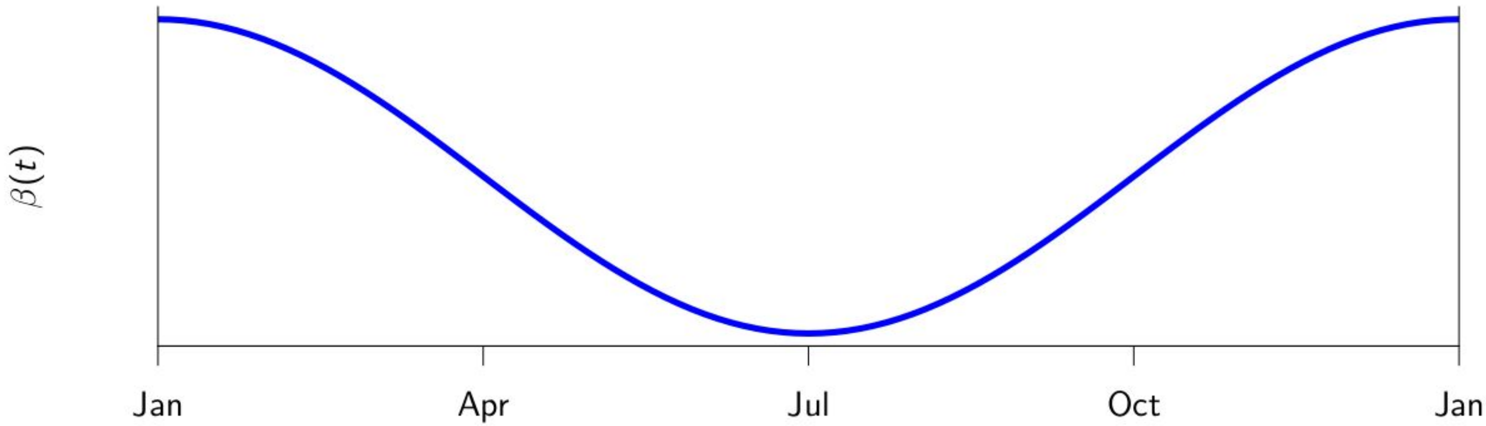
- We accounted for the random variability in the mean infection time ($1/\gamma$) with our Gillespie simulations
  - This almost worked

- Natural next choice is to look at β
  - How is our current utilisation of transmission rate unrealistic?
  - Stochastic effects were already considered
  - But β isn't always constant in time
  - Winter exists

