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Advanced School and Conference on Statistics and Applied Probability in Life Sciences

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Probability, stochastic processes and infectious disease models

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Probability, stochastic processes and infectious disease models

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A general epidemic in a closed population

Susceptible individuals

Exposed, infected but latent (not infectious)

Infectious

Removed (isolation, recovery, death, etc.)

A function capturing interaction between # of “S” and # of “I” individuals over time

The hazard function of the sojourn time T_E during the latent period

The hazard function of the sojourn time T_I during the infectious period

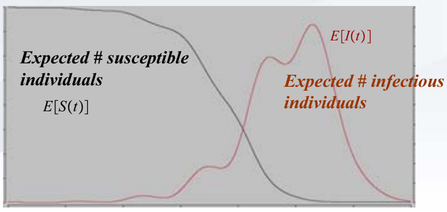
Deterministic:

- a system of integro-differential equations

Stochastic:

- a multivariate semi-Markov process

If the population is closed:
- a highly contagious disease
- a long (but not very variable) latent period



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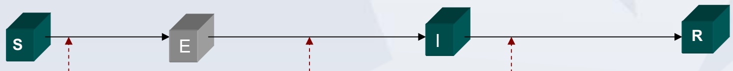

A function capturing interaction between # of "S" and # of "I" individuals over time

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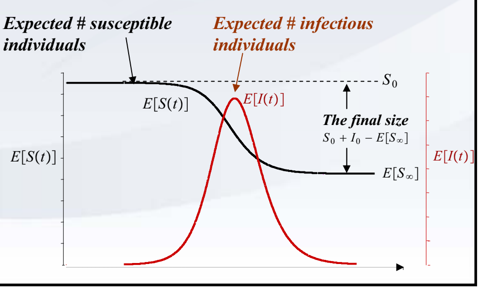
In general

Deterministic:

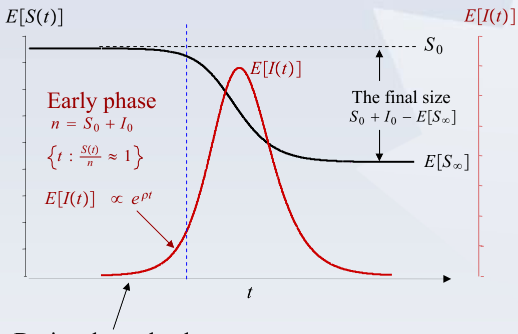
- a system of integro-differential equations

Stochastic:

- a multivariate semi-Markov process



An autonomy of a general epidemic in a simple model

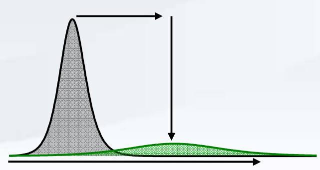


After the early phase,

1. Delay the outbreak (peak) and buy time (e.g. vaccine)
2. Reduce the maximum number of infectious individuals at any time (if constrained by healthcare capacity).
3. Keep the final size as small as possible.

During the early phase,

1. Limit the outbreak to a handful cases and prevent the exponential growth to occur.
2. If an exponential growth has occurred, reduce the initial growth rate ρ
   - This may or may not be a good objective



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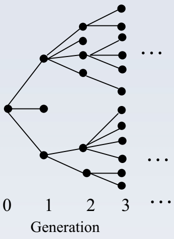
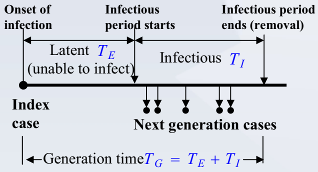
5

Early phase: the depletion of susceptible individuals is ignorable $\left\{ t : \frac{S(t)}{n} \approx 1 \right\}$

1. The branching process
   (the first approximation)





Generation g: a discrete counter, $g = 0, 1, \ldots$

Generation time T_G: from "onset of infection" to "removal" of an infected individual.

N: # of next generation individuals produced by an infected individual during generation time T_G.

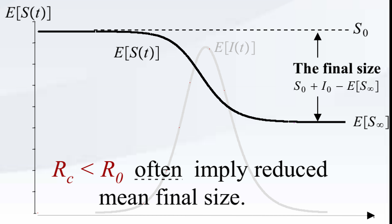
Reproduction number: $R_0 = \mathrm{E}[N]$.

Why care about R_0?

To control the outbreak,

$$R_c = (1 - c)R_0 < R_0$$

1. During the early phase, $R_c < 1 \rightarrow$ with pr. 1, extinction.
2. There is often (not always) a monotone relationship between R_0 and the final size.



$R_c < R_0$ often imply reduced mean final size.

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6

Early phase: the depletion of susceptible individuals is ignorable $\left\{ t : \frac{S(t)}{n} \approx 1 \right\}$

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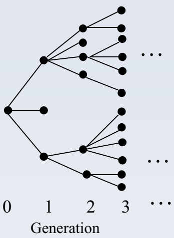
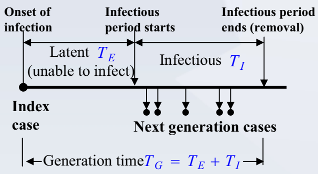
   (the first approximation)





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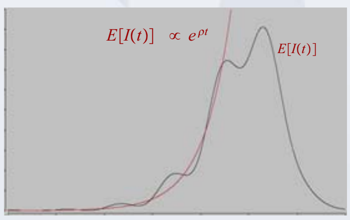
2. The exponential growth
   (the second approximation)



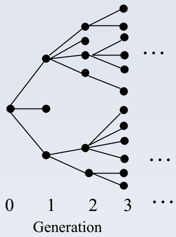
Can one relate R_0 with ρ?

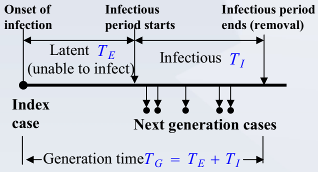
Motivation:

- use empirically observed ρ to deduce R_0
- commonly seen in literature.

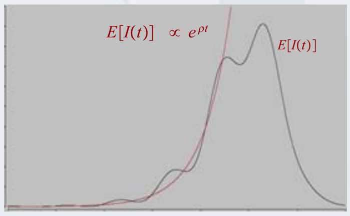
Early phase: the depletion of susceptible individuals is ignorable $\left\{t : \frac{S(t)}{n} \approx 1\right\}$

1. The branching process (the first approximation)





2. The exponential growth (the second approximation)



Reproduction number: $R_0 = E[N]$.

$R_0 = e^{\rho E[T_G]}$ (a familiar formula in ecology, intuitive)

$R_0 = 1 + \rho E[T_G]$ (a familiar formula in mathematical biology)

$R_0 = \frac{\rho E[T_I]}{1-e^{-\rho E[T_I]}}$ (Anderson, R.M. and May R. M, 1991)

$R_0 = 1 + \rho E[T_I]$ (Anderson, R.M. and May R. M, 1991)

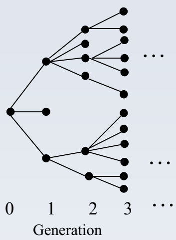
$R_0 = 1 + \rho E[T_G] + f(1-f)(\rho E[T_G])^2$ (Lipsitch et al. 2003)

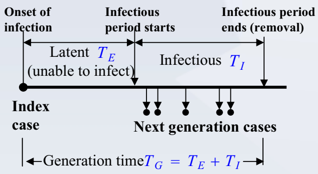
$f = \frac{E[T_E]}{E[T_G]}$

–appears in recent literature (e.g. *Science; Proc. Roy. Soc. Int; etc.*),
– in relation to SARS and Pandemic Influenza

Early phase: the depletion of susceptible individuals is ignorable $\left\{t : \frac{S(t)}{n} \approx 1\right\}$

1. The branching process (the first approximation)





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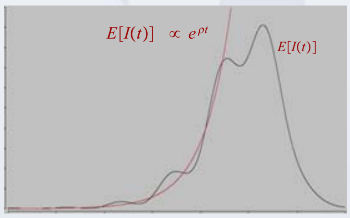


Reproduction number: $R_0 = E[N]$.

