Varying Infectivity and Waning Immunity

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Varying infectivity + waning immunity

- Kermack and McKendrick already in 1932 discussed progressive loss of immunity.
- Let (λ_0, γ_0) and (λ, γ) be two random elements of D^2 such that $0 \le \lambda_0(t), \lambda(t) \le \lambda^*$ and $0 \le \gamma_0(t), \gamma(t) \le 1$, such that $\inf\{t,\ \gamma(t) > 0\} \ge \sup\{t,\ \lambda(t) > 0\}$, and $\lambda(t) = \lambda^0(t) = \gamma(t) = \gamma^0(t) = 0$ for $t < 0$.
- We are given a collection of indep. r.v.'s $\{\lambda_{k,i}, \gamma_{k,i},\ 1 \le k \le N, i \ge 0\}$, where each $(\lambda_{k,0}, \gamma_{k,0})$ has the law of (λ_0, γ_0), and for each $i \ge 1$, each k, $(\lambda_{k,i}, \gamma_{k,i})$ has the law of (λ, γ).
- $A_k^N(t)$ denotes the number of (re)infections of individual $1 \le k \le N$ on the interval $(0, t]$. Next $\zeta_k^N(t) = t - (\sup\{s \in (0, t], A_k^N(s) = A_k^N(s^-) + 1\} \vee 1)$.
- $\gamma_{k,A_k^N(t)}(\zeta_k^N(t))$ is the susceptibility of the k–th indiv. at time t. The total susceptibility is $\mathfrak{S}^N(t) = \sum_{k=1}^N \gamma_{k,A_k^N(t)}(\zeta_k^N(t))$. If someone gets infected at time t, the probability that k is chosen equals $\left(\mathfrak{S}^N(t)\right)^{-1} \gamma_{k,A_k^N(t)}(\zeta_k^N(t))$.

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The functions λ and γ

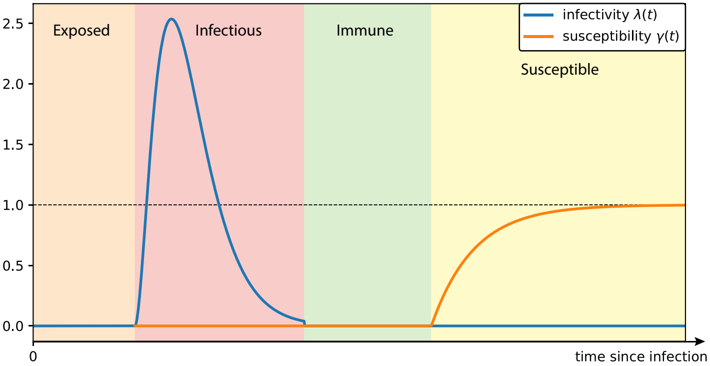

FIGURE – Illustration of the infectivity and susceptibility of an individual from the time of becoming infected, to the time of recovery, and then to time of losing immunity and becoming fully susceptible. The blue curve represents the function $\lambda(t)$ which increases to a certain value and then decreases to zero, and the orange curve represents the function $\gamma(t)$ which gradually increases to 1.

Varying infectivity + waning immunity 2

- It turns out that

$$\bar{\mathfrak{F}}^N(t) = \frac{1}{N}\sum_{k=1}^{N} \lambda_{k,A_k^N(t)}(\zeta_k^N(t)), \quad \bar{\mathfrak{S}}^N(t) = \frac{1}{N}\sum_{k=1}^{N} \gamma_{k,A_k^N(t)}(\zeta_k^N(t)) .$$

