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Modeling of Pandemics and Intervention Strategies: The COVID-19 Outbreak

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Abstract

Since pathogen spillovers and pandemics are unfortunately recurrent in the history of humanity, mathematical approaches to describe and mitigate the spread of infectious diseases have a long tradition. Recently, the COVID-19 pandemic has challenged the scientific community to model, predict, and contain the contagion, especially given the current lack of pharmaceutical interventions such as vaccines and anti-viral drugs targeting the new SARS-CoV-2 coronavirus. The control community has quickly responded by providing new dynamic models of the epidemic outbreak, including both mean-field compartmental models and network-based models, as well as combinations of control approaches and intervention strategies to end the epidemic and recover a new normality. This entry deals with systems-and-control contributions to model epidemics and design effective intervention strategies, with a special focus on the COVID-19 outbreak in Italy.

Keywords

COVID-19 · Epidemics · Epidemiological models · Modeling and control of epidemics · SARS-CoV-2

Introduction

The history of humanity is unfortunately marked by the recurrent appearance of new lethal pathogens and the subsequent spread of devastating epidemics. To better understand and face this threat, epidemiology studies the patterns of disease evolution in a population. The mathematical foundations of contemporary epidemiology have deep roots in the early twentieth century, but simpler models for disease transmission had been conceived even earlier; see Anderson and May (1991), Bailey (1975), Brauer and Castillo-Chavez (2012), Breda et al. (2012), Diekmann and Heesterbeek (2000), Hethcote (2000), House (2012), Keeling and Eames (2005), Kiss et al. (2017), Nowzari et al. (2016), Pastor-Satorras et al. (2015) and the references therein for a thorough survey.

Predictive mathematical models for epidemics are crucial not only to understand and forecast the evolution of epidemic phenomena but also to plan effective control strategies to contain the contagion. The epidemic models

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studied in the literature may be divided into two main classes: mean-field compartmental models (Anderson and May 1991; Bailey 1975; Brauer and Castillo-Chavez 2012; Diekmann and Heesterbeek 2000; Hethcote 2000) and network-based models (House 2012; Keeling and Eames 2005; Kiss et al. 2017; Nowzari et al. 2016; Pastor-Satorras et al. 2015). We discuss both in Section "Mathematical Models and Control Approaches for Epidemics".

Although mathematical models for epidemics have been studied for a long time, the interest of the control community in the topic awakened only recently (Nowzari et al. 2016), with the exception of the pioneering work in Lee and Leitmann (1994) and Leitmann (1998) on control strategies for endemic infectious diseases. A boost of activity was stirred by the COVID-19 pandemic: in China, in the late 2019, a novel strand of Coronavirus denoted SARS-CoV-2 started to spread, causing a severe and potentially lethal respiratory syndrome labeled as COVID-19. Its high infectiousness enabled the virus to soon spread globally, causing a pandemic: on 8 July 2020, the World Health Organization reported 11,669,259 cases and 539,906 deaths worldwide. Given the lack of a vaccine and of anti-viral drugs targeting SARS-CoV-2, sound modeling and prediction approaches were crucial to guide the implementation of non-pharmaceutical interventions: quarantine, social distancing and lockdown, testing and contact tracing, isolation, and use of personal protective equipment (Gatto et al. 2020; Giordano et al. 2020; Hellewell et al. 2020; Kucharski et al. 2020). The availability of open data resources (Alamo et al. 2020) favored the emergence of data-driven approaches and models, and the control community explored approaches to "flatten" (Stewart et al. 2020) or even "crush" the epidemic curve.

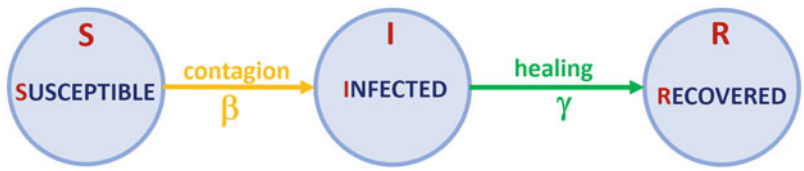
Italy was among the first non-Asian countries being severely affected by COVID-19. On 24 April 2020, the Italian Chapter of the IEEE Control Systems Society organized an online-workshop on *Modeling and Control of the COVID-19 outbreak: How dynamical models can help control the epidemic* to collect the most recent contributions of systems-and-control researchers to the problem of modeling and predicting the dynamics of contagion evolution. Models and approaches tailored to the specificities of the COVID-19 outbreak were proposed as concrete tools to support policymakers in deciding the best intervention strategies.

