

# Recent results on Epidemic Models

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joint work with R. Forien (INRAE), G. Pang (Rice Univ. USA), A.B. Zotsa (AMU)

“A Random Walk in the Land of Stochastic Analysis and Numerical  
Probability”

CIRM Conference in honor of D. Talay

# Kermack and McKendrick, two pioneers

- In 1927, W.O. Kermack and A.G. McKendrick published a paper which proposes a SIR model of propagation of epidemic diseases with an infection–age dependent infectivity and an infection–age dependent recovery rate. In that paper, they treated also the special case of constant infectivity and constant recovery rate.
- That paper was quoted almost 11 000 times, but almost all successors of these pioneers considered only the model with constant rate, which is the following ODE model.

$$\begin{aligned}\frac{dS}{dt}(t) &= -\lambda S(t)I(t), \\ \frac{dI}{dt}(t) &= \lambda S(t)I(t) - \rho I(t), \\ \frac{dR}{dt}(t) &= \rho I(t).\end{aligned}$$

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# Constant vs. non-constant recovery rate

Let  $\mathcal{I}$  denote the length of the infectious period of a typical individual.

- $\mathbb{P}(\mathcal{I} > t) = \exp(-\mu t)$ ,  $t > 0$ , means that  $\mathcal{I}$  follows the exponential distribution with parameter  $\mu$ .
- Let  $t \mapsto \mu(t)$  be measurable from  $\mathbb{R}_+$  into itself, s.t.  $\int_0^\infty \mu(t) dt = +\infty$ . Assume

$$(*) \quad \mathbb{P}(\mathcal{I} > t) = \exp \left( - \int_0^t \mu(s) ds \right), \quad t > 0.$$

It is easy to deduce that  $\mathcal{I}$  has the density

$$f(t) = \mu(t) \exp \left( - \int_0^t \mu(s) ds \right).$$

- Conversely, given a probability density  $f$  on  $\mathbb{R}_+$ , define its hazard function as  $\mu(t) := \left( \int_t^\infty f(s) ds \right)^{-1} f(t)$ , then we have  $(*)$ .
- Assuming that the individuals recover at an infection-age dependent rate allows to choose an arbitrary distribution with density for  $\mathcal{I}$ .

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# Interlude : Poisson process and PRM

- If  $P(t)$  is a standard Poisson process, then  $P(\lambda t)$  is a rate  $\lambda$  Poisson process, and  $P(\int_0^t \lambda(s) ds)$  is a rate  $\lambda(t)$  Poisson process.
- If  $Q$  is a standard PRM on  $\mathbb{R}_+^2$ , i.e.  $Q$  is a sum of Dirac measures at random points, the numbers of points in disjoint subsets are mutually independent, and the number of points in  $A$  follows the  $\text{Poi}(\text{Leb}(A))$  distribution, then

$$\int_0^t \int_0^\infty 1_{u \leq \lambda(s)} Q(ds, du)$$

is a rate  $\lambda(t)$  Poisson process.

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# ODE model as LLN limit of Markov stochastic models 1

- For all  $t \geq 0$ ,  $S^N(t) + I^N(t) + R^N(t) = N$ .
- Suppose that each infectious individual meets others at rate  $\beta$ . With probability the proportion of susceptibles in the population, i.e.  $S^N(t)/N$ , the individual who is met is susceptible, in which case the encounter results in a new infection with probability  $p$ . Let  $\lambda := \beta p$ . Assume that the durations of the infectious periods of the various individuals are i.i.d., with the law  $\text{Exp}(\mu)$ .
- Then (with  $P_{inf}$  and  $P_{rec}$  two independent standard Poisson proc.)

$$S^N(t) = S^N(0) - P_{inf} \left( \lambda \int_0^t N^{-1} S^N(s) I^N(s) ds \right),$$

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- Let  $(\bar{S}^N(t), \bar{I}^N(t), \bar{R}^N(t)) = N^{-1}(S^N(t), I^N(t), R^N(t))$ .
- It follows from the LLN for Poisson processes that  $(\bar{S}^N(t), \bar{I}^N(t), \bar{R}^N(t)) \rightarrow (\bar{S}(t), \bar{I}(t), \bar{R}(t))$ , where

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# SIR model with memory as LLN limit of non-Markov stochastic models