- Our main result is

Theorem

As $N \to \infty$, $(\overline{\mathfrak{S}}^N(t), \bar{\mathfrak{F}}^N(t))$ converges in probability, locally uniformly in t, to the unique solution of

$$\begin{aligned}\overline{\mathfrak{S}}(t) &= \mathbb{E}\left[\gamma^0(t)\exp\left(-\int_0^t \gamma^0(r)\overline{\mathfrak{F}}(r)dr\right)\right] \\ &\quad + \int_0^t \mathbb{E}\left[\gamma(t-s)\exp\left(-\int_s^t \gamma(r-s)\overline{\mathfrak{F}}(r)dr\right)\right]\overline{\mathfrak{S}}(s)\overline{\mathfrak{F}}(s)ds, \\ \overline{\mathfrak{F}}(t) &= \overline{I}(0)\overline{\lambda}^0(t) + \int_0^t \overline{\lambda}(t-s)\overline{\mathfrak{S}}(s)\overline{\mathfrak{F}}(s)ds .\end{aligned}$$

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Varying infectivity + waning immunity 3

- We merge the exposed and infectious individuals into a compartment of "infected individuals", and the Susceptible and Recovered individuals into a compartment of "uninfected individuals". Below are the limits as $N \to \infty$ of the proportions of uninfected and infected individuals, where $\eta^0 = \sup\{t, \lambda_0(t) > 0\}$, $\eta = \sup\{t, \lambda(t) > 0\}$, $F_0^c(t) = \mathbb{P}(\eta^0 > t)$, $F^c(t) = \mathbb{P}(\eta > t)$,

$$\overline{U}(t) = \mathbb{E}\left[1_{t \geq \eta_0} \exp\left(-\int_0^t \gamma_0(r)\bar{\mathfrak{F}}(r)dr\right)\right] + \int_0^t \mathbb{E}\left[1_{t-s \geq \eta} \exp\left(-\int_s^t \gamma(r-s)\bar{\mathfrak{F}}(r)dr\right)\right]\overline{\mathfrak{S}}(s)\overline{\mathfrak{F}}(s)ds,$$

$$\overline{I}(t) = \overline{I}(0)F_0^c(t) + \int_0^t F^c(t-s)\overline{\mathfrak{S}}(s)\overline{\mathfrak{F}}(s)ds\,.$$

- Only the mean of $\lambda(t)$ (and of $\lambda^0(t)$) appears in the above system of equations, while a complicated moment / exponential moment of the random functions $\gamma(t)$ (and $\gamma^0(t)$) appears in the system.

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Limiting equation : existence and uniqueness

- The above Theorem says that $(\overline{\mathfrak{S}}(t), \overline{\mathfrak{F}}(t))$ solves

$$x(t) = \mathbb{E}\left[\gamma^0(t)\exp\left(-\int_0^t \gamma^0(r)y(r)dr\right)\right] + \int_0^t \mathbb{E}\left[\gamma(t-s)\exp\left(-\int_s^t \gamma(r-s)y(r)dr\right)\right] x(s)y(s)ds,$$

$$y(t) = \overline{I}(0)\overline{\lambda}^0(t) + \int_0^t \overline{\lambda}(t-s)x(s)y(s)ds\,.$$

- It is easy to show that if (x, y) solves that equation, then $\forall t \geq 0$,

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- From this we deduce that $x(t) \leq 1$, $y(t) \leq \lambda^*$, and existence and uniqueness of the solution.

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The equation for $A_k(t)$

- Recall that for $1 \le k \le N$, let $A_k^N(t)$ denotes the number of (re)infections of individual k on $(0, t]$, and

$$\zeta_k^N(t) = t - (\sup\{s \in (0,t], A_k^N(s) = A_k^N(s^-) + 1\} \vee 1)$$

- Given $\{Q_k,\ 1 \le k \le N\}$ i.i.d. standard PRM on $\mathbb{R}_+^2$, for each k,

$$A_k^N(t) = \int_0^t \int_0^\infty 1_{u \le \Upsilon_k^N(s^-)} Q_k(ds, du), \text{ where}$$
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The difference between $A_k^N(t)$ and $A_k(t)$

- The above equation has a unique solution.
- Analogously to the SIR case, we show that

$$\mathbb{E}\left[\sup_{0\le t\le T}|A_k^N(t)-A_k(t)|\right]\le C_T N^{-1/2},$$

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- Recall that

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- As a consequence of the LLN, those quantities converge a.s. in D towards $(\mathbb{E}[\gamma_{A(t)}(\zeta(t))], \mathbb{E}[\lambda_{A(t)}(\zeta(t))])$.
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Characterization of $(\bar{\mathfrak{S}}(t), \bar{\mathfrak{F}}(t))$

