Why differential equation based models fail to describe the dynamics of epidemics?

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Abstract

It is of vital importance to understand and track the dynamics of rapidly unfolding epidemics. The health and economic consequences of the current COVID-19 pandemic provide a poignant case. Here we demonstrate that a class of widely used models is fundamentally flawed and cannot account for some important features of the viral spread. We suggest an integral equation based method that can be implemented in most of the reported models. Taking the example of COVID-19 data for New York City, we show that our model yields a significantly larger estimate for the initial basic reproduction rate than other models, much more accurately accounts for the dynamics of the epidemic after restrictive public congregation measures were introduced, and provides a novel way to determine the incubation period. We suggest that no decisions about public health or economic measures should be based on any unimproved model.

Introduction

A commonly used approach to describe the dynamics of epidemics is based on SEIR-type (Susceptible-Exposed-Infectious-Recovered) differential equations [1–5]. Recently these methods have been applied to the COVID-19 pandemic to determine the basic reproduction number [6–11], the incubation period [12–14] and to describe the dynamics of the pandemic [15–22]. In this framework there is no natural and transparent way to account for the delay occurring due to the incubation period of the disease. Even after refinements to try to account for some aspects of this delay [15–17, 23], these models are still plagued by uncontrolled approximations. We suggest that models based on differential equations should not be used, they should be replaced with ones based on an integral equation, which provides a natural setting to implement the time delay. The approach we present is not new, it was already implicit in the original Kermack-McKendric theory proposed in 1927 [24]. Even though several variants of that

model with various degrees of precision circulate in the current literature [25–28], their superiority over the differential equation based method has not been widely recognized.

We emphasize that in the form presented below, the integral equation based approach is neither technically nor conceptually more complicated than the one based on differential equations. More importantly, it gives a much more realistic representation of the epidemic dynamics. We demonstrate this by comparing how the two types of approach describe the New York City data [29], taken from the currently ongoing COVID-19 pandemic. Firstly, we show that even in the initial simple exponential phase of the epidemic, the correct, integral equation based model can give a vastly larger estimate for R_0, the basic reproduction rate. Secondly, we show that the oscillations in the graph of the number of newly infected people after restrictive public interaction measures were introduced, is well described by the integral equation model. This is a generic feature of COVID-19 data, seen in several countries, and there is no simple way the differential equation based models could explain it.

Our comparison here is based on a simple SEIR-type differential equation model and its integral equation counterpart containing the same variables, but a different time evolution. It can be seen from our general discussion that the differences we find are generic features of the two types of models and carry over to more sophisticated versions of these models. We cannot take on the task of performing a similar comparison for all the models currently accepted by the community, but we urge everyone to test how different their results are between the two approaches in the case of the particular models they use. Finally, based on our findings, we suggest that in the future, decisions about public health measures should be based solely on models relying on the integral equation approach, and the differential equation based approaches should be completely abandoned.

Integral equation description for discrete and continuous time evolution

The mathematical modeling of how infectious diseases spread is almost exclusively based on compartmental models. In this framework the population is divided into different categories and a dynamical model is set up to describe how the number of individuals in each category evolves with time. A simple model of this type is the so called SEIR model, in which the compartments are susceptible (not yet infected), exposed and infected (but not yet capable of infecting others), infectious, and recovered (not capable of infecting others any more). In its simplest form the model is characterized by three parameters, α, β, γ that determine the transition rates among different compartments through the following set of differential equations:

$$\frac{dS}{dt} = -\beta \frac{I}{N} S, \qquad \frac{dE}{dt} = \beta \frac{I}{N} S - \alpha E, \qquad \frac{dI}{dt} = \alpha E - \gamma I, \qquad \frac{dR}{dt} = \gamma I, \tag{1}$$

where $S(t), E(t), I(t)$ and $R(t)$ are the number of susceptible, exposed, infectious and recovered individuals, all functions of the time, and $N = S + E + I + R$ is the total population.