Seasonal Forcing

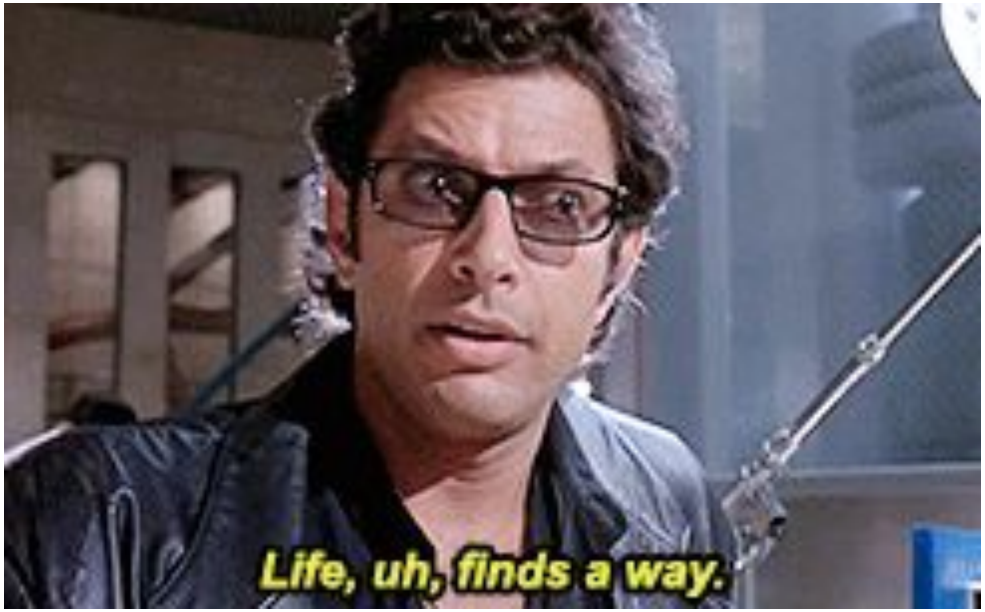
- β is really a function of time

$$\beta(t) = \bar{\beta}\,(1 + \alpha\,\cos(2\,\pi\,t))$$

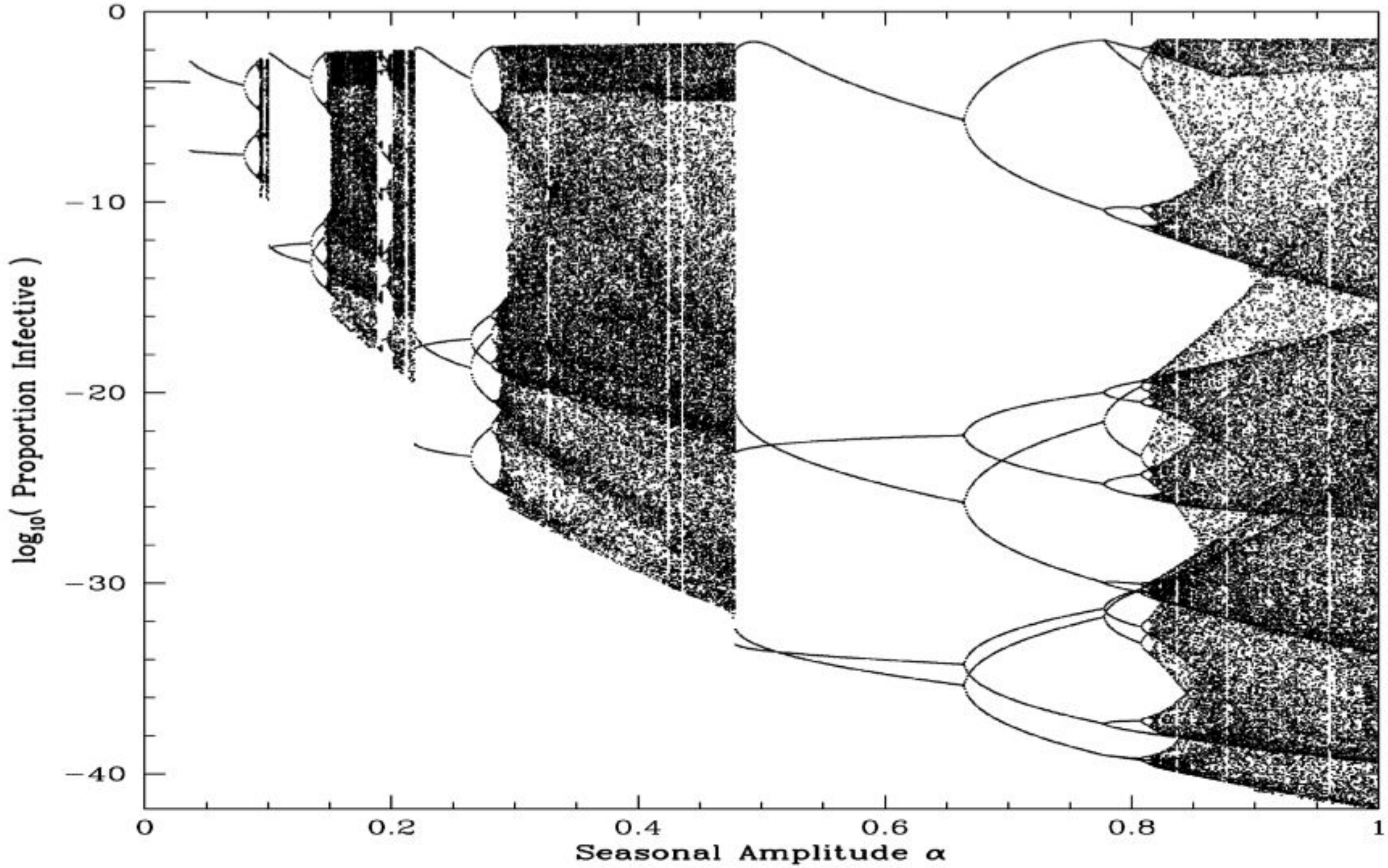


Seasonal Forcing

- By adding a forcing term to our model we expect to see new qualitative dynamics
  - Any guesses? (Hint: pendulum)