- Recall that $(\bar{\mathfrak{S}}(t), \bar{\mathfrak{F}}(t))$ is characterized as the unique solution of

$$x(t) = \mathbb{E}\left[\gamma^0(t)\exp\left(-\int_0^t \gamma^0(r)y(r)dr\right)\right] + \int_0^t \mathbb{E}\left[\gamma(t-s)\exp\left(-\int_s^t \gamma(r-s)y(r)dr\right)\right]x(s)y(s)ds,$$

$$y(t) = \bar{I}(0)\bar{\lambda}^0(t) + \int_0^t \bar{\lambda}(t-s)x(s)y(s)ds\,.$$

- Hence what we have to show is that $(\mathbb{E}[\gamma_{A(t)}(\zeta(t))], \mathbb{E}[\lambda_{A(t)}(\zeta(t))])$ solves the above system of equations.

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y(t) &= \overline{I}(0)\overline{\lambda}^0(t) + \int_0^t \overline{\lambda}(t-s)x(s)y(s)ds\,.
\end{aligned}
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- Hence what we have to show is that $(\mathbb{E}[\gamma_{A(t)}(\zeta(t))], \mathbb{E}[\lambda_{A(t)}(\zeta(t))])$ solves the above system of equations.

Proof of $(\mathbb{E}[\gamma_{A(t)}(\zeta(t))], \mathbb{E}[\lambda_{A(t)}(\zeta(t))]) = (\bar{\mathfrak{S}}(t), \bar{\mathfrak{F}}(t))$

- We start with $\mathbb{E}[\gamma_{A(t)}(\zeta(t))]$.

$$\gamma_{A(t)}(\zeta(t)) = \gamma_0(t)1_{A(t)=0} + \sum_{i\ge 1}\gamma_i(t-\tau_i)1_{A(t)=i}$$

$$\begin{aligned}\mathbb{E}[\gamma_0(t)1_{A(t)=0}] &= \mathbb{E}[\gamma_0(t)\mathbb{P}(A(t)=0|\gamma_0)] \\ &= \mathbb{E}\left[\gamma_0(t)\exp\left(-\int_0^t \gamma_0(r)\bar{\mathfrak{F}}(r)dr\right)\right]\end{aligned}$$

- Let $\mathcal{F}_t = \sigma\{(\lambda_i,\gamma_i)_{i\le A(t)}, Q|_{[0,t]\times\mathbb{R}_+}\}$. $Q|_{(\tau_i,t]\times\mathbb{R}_+}$ and $\mathcal{F}_{\tau_i}$ are independent. Hence $\mathbb{P}(A(t)=i|\mathcal{F}_{\tau_i}) = \exp\left(-\int_{\tau_i}^t \gamma_i(r-\tau_i)\bar{\mathfrak{F}}(r)dr\right)$

$$\begin{aligned}\mathbb{E}\sum_{i\ge 1}\gamma_i(t-\tau_i)1_{A(t)=i} &= \sum_{i\ge 1}\mathbb{E}\left[\gamma(t-\tau_i)\exp\left(-\int_{\tau_i}^t \gamma(r-\tau_i)\bar{\mathfrak{F}}(r)dr\right)\right] \\ &= \mathbb{E}\int_0^t \gamma(t-s)\exp\left(-\int_s^t \gamma(r-s)\bar{\mathfrak{F}}(r)dr\right)dA(s)\end{aligned}$$

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- Next

$$\mathbb{E}\int_0^t \mathbb{E}\left[\gamma(t-s)\exp\left(-\int_s^t \gamma(r-s)\bar{\mathfrak{F}}(r)dr\right)\right]dA(s)$$
$$= \mathbb{E}\int_0^t \gamma(t-s)\exp\left(-\int_s^t \gamma(r-s)\bar{\mathfrak{F}}(r)dr\right)\mathbb{E}[\gamma_{A(s)}(\zeta(s)]\bar{\mathfrak{F}}(s)ds$$

