Epidemiological dynamics with fine temporal resolution

Yaroslav Ispolatov\textsuperscript{1,*}

\textsuperscript{1} Departamento de Física, Universidad de Santiago de Chile,
Casilla 302, Correo 2, Santiago, Chile

Abstract

To better predict the dynamics of spread of COVID-19 epidemics, it is important not only to investigate the network of local and long-range contagious contacts, but also to understand the temporal dynamics of infectiousness and detectable symptoms. Here we present a model of infection spread in a well-mixed group of individuals, which usually corresponds to a node in large-scale epidemiological networks. The model uses delay equations that take into account the duration of infection and is based on experimentally-derived time courses of viral load, virus shedding, severity and detectability of symptoms. We show that because of an early onset of infectiousness, which is reported to be synchronous or even precede the onset of detectable symptoms, the tracing and immediate testing of everyone who came in contact with the detected infected individual reduces the spread of epidemics, hospital load, and fatality rate. We hope that this more precise node dynamics could be incorporated into complex large-scale epidemiological models to improve the accuracy and credibility of predictions.

\*Electronic address: jaros007@gmail.com
I. INTRODUCTION

In less than 3 months the COVID-19 pandemics has brought the entire world to a halt. To an extend, such a rapid spread of infection is caused by its peculiar dynamics. According to the general paradigm of epidemiology, a severe or deadly disease usually does not spread too far as the infected individuals quickly become incapacitated or die, thus limiting the secondary infections. Apparently, such was the case of recent epidemics of SARS, MERS, and Ebola. Conversely, the diseases with less severe symptoms, such as common colds, spread wider as the symptoms do not limit the mobility and social contacts of the bearers. From what has already become known about the COVID-19, the infection exhibits both those attributes: At the early stages of infection, an already highly contagious bearer may still remains asymptomatic [1-4]. In addition, an infected and infectious individual may stay completely asymptomatic through the course of the disease. The complications that severely limit mobility and sometimes lead to death usually arrive in the second week after the onset of symptoms or even later ([5]). This fairly unusual disease dynamics necessitates more complex mitigation strategies and, thus, epidemiological models. For example, various lockdown criteria and schedules for imposing and exiting quarantine, such as cyclic lockdown-exit scenario proposed in [6], require accurate predictors of disease dynamics and contagiousness in both the symptomatic and asymptomatic parts of population, especially given the current lack of population-wide testing for active viruses and antibodies.

Here we propose an extension of the traditional SEIR epidemiological node dynamics that takes into account the actual time courses of viral load, detectable symptoms, and virus shedding. It serves to better quantify the processes of infection, possible quarantine, and recovery or death. To do so, we replace the continuous or discrete transition from Exposed to Infected, traditionally used in the epidemiological models, by keeping track of the progress of individual disease and expressing the probability of infection or detection as functions of the disease duration. This results in replacing the traditional SEIR ordinary differential equations by the delay differential equations similar to [7, 8]. The temporal changes in the infectiousness and severity of symptoms determine the number of secondary infection and serve as an indicator detectability of symptoms and subsequent restrictions in contacts. The time courses of infectiousness and severity of symptoms are taken directly from clinical data or approximated by functional fits to that data. The model confirms that a rapid tracing and testing the contacts, rather than reacting to the detectable symptoms, noticeably restricts the spread of the infection and makes quantitative predictions about level of
II. THE MODEL

We consider a single “node” of epidemiological models, which represents a well-mixed part of the global population and consists of Susceptible (S), Infected (I), Quarantined (Q), Recovered (R), and deceased (D) individuals. The susceptible individuals, whose concentration at time $t$ is denoted by $S(t)$, may pick up a disease from an infected individuals, whose infection could be either undetected or detected. The individuals with detected symptoms are considered quarantined, so the infectiousness of detected individuals is less than that of the undetected ones by factor $\chi < 1$. The concentrations of undetected and quarantined infected individuals are denoted as $I(\tau, t)$ and $Q(\tau, t)$, where the variable $\tau$, $0 \leq \tau \leq t$, is the time when the individual was infected. Quantitatively, the infection of susceptibles occurs at the rate

$$\frac{dS(t)}{dt} = -S(t)C_I \int_0^t \Gamma_I(t - \tau) [I(\tau, t) + \chi Q(\tau, t)] d\tau. \quad (1)$$

The empirically derived function $\Gamma_I(t - \tau)$, which depends on the duration of a particular infection $t - \tau$, is one of the key features of our model. It shows how contagious an individual is at a particular stage of infection. This information is based on clinical data (viral load measured via swabs and blood tests) and can be entered the form of a table or histogram (normally with daily bins [2, 5]) or a functional fit to the data, e.g. Gamma distributions used in [1, 2].

