Epidemic models with uncertainty - application to influenza

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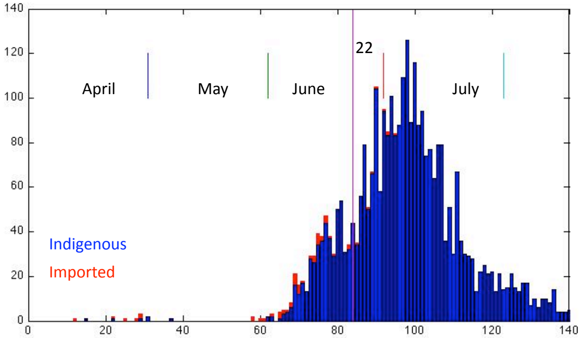
H1N1 (swine flu) in New Zealand, 2009



- We estimated $\mathcal{R}_0 = 1.25$, confidence interval $(1.07, 1.47)$.

  Roberts & Nishiura (2011) *PLoS One* 6:e17835.

Introduction

- Epidemic models: the *SIR* model with uncertainty.
- The Kermack-McKendrick model and swine flu.
- Seasonal influenza and a two-strain model.

- Thanks for funding to
  - **The Marsden Fund** MAU0809, MAU1106
  - **The Health Research Council** 10/754

MARSDEN FUND
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hrc Health Research Council of New Zealand
Te Kaunihera Rangahau Hauora o Aotearoa

The *SIR* epidemic model - scaled time

Proportions: Susceptible $\frac{\mathrm{d}x}{\mathrm{d}t} = -\mathcal{R}_0 xy$ Infectious $\frac{\mathrm{d}y}{\mathrm{d}t} = \mathcal{R}_0 xy - y$

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- The final size, $\mathcal{P} = x_0 - x_\infty$, solves

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- $\mathcal{R}_0$ is the **basic reproduction number**.

The SIR model with uncertainty

- Replace $\mathcal{R}_0$ with $\mathcal{R}_0 + \rho\theta$.

$$\begin{aligned}\dot{x}(t) &= -\left(\mathcal{R}_0 + \rho\theta\right) xy \\ \dot{y}(t) &= \left(\mathcal{R}_0 + \rho\theta\right) xy - y\end{aligned}$$

- initial conditions $x_0 < 1$ and $y_0 \ll 1$.

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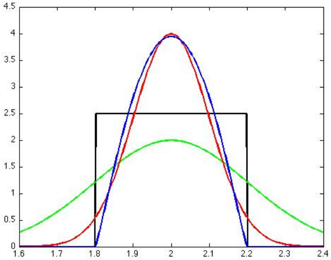
$$\dot{y}(t) = \left(\mathcal{R}_0 + \rho\theta\right) xy - y$$

- initial conditions $x_0 < 1$ and $y_0 \ll 1$.
- $\theta \in [-1, 1]$ has pdf

$$\mathcal{U} : \quad w(\theta) = 1/2 \quad \text{or}$$
$$\mathcal{B} : \quad w(\theta) = k\left(1 - \theta^2\right)^\beta$$

where k is a normailsing constant. We will use $\beta = 1.19$.

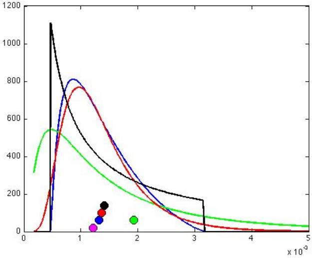


- pdfs for $\mathcal{R}_0 + \rho\theta$ with $w(\theta) \sim$
  - $\mathcal{U}$ (black)
  - $\mathcal{B}$ (blue)
  - $\mathcal{N}(0, 1)$ (green)
  - $\mathcal{N}\left(0, \frac{1}{2}\right)$ (red).
- $\mathcal{R}_0 = 2$, $\rho = 0.2$.