This entry illustrates classical mathematical models of epidemic spreading and recently proposed models tailored to the COVID-19 outbreak. It discusses the insight these models provide to help contain the contagion and manage the epidemic phases and surveys novel approaches for the control of epidemics with systems-and-control methodologies.

Mathematical Models and Control Approaches for Epidemics

Compartmental Models

Classical models for epidemic outbreaks are compartmental models; of these, the simplest model capturing the qualitative evolution of an epidemic phenomenon is the SIR model visualized in Fig. 1, introduced in the seminal work (Kermack and McKendrick 1927) to describe the human-to-human transmission of



Modeling of Pandemics and Intervention Strategies: The COVID-19 Outbreak, Fig. 1 Graph representation of the mean-field compartmental epidemiological *SIR model*: Susceptible-Infected-Recovered

infectious diseases. Compartmental models are mean-field models, where all the parameters represent averaged values over the whole population and do not aim at describing the specific situation of a single individual. They rely on some simplifying assumptions:

- births, deaths (other than those due to the disease), and any other demographic processes either are absent or compensate for each other during the considered period of time, so that the total population is constant;
- the population can be partitioned into mutually exclusive classes, or compartments, depending on the stage of the disease: for the SIR model, each individual is either susceptible to infection (S), infected and infectious (I), and recovered and permanently immune (R); alternatively, R may stand for removed, namely, either recovered and immune or dead;
- the population is large and it is randomly and homogeneously mixed, so that infections occur according to the mass-action law, i.e., depending on the product between the amount of susceptible individuals and of infectious individuals, with rate constant β;
- recovery (or recovery, death, and removal) from the infection occurs with rate constant γ.

To understand how the transitions between the various stages are modeled, we can adopt an analogy and represent individuals belonging to different compartments as particles or chemical species, whose concentrations evolve according to given interaction rules or reactions, each associated with a possible transition among compartments. Each "reaction" corresponds to a given "stoichiometric" law and a "reaction" rate. Then, the SIR model visualized in Fig. 1 is described by the equivalent chemical reactions $S + I \overset{\beta}{\rightharpoonup} 2I$ and $I \overset{\gamma}{\rightharpoonup} R$, which correspond to the positive dynamical system

$$\frac{ds}{dt}(t) = -\beta s(t) i(t) \tag{1}$$

$$\frac{di}{dt}(t) = \beta s(t) i(t) - \gamma i(t) \tag{2}$$

$$\frac{dr}{dt}(t) = \gamma i(t) \tag{3}$$

where $s(t)$, $i(t)$, and $r(t)$ denote, respectively, the fraction of susceptible, infected, and recovered individuals (which can be seen as the normalized concentrations of the equivalent chemical species S, I, and R) and $s(t) + i(t) + r(t) \equiv 1$ (the total population is constant, which can be seen as a conservation law). Equation (3) may be neglected, since r does not influence the other variables and its evolution can be obtained by difference: $r(t) = 1 - s(t) - i(t)$. The involved parameters are the transmission coefficient β, depending both on intrinsic features of the pathogen/infection and on the intensity of interactions among individuals, and the recovery/removal coefficient γ, depending on the average time before an individual recovers or dies from the infection; the average duration of infectiousness is $1/\gamma$. The system is positive: starting from nonnegative initial conditions, all the system variables preserve nonnegative values for their whole evolution.

We consider initial conditions with $s(0) \approx 1$, while $0 < i(0) \ll 1$ and $r(0) = 0$.

In the initial stages of the epidemic, the SIR model yields an exponential growth, or decay. In fact, since initially $s \approx 1$,

$$\frac{di}{dt}(t) \approx (\beta - \gamma) i(t), \tag{4}$$

which has the explicit exponential solution

$$i(t) \approx i(0) e^{(\beta - \gamma)t}. \tag{5}$$

Let us define the *basic reproduction number* R_0, corresponding to the average number of secondary infections caused by a primary case introduced in a fully susceptible population (Anderson and May 1991; Brauer and Castillo-Chavez 2012), as

$$R_0 \doteq \frac{\beta}{\gamma}. \tag{6}$$

Then, Eq. (5) represents an exponential growth if $\beta - \gamma > 0$, namely, $R_0 = \frac{\beta}{\gamma} > 1$, and an exponential decay if $\beta - \gamma < 0$, namely, $R_0 = \frac{\beta}{\gamma} < 1$.