$R_0 = e^{\rho E[T_G]}$

$R_0 = 1 + \rho E[T_G]$ $\quad R_0 = 1 + \rho E[T_I]$

$R_0 = \frac{\rho E[T_I]}{1-e^{-\rho E[T_I]}}$

$R_0 = 1 + \rho E[T_G] + f(1-f)(\rho E[T_G])^2$

$f = \frac{E[T_E]}{E[T_G]}$

All are special cases of Anderson, D. and Watson, R. (*Biometrika*, 1980)

$$\boxed{R_0 = (1+\rho\nu\phi_1)^{\frac{1}{\phi_1}} \frac{\rho\mu}{1-(1+\rho\mu\phi_2)^{-\frac{1}{\phi_2}}}}$$

$\nu = E[T_E]$, $var[T_E] = \phi_1 \nu^2$

$\mu = E[T_I]$, $var[T_I] = \phi_2 \mu^2$

Early phase: the depletion of susceptible individuals is ignorable $\left\{ t : \frac{S(t)}{n} \approx 1 \right\}$

Anderson, D. and Watson, R. (*Biometrika*, 1980)

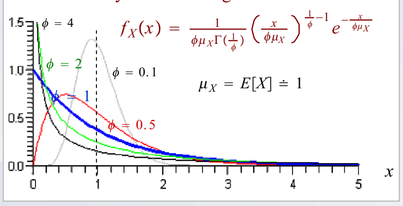
$$R_0 = (1+\rho\nu\phi_1)^{\frac{1}{\phi_1}} \frac{\rho\mu}{1-(1+\rho\mu\phi_2)^{-\frac{1}{\phi_2}}}$$

$E[T_E] = \nu,\ var[T_E] = \phi_1\nu^2$

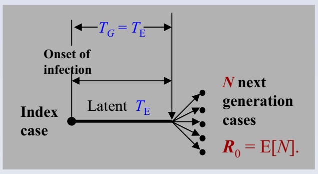
$E[T_I] = \mu,\ var[T_I] = \phi_2\mu^2$

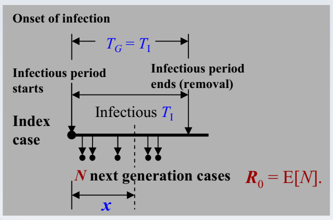
Assumptions: The latent period T_E and infectious period T_I are independent, gamma distributed

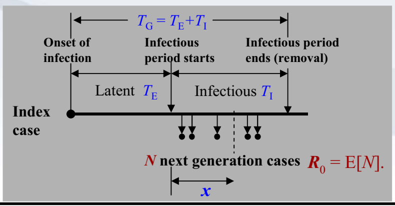
Probability densities for gamma distribution



Classes of branching processes (BP):

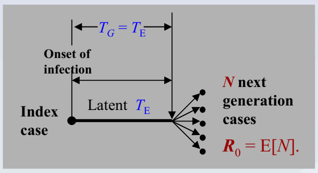




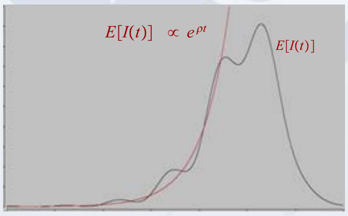


1. Galton-Watson BP:
   - infectious period degenerated to a point $T_I \to 0$
   - latent period is a constant $T_E = \nu$, zero variance
2. Bellman-Harris BP:
   - infectious period degenerated to a point $T_I \to 0$
   - latent period follows an arbitrary distribution with $E[T_E] = \nu$
3. Crump-Mode-Jagers (CMJ) BP:
   - $T_E = 0$;
   - next generation cases: counting process $\{K(x)\}$
   - $\{K(x)\}$ has stationary increment
   - random infection period T_I with $E[T_I] = \mu$
   - T_I serves as a random stopping time for $\{K(x)\}$
4. Bellman-Harris + CMJ BP:
   - latent period has a distribution, $E[T_E] = \nu$
   - infection period T_I has a distribution, $E[T_I] = \mu$
   - next generation cases: counting process $\{K(x)\}$
   - T_I serves as a random stopping time for $\{K(x)\}$

Classes of branching processes (BP) in relation to ρ



$R_0 = f(\rho)$?



Special cases of Anderson, D. and Watson, R. (*Biometrika*, 1980)

$$\boxed{R_0 = (1+\rho\nu\phi_1)^{\frac{1}{\phi_1}} \frac{\rho\mu}{1-(1+\rho\mu\phi_2)^{-\frac{1}{\phi_2}}}}$$

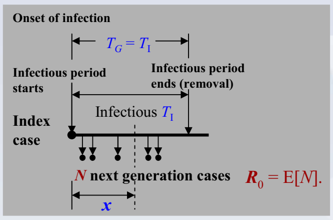
1. Galton-Watson BP:
   - infectious period degenerated to a point $T_I \to 0$
   - latent period is a constant $T_E = \nu$, zero variance

$R_0 = e^{\rho E[T_G]}$

2. Bellman-Harris BP:
   - infectious period degenerated to a point $T_I \to 0$
   - latent period follows exponential distribution with $E[T_E] = \nu$

$R_0 = 1 + \rho E[T_G]$

Classes of branching processes (BP) in relation to ρ



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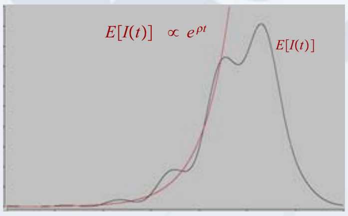

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   - $T_E = 0$;
   - next generation cases: counting process $\{K(x)\}$
   - $\{K(x)\}$ has stationary increment
   - random infection period T_I with $E[T_I] = \mu$
   - T_I serves as a random stopping time for $\{K(x)\}$

– T_I is not random $E[T_I] = \mu$, $var[T_I] = 0$

$R_0 = \frac{\rho E[T_I]}{1-e^{-\rho E[T_I]}}$

– T_I exponentially distributed, $E[T_I] = \mu$

$R_0 = 1 + \rho E[T_I]$

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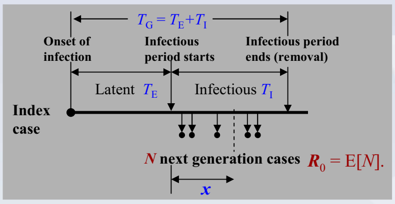
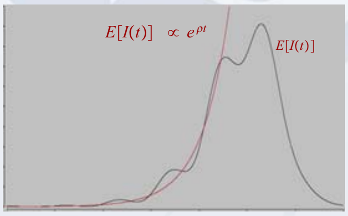
Classes of branching processes (BP) in relation to ρ



$R_0 = f(\rho)$?



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$$\boxed{R_0 = (1+\rho\nu\phi_1)^{\frac{1}{\phi_1}} \frac{\rho\mu}{1-(1+\rho\mu\phi_2)^{-\frac{1}{\phi_2}}}}$$

4. Bellman-Harris + CMJ BP:
   - latent period has a distribution, $E[T_E] = \nu$
   - infection period T_I has a distribution, $E[T_I] = \mu$
   - next generation cases: counting process $\{K(x)\}$
   - T_I serves as a random stopping time for $\{K(x)\}$

a) constant latent & infectious periods

$$R_0 = e^{\rho E[T_E]} \frac{\rho[T_I]}{1-e^{-\rho[T_I]}}$$

b) latent and infectious period are exponential

$$R_0 = 1 + \rho E[T_G] + f(1-f)(\rho E[T_G])^2$$

$$f = \frac{E[T_E]}{E[T_G]}$$

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Classes of branching processes (BP) in relation to ρ

Special cases of Anderson, D. and Watson, R. (*Biometrika*, 1980)

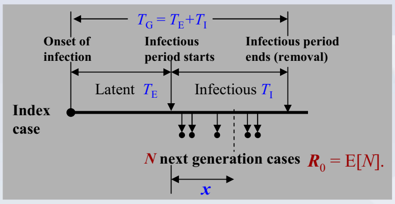
$$\boxed{R_0 = (1+\rho\nu\phi_1)^{\frac{1}{\phi_1}} \frac{\rho\mu}{1-(1+\rho\mu\phi_2)^{-\frac{1}{\phi_2}}}}$$

This is one of an extensive list of results by Anderson, D. and Watson, R. (1980) concerning SEIR models with gamma distributed latent and infectious periods.