The gain in the number of undetected infected individuals, described by the first term in (2), comes from the new infections described above. The delta-function $\delta(t - \tau)$ indicates that the beginning of a new infection occurs at the current time $t$. The loss term describes the detection of infection and thus the conversion of detected individuals into the quarantined ones. It is assumed to be happening with the rate dependent on the severity of symptoms given by the function $\Gamma_S(t - \tau)$. This function is another key element of our model and is based on the empirical data of the temporal evolution of severity of symptoms, and most importantly, on the time of the onset of detectable symptoms. The epidemiological dynamics as well as the clinical data [1, 2, 9] indicate that the transmissivity of the infection may start before the symptoms onset, which means that the infection function $\Gamma_I(t - \tau)$ may start to increase and even reach its maximum earlier than the symptom function $\Gamma_S(t - \tau)$ does. Similarly to $\Gamma_I(t - \tau)$, the symptom function $\Gamma_S(t - \tau)$ can be tabulated based on clinical data or approximated by a fit to that data. The last term in Eq. (2)
describes resolution of a disease after a typical duration of $\tau^* \sim 20$ days, resulting in recovery or death of a patient.

$$\frac{\partial I(\tau, t)}{\partial t} = \delta(t - \tau) C_I S \int_0^t \Gamma_I(t - t') \times [I(\tau', t) + \chi Q(\tau', t)] \, dt' - I(\tau, t) [C_S \Gamma_S(t - \tau) + \delta(t - \tau - \tau^*)]$$

(2)

The concentration of quarantined individuals increases via the detection of so far undetected infected individuals and decreases on the $\tau^*$th day of the disease as individuals recover or die (3),

$$\frac{\partial Q(\tau, t)}{\partial t} = I(\tau, t) C_S \Gamma_S(t - \tau) - Q(\tau, t) \delta(t - \tau - \tau^*).$$

(3)

The approximation of a “sudden recovery” or a possible “sudden death” on the $\tau^*$th day of the disease does not affect the dynamics of infection as it has been observed that individuals destined either to recover or die lose infectiousness in about a week after the onset of symptoms, which is well in advance of $\tau^*$ [1–3]. The approximation does slightly affect the death and recovery running statistics but not the final number of recovered and dead by the end of epidemics. We assume that the quarantined individuals receive better care and have lower death rate than the undetected ones. This is reflected by the coefficient $\nu < 1$.

$$\frac{dD(t)}{dt} = C_D \delta(t - \tau - \tau^*) [I(\tau, t) + \nu Q(\tau, t)].$$

(4)

The individuals who do not die, recover (5),

$$\frac{dR(t)}{dt} = \delta(t - \tau - \tau^*) \{I(\tau, t) [1 - C_D] + Q(\tau, t) [1 - C_D \nu]\}.$$

(5)

The constants $C_I$ in (1), $C_S$ in (2), and $C_D$ in (4) are fitted to reproduce the empirical infection, detection of infection (quarantining), and death rates. As in [1, 3], we use Gamma distributions to fit the temporal evolution of infectiousness $\Gamma_I(t - \tau)$ and severity of symptoms $\Gamma_S(t - \tau)$,

$$\Gamma(y) = \frac{x^{k-1}}{(k-1)!} \theta^k \exp(-y/\theta), \langle y \rangle = k\theta.$$

(6)