In the initial phase of a rapidly developing epidemic, the situation we are concerned with here, $S/N \approx 1$, which we will assume. The generalization to include S as a dynamical parameter, to consider births and deaths or other parameters is straightforward. With this approximation the two functions describing the dynamics are $E(t)$ and $I(t)$. At this point it is instructive to introduce t_e and and t_i, the average

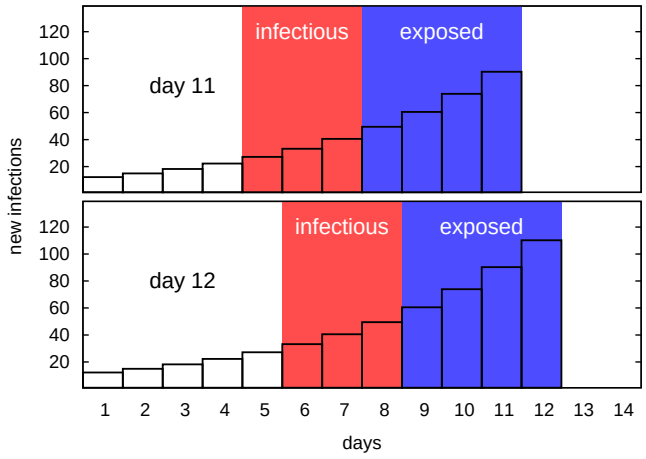

Figure 1: The number of new infections per day, shown up to the eleventh (top) and the twelfth day (bottom) of the epidemic. The blue area represents those that are infected, but not yet infectious, i.e. people who were exposed between today and $t_e = 4$ days ago. The red area represents those that are infectious, i.e. people who were exposed more than t_e days ago, but not more than $t_e + t_i = 7$ days ago. In the SEIR model the number of people who cease to be infectious from day 11 to day 12 is equal to the daily average of the red area in the top panel. In reality, however, only people in the leftmost red histogram, here a much smaller number, cease to be infectious. Similarly, in the SEIR model the number of people who become infectious is the daily average of the blue area, when in reality it is only people in the leftmost bar of the blue area who become infectious from day 11 to day 12. Clearly the only case when the SEIR model correctly represents the situation is when the number of newly infected people per day is constant in time.

days an individual spends in the categories E and I respectively. It is convenient to write the equations in terms of these parameters and the basic reproduction rate, R_0, using the simple relations $\alpha = 1/t_e$, $\beta = R_0/t_i$ and $\gamma = 1/t_i$.

With these new parameters the simplified form of the differential equations valid for the initial stage when $S/N \approx 1$ is

$$\frac{d}{dt}\begin{pmatrix} E \\ I \end{pmatrix} = \begin{pmatrix} -1/t_e & R_0/t_i \\ 1/t_e & -1/t_i \end{pmatrix} \begin{pmatrix} E \\ I \end{pmatrix}. \tag{2}$$

There is, however, a fundamentally wrong assumption underlying Eq. (2). Let us assume that for every day t in the past we know how many individuals became infected on that day, and denote their number with $\rho(t)$. This can be depicted in a histogram with time flowing from left to right along the horizontal axis (Fig. 1). Based on this information we would like to estimate $\rho(t+1)$, the number of individuals becoming infected on the following day. For the sake of simplicity let us assume that anyone exposed to the infection will become infected, but will not be infectious for t_e days. Such a person will become infectious t_e days after exposure and will remain in this category for an additional t_i days, after which he is isolated and ceases to be capable of infecting others. In the simplest version of the model t_e and t_i can represent averages, but later on we will indicate how to generalize the model by using continuous distributions. In Fig. 1 the blue area represents those in category E, with $t_e = 4$, and the red area those in I, with $t_i = 3$. Now, exactly as in the SEIR model, described above, the number of newly

infected on the following day, day 12 in the figure, will be

$$\rho(t+1) = \beta \sum_{\tau=t-t_i-t_e}^{t-t_e-1} \rho(\tau), \qquad \beta = \frac{R_0}{t_i} \tag{3}$$

where the sum is the total number of infectious individuals at time t, i.e. the red area in the top panel of Fig. 1. At this point we can depict the situation at time $t+1$ simply by shifting both the blue and the red region, showing the people in category E and I, one day forward to the right (bottom panel of Fig. 1). From this point on the same procedure can be further iterated day by day: on each day we calculate the number of newly infected for the following day and shift the windows delineating the exposed and the infectious by one day forward.

Let us now see how the number of exposed and infectious people evolve in time according to the SEIR model of Eq. (2). In the SEIR model the rates at which individuals flow out of the pools E and I are proportional to the number of people in the respective pools (see the explanation below Fig. 1). In reality, however, the number of people entering (leaving) the I and E pool is represented by the rightmost (leftmost) histogram bars of the respective red and blue regions. In a rapidly changing situation the SEIR model gives a very bad description of reality.