- Let us go back to the general model of Kermack–McKendrick, first with a fixed infectivity  $\lambda$ , during an infectious period of length  $\mathcal{I}$ , where  $P(\mathcal{I} \leq t) = F(t)$ . The infection age recovery rate is the hazard function of  $\mathcal{I}$ , i.e.  $\mu(t) := f(t)/F^c(t)$ , if  $f$  is the density of  $F$ , and  $F^c(t) := 1 - F(t)$ , i.e.  $\mathbb{P}(\mathcal{I} > t) = \exp(-\int_0^t \mu(s)ds)$ .
- Then the stochastic model is non Markov, unless if  $F$  is an exponential distribution (i.e.  $\mu$  is constant).
- $(\bar{S}^N(t), \bar{I}^N(t), \bar{R}^N(t)) \rightarrow (\bar{S}(t), \bar{I}(t), \bar{R}(t))$  as  $N \rightarrow \infty$ , where

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# Central limit theorem

Define  $\hat{S}^N := \sqrt{N}(\bar{S}^N - \bar{S})$ , and similarly for  $\hat{I}^N$ ,  $\hat{R}^N$ . If those converge at time 0, then we have

## Theorem

As  $N \rightarrow \infty$ ,

$$(\hat{S}^N, \hat{I}^N, \hat{R}^N) \Rightarrow (\hat{S}, \hat{I}, \hat{R}) \text{ in } D^3,$$

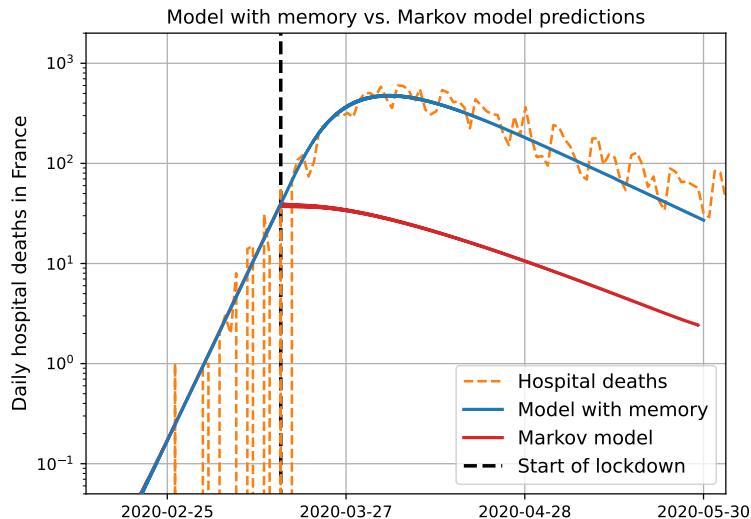
where the limit  $(\hat{S}, \hat{I}, \hat{R})$  is the unique solution to the following set of stochastic Volterra integral equations driven by Gaussian processes :

$$\hat{S}(t) = -\hat{I}(0) - \lambda \int_0^t \left( \hat{S}(s)\bar{I}(s) + \bar{S}(s)\hat{I}(s) \right) ds - \hat{M}_A(t),$$

$$\hat{I}(t) = \hat{I}(0)F_0^c(t) + \hat{I}_0(t) + \hat{I}_1(t) + \lambda \int_0^t F^c(t-s) \left( \hat{S}(s)\bar{I}(s) + \bar{S}(s)\hat{I}(s) \right) ds,$$

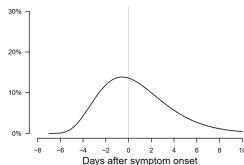
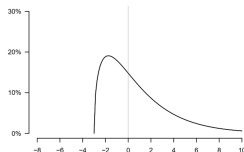
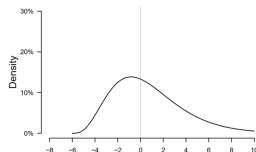
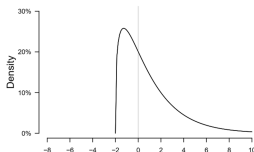
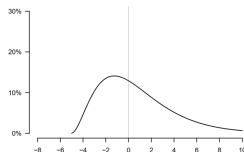
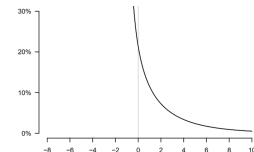
$$\hat{R}(t) = \hat{I}(0)F_0(t) + \hat{R}_0(t) + \hat{R}_1(t) + \lambda \int_0^t F(t-s) \left( \hat{S}(s)\bar{I}(s) + \bar{S}(s)\hat{I}(s) \right) ds.$$

# Model with constant vs. infection age dependent recovery rate for the Covid



## NATURE MEDICINE

## BRIEF COMMUNICATION



# Varying infectivity

- Let  $\{\lambda(t), t \geq 0\}$  be a random function with  $\geq 0$  values. If
$$\mathcal{E} = \inf\{t > 0, \lambda(t) > 0\} \quad \mathcal{I} = \inf\{t > 0, \lambda(\mathcal{E} + t + r) = 0, \forall r > 0\}.$$

Then  $\mathcal{E}$  is the exposed period,  $\mathcal{I}$  the infectious period.

