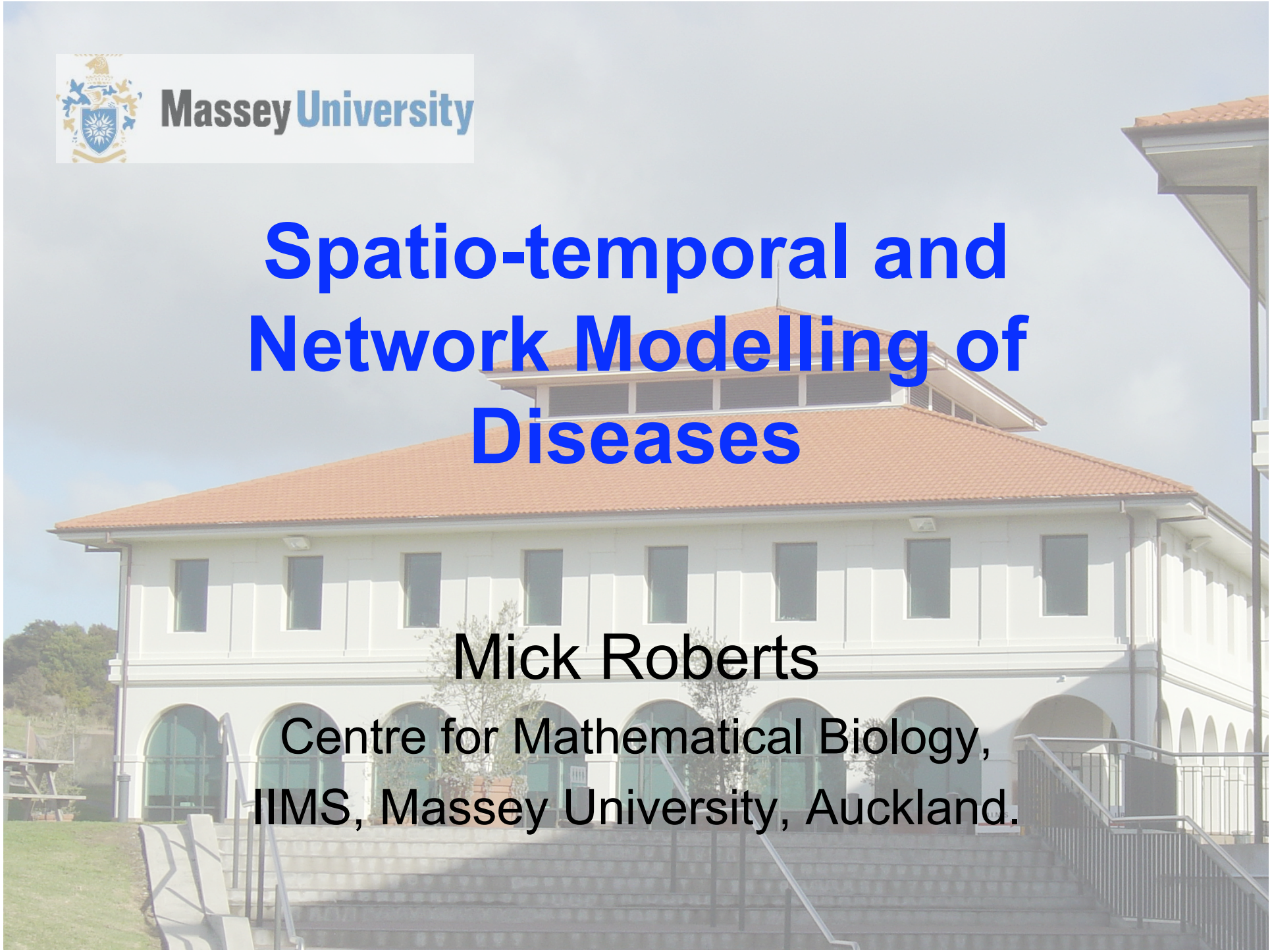

Spatio-temporal and Network Modelling of Diseases

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The next generation matrix and $\mathcal{R}_0$

- We define the **Basic Reproduction Number** $\mathcal{R}_0$ to be the largest eigenvalue of the next generation matrix $\mathbf{K}$, where $K_{i\,j}$ is the expected number of infections of Type i due to a single infection of Type j, in a fully susceptible population.