The exponential phase $y(t,\theta) = y_0 e^{(\mathcal{R}_0+\rho\theta)x_0 t - t}$

- The expected value of $y(t)$ is

$$\begin{aligned}\mathbb{E}(y) &= \int_\Omega y(t,\theta) w(\theta)\,\mathrm{d}\theta \\ &= y_0 e^{\mathcal{R}_0 x_0 t - t} \underbrace{\int_\Omega e^{\rho\theta x_0 t} w(\theta)\,\mathrm{d}\theta}_{>1}\end{aligned}$$



- Dots at means, magenta dot at deterministic solution.
- Parameter values $\mathcal{R}_0 = 2$, $\rho = 0.2$, $x_0 = 1 - 10^{-5}$, $y_0 = 10^{-5}$. $t = 4.8$

- pdfs for $y(t,\theta)$ with $w(\theta) \sim$
  - $\mathcal{U}$ (black)
  - $\mathcal{B}$ (blue)
  - $\mathcal{N}(0,1)$ (green)
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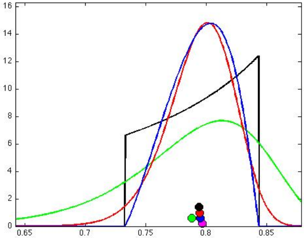
The final size $\mathcal{P}(\theta)$

- The proportion infected in the epidemic solves

$$\mathcal{R}_0+\rho\theta+\frac{1}{\mathcal{P}(\theta)}\log\left(1-\frac{\mathcal{P}(\theta)}{x_0}\right)=0$$

- The pdf of $\mathcal{P}$ is $w(\theta)/\mathcal{P}'(\theta)$.



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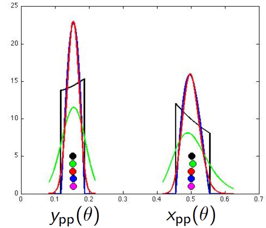
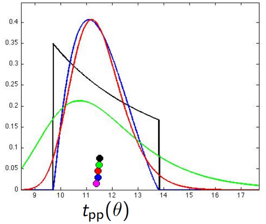
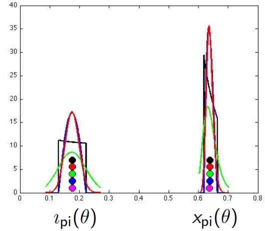
Peak value distributions

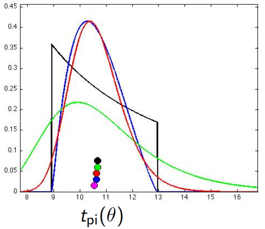
- Peak prevalence.





- Peak incidence.





- pdfs with $w(\theta) \sim \mathcal{U}$ (black); $\mathcal{B}$ (blue); $\mathcal{N}(0,1)$ (green); $\mathcal{N}\left(0, \frac{1}{2}\right)$ (red).

The Galerkin solution

- Reminder: the *SIR* model

$$\dot{x}(t) = -\mathcal{R}_0 xy \qquad \dot{y}(t) = \mathcal{R}_0 xy - y$$

- Expand over θ in orthogonal polynomials. Substitute

$$x(t,\theta) = \sum_{i=1}^{\infty} x_i(t)\phi_i(\theta) \qquad y(t,\theta) = \sum_{i=1}^{\infty} y_i(t)\phi_i(\theta)$$

to obtain

$$\sum_{i=1}^{\infty} \dot{x}_i(t)\phi_i(\theta) = -\left(\mathcal{R}_0 + \rho\theta\right) \sum_{i=1}^{\infty}\sum_{j=1}^{\infty} x_i(t) y_j(t)\phi_i(\theta)\phi_j(\theta)$$

$$\sum_{i=1}^{\infty} \dot{y}_i(t)\phi_i(\theta) = -\sum_{i=1}^{\infty} \dot{x}_i(t)\phi_i(\theta) - \sum_{i=1}^{\infty} y_i(t)\phi_i(\theta)$$

Expectation and inner product

- Choose $\{\phi_i(\theta)\}$ so that

$$\mathbb{E}\left(\phi_i\phi_j\right) = \int_{-1}^{1} \phi_i(\theta)\phi_j(\theta)w(\theta)\,\mathrm{d}\theta = 0 \quad \text{if} \quad i \neq j$$