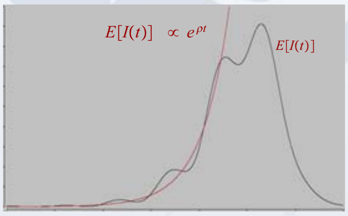
– proof is limited to Erlang distributions where $\kappa_1 = \phi_1^{-1}$ and $\kappa_2 = \phi_2^{-1}$ take integer values

Cases	ν	μ	ϕ_1	ϕ_2	$\mathbf{R}_0$
C1 √	ν	$\to 0$	$\to 0$	ϕ_2	$e^{\rho\nu}$
C2 √	ν	$\to 0$	$= 1$	ϕ_2	$1+\rho\nu$
C3	ν	$\to 0$	ϕ_1	ϕ_2	$(1+\rho\nu\phi_1)^{\frac{1}{\phi_1}}$
C4 √	0	μ	ϕ_1	$\to 0$	$\frac{\rho\mu}{1-e^{-\rho\mu}}$
C5 √	0	μ	ϕ_1	$= 1$	$1+\rho\mu$
C6	0	μ	ϕ_1	ϕ_2	$\frac{\rho\mu}{1-(\mu\rho\phi_2+1)^{-\frac{1}{\phi_2}}}$
C7 √	ν	μ	$\to 0$	$\to 0$	$e^{\rho\nu}\frac{\rho\mu}{(1-e^{-\rho\mu})}$
C8	ν	μ	$= 1$	$\to 0$	$\frac{(1+\rho\nu)\rho\mu}{1-e^{-\rho\mu}}$
C9	ν	μ	ϕ_1	$\to 0$	$\frac{(1+\rho\nu\phi_1)^{\frac{1}{\phi_1}}\rho\mu}{1-e^{-\rho\mu}}$
C10	ν	μ	$\to 0$	$= 1$	$e^{\rho\nu}(1+\rho\mu)$
C11 √	ν	μ	$= 1$	$= 1$	$(1+\rho\nu)(1+\rho\mu)$
C12	ν	μ	ϕ_1	$= 1$	$(1+\rho\nu\phi_1)^{\frac{1}{\phi_1}}(1+\rho\mu)$
C13	ν	μ	$\to 0$	ϕ_2	$e^{\rho\nu}\frac{\rho\mu}{1-(\mu\rho\phi_2+1)^{-\frac{1}{\phi_2}}}$
C14	ν	μ	$= 1$	ϕ_2	$\frac{(1+\rho\nu)\rho\mu}{1-(\mu\rho\phi_2+1)^{-\frac{1}{\phi_2}}}$
General	ν	μ	ϕ_1	ϕ_2	$\frac{(\rho\nu\phi_1+1)^{\frac{1}{\phi_1}}\rho\mu}{1-(\rho\mu\phi_2+1)^{-\frac{1}{\phi_2}}}$

Classes of branching processes (BP) in relation to ρ



$R_0 = f(\rho)$?



General result (Yan, P. 2007): $\boxed{R_0 = \dfrac{\mu}{\mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho)}}$

- $x = 0$: the beginning of infectious period
- next generation cases: counting process $\{K(x)\}$

$$K(x) \overset{\text{def.}}{=} \text{cumulative number of infectious contacts by time } x$$

- $\{K(x)\}$: stationary increment $E\{K(x)\} = \beta x$

$R_0 = \beta\mu$

- T_E and T_I are independently, arbitrarily distributed, with Laplace transforms

$$\mathcal{L}_E(\rho) = \int e^{-\rho x} f_{T_E}(x)dx \qquad \mathcal{L}_I^*(\rho) = \int e^{-\rho x}\overline{F}_{T_I}(x)dx = \frac{1-\mathcal{L}_I(\rho)}{\rho}$$

probability density of latent period

survivor function of infectious period

General result: $\boxed{\beta\mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho) = 1}$

Special cases of $R_0 = \dfrac{\mu}{\mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho)}$

1. If both the latent period T_E and infectious period T_I are gamma distributed,

$$\mathcal{L}_E(\rho) = \left(\frac{1}{1+\rho\nu\phi_1}\right)^{\frac{1}{\phi_1}} \qquad \mathcal{L}_I^*(\rho) = \frac{1-(1+\rho\mu\phi_2)^{-\frac{1}{\phi_2}}}{\rho} \quad \rightarrow \quad R_0 = (1+\rho\nu\phi_1)^{\frac{1}{\phi_1}}\frac{\rho\mu}{1-(1+\rho\mu\phi_2)^{-\frac{1}{\phi_2}}}$$

2. If both the latent period T_E and infectious period T_I are inverse-Gaussian,

$$\mathcal{L}_E(\rho) = \exp\left(\frac{1-\sqrt{1+2\nu\phi_1\rho}}{\phi_1}\right) \qquad \mathcal{L}_I^*(\rho) = \frac{1-\exp\left(\frac{1-\sqrt{1+2\mu\phi_2\rho}}{\phi_2}\right)}{\rho} \quad \rightarrow \quad R_0 = \frac{1}{\exp\left(\frac{1-\sqrt{1+2\nu\phi_1\rho}}{\phi_1}\right)} \times \frac{\rho\mu}{1-\exp\left(\frac{1-\sqrt{1+2\mu\phi_2\rho}}{\phi_2}\right)}$$

3. If T_E is inverse-Gaussian and T_I is gamma

$$R_0 = \frac{1}{\exp\left(\frac{1-\sqrt{1+2\nu\phi_1\rho}}{\phi_1}\right)} \times \frac{\rho\mu}{1-(1+\rho\mu\phi_2)^{-\frac{1}{\phi_2}}}$$

4. If T_E is gamma and T_I is inverse-Gaussian

$$R_0 = (\rho\nu\phi_1 + 1)^{\frac{1}{\phi_1}}\frac{\rho\mu}{1-\exp\left\{\frac{1-\sqrt{1+2\mu\phi_2\rho}}{\phi_2}\right\}}$$

⋮

Cases	ν	μ	ϕ_1	ϕ_2	R_0	Remarks
C1	ν	$\to 0$	$\to 0$	ϕ_2	$e^{\rho\nu} = e^{\rho T_G}$	as C1 in gamma T_E and T_I
C2	ν	$\to 0$	$= 1$	ϕ_2	$\frac{1}{\exp\left(1-\sqrt{1+2\nu\rho}\right)}$	
C3	ν	$\to 0$	ϕ_1	ϕ_2	$\exp\left(\frac{1-\sqrt{1+2\nu\phi_1\rho}}{\phi_1}\right)$	
C4	0	μ	ϕ_1	$\to 0$	$\frac{\rho\mu}{1-e^{-\rho\mu}}$	as C4 in gamma T_E and T_I
C5	0	μ	ϕ_1	$= 1$	$\frac{\rho\mu}{1-\exp\left(1-\sqrt{1+2\mu\rho}\right)}$	
C6	0	μ	ϕ_1	ϕ_2	$\frac{\rho\mu}{1-\exp\left(\frac{1-\sqrt{1+2\mu\phi_2\rho}}{\phi_2}\right)}$	
C7	ν	μ	$\to 0$	$\to 0$	$e^{\rho\nu}\frac{\rho\mu}{1-e^{-\rho\mu}}$	as C7 in gamma T_E and T_I
⋮	⋮	⋮	⋮	⋮	⋮	⋮

From special cases to general cases

$R_0 = e^{\rho E[T_G]}$ $\quad$ $R_0 = 1 + \rho E[T_G]$

$R_0 = 1 + \rho E[T_G] + f(1-f)(\rho E[T_G])^2$

$\vdots$

special cases of

$$R_0 = (1+\rho\nu\phi_1)^{\frac{1}{\phi_1}} \frac{\rho\mu}{1-(1+\rho\mu\phi_2)^{-\frac{1}{\phi_2}}}$$

$$R_0 = \frac{\rho\mu}{\exp\left(\frac{1-\sqrt{1+2\nu\phi_1\rho}}{\phi_1}\right)\left[1-\exp\left(\frac{1-\sqrt{1+2\mu\phi_2\rho}}{\phi_2}\right)\right]}$$