- If the system is in state $\mathbf{w}$, then (in a susceptible population)

$$\lim_{n\to\infty} \frac{1}{(\mathcal{R}_0)^n}\mathbf{K}^{n+1}\mathbf{w} = \mathbf{K}\mathbf{v} = \mathcal{R}_0\mathbf{v}$$

- $\mathbf{K}$ is dimensionless, and relates *infection-generations*.

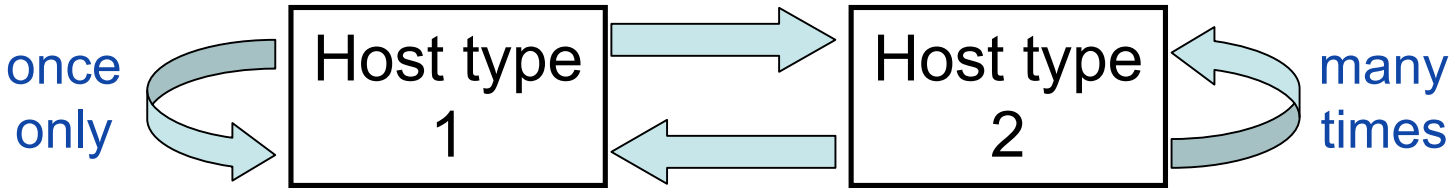
For example:

- For an STI, Types could be male, female.
- For a vector transmitted infection, Types could be human, mosquito.
- The **Next Generation Matrix** is

$$\mathbf{K} = \begin{pmatrix} 0 & K_{12} \\ K_{21} & 0 \end{pmatrix}$$

- The **Basic Reproduction Number** is $\mathcal{R}_0 = \sqrt{K_{12}K_{21}}$.

The type reproduction number



- The expected number of infected hosts of Type 1 that would arise from a single infected host of Type 1 in an otherwise susceptible population.
- This only makes sense if $\mathcal{R}_0$ *for Type 2* is less than one.

The type reproduction number: 2 types

- The type reproduction number is like the basic reproduction number, but focuses on a subset of host *types at infection*.
- For example, with two types

$$\begin{aligned}\mathcal{T} &= K_{11} + K_{12}K_{21} + K_{12}K_{22}K_{21} + K_{12}K_{22}^2K_{21} + \ldots \\ &= K_{11} + \frac{K_{12}K_{21}}{1 - K_{22}}\end{aligned}$$

  This requires $K_{22} < 1$.

- If $K_{22} > 1$ then Type 2 is a **reservoir of infection**.

The type reproduction number: many types

- To focus on ℓ out of n types, define a projection matrix $P_{i\,i} = 1$ for $i = 1 \ldots \ell$, $P_{i\,j} = 0$ otherwise.
- Now define a *reduced* next generation matrix:

$$\mathbf{M} = \mathbf{K}\left(\mathbf{I} - (\mathbf{I} - \mathbf{P})\,\mathbf{K}\right)^{-1}$$

- This requires $\|(\mathbf{I} - \mathbf{P})\,\mathbf{K}\| < 1$. If not, the *out of focus* types form a **reservoir of infection**.
- The type reproduction number is $\mathcal{T} = \|\mathbf{M}\|$.

Infection control

- It has been proved that $\mathcal{T} < 1 \Leftrightarrow \mathcal{R}_0 < 1$.
- To eliminate infection you must:
  - protect a proportion v of all types, where $v > 1 - \frac{1}{\mathcal{R}_0}$; or of focus types, where $v > 1 - \frac{1}{\mathcal{T}}$;
  - reduce transmission time of all types by a proportion $w > 1 - \frac{1}{\mathcal{R}_0}$; or of focus types by $w > 1 - \frac{1}{\mathcal{T}}$.

References

- Roberts & Heesterbeek: A new method for estimating the effort required to control infectious diseases. *Proc. R Soc. B* 270 (2003):1359-64.
- Heesterbeek & Roberts: The type-reproduction number $\mathcal{T}$ in models for infectious disease control. *Math. Biosci.* 206 (2007): 3-10.
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Structured integral equation models

- Integral equation models provide an ideal vehicle for analysing epidemics of emerging infectious diseases.
- Contact and transmission functions are explicitly represented, and easily modified to reflect control interventions. We are not restricted to flow rates between compartments.
  - . . . most people keep referring to the [*SIR*] model as *the* Kermack and McKendrick model. This should stop! (Diekmann *et al.* 1995)
  - This is the classic Kermack-McKendrick (1927) model (Murray 2002).