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- When truncated, the equations are

$$\begin{aligned} \dot{x}_\ell(t) &= -\,\mathbf{x}.\left(\mathcal{R}_0\mathbf{A}_\ell + \rho\mathbf{B}_\ell\right)\mathbf{y} \\ \dot{y}_\ell(t) &= \mathbf{x}.\left(\mathcal{R}_0\mathbf{A}_\ell + \rho\mathbf{B}_\ell\right)\mathbf{y} - y_\ell \end{aligned}$$

  with $\mathbf{x} = (x_1, x_2, \ldots, x_N)'$, similarly $\mathbf{y}$ (prime is transpose). The $N \times N$ matrices have components

$$A_{\ell\,i\,j} = \frac{\mathbb{E}\left(\phi_i\phi_j\phi_\ell\right)}{\mathbb{E}\left(\phi_\ell^2\right)} \qquad B_{\ell\,i\,j} = \frac{\mathbb{E}\left(\theta\phi_i\phi_j\phi_\ell\right)}{\mathbb{E}\left(\phi_\ell^2\right)}$$

- The initial conditions are $\mathbf{x}(0) = x_0\mathbf{e}$ and $\mathbf{y}(0) = y_0\mathbf{e}$, with $\mathbf{e} = (1, 0, \ldots, 0)'$.

Polynomial bases

- If $w \sim \mathcal{U}$, a uniform distribution, use Legendre polynomials:

$$\phi_i(\theta) = P_{i-1}(\theta) \qquad P_0(\theta) = 1 \quad P_1(\theta) = \theta$$
$$P_{\ell+1}(\theta) = \frac{2\ell+1}{\ell+1}\theta P_\ell(\theta) - \frac{\ell}{\ell+1}P_{\ell-1}(\theta)$$

Xiu (2010) Numerical methods for stochastic computations. Princeton UP.

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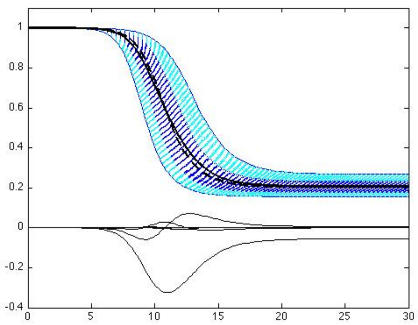
- If $w \sim \mathcal{B}$, a beta distribution, use Jacobi polynomials:

$$\phi_i(\theta) = J_{i-1}^{(\beta)}(\theta) \qquad J_0^{(\beta)}(\theta) = 1 \quad J_1^{(\beta)}(\theta) = (\beta+1)\,\theta$$
$$\begin{aligned} J_{\ell+1}^{(\beta)}(\theta) = {} & \frac{(2\ell+2\beta+1)\,(\ell+\beta+1)}{(\ell+1)\,(\ell+2\beta+1)}\theta J_\ell^{(\beta)}(\theta) \\ & - \frac{(\ell+\beta)\,(\ell+\beta+1)}{(\ell+1)\,(\ell+2\beta+1)} J_{\ell-1}^{(\beta)}(\theta) \end{aligned}$$

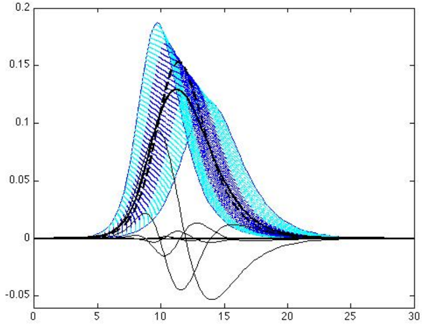
Xiu (2010) Numerical methods for stochastic computations. Princeton UP.

Numerical solution: $w \sim \mathcal{U}$, uniform distribution.

- Proportion susceptible.



- Proportion infectious.



- Solid lines are expected values, $\mathbb{E}(y(t))$.
- Dashed lines are deterministic solution, $y(t, 0)$.
- Blue cloud is $y(t, \theta)$, $-1 \leqslant \theta \leqslant 1$.
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Numerical solution: $w \sim \mathcal{B}$, beta distribution.