When the complete dynamics in Eqs. (1)–(3) are considered without approximations, including later stages of infection, the value of R_0 still has a key role in determining the epidemic outcome. Denote by $\bar{s}$, $\bar{i}$, and $\bar{r}$ the asymptotic equilibrium value. Starting from an initial condition with $i(0) > 0$, it must be $\bar{s} < s(0)$, since $s(t)$ is monotonically decreasing in view of Eq. (1), while $\bar{r} > r(0)$, since $r(t)$ is monotonically increasing in view of Eq. (3). If $R_0 s(0) < 1$ (hence $R_0 s(t) < 1$ for all $t \geq 0$, being $s(t)$ decreasing), the fraction of infected population decreases, because $\frac{di}{dt} < 0$, as can be seen from (2), until $i(t)$ reaches zero; then there is no outbreak and infections spontaneously decay. Conversely, if $R_0 s(0) > 1$, the fraction of infected population is initially increasing, because $\frac{di}{dt} > 0$. However, since $s(t)$ is decreasing, $R_0 s(t)$ decreases too: it reaches from above the threshold 1 and then goes below. Therefore, the fraction of infected population reaches a peak, at the time t^* such that $R_0 s(t^*) = 1$, and eventually decreases to zero (because, for $t > t^*$, $R_0 s(t) < 1$).

Any equilibrium of the system is such that there are no infected individuals, $\bar{i} = 0$: the generic equilibrium has the form $(\bar{s}, 0, \bar{r})$, with $\bar{s} + \bar{r} = 1$. To ensure stability, the equilibrium value of s must be such that $R_0 \bar{s} < 1$.

If we consider the sum of Eqs. (1) and (2), we obtain

$$\frac{ds}{dt}(t) + \frac{di}{dt}(t) = -\gamma i(t). \tag{7}$$

Integration of Eq. (7) yields

$$\int_0^t i(\tau) d\tau = \frac{1}{\gamma}[s(0) - s(t) + i(0) - i(t)]. \tag{8}$$

Also, integrating Eq. (1) divided by s gives

$$\log\left(\frac{s(0)}{s(t)}\right) = \beta \int_0^t i(\tau) d\tau \tag{9}$$

and substituting Eq. (8) into Eq. (9) gives

$$\log\left(\frac{s(0)}{s(t)}\right) = \underbrace{\frac{\beta}{\gamma}}_{R_0} [s(0) - s(t) + i(0) - i(t)]. \tag{10}$$

Rearranging Eq. (10) computed at time $t = t^*$, where t^* is defined above, allows us to compute the peak value $i^{\max}$ of i, which is achieved for $s^* = s(t^*) = \frac{1}{R_0}$:

$$i^{\max} = i(0) + s(0) - \frac{1}{R_0}[1 + \log(R_0 s(0))]. \tag{11}$$

If we start from an initial condition with $r(0) = 0$, hence $s(0) + i(0) = 1$, Eq. (10) allows us to compute the equilibrium value of the susceptible population as the unique positive root of the equation

$$\log\left(\frac{s(0)}{\bar{s}}\right) = R_0[1 - \bar{s}], \tag{12}$$

known as *final size relation*. The quantity $1 - \bar{s} = \bar{r}$, called *attack rate* by the epidemiologists, corresponds to the fraction of the population having experienced the disease during the epidemic.

Several extensions of the SIR model were proposed, taking into account additional infection stages: for instance, the SEIR (Susceptible, Exposed, Infectious, Recovered) model, shown in Fig. 2, considers a latency stage when the infected person is not yet infectious.

The SEIR model is described by the equivalent chemical reactions $S + I \xrightarrow{\beta} E + I$, $E \xrightarrow{\kappa} I$, $I \xrightarrow{\gamma} R$, corresponding to the positive dynamical system

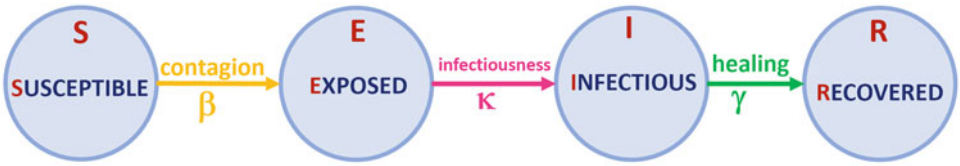
$$\frac{ds}{dt}(t) = -\beta s(t) i(t) \tag{13}$$

$$\frac{de}{dt}(t) = \beta s(t) i(t) - \kappa e(t) \tag{14}$$

$$\frac{di}{dt}(t) = \kappa e(t) - \gamma i(t) \tag{15}$$

$$\frac{dr}{dt}(t) = \gamma i(t) \tag{16}$$

where $s(t)$, $e(t)$, $i(t)$, and $r(t)$ denote, respectively, the fraction of susceptible, exposed,



Modeling of Pandemics and Intervention Strategies: The COVID-19 Outbreak, Fig. 2 Graph representation of the mean-field compartmental epidemiological *SEIR model*: Susceptible-Exposed-Infectious-Recovered

infectious, and recovered individuals and $s(t) + e(t) + i(t) + r(t) \equiv 1$. In this case, all possible equilibria have the form $(\bar{s}, 0, 0, \bar{r})$ with $\bar{s} + \bar{r} = 1$.