We choose to set $k = 3$ to mimic that both the infectiousness and symptoms grow slower than linearly immediately after the infection and assign the values of scale parameters $\theta_I$ and $\theta_S$ in the range derived from epidemiological and clinical data in [1,9]. Specifically, the mean serial interval $\langle T_I \rangle$, defined as the duration between symptom onsets of successive cases in a transmission chain,
and the incubation period $\langle T_S \rangle$, defined as the time between infection and onset of symptoms, were reported in [1] as $\langle T_I \rangle = 5.8$ and $\langle T_S \rangle = 5.2$, and in [9] as $\langle T_I \rangle = 7.0$ and $\langle T_S \rangle = 4.8$. In the example below we use the average times from [1]. From the definition, the mean serial interval corresponds to the mean infectiousness time, so we find it natural to assume that $\theta_I = \langle T_I \rangle / 3 \approx 1.93$. The factor 3 appears because the mean of the 3-rd order ($k = 3$ in (6)) Gamma-distribution is triple the scaling parameter. The evaluation of $\theta_S$, the scale parameter in the distribution of severity of the symptoms, requires a different argument. We assume that the onset of symptoms is registered when their severity reaches its maximum, which for the 3-rd order Gamma distribution occurs at $y = 2\theta$. Hence, we assume that $\theta_S = \langle T_S \rangle / 2 \approx 2.6$.

III. RESULTS

In Fig. 1 we show an example of temporal dynamics of the model. The values of constants $C_I, C_S, C_R$ were chosen to reproduce the reported doubling period of infection at its early stages $\approx 5$ days and mortality $\approx 4\%$. Now we show how the timing of detection and quarantining affects the spread of infection and the eventual outcome of the epidemics. Keeping the rest of parameters the same, we vary the parameter $\theta_S$, which controls the time when the detectability rate is at its maximum. In Fig. 2 we show the fractions of dead, recovered, and remaining susceptible after the infection is over, that is, when the sufficient herd immunity is reached. These fractions in Fig. 2 correspond to the respective fractions at the final time ($t = 200$ days) in Fig. 1. Also similarly to Fig. 1 we show what fraction of infected individuals were detected as infected through the course of their disease, and what fraction of infections was never detected. It follows from Fig. 2 that the earlier detection reduces the death rate severalfold and almost doubles the number of never infected susceptible.

A quick detection of new infection is normally done through contact tracing and testing. We account for these measures by simply shifting the maximum of detectability of symptoms to earlier time, leaving the detection efficiency at the postulated sub-ideal level. Nevertheless, the beneficial epidemiological effect of even such sub-optimal early detection is clearly pronounced. Conversely, even a short delay in contact tracing or processing of the test results, corresponding to an increase in $\theta_S$, brings in more infections and higher fatality rate.
FIG. 1: Temporal dynamics of fractions of dead (black), recovered (red), undetected infected (green), detected infected (blue), and susceptible (orange) individuals for the following parameters: The infection rate coefficient $C_I = 2$, the coefficient in the rate of detection of infected $C_S = 0.5$, the death rate coefficient $C_R = 0.07$, the attenuation of death rate and infectiousness after the detection of the disease $\nu = 0.5$ and $\chi = 0.2$. The characteristic times of distribution of infectiousness $\theta_I = 1.93$ and symptom severity $\theta_S = 2.6$ were derived from the data presented in [1].

IV. CONCLUSION

In this note we suggest to improve the current epidemiological models by incorporating the history of infections into a single node dynamics. The resulting delay equations are only slightly more complex than the traditional SLIR ordinary differential equation models, yet they allow one to make precise and credible predictions of the effects of early detection and isolation of infected individuals, including pre-symptomatic ones, on the spread of infection. This is especially relevant to the current COVID-19 epidemics, where the infectiousness was shown to increase syn-
FIG. 2: The fraction of susceptible (black), recovered (red), never detected infected (green), detected infected (blue) and never infected susceptible (orange) individuals as the functions of the time of maximal detectability of infection (maximum of symptoms) \(\langle T_s \rangle = 3\theta_s\). The remaining parameters are the same as in Fig. 1.

chronously or even ahead of the visible onset of symptoms. We believe that this simple approach could fitted to the clinical data and the data from detailed epidemiological case studies, and then incorporated as the modified single node dynamics into large-scale network-based epidemiological models.
V. APPENDIX: SIMILARITY OF SLAIR MODEL AND DELAY EQUATION SOLUTIONS.