$\vdots$

special cases of

$$\beta\mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho) = 1$$

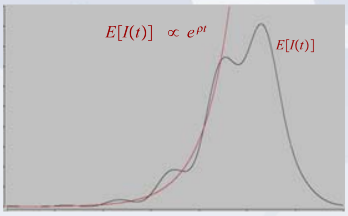
special cases of Euler-Lotka equation (Lotka, 1925)

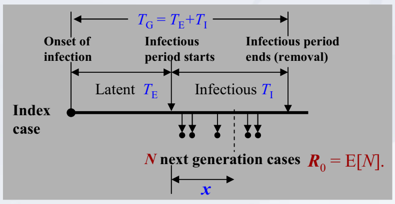
$$\int_0^\infty e^{-\rho\tau}\beta(\tau)A(\tau)d\tau = 1$$

$$A(\tau) = \Pr\{T_E \le \tau \cap T_E + T_I > \tau\}$$

$$\beta(\tau) = \begin{cases} 0 & \text{if } \tau \le T_E \\ \beta(x) = \frac{d}{dx}K(x) & \text{if } \tau > T_E, T_I > \tau - T_E \end{cases}$$

$K(x) \overset{\text{def.}}{=}$ cumulative number of infectious contacts by time x





How does the distribution of T_E shape the initial growth ρ?

$$\beta\mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho) = 1$$

When β and the distribution of the infectious period T_I is given:

- the longer is T_E in *stochastic order*,
  - $\leftrightarrow$ larger survival function $\bar{F}_E(x) = \Pr\{T_E > x\}$ for all x

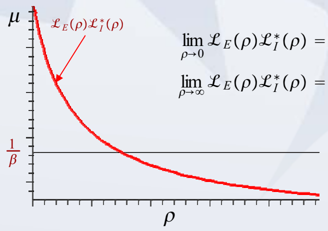
$\rightarrow$ the longer is T_E in *Laplace order*,
- $\leftrightarrow$ smaller $\mathcal{L}_E(\rho)$

$\longrightarrow$ the smaller is the growth rate ρ

Give the infectious period T_I distribution and β

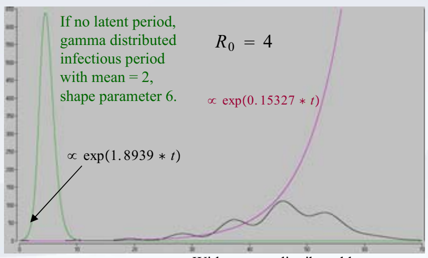
— the same R_0

If ρ is empirically observed, one may under estimate R_0 if one assumes a latent period distribution which is shorter than it should.



$$\lim_{\rho\to 0}\mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho) = \mu > \frac{1}{\beta}$$

$$\lim_{\rho\to\infty}\mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho) = 0.$$



With gamma distributed latent period: mean = 8, shape = 70

How does the distribution of T_I shape the initial growth ρ?

$$\beta \mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho) = 1$$

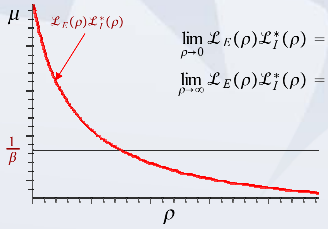
When β and the distribution of T_E is given:

- the shorter is T_I in *stochastic order*,

→ the shorter is T_I in *Laplace order*,

↔ smaller $\mathcal{L}^*_I(\rho)$

⟶ the smaller is the growth rate ρ



$$\lim_{\rho\to 0} \mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho) = \mu > \frac{1}{\beta}$$

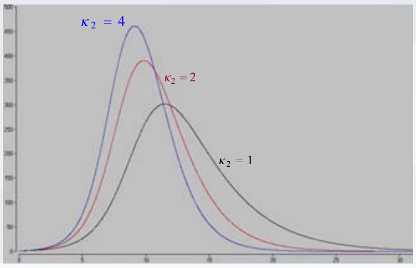
$$\lim_{\rho\to \infty} \mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho) = 0.$$

Gamma dist^ed infectious period T_I

$$\mathcal{L}_I^*(\rho) = \frac{1-\left(1+\frac{\rho\mu}{\kappa}\right)^{-\kappa}}{\rho}$$

For the same mean μ,

- the larger is the shape para. $\kappa = \phi_2^{-1}$
  (smaller is the variance $var[T_I] = \phi_2\mu^2$)
- the larger is the value of $\mathcal{L}_I^*(\rho)$



If ρ is empirically observed, one may over estimate R_0 if assuming exponentially distributed infection period if $var[T_I] < \mu^2$

How does the distribution of T_I shape the initial growth ρ?

$$\beta \mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho) = 1$$

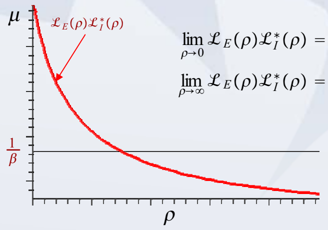
When β and the distribution of T_E is given:

- the shorter is T_I in *stochastic order*,

→ the shorter is T_I in *Laplace order*,

↔ smaller $\mathcal{L}^*_I(\rho)$

⟶ the smaller is the growth rate ρ



$$\lim_{\rho\to 0} \mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho) = \mu > \frac{1}{\beta}$$

$$\lim_{\rho\to \infty} \mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho) = 0.$$

Gamma dist^ed infectious period T_I

$$\mathcal{L}_I^*(\rho) = \frac{1-\left(1+\frac{\rho\mu}{\kappa}\right)^{-\kappa}}{\rho}$$

For the same shape parameter κ:

- the larger is the mean value μ → the larger is the growth rate ρ
- the larger is the value of $\mathcal{L}_I^*(\rho)$ → but it also increases $R_0 = \beta\mu$.

How do β and $\mu = E[T_I]$ shape the initial growth ρ?

How do β and $\mu = E[T_I]$ shape the initial growth ρ?

$$\beta \mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho) = 1$$

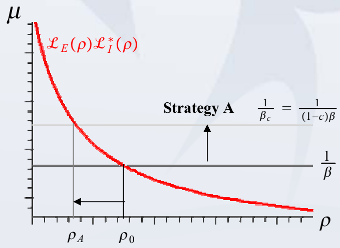
$$R_0 = \beta\mu$$

Consider two strategies at reducing R_0

$$R_c = (1-c)R_0 < R_0$$

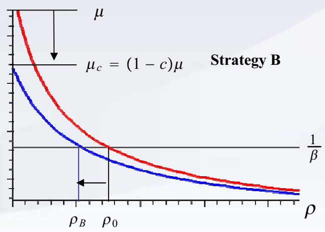
Strategy A $\quad \beta_c = (1-c)\beta \quad \mu_c = \mu$

Strategy B $\quad \mu_c = (1-c)\mu \quad \beta_c = \beta$



If there is a constraints in health care resources, such as limited capacity of hospital beds, it may be advantageous to set reduction of ρ as one of the public health management objectives.

Two R_c – equivalent strategies may not have the same amount of impact on reduction of ρ.



How long it takes to infect a person? — the distribution of the transmission interval

Motivation: Review the formula $R_0 = 1 + \rho E[T_G] + f(1-f)(\rho E[T_G])^2 \qquad f = \frac{E[T_E]}{E[T_G]}$

Lipsitch et al. (*Science*, 2003) called $E[T_G]$ the *mean serial interval*, defined as the time from the onset of symptoms in an index case to the onset of symptoms in a subsequent case infected by the index patient.

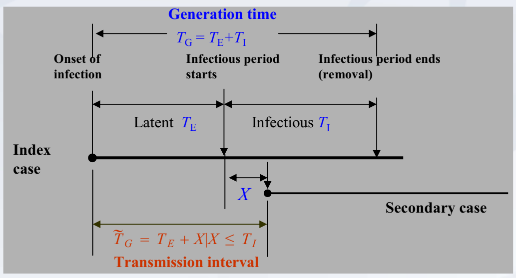
We have seen that it is valid if

1. T_E and T_I are both exponential;
2. T_E and T_I are independent;
3. $T_G = T_E + T_I$

Lipsitch et al. (2003) postulated

$$E[T_G] = E[T_E] + E[T_I]$$

(mean generation time)



$\tilde{T}_G \overset{\text{Def.}}{=}$ from infection of an individual to the infection of a secondary case by that individual

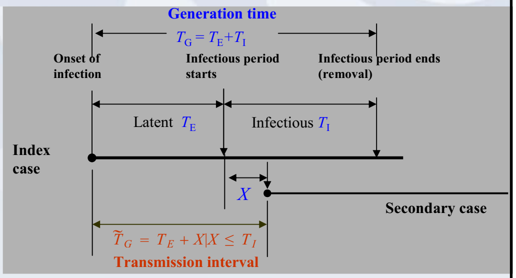
— Wallinga and Lipstich *(Proc. Roy. Soc. B; 2007)*

- use empirically observed or approximated $\tilde{T}_G$ to deduce R_0

How long it takes to infect a person? — the distribution of the transmission interval

1. $E[\tilde{T}_G] = E[T_E] + \text{fraction of } E[T_I]$
   What is this fraction?