The Kermack-McKendrick model

The incidence of an emerging infection $\imath(t)$ may be calculated from:

$$\imath(t) = \delta(t) + s(t) \int_0^\infty p(\tau)\kappa(\tau)\imath(t-\tau)\,\mathrm{d}\tau$$

- $\delta(t)$ is the incidence of the index case;
- $p(\tau)$ is the probability of transmission given contact;
- $\kappa(\tau)$ is the contact rate;
- τ is the time since exposure to infection.

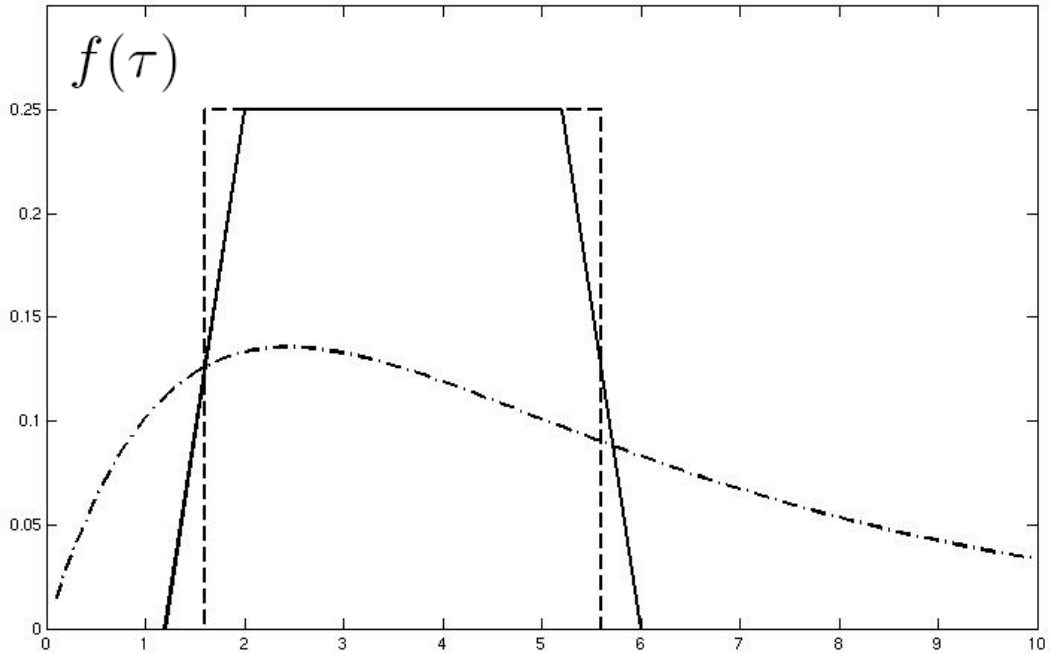
The Kermack-McKendrick model - 2

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

- $\mathcal{R}_0$ is the basic reproduction number;
- $f(\tau)$ is a probability density;
- N is the population size, $s(t) = S(t)/N$.
- The numbers in the population susceptible and removed at time t are