At this point the objection could be raised that we have been comparing the continuous SEIR model with a discretized model. However, the framework presented in the histograms can be easily generalized from days to arbitrarily fine time steps. In the limit of infinitely fine time steps dt, we can choose the height of the histogram bars $\rho(t)$ such that $\rho(t)dt$ be the number of people becoming infected in the time interval $[t, t+dt]$. In this case the sum in the right hand side of Eq. (3) becomes an integral and the equation can be rewritten as

$$\rho(t) = \beta \int_{t-t_i-t_e}^{t-t_e} \rho(\tau)\, d\tau, \qquad \beta = \frac{R_0}{t_i}. \tag{4}$$

We emphasize that only this continuous version of the model describes the real situation properly.

Determination of R_0, the example of New York City

We illustrate the failure of the SEIR model in two examples. First let us consider the case of constant $R_0 > 1$ which leads to the exponentially growing solution with exponent λ, i.e. all relevant quantities ($E(t), I(t)$ of SEIR and $\rho(t)$ of the integral equation) are proportional to $\exp(\lambda t)$. A simple substitution gives:

$$R_0^{(\text{SEIR})} = 1 + \lambda(t_e + t_i) + \lambda^2 \cdot t_e t_i \qquad \text{and} \qquad R_0^{(\text{integral})} = \frac{t_i \lambda}{e^{-\lambda t_e} - e^{-\lambda(t_e+t_i)}} \tag{5}$$

Solving the discretized equation (3) with time step Δt leads to $R_0^{(\text{discretized})} = (e^{\lambda \Delta t} - 1)/(\lambda \Delta t) \cdot R_0^{(\text{integral})}$. Figure 2 shows these three R_0 (SEIR, integral equation, discretized integral equation) using realistic parameters that describe the initial phase of the pandemic in New York City. There is a striking difference between the SEIR and integral equation predictions. While the SEIR result is largely insensitive to the split of the total incubation period into t_e and t_i, this is not the case for the solution of the integral equation. The true value of R_0 can be 3-4 times larger than the one predicted by the SEIR model. For $t_i \approx 2$ days which, as we will later see, provides a reasonable description of the daily reported cases, R_0

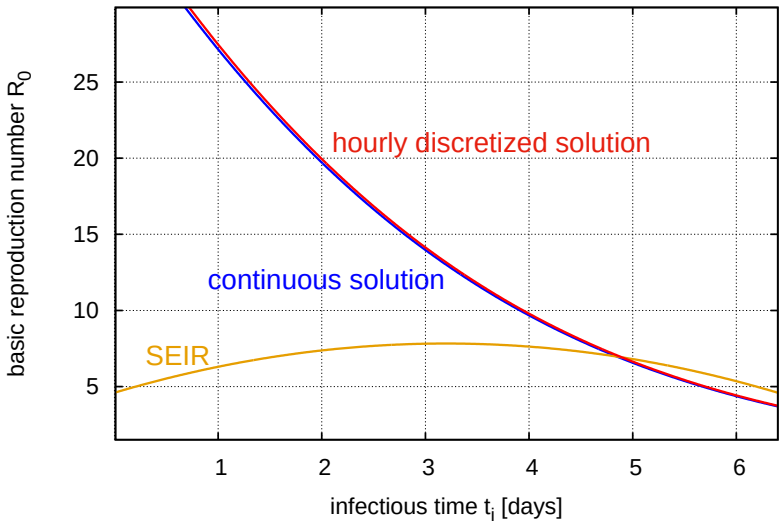

Figure 2: R_0 as a function of t_i, the infectious part of the incubation period. The total incubation period is taken to be $t_e + t_i$=6.4 days [13] and the exponential growth parameter is $1/\lambda = 1.78$ days which describe the growing phase of the New York City data [29] well. The orange color curve with the maximum shows the prediction based on the SEIR model of eq. (2). The blue and red lines correspond to the solution of the integral equation (4) and its discretized version (3) with an hourly time step, respectively. Their agreement indicate that such a discretization is sufficient. A daily discretization would give 34% higher R_0 values.

can be as high as 20. R_0 is, of course region dependent. Less populated areas can have much smaller R_0 values.

One might think that this difference is only due to the relatively large incubation period (as compared to the characteristic growth time of the pandemic) and the SEIR model gives reliable estimates for small incubation periods. Surprisingly this is not the case. A trivial expansion of $R_0^{(\text{integral})}$ in λt_e and λt_i yields $R_0^{(\text{integral})} \approx 1 + \lambda(t_e + t_i/2) + \lambda^2(t_e^2/2 + t_e t_i/2 + t_i^2/12) + \mathcal{O}(\lambda^3)$ which is clearly different from the SEIR result.