2. If T_E and T_I are exponential, independent, and next generation cases from Poisson process
   $E[\tilde{T}_G] = E[T_E] + E[T_I] = E[T_G]$?
   $\tilde{T}_G$ and T_G identically distributed ?



3. Can one determine the distribution for $\tilde{T}_G$?

Two recent publications:
   i. Wallinga and Lipstich *(Proc. Royal Society. B; 2007)*
   ii. Roberts and Heesterbeek *(The Journal of Math. Biolgy; 2007)*

Normalize the kernel of: $\int_0^\infty e^{-\rho\tau}\beta(\tau)A(\tau)d\tau = 1$ (Euler-Lotka) $\longrightarrow$ $g(\tau) = \frac{\beta(\tau)A(\tau)}{\int_0^\infty \beta(\tau)A(\tau)d\tau}$

postulate: $\tilde{T}_G$ is identically distributed with a *r.v.* defined by *p.d.f.* $g(\tau)$

$E[\tilde{T}_G] = \int_0^\infty \tau g(\tau)d\tau$

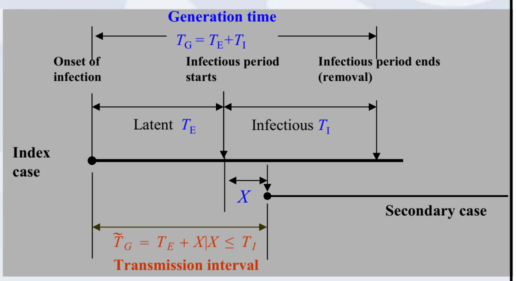
by consequence: the answers to questions in 2. are "yes".

How long it takes to infect a person? — the distribution of the transmission interval

Yan, P. *(on-going)*

Assumptions:

1. $\{K(x)\}$ Poisson process (β)
2. T_I arbitrary distribution:
   $\bar{F}_I(x) = \Pr\{T_I > x\}$
   Laplace transform $\mathcal{L}_I(\beta)$ exists
3. X and T_I are independent



$\rightarrow$ $\Pr\{X \le T_I\} = \int_0^\infty (1 - e^{-\beta x}) f_I(x)dx = 1 - \mathcal{L}_I(\beta)$

$\rightarrow$ $f_X(x|X \le T_I) = \frac{\beta e^{-\beta x}\bar{F}_I(x)}{1-\mathcal{L}_I(\beta)} = \frac{e^{-\beta x}\bar{F}_I(x)}{\mathcal{L}_I^*(\beta)}$

$f_I(x) = -\frac{d}{dx}\bar{F}_I(x)$

$\mathcal{L}_I^*(\beta) = \int_0^\infty e^{-\beta x}\bar{F}_I(x)dx = \frac{1-\mathcal{L}_I(\beta)}{\beta}$

$E[X|X \le T_I] = \frac{1}{\mathcal{L}_I^*(\beta)}\int_0^\infty x e^{-\beta x}\bar{F}_I(x)dx = -\frac{1}{\mathcal{L}_I^*(\beta)}\frac{d}{d\beta}\mathcal{L}_I^*(\beta) = \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)]$

$\rightarrow$ $f_{\tilde{T}_G} = f_{T_E} \circ f_{X|X \le T_I}$ (convolution)

$E[\tilde{T}_G] = E[T_E] + E[X_1|X_1 \le T_I] = \nu + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)]$

How long it takes to infect a person? — the distribution of the transmission interval

Yan, P. *(on-going)*

assuming new infections follow Poisson process

$$f_{\tilde{T}_G} = f_{T_E} \circ f_{X|X\le T_I}$$

$$f_X(x|X \le T_I) = \frac{\beta e^{-\beta x}\overline{F}_I(x)}{1-\mathcal{L}_I(\beta)} = \frac{e^{-\beta x}\overline{F}_I(x)}{\mathcal{L}_I^*(\beta)}$$

$$E[\tilde{T}_G] = \nu + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)]$$

$$E[X|X \le T_I] = \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)]$$

Wallinga and Lipsitch, Roberts and Heesterbeek

$$g(\tau) = \frac{\beta(\tau)A(\tau)}{\int_0^\infty \beta(\tau)A(\tau)d\tau} = \frac{\overline{F}_{E+I}(\tau)-\overline{F}_E(\tau)}{\mu}$$

$\overline{F}_{E+I}(\tau) =$ survival function of $T_G = T_E + T_I$

$\overline{F}_E(\tau) =$ survival function of T_E

If T_I is gamma distributed with mean μ and shape parameter κ: $\mathcal{L}_I^*(\beta) = \frac{1-\mathcal{L}_I(\beta)}{\beta} = \frac{\left(\frac{\beta\mu}{\kappa}+1\right)^\kappa-1}{\beta\left(\frac{\beta\mu}{\kappa}+1\right)^\kappa}$

Yan, P. *(on-going)*

$$E[\tilde{T}_G] = \nu + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)]$$
$$= \nu + \left(\frac{1}{\beta} + \frac{\mu\kappa^{\kappa+1}}{(\kappa+\beta\mu)(\kappa^\kappa-(\kappa+\beta\mu)^\kappa)}\right)$$
$$= \nu + \left(\frac{1}{R_0} + \frac{\kappa^{\kappa+1}}{(R_0+\kappa)(\kappa^\kappa-(R_0+\kappa)^\kappa)}\right)\mu$$

Roberts and Heesterbeek (2007)

$$\int_0^\infty \tau g(\tau)d\tau = \nu + \frac{\kappa+1}{2\kappa}\mu$$

$$\boxed{g(\tau) \ne f_{\tilde{T}_G}, \quad \int \tau g(\tau)d\tau \ne \nu + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)]}$$

How long it takes to infect a person? — the distribution of the transmission interval

If T_I is gamma distributed with mean μ and shape parameter κ: $\mathcal{L}_I^*(\beta) = \frac{1-\mathcal{L}_I(\beta)}{\beta} = \frac{\left(\frac{\beta\mu}{\kappa}+1\right)^\kappa-1}{\beta\left(\frac{\beta\mu}{\kappa}+1\right)^\kappa}$

Yan, P. *(on-going)*

$$E[\tilde{T}_G] = \nu + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)]$$
$$= \nu + \left(\frac{1}{\beta} + \frac{\mu\kappa^{\kappa+1}}{(\kappa+\beta\mu)(\kappa^\kappa-(\kappa+\beta\mu)^\kappa)}\right)$$
$$= \nu + \left(\frac{1}{R_0} + \frac{\kappa^{\kappa+1}}{(R_0+\kappa)(\kappa^\kappa-(R_0+\kappa)^\kappa)}\right)\mu$$

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$$\int_0^\infty \tau g(\tau)d\tau = \nu + \frac{\kappa+1}{2\kappa}\mu$$

$$\boxed{g(\tau) \ne f_{\tilde{T}_G}, \quad \int \tau g(\tau)d\tau \ne \nu + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)]}$$

Example 1: *Infectious period is constant*

$$\kappa \to \infty \; (var[T_I] = \frac{\mu^2}{\kappa} \to 0)$$

$$\lim_{\kappa\to\infty}\left(\frac{1}{R_0} + \frac{\kappa^{\kappa+1}}{(R_0+\kappa)(\kappa^\kappa-(R_0+\kappa)^\kappa)}\right) = \frac{1}{R_0} + \frac{1}{1-e^{R_0}}$$

$$E[\tilde{T}_G] \to \nu + \left(\frac{1}{R_0} + \frac{1}{1-e^{R_0}}\right)\mu$$

$$\int_0^\infty \tau g(\tau)d\tau = \nu + \frac{\kappa+1}{2\kappa}\mu \to \nu + \frac{1}{2}\mu$$