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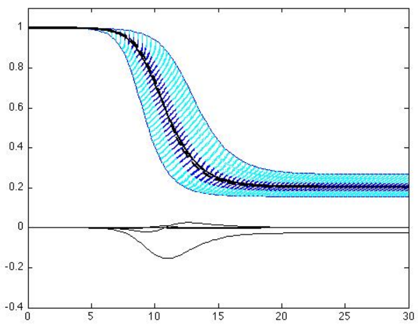

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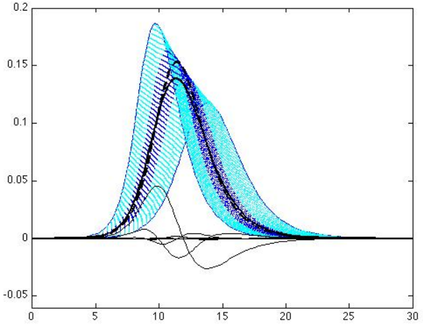

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Some comments

- We have replaced two equations with $2N$ equations, but we only need to solve these once.
- The ODEs are solved numerically, but constructed analytically via recurrence relationships. For example, if $w \sim \mathcal{B}$ then $\mathbb{E}\left(\theta^{n+2}\right) = \frac{n+1}{n+2\beta+3}\mathbb{E}\left(\theta^{n}\right)$ if n even, and zero if n odd.
- If $w \sim \mathcal{N}$, a normal distribution, we use Hermite polynomials. Convergence problems were experienced.
- **Everything is deterministic.**

Roberts (2013) *J. Math. Biol.* 66:1463-1474.

Pandemic influenza

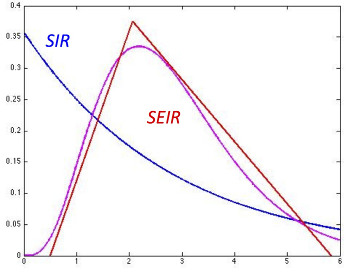
- The Kermack-McKendrick model

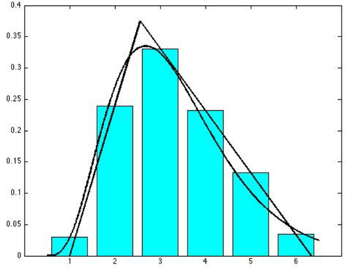
$$\imath(t) = \jmath(t) + \mathcal{R}_0 x(t) \int_0^\infty f(\tau)\imath(t-\tau)\,\mathrm{d}\tau$$

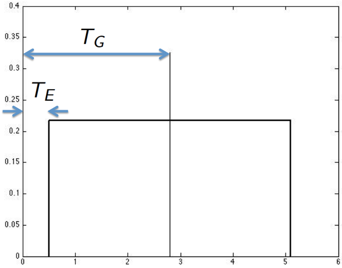
$$x(t) = x_0 - \frac{1}{N}\int_0^t \imath(u)\,\mathrm{d}u$$

- where
  - $\mathcal{R}_0$ is the basic reproduction number
  - $\imath(t)$ is the local incidence of infection
  - $\jmath(t)$ is the incidence of imported cases
  - $f(\tau)$ is the probability distribution of infection-generation intervals
  - $x(t)$ and $y(t)$ are the proportions of the population (size N) that are susceptible or infected (prevalence).

Infection-generation intervals $f(\tau)$







- T_G Mean $= 2.8$ days.
- T_G S.D. $= 1.12$ days.
- Pre-infectious period
- $T_E = 0.5$ days.

Interlude: estimating $\mathcal{R}_0$.