The precise determination of R_0 for the initial phase of the pandemic in New York City is beyond the scope of this paper but the message is clear: *no determination of R_0 should be based on differential equation based models such as SEIR.*

The effect of decreasing R_0, delay and oscillation

The parameter R_0 in both the SEIR- and the integral equations is in general time dependent. The most important goal of the first restrictive measures was to decrease the value of R_0 as fast as possible and bring it below the critical value of 1. In the following we study how the different models react to a sudden decrease of R_0 and compare them qualitatively to the daily reported new cases in New York City [29]. To simplify our discussion we will assume that all cases are reported exactly after the incubation period, i.e.

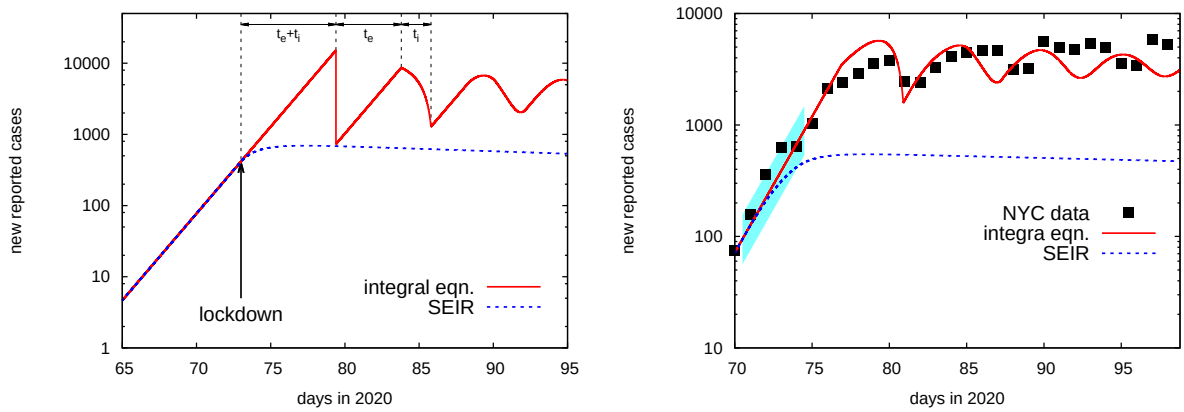

Figure 3: *Left:* time evolution of new reported cases after a lockdown on day 73 in the case of the SEIR and integral equation models. For the initial phase of the pandemic $1/\lambda = 1.78$ days, $t_e = 4.4$ days and t_i=2 days was used. This corresponds to $R_0^{\rm SEIR} = 7.37$ and $R_0^{\rm integral} = 19.7$. The value of R_0 was instantaneously decreased to 0.95 in both cases on day 73. The difference between the two models is quite dramatic. The SEIR solution reacts immediately and turns smoothly to a decreasing exponential function. The solution of the integral equation is qualitatively different. There is a delay of $t_e + t_i$ after which the effect of the lockdown becomes visible, then an oscillation follows. The characteristic scales of this oscillation are indicated in the figure. *Right:* time evolution of the new reported cases after a gradual lockdown from day 71 to day 74 confronted with the data of New York City. The initial parameters are the same as for the left panel. R_0 is now decreased to 0.95 linearly in time during this four day period in both models. The main features of the curves are similar to the left panel but the amplitude of the oscillation is reduced, making it similar to the real data. Note that we did not fit our model to the data. This plot is an illustration that the main features (delay and oscillation) of the data are well captured by the integral equation and neither of these is reproduced by SEIR.

$t_e + t_i$ time after first exposure. In the case of the SEIR model the rate of people leaving the incubation phase is $dR/dt = \gamma I$ while in the case of the integral equation it is $\rho(t - t_e - t_i)$. These two functions will be referred to as "reported new cases" in the following. If we assume that the majority of cases are reported when symptoms emerge, it follows that any change in the parameters will only show up $t_e + t_i$ days later in the data. Any reasonable model should be able to naturally account for this delay. Quantities in differential equations react immediately to any change of the parameters, thus no differential equation based model (such as SEIR or its simple extensions) is expected to explain such a delay. The integral equation (4), on the other hand, naturally provides a delay.

The simplest possibility is to assume that R_0 decreases instantaneously after a successful lockdown. The left panel of Figure 3 shows how the reported new cases evolve after a lockdown happens on March 13 (day 73 of 2020) which reduces R_0 to 0.95. A more realistic situation is shown in the right panel of Figure 3. Here the value of R_0 was gradually decreased from March 11 to March 14. In both cases it is clear that the expected delay, which is clearly visible in the data, is only explained by the integral equation. The reported data of many countries show an interesting oscillation after the effect of a lockdown starts to show up. This feature is also naturally described by the integral equation.