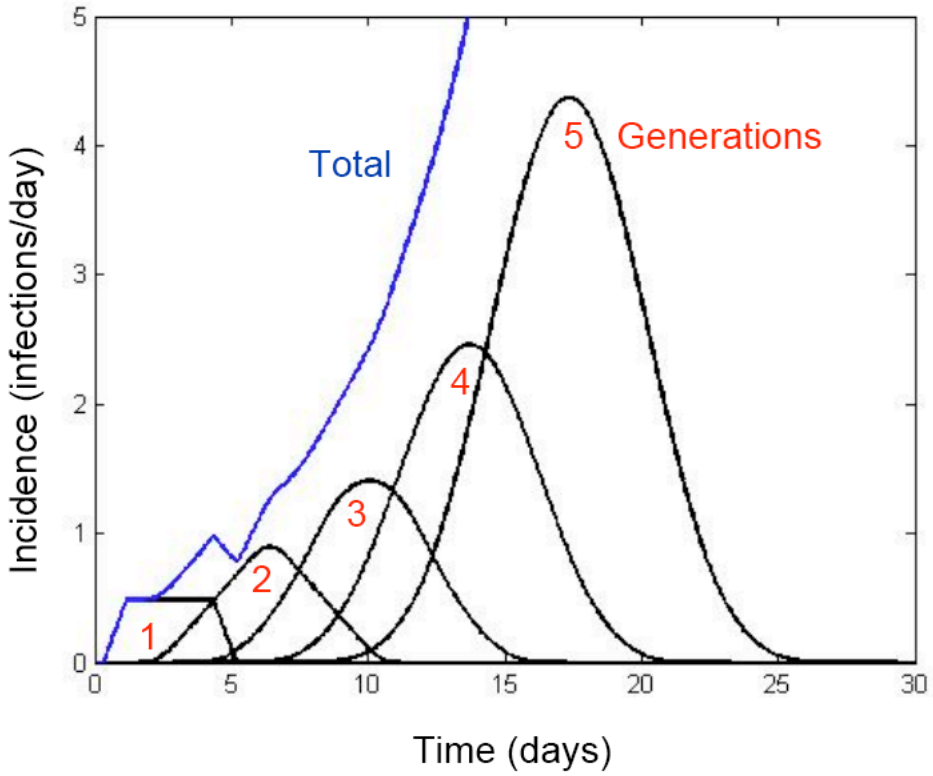
$$S(t) = N - \int_0^t \imath(u)\,\mathrm{d}u \qquad R(t) = \int_0^\infty g(\tau)\imath(t-\tau)\,\mathrm{d}\tau$$

The integral kernel



$$f(\tau) = \frac{\gamma\nu}{\gamma - \nu}\left(e^{-\nu\tau} - e^{-\gamma\tau}\right)$$