We assume that to each individual is attached a copy  $\lambda_i(t)$ , where the  $\lambda_i$  are i.i.d. To the initially infected individuals are attached copies  $\lambda_j^0(t)$  of another type of infectivity function.

- We request that  $\lambda$  belongs a.s. to the Skorohod space  $D$ , and that  $\sup_{t \geq 0} \lambda(t) \leq \lambda^*$ , where  $\lambda^*$  is a given constant. Then one can establish a law of large numbers as  $N \rightarrow \infty$  of the corresponding individual based model. Define the total force of infection

$$\mathfrak{F}^N(t) = \sum_{j=1}^{I^N(0)} \lambda_j^0(t) + \sum_{i=1}^{A^N(t)} \lambda_i(t - \tau_i^N) = \lambda \times \# \text{ of infectious indiv.}$$

$$A^N(t) = \sum_{i \geq 1} 1_{(0, t]}(\tau_i^N) \text{ counts the number of indiv. infected on } (0, t].$$

# Varying infectivity

- Let  $\{\lambda(t), t \geq 0\}$  be a random function with  $\geq 0$  values. If  $\mathcal{E} = \inf\{t > 0, \lambda(t) > 0\}$   $\mathcal{I} = \inf\{t > 0, \lambda(\mathcal{E} + t + r) = 0, \forall r > 0\}$ . Then  $\mathcal{E}$  is the exposed period,  $\mathcal{I}$  the infectious period. We assume that to each individual is attached a copy  $\lambda_i(t)$ , where the  $\lambda_i$  are i.i.d. To the initially infected individuals are attached copies  $\lambda_j^0(t)$  of another type of infectivity function.
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# Varying infectivity : the LLN

- Let  $S^N(t), I^N(t), R^N(t)$  denote resp. the number of susceptible, infected and recovered indiv. in the population.  
 $S^N(t) + I^N(t) + R^N(t) = N$ . Let  $\bar{S}^N = N^{-1}S^N$ , same with  $I$  and  $R$ .
- $(\bar{S}^N(t), \bar{\mathfrak{S}}^N(t), \bar{I}^N(t), \bar{R}^N(t)) \rightarrow (\bar{S}(t), \bar{\mathfrak{S}}(t), \bar{I}(t), \bar{R}(t))$  as  $N \rightarrow \infty$ ,  
where, with  $\bar{\lambda}(t) = \mathbb{E}[\lambda(t)]$ ,  $\bar{\lambda}^0(t) = \mathbb{E}[\lambda^0(t)]$ ,  $F = \text{d.f. of } \mathcal{E} + \mathcal{I}$ ,

$$\bar{S}(t) = \bar{S}(0) - \int_0^t \bar{S}(s) \bar{\mathfrak{S}}(s) ds,$$

$$\bar{\mathfrak{S}}(t) = \bar{I}(0) \bar{\lambda}^0(t) + \int_0^t \bar{\lambda}(t-s) \bar{S}(s) \bar{\mathfrak{S}}(s) ds,$$

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

- Equivalent to the equations in the 1927 paper of Kermack - McKendrick. We also have a CLT (with more assumptions on  $\lambda$ ).

# Varying infectivity : the LLN

- Let  $S^N(t), I^N(t), R^N(t)$  denote resp. the number of susceptible, infected and recovered indiv. in the population.  
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- We note that this SDE is an SDE whose coefficients depend upon the law of the solution. Such an SDE is called a McKean–Vlasov equation. This type of equation appears in the theory of “propagation of chaos”, see A.S Sznitman’s celebrated St Flour lecture notes. This version of the LLN can be interpreted as a propagation of chaos type of result.

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## Alternative description : a PDE model

- Let us introduce the **age of infection** explicitly in our model. We define  $\mathfrak{I}^N(t, \alpha)$  as the number of infected individuals who have been infected for a duration  $\leq \alpha$ . Again  $\bar{\mathfrak{I}}^N(t, \alpha) := N^{-1}\mathfrak{I}^N(t, \alpha)$ . Then one can show that as  $N \rightarrow \infty$ ,  $\bar{\mathfrak{I}}^N(t, \alpha) \rightarrow \bar{\mathfrak{I}}(t, \alpha)$  in probability, locally uniformly in  $t$  and  $\alpha$ , and we have

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# Time of extinction of an epidemic

This is joint work with I. Drame and A. Mougabe-Peurkor.