- The infection generation interval is $T_G = \int_0^\infty \tau f(\tau)\,\mathrm{d}\tau$.
- During the initial exponential phase of an epidemic

$$\mathcal{R}_0 \int_0^\infty e^{-r\tau} f(\tau)\,\mathrm{d}\tau = 1$$

- For an *SEIR* model with $T_G = T_E + T_I$

$$\mathcal{R}_0^{\mathrm{exp}} = 1 + rT_G + r^2 T_E \left(T_G - T_E\right)$$

- For a fixed-period model with $T_G = T_E + T_I/2$

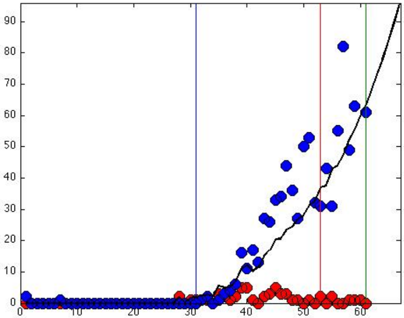
$$\mathcal{R}_0^{\mathrm{fix}} = \frac{r\left(T_G - T_E\right)}{\sinh r\left(T_G - T_E\right)} e^{rT_G}$$

- We always have $1 + rT_G \leqslant \mathcal{R}_0^{\mathrm{exp}} < \mathcal{R}_0^{\mathrm{fix}} \leqslant e^{rT_G}$

  Roberts & Heesterbeek (2007) *J. Math. Biol.* 55:803-816.

Pandemic forecasting

- Curve fit to data



- Blue: local transmission; Red: imported cases.
- We estimated $\mathcal{R}_0 = 1.25$, confidence interval $(1.07, 1.47)$.

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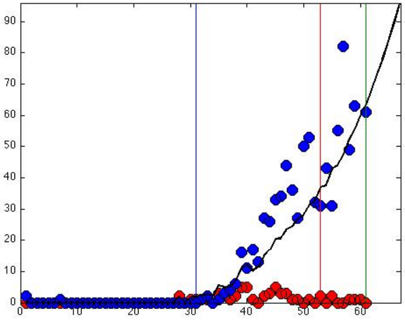
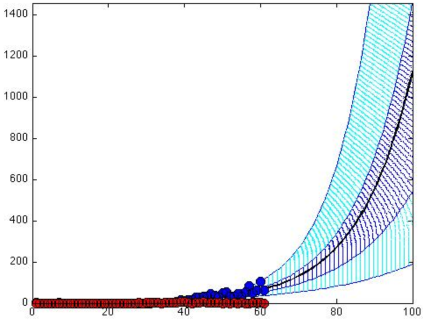


- The prediction

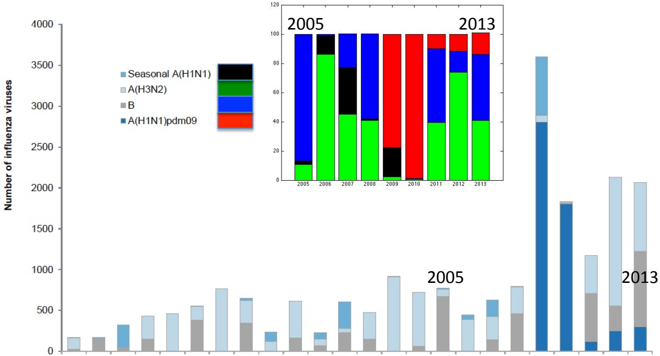


- Blue: local transmission; Red: imported cases.
- We estimated $\mathcal{R}_0 = 1.25$, confidence interval $(1.07, 1.47)$.
- Beta distribution with quartiles shaded.

Pandemic becomes seasonal

- The Galerkin method deals with uncertainty in parameter estimates. The models are neither chaotic nor stochastic.
- Projections of incidence during the exponential phase have wide confidence limits. *Prediction is very difficult, especially about the future (Bohr attrib.).*
- Cross-immunity between influenza A subtypes is still an open question.

Seasonal influenza in New Zealand



	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13
Seasonal A(H1N1)(%)	1	8	86	0	0	1	0	4	47	0	36	54	0	0	0	2	13	32	1	20	0	0	0	0
A(H3N2)(%)	83	0	3	66	99	30	99	43	52	74	33	8	68	100	91	11	86	45	41	2	1	40	74	41
B(%)	16	92	11	34	1	69	1	53	1	26	31	38	32	0	9	87	1	23	58	0	1	50	14	45
A(H1N1)pdm09(%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	78	99	10	12	15

- Influenza survey summary for New Zealand, 1990-2013.