Infection generations

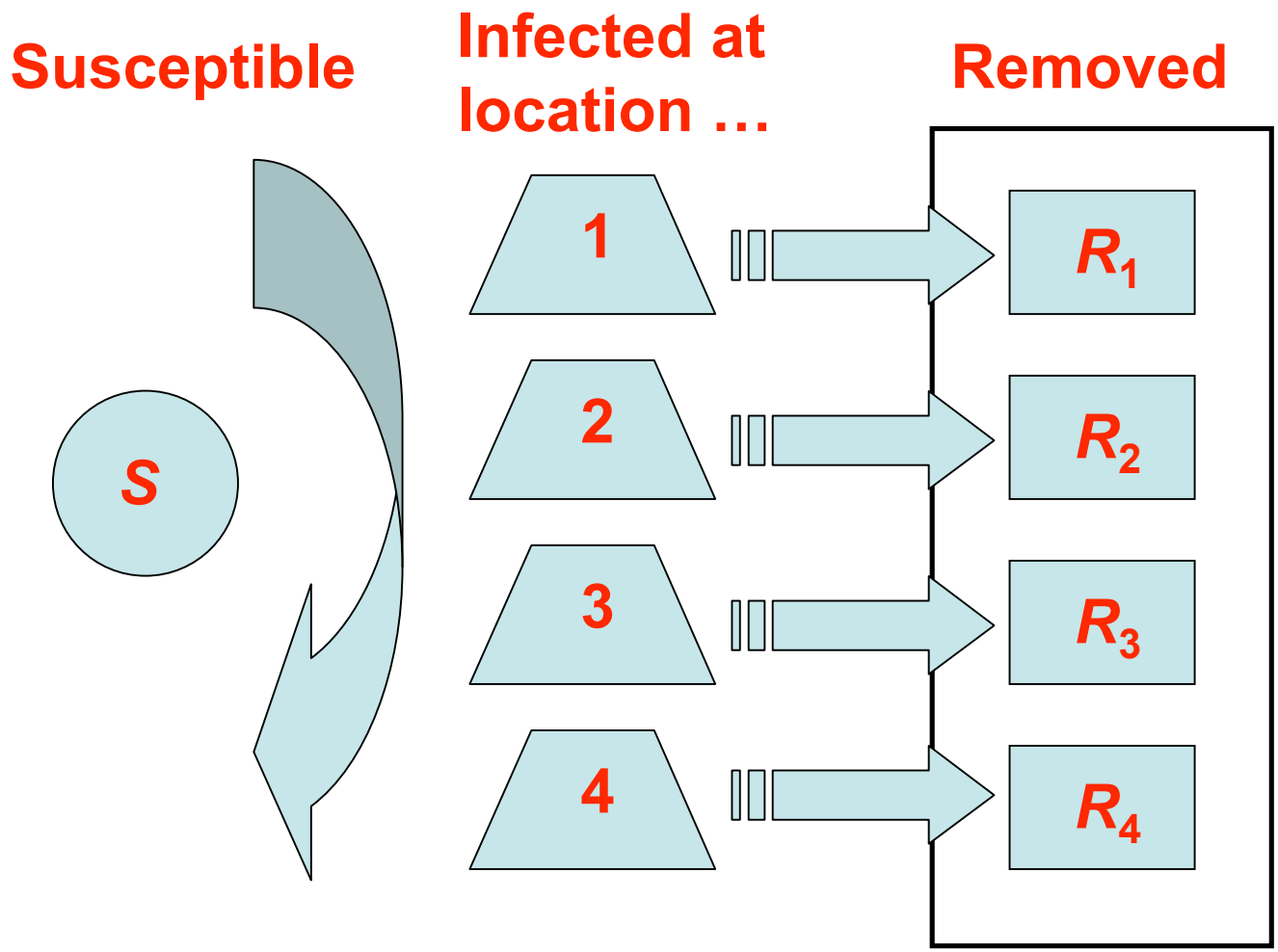


- With $s(t) \approx 1$ the first generation solution is $\imath_1(t) = \mathcal{R}_0 f(t)$.
- Subsequent infection generations are found from

$$\imath_{k+1}(t) = \mathcal{R}_0 s(t) \int_0^\infty f(\tau)\imath_k(t-\tau)\,\mathrm{d}\tau$$

- The result is $\imath(t) = \sum_{k=1}^{\infty} \imath_k(t)$.

Adding some structure



Adding some structure - 2

- The location of exposure confers a unique infection type.

$$\boldsymbol{\imath}(t) = \delta(t)\mathbf{e} + \mathcal{R}_0 s(t) \int_0^\infty f(\tau)\mathbf{W}\boldsymbol{\imath}(t-\tau)\,\mathrm{d}\tau$$

where $\|\mathbf{W}\| = 1$. For example:

$$\mathbf{W} = \begin{pmatrix} 0 & w_1 & w_1 & w_1 \\ w_2 & w_2 & 0 & w_2 \\ w_3 & 0 & w_3 & w_3 \\ w_4 & w_4 & w_4 & w_4 \end{pmatrix}$$

1. Within the household;
2. At school/work;
3. In the wider community;
4. Within a healthcare facility.

Adding some structure - 3

- The incidence of infection is

$$\boldsymbol{\imath}(t) = \delta(t)\mathbf{e} + \mathcal{R}_0 s(t) \int_0^\infty f(\tau)\mathbf{W}\boldsymbol{\imath}(t-\tau)\,\mathrm{d}\tau$$