- Combining with the result for the first term, we have proved that

$$\mathbb{E}[\gamma_{A(t)}(\zeta(t)] = \mathbb{E}\left[\gamma_0(t)\exp\left(-\int_0^t \gamma_0(r)\bar{\mathfrak{F}}(r)dr\right)\right]$$
$$+\,\mathbb{E}\int_0^t \gamma(t-s)\exp\left(-\int_s^t \gamma(r-s)\bar{\mathfrak{F}}(r)dr\right)\mathbb{E}[\gamma_{A(s)}(\zeta(s)]\bar{\mathfrak{F}}(s)ds$$

This proves that $\mathbb{E}[\gamma_{A(t)}(\zeta(t)] = \bar{\mathfrak{S}}(t)$.

- Now

$$\lambda_{A(t)}(\zeta(t)) = \lambda_0(t)1_{A(t)=0} + \sum_{i\geq 1}\lambda_i(t-\tau_i)1_{A(t)=i}$$
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Proof of $\mathbb{E}[\lambda_{A(t)}(\zeta(t))] = \bar{\mathfrak{F}}(t)$

- We have

$$
\begin{aligned}
\mathbb{E}[\lambda_{A(t)}(\zeta(t))] &= \mathbb{E}[\lambda_0(t)] + \mathbb{E}[\sum_{i\geq 1} \lambda_i(t-\tau_i)] \\
&= \mathbb{E}[\lambda_0(t)|\eta_0 > 0]\mathbb{P}(\eta_0 > 0) + \mathbb{E}[\lambda_0(t)|\eta_0 = 0]\mathbb{P}(\eta_0 = 0) \\
&\quad + \mathbb{E}[\sum_{i\geq 1} \lambda(t-\tau_i)] \\
&= \bar{\lambda}_0(t)\bar{I}(0) + \mathbb{E}\int_0^t \bar{\lambda}(t-s)dA(s) \\
&= \bar{\lambda}_0(t)\bar{I}(0) + \int_0^t \bar{\lambda}(t-s)\mathbb{E}[\gamma_{A(s)}(\zeta(s)]\bar{\mathfrak{F}}(s)ds \\
&= \bar{\lambda}_0(t)\bar{I}(0) + \int_0^t \bar{\lambda}(t-s)\bar{\mathfrak{S}}(s)\bar{\mathfrak{F}}(s)ds
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&= \mathbb{E}[\lambda_0(t)|\eta_0>0]\mathbb{P}(\eta_0>0) + \mathbb{E}[\lambda_0(t)|\eta_0=0]\mathbb{P}(\eta_0=0) \\
&\quad + \mathbb{E}[\sum_{i\geq 1}\lambda(t-\tau_i)] \\
&= \bar{\lambda}_0(t)\bar{I}(0) + \mathbb{E}\int_0^t \bar{\lambda}(t-s)dA(s) \\
&= \bar{\lambda}_0(t)\bar{I}(0) + \int_0^t \bar{\lambda}(t-s)\mathbb{E}[\gamma_{A(s)}(\zeta(s)]\bar{\mathfrak{F}}(s)ds \\
&= \bar{\lambda}_0(t)\bar{I}(0) + \int_0^t \bar{\lambda}(t-s)\bar{\mathfrak{S}}(s)\bar{\mathfrak{F}}(s)ds
\end{aligned}$$

- Hence $\mathbb{E}[\lambda_{A(t)}(\zeta(t))] = \bar{\mathfrak{F}}(t)$.

Comparison with the Markovian SIRS model

- Let $\gamma_* = \lim_{t\to\infty} \gamma(t)$. If $R_0 > \mathbb{E}[1/\gamma_*]$, under then we have unique endemic equilibrium, and we can compute the force of infectivity at equilibrium.
- If we compare that level of infectivity in the population with the one in a Markovian model with abrupt loss of immunity, and the same integrated mean immunity, we see that it is higher in the waning immunity model.
- This was first established numerically, in the case of a Markovian model, with a loss of immunity by jumps, by Britton and Khalifi.

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