One remark is in order. The incubation period of 6.4 days is accidentaly very close to the weakly

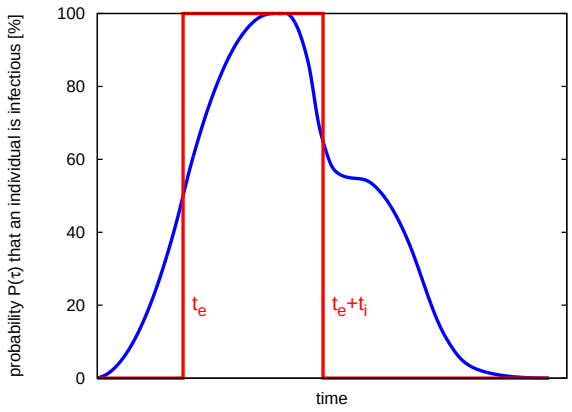

Figure 4: Two possible choices for the $P(\tau)$ probability at which an individual is infectious τ time after exposure. The red curve corresponds to fix t_e and t_i. The blue curve shows a more realistic scenario. The small plateau or even a second peak at larger times may correspond to people who are symptom free and are therefore infectious for a longer period, possibly until they naturally recover.

cycle of 7 days. Thus, the oscillation might in principle be just a weekend effect. Looking at the weekend during the strongly exponential growth with enough statistics (March 14, Saturday to March 16, Monday) one observes less cases during Saturday and Sunday and an accordingly higher number of cases on Monday than the average exponential growth would predict. Correcting the data for this effect later would weaken but not eliminate the observed oscillation, it seems to be a real effect. This is also supported by the fact that different countries have minima and maxima of their oscillation on different days (e.g. in Italy the minima are on Mondays and Tuesdays, in the Netherlands they are on Tuesdays). The main message, however, is again clear: *no differential equation based model should be used to predict the evolution of the pandemic.*

It is in principle possible to determine the incubation time t_e and t_i from this oscillatory pattern. Taking the distance of subsequent minima we determined $t_e + t_i$. Using data of New York City, Italy, Spain, Germany, and the Netherlands [29, 30] the period of the oscillations seems quite robust and is around $t_e + t_i = 7.4$ days on average with a spread of 0.2 days.

Once t_e and t_i are known, one can solve eqn (4) for $\beta(t)$ or equivalently $R_0(t)$ by taking $\rho(t)$ and the (numerical) integral from the actual data. In this way one can continuously monitor the effect of restrictive or easing measures.

Conclusions and Outlook

In the previous sections we illustrated the failure of the SEIR model in a simple approximation when both t_e and t_i are fixed. In reality the incubation period is described by a probability function $P(\tau)$ which gives the probability that a person is infectious a time τ after exposure. Figure 4 shows the probability function corresponding to fixed t_e and t_i and a sketch for a more general choice. The integral equation

(4) can easily be generalized to include P:

$$\rho(t) = \beta \int_0^\infty \rho(t-\tau)P(\tau)d\tau, \qquad R_0 = \beta \int_0^\infty P(\tau)d\tau. \tag{6}$$

In general, the transmission rate β also changes in time since new restrictive measures can be implemented. This can also be incorporated into the equation, however, in that case R_0 might not have a transparent interpretation. This equation has been around in the literature for a long time (see e.g. [25–27]) but unfortunately it has not yet been widely adopted. Any evolution computed using this equation is expected to have qualitatively similar features (delay and oscillation) as in the simple approximation presented above. The SEIR model is not a good approximation of this integral equation even if the $P(\tau)$ probability is built into its parameters.

For later stages of a pandemic when $S/N < 1$ the integral equation can be generalized to include S as well:

$$\rho(t) = \beta \frac{S(t)}{N} \int_0^\infty \rho(t-\tau)P(\tau)d\tau, \qquad S(t) = N - \int_{-\infty}^t \rho(\tau)d\tau. \tag{7}$$

Any further extension which can be included in the SEIR equations (e.g. birth and death rate, day/night differences, inhomogeneities, metapopulation systems, etc.) can also be naturally included in the integral equation formalism.

We demonstrated that the widely used differential equation based models of epidemiology, in particular the SEIR model, are fundamentally flawed. They may significantly underestimate R_0 and fail to reproduce the expected time delay in reported cases after a reduction of R_0. We suggest using the integral equation formalism instead, which has originally been developed almost 100 years ago. We presented a simple way to implement this equation in numerical simulations which is not more complicated than the numerical solution of the SEIR equations. Any further improvement should be based on the integral equation formalism and not on differential equations.

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