- In the beginning $s(t) \simeq 1$, so

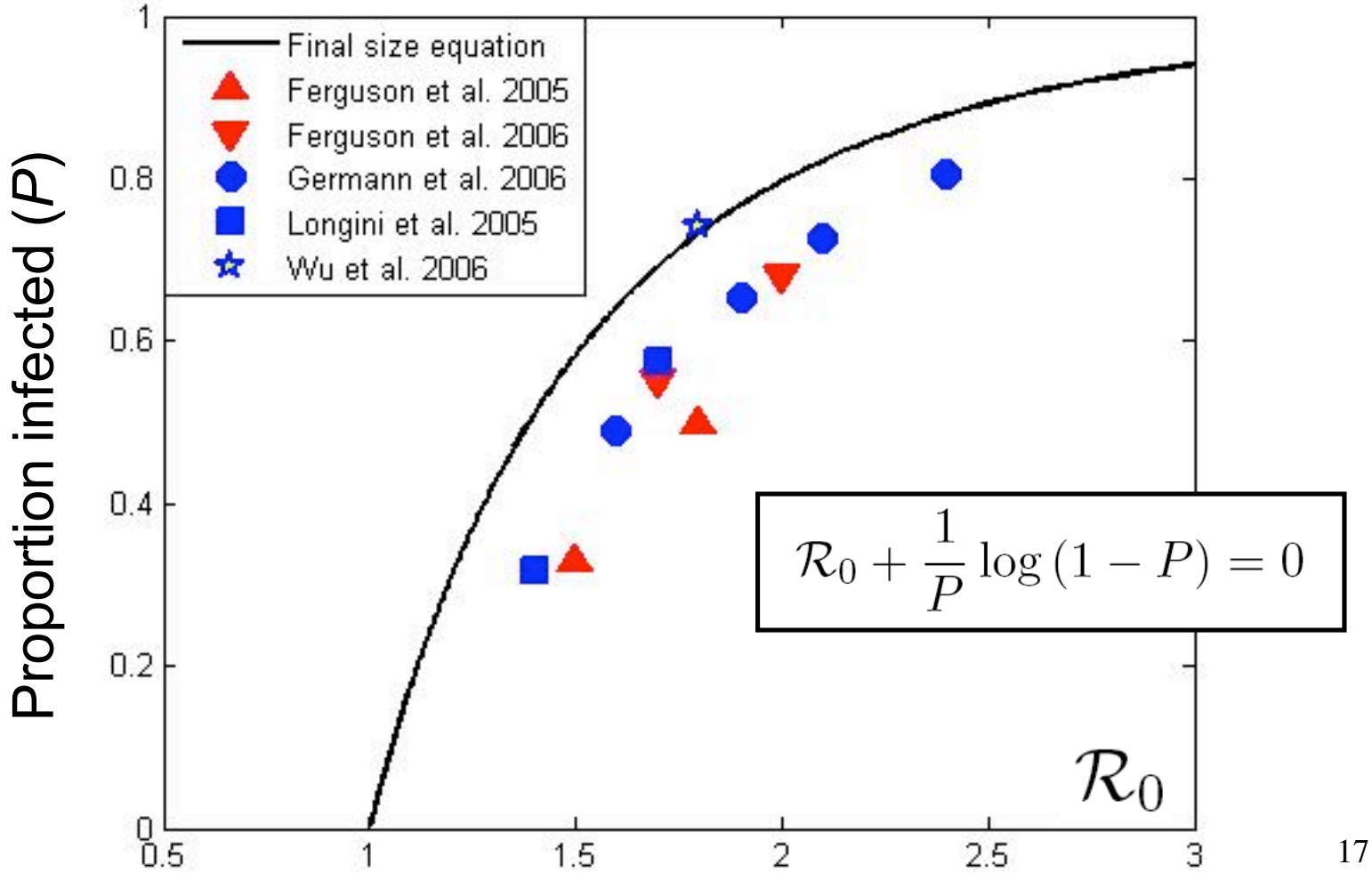
$$\overline{\boldsymbol{\imath}}(\omega) \simeq \left(\mathbf{I} - \mathcal{R}_0\overline{f}(\omega)\mathbf{W}\right)^{-1}\mathbf{e}$$

  and $|\boldsymbol{\imath}| \simeq e^{rt}$ where $\mathcal{R}_0\overline{f}(r) = 1$.

- The proportion infected in an epidemic is $|\mathbf{p}|$ where

$$\mathcal{R}_0 + \frac{1}{|\mathbf{p}|}\log\left(1 - |\mathbf{p}|\right) = 0 \qquad \mathbf{W}\mathbf{p} = \mathbf{p}$$

The final size equation



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- Aldis & Roberts: An integral equation model for the control of a smallpox outbreak. *Math. Biosci.* 195(2005):1-22.
- Roberts *et al.*: A model for the spread and control of pandemic influenza in an isolated geographical region. *J. R. Soc. Interface* 4(2007): 325-30.

What about networks?

- A statistic as useful as $\mathcal{R}_0$, but defined on a network must:
  - be easily derived from the network structure;
  - have a biological interpretation;
  - tell us something useful -
    - threshold property for (large) epidemics,
    - control effort for elimination,
    - final size of the epidemic,
    - ...
- Is it possible to define and derive such a property?

The end