If constrained by $R_0 > 1$
(a necessary condition for r > 0)

$$\nu + \left(\frac{1}{R_0} + \frac{1}{1-e^{R_0}}\right)\mu \le \nu + \frac{e-2}{e-1}\mu < \nu + \frac{1}{2}\mu$$

How long it takes to infect a person? — the distribution of the transmission interval

If T_I is gamma distributed with mean μ and shape parameter κ: $\mathcal{L}_I^*(\beta) = \frac{1-\mathcal{L}_I(\beta)}{\beta} = \frac{\left(\frac{\beta\mu}{\kappa}+1\right)^{\kappa}-1}{\beta\left(\frac{\beta\mu}{\kappa}+1\right)^{\kappa}}$

Yan, P. *(on-going)*

$$
\begin{aligned}
E[\tilde{T}_G] &= \nu + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)] \\
&= \nu + \left(\frac{1}{\beta} + \frac{\mu\kappa^{\kappa+1}}{(\kappa+\beta\mu)(\kappa^{\kappa}-(\kappa+\beta\mu)^{\kappa})}\right) \\
&= \nu + \left(\frac{1}{R_0} + \frac{\kappa^{\kappa+1}}{(R_0+\kappa)(\kappa^{\kappa}-(R_0+\kappa)^{\kappa})}\right)\mu
\end{aligned}
$$

Roberts and Heesterbeek (2007)

$$\int_0^\infty \tau g(\tau)d\tau = \nu + \frac{\kappa+1}{2\kappa}\mu$$

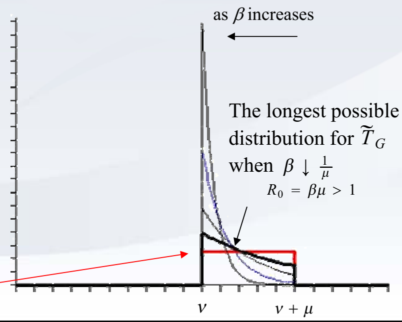
$$\boxed{\begin{aligned} &g(\tau) \neq f_{\tilde{T}_G}, \\ &\int \tau g(\tau)d\tau \neq \nu + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)] \end{aligned}}$$

Example 1: *Infectious period is constant if latent period is also constant*

$$
f_{\tilde{T}_G}(\tau|X_1 \le \mu) = \begin{cases} \frac{\beta e^{-\beta(\tau-\nu)}}{1-e^{-\beta\mu}}, & \text{if } \nu < \tau \le \nu+\mu \\ 0, & \text{otherwise.} \end{cases}
$$

$$
\begin{aligned}
E[\tilde{T}_G] &= \int_\nu^{\nu+\mu} \frac{\beta\tau e^{-\beta(\tau-\nu)}}{1-e^{-\beta\mu}}d\tau \\
&= \nu + \left(\frac{1}{R_0} + \frac{1}{1-e^{R_0}}\right)\mu \le \nu + \frac{e-2}{e-1}\mu < \nu + \frac{1}{2}\mu
\end{aligned}
$$

$$
g(\tau) = \begin{cases} \frac{1}{\mu}, & \text{if } \nu < \tau \le \nu+\mu \\ 0, & \text{otherwise.} \end{cases}
\qquad \int_0^\infty \tau g(\tau)d\tau = \nu + \frac{\mu}{2}
$$



How long it takes to infect a person? — the distribution of the transmission interval

If T_I is gamma distributed with mean μ and shape parameter κ: $\mathcal{L}_I^*(\beta) = \frac{1-\mathcal{L}_I(\beta)}{\beta} = \frac{\left(\frac{\beta\mu}{\kappa}+1\right)^{\kappa}-1}{\beta\left(\frac{\beta\mu}{\kappa}+1\right)^{\kappa}}$

Yan, P. *(on-going)*

$$
\begin{aligned}
E[\tilde{T}_G] &= \nu + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)] \\
&= \nu + \left(\frac{1}{\beta} + \frac{\mu\kappa^{\kappa+1}}{(\kappa+\beta\mu)(\kappa^{\kappa}-(\kappa+\beta\mu)^{\kappa})}\right) \\
&= \nu + \left(\frac{1}{R_0} + \frac{\kappa^{\kappa+1}}{(R_0+\kappa)(\kappa^{\kappa}-(R_0+\kappa)^{\kappa})}\right)\mu
\end{aligned}
$$

Roberts and Heesterbeek (2007)

$$\int_0^\infty \tau g(\tau)d\tau = \nu + \frac{\kappa+1}{2\kappa}\mu$$

$$\boxed{\begin{aligned} &g(\tau) \neq f_{\tilde{T}_G}, \\ &\int \tau g(\tau)d\tau \neq \nu + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)] \end{aligned}}$$

Example 2: *Infectious period is exponential* $\kappa = 1$

$$\left(\frac{1}{R_0} + \frac{\kappa^{\kappa+1}}{(R_0+\kappa)(\kappa^{\kappa}-(R_0+\kappa)^{\kappa})}\right)\Bigg|_{\kappa=1} = \frac{1}{R_0+1}$$

$$E[\tilde{T}_G] = \nu + \frac{1}{R_0+1}\mu$$

$$\int_0^\infty \tau g(\tau)d\tau = \nu + \frac{\kappa+1}{2\kappa}\mu = \nu + \mu$$

If constrained by $R_0 > 1$
(a necessary condition for r > 0)

$$E[\tilde{T}_G] \le \nu + \frac{1}{2}\mu < \nu + \mu$$

How long it takes to infect a person? — the distribution of the transmission interval

If T_I is gamma distributed with mean μ and shape parameter κ: $\mathcal{L}_I^*(\beta) = \frac{1-\mathcal{L}_I(\beta)}{\beta} = \frac{\left(\frac{\beta\mu}{\kappa}+1\right)^{\kappa}-1}{\beta\left(\frac{\beta\mu}{\kappa}+1\right)^{\kappa}}$

Yan, P. *(on-going)*

$$E[\widetilde{T}_G] = \nu + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)]$$
$$= \nu + \left(\frac{1}{\beta} + \frac{\mu\kappa^{\kappa+1}}{(\kappa+\beta\mu)(\kappa^{\kappa}-(\kappa+\beta\mu)^{\kappa})}\right)$$
$$= \nu + \left(\frac{1}{R_0} + \frac{\kappa^{\kappa+1}}{(R_0+\kappa)(\kappa^{\kappa}-(R_0+\kappa)^{\kappa})}\right)\mu$$

Roberts and Heesterbeek (2007)

$$\int_0^\infty \tau g(\tau)d\tau = \nu + \frac{\kappa+1}{2\kappa}\mu$$

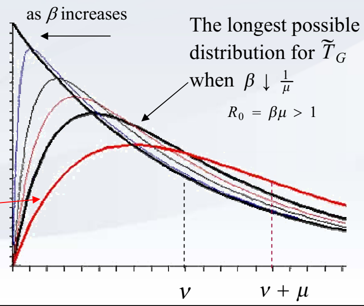
$$\boxed{\begin{array}{c} g(\tau) \neq f_{\widetilde{T}_G}, \\ \int \tau g(\tau)d\tau \neq \nu + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)] \end{array}}$$

Example 2: *Infectious period is exponential* $\kappa = 1$
if latent period is also exponential

$$f_{\widetilde{T}_G}(\tau | X \le T_I) = \frac{\beta\mu+1}{(\beta\mu+1)\nu-\mu}\left(e^{-\frac{\tau}{\nu}} - e^{-\frac{\beta\mu+1}{\mu}\tau}\right)$$

$$E[\widetilde{T}_G] = \nu + \frac{\mu}{\beta\mu+1}$$
$$= \nu + \frac{1}{1+R_0}\mu \le \nu + \frac{\mu}{2} < \nu + \mu$$

$$g(\tau) = \frac{1}{\nu-\mu}\left(e^{-\frac{\tau}{\nu}} - e^{-\frac{\tau}{\mu}}\right)$$
$$\int_0^\infty \tau g(\tau)d\tau = \nu + \mu$$



Synthesis: R_0, $E[\widetilde{T}_G]$ and ρ $\quad (R_0 = \beta\mu)$

$E[\widetilde{T}_G]$ is determined by β and by the distribution for T_I; not by the distribution of T_E except for its mean.

$$E[\widetilde{T}_G] = \nu + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)]$$

IF, big if, $E[\widetilde{T}_G]$ can be derived from data, one can use

$$\frac{E[\widetilde{T}_G]-\nu}{\mu} = \frac{E[X|X \le T_I]}{\mu} = \frac{1}{\mu}\frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)] = f(R_0;\ \mu,\ \phi, \cdots)$$

to derive R_0 in the absence of knowledge of ρ.