Seasonal Forcing

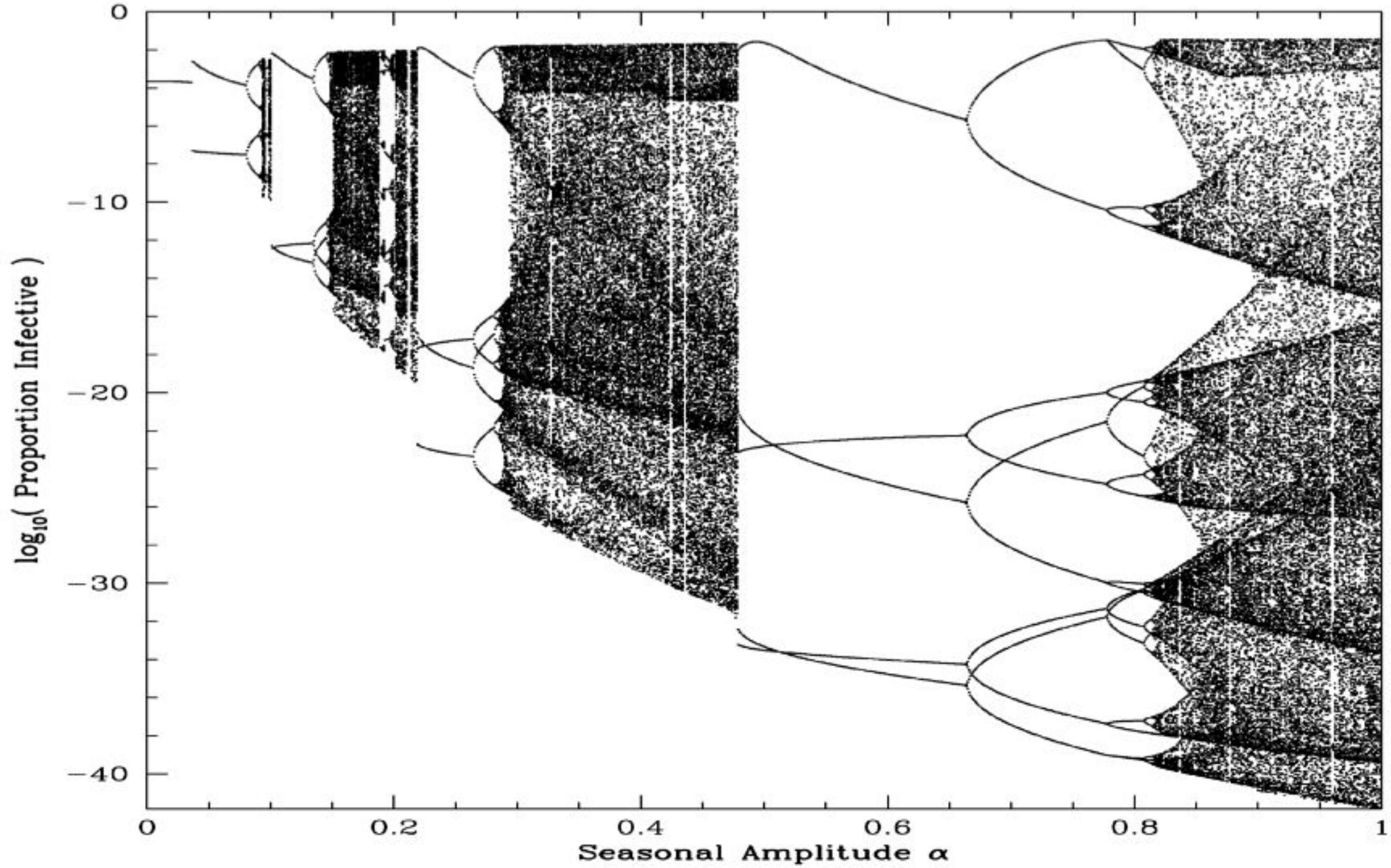


Olsen LF, Schaffer WM, 1990, Science 249, 499–504

Seasonal Forcing

- For correct parameter values can have damped or undamped oscillatory behaviour
- Periodic behaviour for a wide variety of periods
- Chaos
    - Pro: Explains the irregular behaviour we observed in post-vaccine measles