The standard Susceptible ($S(t)$), Latent ($L(t)$), Infected ($I(t)$), and Removed ($R(t)$) or “SLIR” model is usually formulated in terms of ordinary differential equations,

\[
\begin{align*}
\frac{dS}{dt} &= -\alpha SL \\
\frac{dL}{dt} &= \alpha SL - \beta L \\
\frac{dI}{dt} &= \beta L - \gamma I \\
\frac{dR}{dt} &= \gamma I
\end{align*}
\]

At the early stages of infection the majority of population is susceptible $S(t) \approx S_0 = 1$. Here $S, L, I, R$ denote fractions of populations, so $S + L + I + R = 1$. The system becomes a linear system with the solution presented by a sum of increasing (first term) and decreasing (second term) exponential functions,

\[
\begin{pmatrix} L(t) \\ I(t) \end{pmatrix} = I_0 \begin{pmatrix} \frac{-\alpha}{\sqrt{\beta-\gamma}^2 + 4\beta\alpha} & \frac{-\beta}{\sqrt{\beta-\gamma}^2 + 4\beta\alpha} \\ \frac{-\alpha}{\sqrt{\beta-\gamma}^2 + 4\beta\alpha} & \frac{-\gamma}{\sqrt{\beta-\gamma}^2 + 4\beta\alpha} \end{pmatrix} \exp \left( \frac{\sqrt{(\beta-\gamma)^2 + 4\beta\alpha} - (\beta + \gamma) t}{2} \right) + I_0 \begin{pmatrix} \frac{-\alpha}{\sqrt{\beta-\gamma}^2 + 4\beta\alpha} & \frac{\beta}{\sqrt{\beta-\gamma}^2 + 4\beta\alpha} \\ \frac{-\alpha}{\sqrt{\beta-\gamma}^2 + 4\beta\alpha} & \frac{\gamma}{\sqrt{\beta-\gamma}^2 + 4\beta\alpha} \end{pmatrix} \exp \left( \frac{-\sqrt{(\beta-\gamma)^2 + 4\beta\alpha} - (\beta + \gamma) t}{2} \right).
\]

Here $I_0$ is the initial number of infected individuals, and $L(t = 0) = 0$. By adjusting constants $\alpha, \beta, \gamma$ the model can be fitted to the observed exponential growth of infection at its early stage.

The delay equation takes into account that an infected individual becomes infectious only after time $\tau_I$ and recovers or dies around time $\tau_R > \tau_I$,

\[
\frac{dI}{dt} = S(t)\beta I(t - \tau_I) - \gamma I(t - \tau_R)
\]

Assuming again that we analyze the early stages of infection, $S = S_0 = 1$, we seek the solution in the exponential form, $I(t) = I_0 \exp(\delta t)$, where $I_0$ is the initial number of infected individuals. Taking into account that $\beta > \gamma$ for the infection growth, the resulting transcendental equation for $\delta$ always has a solution,

\[
\delta = \beta \exp(-\delta \tau_I) - \gamma \exp(\delta \tau_R) \equiv \phi(\delta).
\]
This can be concluded by observing that the function $\phi(\delta)$, defined by the right hand side of (12) changes from $\beta - \gamma > 0$ for $\delta = 0$ to $0$ for $\delta = +\infty$ either monotonously decreasing when $\beta \tau_I > \gamma \tau_R$, or going through a maximum in the opposite case. It is possible to find the approximate solution of the Eq. (12). For example, at early stages of infection when recovery and death are not yet happening (i.e. for $t < \tau_R$) or for a rapidly developing infection, the recovery term vanishes or becomes insignificant. In the limits of short ($\beta \tau_I \ll 1$) and long ($\beta \tau_I \gg 1$) infectiousness delay, $\delta$ can be approximated as

$$\delta \approx \frac{\beta}{1 + \beta \tau_I}, \quad \text{when } \beta \tau_I \ll 1,$$

or

$$\delta \approx \frac{\ln(\beta \tau_I) - \ln(\ln(\beta \tau_I))}{\tau_I} \quad \text{when } \beta \tau_I \gg 1.$$

Since both the ODE and delay equations can exhibit any desirable exponential growth for the early stages of infection, the former is used much more often as it is simpler mathematically and can be implemented utilizing standard ODE integrators. However, as shown in our text, the delay equations provide the additional information about the age of infection. Such information is essential for making correct predictions of the effects and timing of detection and quarantining on the spread of infection [7, 8].

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