- Suppose we are in a situation where, starting from  $t = t_0$ , an epidemic is declining (i.e. the mean number of susceptible individuals which an infected infects  $R_{eff} < 1$ ), while the total number of infected individuals is  $M \ll N$ , the size of the population. Then deterministic models are no longer valid, the epidemic is well approximated by a sub-critical branching process, which decays essentially like an exponential  $e^{-\rho(t-t_0)}$ .
- The approximating branching process associated to our varying infectivity model is a non-Markov continuous time branching process. We could derive an equation for the distribution function of the time of extinction, given that a unique infected individual got infected at time  $t_0$ .
- If we compare the time of extinction in our model with that of a Markov SIR model with the same  $R_{eff}$  and the same  $\rho$ , we see that the Markov model underestimates the time of extinction.



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- Let  $s_k(t)$  be the susceptibility of the  $k$ -th indiv. at time  $t$ . The total susceptibility is  $\mathfrak{S}^N(t) = \sum_{k=1}^N s_k(t)$ . If someone gets infected at time  $t$ , the probability that  $k$  is chosen equals  $(\mathfrak{S}^N(t))^{-1} s_k(t)$ .
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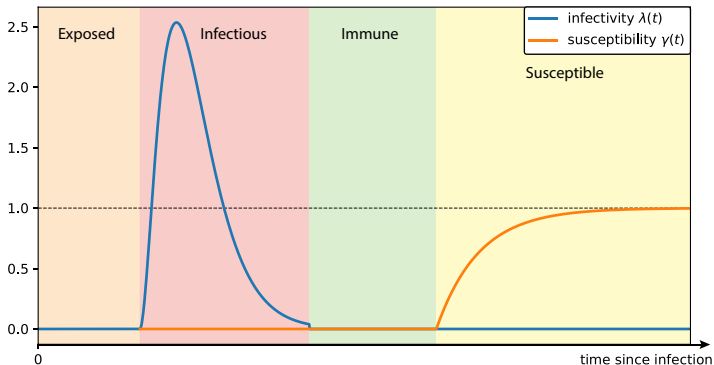
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# The functions $\lambda$ and $\gamma$



**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 + immunity/susceptibility 2

$$\mathfrak{S}^N(t) = \sum_{k=1}^N \gamma_k^0(t) 1_{t < \eta_k^{N,0}} + \sum_{i=1}^{A^N(t)} \gamma_i(t - \tau_i^N) 1_{t < \eta_i^N},$$

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where  $\eta_k^{N,0}$  is the time of (re)infection of the  $k$ -th individual, who is either initially susceptible (then  $\gamma_k^0(t) \equiv 1$ ), or initially infected (then  $\gamma_k^0(0) = 0$ ), and  $\eta_i^N$  is the time of reinfection of the  $i$ -th newly infected individual.  $Q$  is a standard PRM on  $\mathbb{R}_+^2$ ,  $\tau_i^N$ 's = jump times of  $A^N(t)$  i.e. the times of the “new” infections, those which happen after time 0.

# Varying infectivity + immunity/susceptibility 3

- Define  $(\bar{\mathfrak{S}}^N(t), \bar{\mathfrak{I}}^N(t)) = (N^{-1}\mathfrak{S}^N(t), N^{-1}\mathfrak{I}^N(t))$ .
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## Theorem

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

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- We combine the exposed and infectious individuals into unique compartment of “infected individuals”. Similarly, we put the Susceptible and Recovered individuals into a unique compartment of susceptible individuals, where the recovered have susceptibility 0. The limits as  $N \rightarrow \infty$  of the proportions of susceptible and infected individuals are given by the following formulas, where  $F$  (resp.  $F_0$ ) denote the d.f. of the duration of the infected period of newly infected individuals (resp. of initially infected individuals).

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# Comparison with the models of Kermack and McKendrick

- In case of the SIR model with infection–age infectivity and recovery rate, the LLN deterministic model we obtain is exactly the model which appears in the 1927 paper of Kermack and McKendrick. We start with i.i.d.  $\lambda_i(t)$ 's, and we obtain the Kermack and McKendrick model with  $\mathbb{E}[\lambda(t)]$ .
- In case of the SIRS model with infection age infectivity and recovery rate, and varying susceptibility, our model in general is quite different, since it involves not only the expectation of the random functions  $\gamma(t)$ . However, in case  $\gamma_i(t) = \rho(t - \xi_i)$ , where  $\xi_i$  is the time of recovery and  $\rho$  is a deterministic function (which is 0 on  $\mathbb{R}_-$ ), then our LLN deterministic model coincides with the model of the 1932 paper of Kermack and McKendrick.

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# The effect of waning immunity upon endemicity

- Britton and Khalifi have compared progressive loss of immunity to the unrealistic behavior which is assumed in almost all models, where individuals jump instantaneously from full immunity to full susceptibility.
- They show that, with the same mean susceptibility, progressive loss of immunity induces a more severe endemic situation, and requires a higher vaccination coverage to avoid an endemic situation.
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HAPPY BIRTHDAY  
DENIS !