Seasonal Forcing



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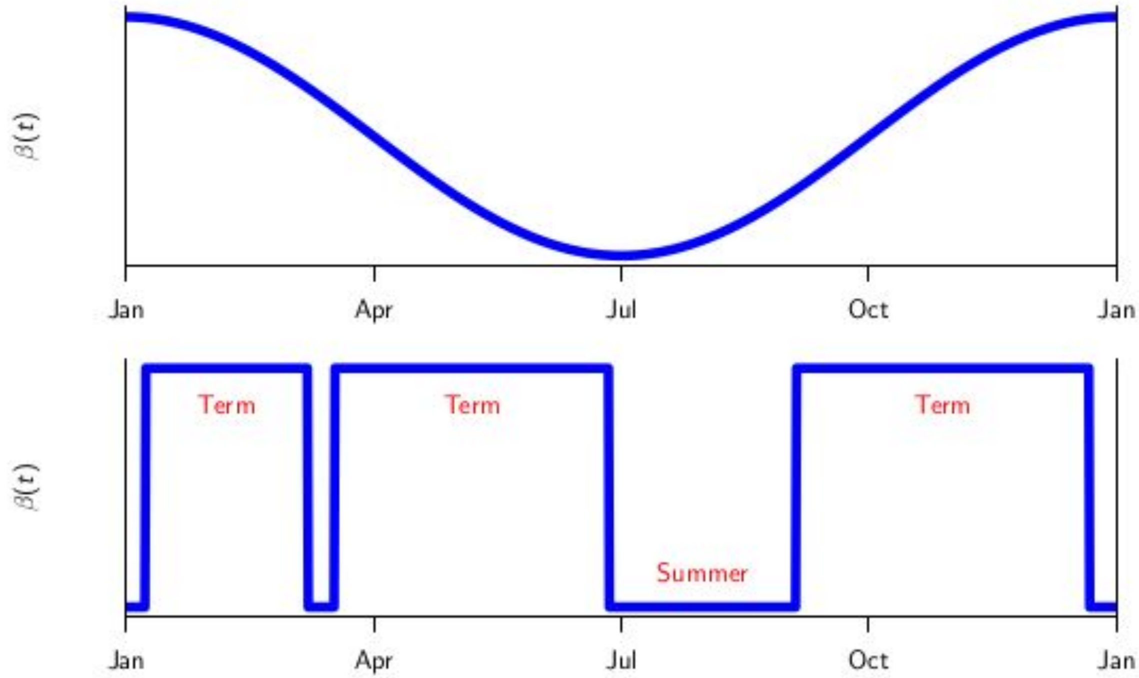
Seasonal Forcing and Age Structure

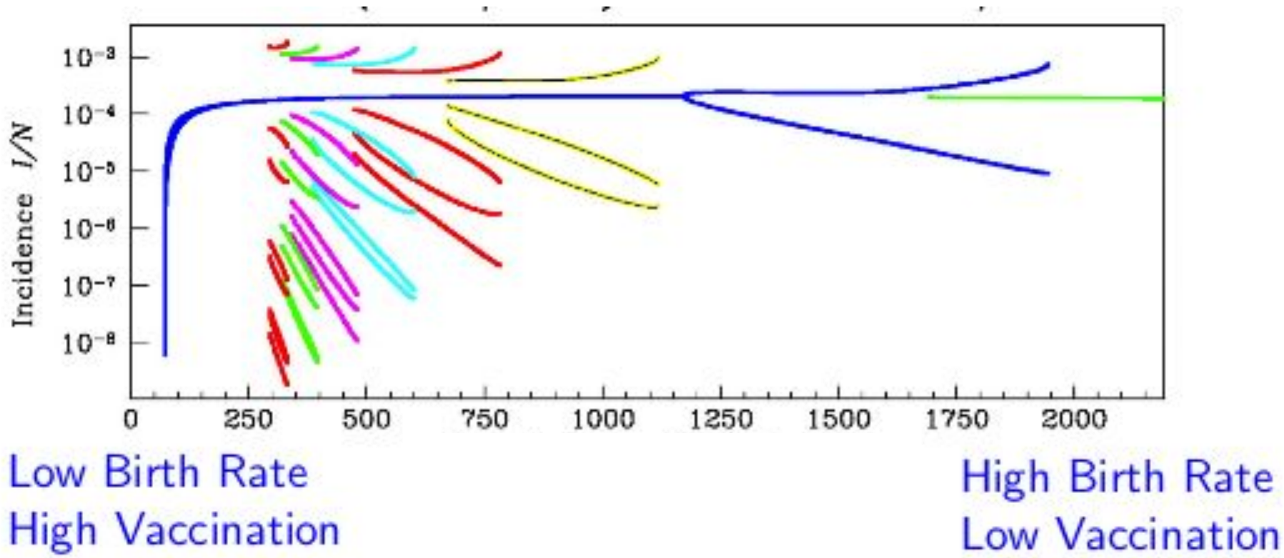
- Age structured models
  - Different beta rates for each age group (0-1, 1-2, ... , 21+)
  - Different beta rates BETWEEN each age group
  - 84 ODEs, 500 parameters
    - Spatial data too (by county)
    - ~6000 ODES, ~1500 Parameters
    - Matches the data indistinguishably!

Think of the Children!



Think of the Children!

- Replicates the results of the Age and Spatial distributed model
  - Much simpler



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

Review

- Simple SIR model with vital dynamics and vaccination
  - Oscillations damp out
- Stochastic version of that model
  - Undamped oscillations at one frequency
- Sinusoidally forced Transmission rate
  - Oscillations at multiple periods!
  - Chaos
    - Rapid extinction of pathogen
    - Extreme sensitivity to amplitude
- School-term forcing
  - Very good description of measles dynamics in London
  - Multiple frequencies of oscillation
  - Fails at long term changes in dynamics (~10 years)

Thanks!

Slides available online

http://www.beastman.ca/epidemic