A two-subtype influenza model

- The proportion of the population infectious:

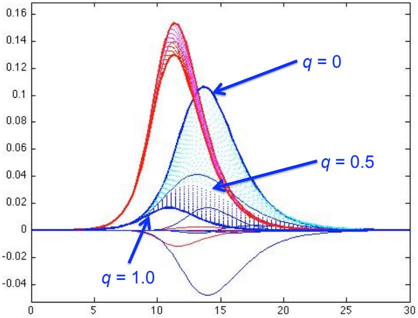
$$\dot{y}^s = \mathcal{R}_0^s x^s y^s - y^s \qquad s = 1, 2$$

- The function $x^s(t) = 1 - u^s + (1 - q)(u^s - z^s)$ is the *relative susceptibility* of the population.
  - A proportion z^s is specifically protected.
  - A proportion u^s is non-specifically protected.
  - $q = 0$ for no cross-protection.
  - $q = 1$ for complete cross-protection.

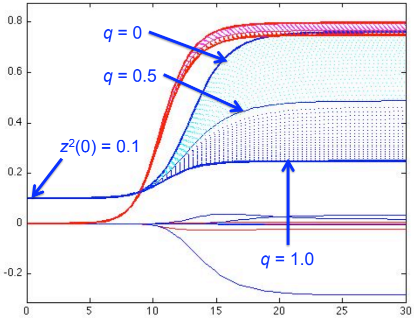
  Assumptions
  - The epidemic is confined to one season.
  - Neglect virus evolution within season.
  - No cross-subtype protection between seasons.

Numerical solution - different immune proportions

- y^s, proportions infected.



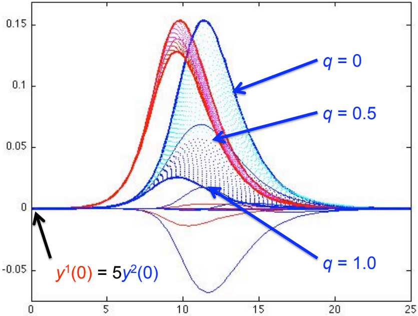
- z^s, specifically protected.

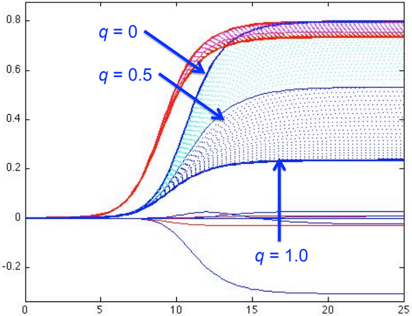


- Cyan and magenta clouds are $y^s(t,q)$, $z^s(t,q)$, $0 < q < 0.5$.
- Blue and red clouds are $y^s(t,q)$, $z^s(t,q)$, $0.5 < q < 1$.
- Thin lines are solutions $y^s_i(t), z^s_i(t)$.
- Parameters: $\mathcal{R}^s_0 = \mathcal{R}^r_0 = 2$, $y^s_0 = y^r_0 = 10^{-5}$, $z^s_0 = 0$ red, $z^r_0 = 0.1$ blue.

Numerical solution - different initial infecteds

- y^s, proportions infected.
- z^s, specifically protected.



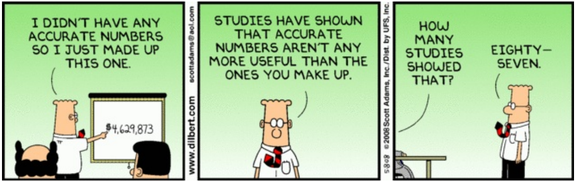


- Colours as in previous slide.
- Parameters: $\mathcal{R}_0^s = \mathcal{R}_0^r = 2$, $y_0^s = 5 \times 10^{-5}$, red, $y_0^r = 10^{-5}$, blue, $z_0^s = z_0^r = 0$.

Roberts (2012) *ANZIAM Journal* 54:108-115

Other work

- Hickson & Roberts (2014) How population heterogeneity in susceptibility and infectivity influences epidemic dynamics. *J. Theor. Biol.* 350:70-80.



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THE END