If gamma distributed T_I: $\frac{E[\widetilde{T}_G]-\nu}{\mu} = \frac{(\phi R_0+1)\left[(\phi R_0+1)^{\frac{1}{\phi}}-1\right]-R_0}{R_0(\phi R_0+1)\left[(\phi R_0+1)^{\frac{1}{\phi}}-1\right]}$ $\quad R_0$ can be solved numerically.

ρ is determined by β, by the distribution for T_I and by the distribution of T_E

$$\beta\mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho) = 1 \qquad R_0 = \frac{\mu}{\mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho)}$$

One can not deduce R_0 by empirically observed ρ and $\mu = E[T_I]$ alone. One needs detailed distributions for both T_E and T_I.

There is no general relationship between ρ and $E[\widetilde{T}_G]$. Special case: $E[\widetilde{T}_G] = \nu + \frac{\mu}{(1+\rho\nu)(1+\rho\mu)+1}$
(exponential)

Simulation

Assumptions

1. Gamma distributed latent period T_E : mean $v = 19$ days and shape parameter *70*
2. Gamma distributed pre-symptom infectious period $T_I^{(1)}$: mean $\mu_1 = 1.5$ days and shape parameter *70*
3. Gamma distributed pre-symptom infectious period $T_I^{(2)}$: mean $\mu_2 = 5.5$ days and shape parameter *6*
4. $\beta = 1.001127 \quad \mu = \mu_1 + \mu_2 = 7$

$\boxed{R_0 = 1.001127 \times 7 = 7.0079}$

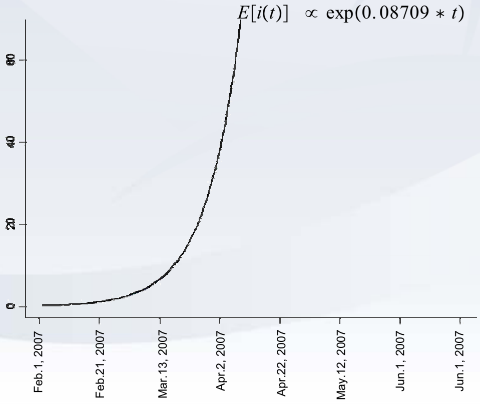
Modification of $R_0 = \dfrac{\mu}{\mathcal{L}_E(\rho)\mathcal{L}_I^*(\rho)}$

$\longrightarrow R_0 = \dfrac{\rho\mu}{\mathcal{L}_E(\rho)\left[1-\mathcal{L}_I^{(1)}(\rho)\mathcal{L}_I^{(2)}(\rho)\right]}$

numeric solution: $\rho = 0.08709$

Initial growth:

$E[i(t)] \propto \exp(0.08709 * t)$



Simulation

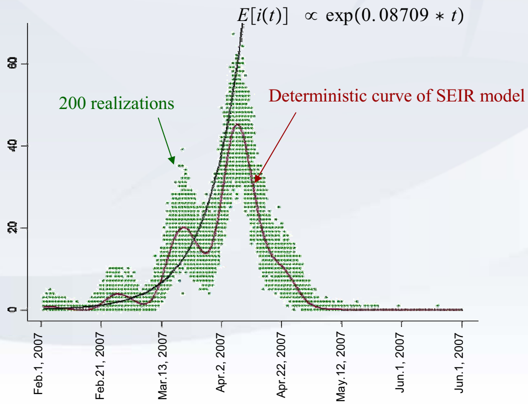
Assumptions

1. Gamma distributed latent period T_E : mean $v = 19$ days and shape parameter *70*
2. Gamma distributed pre-symptom infectious period $T_I^{(1)}$: mean $\mu_1 = 1.5$ days and shape parameter *70*
3. Gamma distributed pre-symptom infectious period $T_I^{(2)}$: mean $\mu_2 = 5.5$ days and shape parameter *6*
4. $\beta = 1.001127 \quad \mu = \mu_1 + \mu_2 = 7$

$\boxed{R_0 = 1.001127 \times 7 = 7.0079}$

$\longrightarrow \rho = 0.08709$

- Use integro-differential equations to calc. a deterministic curve *($S_0 = 1550$, $I_0 = 1$)*
- Simulate # daily new infections as a non-homogenous Poisson process with the deterministic curve as its intensity function (200 realizations)



Simulation

Assumptions

1. Gamma distributed latent period T_E : mean v =*19* days and shape parameter *70*
2. Gamma distributed pre-symptom infectious period $T_I^{(1)}$: mean μ_1=*1.5* days and shape parameter *70*
3. Gamma distributed pre-symptom infectious period $T_I^{(2)}$: mean μ_2=*5.5* days and shape parameter *6*
4. $\beta = 1.001127 \quad \mu = \mu_1 + \mu_2 = 7$

$\boxed{R_0 = 1.001127 \times 7 = 7.0079}$

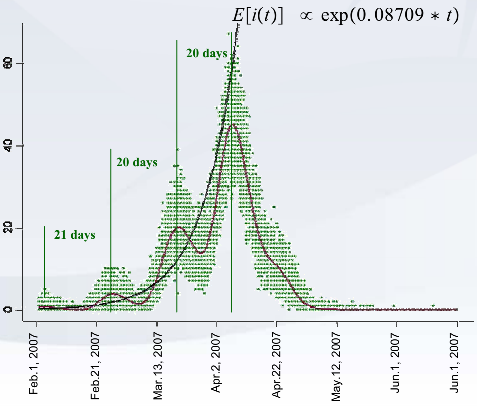
→ $\rho = 0.08709$

- Simulate # daily new infections (200 realizations)

- Use $E[\tilde{T}_G] = v + \frac{d}{d\beta}[-\log \mathcal{L}_I^*(\beta)]$

→ $E[\tilde{T}_G] = 19 + 0.82141 = 19.82141$ (theoretically predicted)

Question: Can the difference between modes be a proxy for $E[\tilde{T}_G]$ *?*



Simulation

Assumptions

1. Gamma distributed latent period T_E : mean v =*19* days and shape parameter *70*
2. Gamma distributed pre-symptom infectious period $T_I^{(1)}$: mean μ_1=*1.5* days and shape parameter *70*
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4. $\beta = 1.001127 \quad \mu = \mu_1 + \mu_2 = 7$

$\boxed{R_0 = 1.001127 \times 7 = 7.0079}$

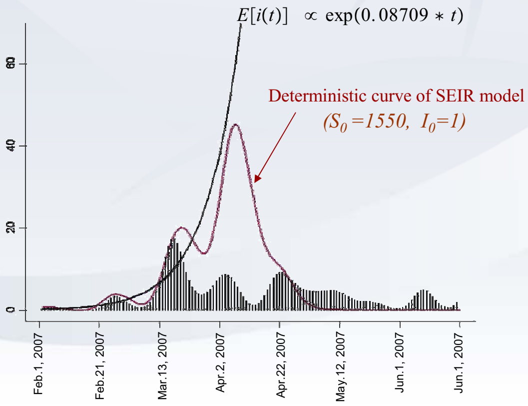
Reality check:

Statistically estimated (back-calculation) # mumps by date of infection in Nova Scotia, Canada, using illness data

1. *Early departure from exp. growth*

Depletion of susceptibles is faster than expected (e.g. intervention)

or S_0 may be too large in the simulation model.

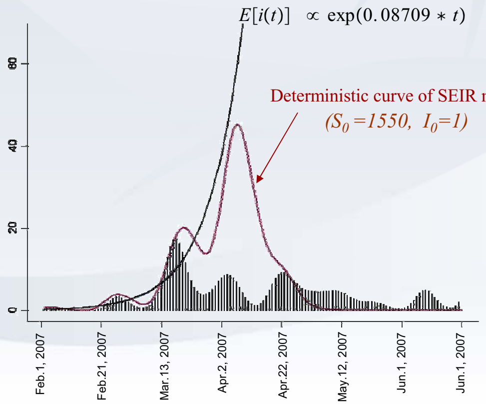


Simulation

Assumptions

1. Gamma distributed latent period T_E : mean $v = 19$ days and shape parameter 70
2. Gamma distributed pre-symptom infectious period $T_I^{(1)}$: mean $\mu_1 = 1.5$ days and shape parameter 70
3. Gamma distributed pre-symptom infectious period $T_I^{(2)}$: mean $\mu_2 = 5.5$ days and shape parameter 6
4. $\beta = 1.001127 \quad \mu = \mu_1 + \mu_2 = 7$

$\boxed{R_0 = 1.001127 \times 7 = 7.0079}$



Reality check:

Statistically estimated (back-calculation) # mumps by date of infection in Nova Scotia, Canada, using illness data

2. *More sustained outbreak than predicted*

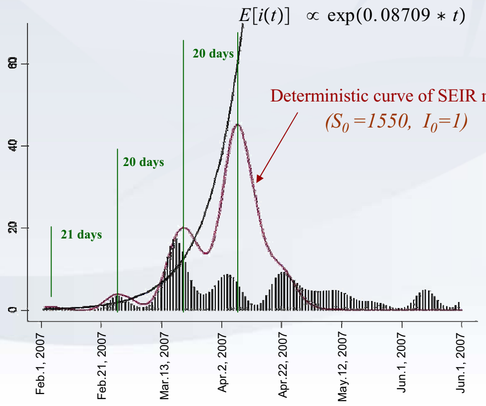
The closed population model in simulation may be not incorrect.

Simulation

Assumptions

1. Gamma distributed latent period T_E : mean $v = 19$ days and shape parameter 70
2. Gamma distributed pre-symptom infectious period $T_I^{(1)}$: mean $\mu_1 = 1.5$ days and shape parameter 70
3. Gamma distributed pre-symptom infectious period $T_I^{(2)}$: mean $\mu_2 = 5.5$ days and shape parameter 6
4. $\beta = 1.001127 \quad \mu = \mu_1 + \mu_2 = 7$

$\boxed{R_0 = 1.001127 \times 7 = 7.0079}$



Reality check:

Statistically estimated (back-calculation) # mumps by date of infection in Nova Scotia, Canada, using illness data

3. *Shorter "serial intervals" than what model predicted*

May suggest that the assumed mean latent period = 19 days a bit too long for mumps.

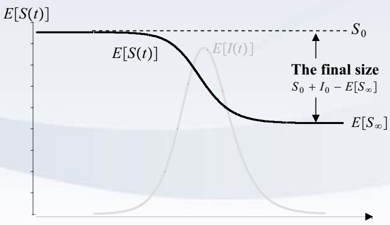
About the final size

There is very often (not always) a monotone relationship between R_0 and the final size.

$$\frac{S_0+I_0-E[S_\infty]}{n} \overset{asymp.}{\sim} N(\eta,\sigma^2) \qquad \sigma^2 = \frac{\eta(1-\eta)}{(1-R_0\eta)^2} + \frac{\eta^2(var[N]-R_0)(1-\eta+\varepsilon)}{(1-R_0\eta)^2}$$

$\eta = \lim_{n\to\infty} \frac{S_0+I_0-E[S_\infty]}{n}$ is the root of $1-\eta = \exp(-R_0(\eta+\varepsilon))$ the final size equation

$$\varepsilon = \frac{I_0}{S_0}$$



The final size equation

$$1-\eta = \exp(-R_0(\eta+\varepsilon)) \qquad \varepsilon = \frac{I_0}{S_0}$$

Early appearance in Kermack and Mckendrick (1927).

1. Ma and Earn (2006) (integro-differential equations) showed that it holds in general settings
   - Homogeneous mixing (all susceptibles and infectives are of the same kind), the final size is invariant if,
     1. existing a latent period & arbitrarily distributed infectious period;
     2. any # infectious stages and/or a stage during which infectives are isolated.
   - The final size equations are valid under certain situations with heterogeneous mixing.

2. They are valid, as long as the conditions that the conditions that the force of infection at time t can be expressed by $\beta E[I(t)]$,

$$\int_0^\infty E[I(t)]dt = -\frac{\log(1-\eta)}{\beta} \quad \text{is invariant.}$$

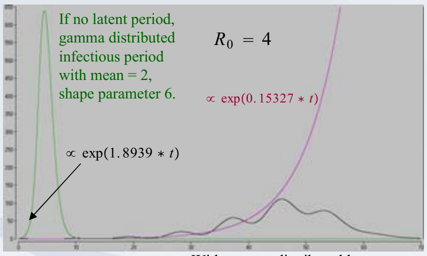
3. Ludwig (1975); von Bahr and Martin-Löf (1980); Scalia-Tomba (1985); Martin-Löf (1986); Lefèvre and Picard (1995); etc.

$$\frac{S_0+I_0-S_\infty}{n} \overset{asymp.}{\sim} N(\eta,\sigma^2)$$

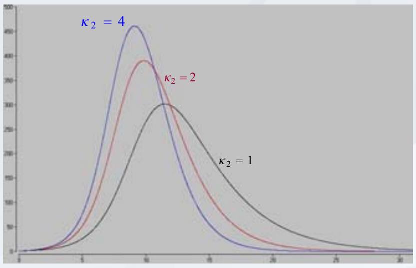
From generality of final size equations

$$1 - \eta = \exp(-R_0(\eta + \varepsilon)) \qquad \varepsilon = \frac{I_0}{S_0} \qquad \int_0^\infty E[I(t)]dt = -\frac{\log(1-\eta)}{\beta}$$

The areas covered by the following curves are identical.



With gamma distributed latent period: mean = 8, shape = 70



A modification of the final size equations including intervention

To control the outbreak, $R_c = (1-c)R_0 < R_0$

Without intervention: $1 - \eta = \exp(-R_0(\eta + \varepsilon))$

With intervention: $1 - \eta = \exp(-(1-c)R_0(\eta + \varepsilon))$

Some intervention may be quantifiable (e.g. amount of antiviral doses) with a demand.

To achieve reduction of R_0 by a factor of $0 < c < 1$, one needs to pay a price $P^{(c)}$

- assuming that $P^{(c)}$ is proportional to the final size (e.g. antiviral drugs are only applied to those who are infected)

  $$1 - \eta = \exp(-(1-c)R_0(\eta - cP^{(c)})), \quad \varepsilon \approx 0$$

  (a joint work with Dr. Fan Zhang at PHAC)

  ⟶ implying that the controlled final size to be determined by input $P^{(c)}$

- This may be conducted under constraints $P^{(c)} \leq P^{\text{limit}}$

  ⟶ use final size equations to set an Operations Research agenda.

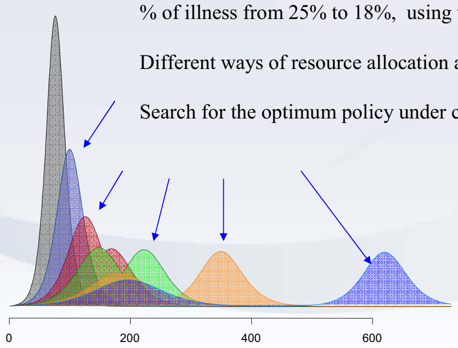
Use final size equations to set an Operations Research agenda.

- Reduce the final size (consequently, hospitalization, death, etc.) as much as possible

$$\text{min} \;:\; w_0 \times \text{overall mortality} + w_1 \times \text{hospitalization} + w_2 \times \text{absenteeism} + \cdots$$

- Constraints: limited resources such as fixed amount of antiviral drugs at disposal.

If no intervention, 25% population expected ill



If effective use up all the limited resource, at the best one reduces the % of illness from 25% to 18%, using the modified final size eqn.

Different ways of resource allocation are size-equivalent (18%).

Search for the optimum policy under constraint:

1. Delay the first wave may buy time for a vaccine to arrive
2. Reduce the peak level may make it easier to health care to manage