More complex models were proposed to better describe the specific features of a given disease; for instance, the SEQIJR model put forth in Gumel et al. (2004) is tailored to SARS. The reader is referred to Anderson and May (1991), Bailey (1975), Brauer and Castillo-Chavez (2012), Diekmann and Heesterbeek (2000), and Hethcote (2000) for further details on extended compartmental models for epidemic spreading and their analysis.

Network-Based Models

Network-based models embed compartmental models into a graph-theoretic framework: the interacting population is represented by a graph where the nodes are associated with individuals, whose state corresponds to one of the stages in compartmental models (e.g., susceptible, infected, recovered, and immune), and the links among them are associated with human-to-human interactions that can potentially lead to contagion. The transmission rate is no longer an averaged value for a well-mixed population, but is tailored to each specific node, depending on its connectivity degree and on the state of its neighboring nodes. Both stochastic and deterministic population models, and both stochastic and deterministic network models, can be adopted. The models can then describe how the total number of nodes at each of the infection stages evolves over time, depending on the initial conditions and the network topology, by monitoring the fractions of nodes in each stage at each time instant (in a deterministic framework), or the probability that a node belongs to a given stage (in a stochastic framework, based on the evaluation of expectations and moment closures). Network epidemics can also be seen as a percolation phenomenon (House 2012; Pastor-Satorras et al. 2015).

Network-based models also include agent-based models, typically spatially structured, which consider the discrete nature of individuals and their mobility and interaction patterns in a stochastic framework. These models are extremely complex and detailed, since they rely on the construction of a synthetic population reproducing each individual and her/his neighborhood and movements; hence, efficient data-driven computational approaches are needed.

In meta-population models, each node of the network corresponds not to a single individual in the population, but to a group of multiple individuals. We can also consider networked models where each node is associated with a compartmental dynamical system, describing local epidemic spreading, and each link represents mobility between local communities, which spreads the epidemic to larger geographic areas (Mei et al. 2017; Paré et al. 2018; Ye et al. 2020).

For more information on epidemics on networks, the reader is referred to House (2012), Keeling and Eames (2005), Kiss et al. (2017), Nowzari et al. (2016), and Pastor-Satorras et al. (2015).

Control Approaches

Several approaches were considered to mitigate the effects of an epidemic outbreak. In a compartmental SIR model, clearly the epidemics can be suppressed by increasing the recovery rate γ (thanks to improved treatment for infected individuals) and decreasing the transmission rate

β (which can be achieved by raising awareness, use of personal protective equipment, social distancing, quarantining and isolating infected individuals, or even travel limitations and lockdown), so that $R_0 = \beta/\gamma$ becomes as small as possible, at least smaller than 1 to make the epidemic phenomenon decay.

In network-based epidemic models, with the constraint of a limited budget, one may be interested in optimally investing fixed resources to reduce at best the spreading of the disease, so as to minimize the quantity $\lambda_{\max}(B - \Gamma)$, where $\lambda_{\max}$ denotes the dominant eigenvalue, B is the matrix of infection rates β_{ij} among nodes, and Γ is the diagonal matrix of recovery rates γ_i for the individual nodes. Two possible strategies can be devised for spectral control and optimization: in order to reduce $\lambda_{\max}$, either network nodes or network links can be removed. This corresponds to isolation/quarantine for some individuals (node removal) and to social distancing (link removal).

Optimal control approaches were proposed, relying on Pontryagin's maximum principle, to minimize the cost of the epidemics, which combines the cost of infection and the cost of treatment or vaccination (Bloem et al. 2009; Forster and Gilligan 2007; Hansen and Day 2011; Morton and Wickwire 1974), so as to design an optimal treatment plan, or vaccination plan. Robust control approaches were also proposed to control the spreading of infectious diseases, seen as an uncertain dynamical system (Lee and Leitmann 1994; Leitmann 1998). Given the complexity of the problem, numerous heuristic feedback control approaches were put forth as well. The reader is referred to Nowzari et al. (2016) for a comprehensive survey of the control of spreading processes.

Modeling and Control of the COVID-19 Outbreak

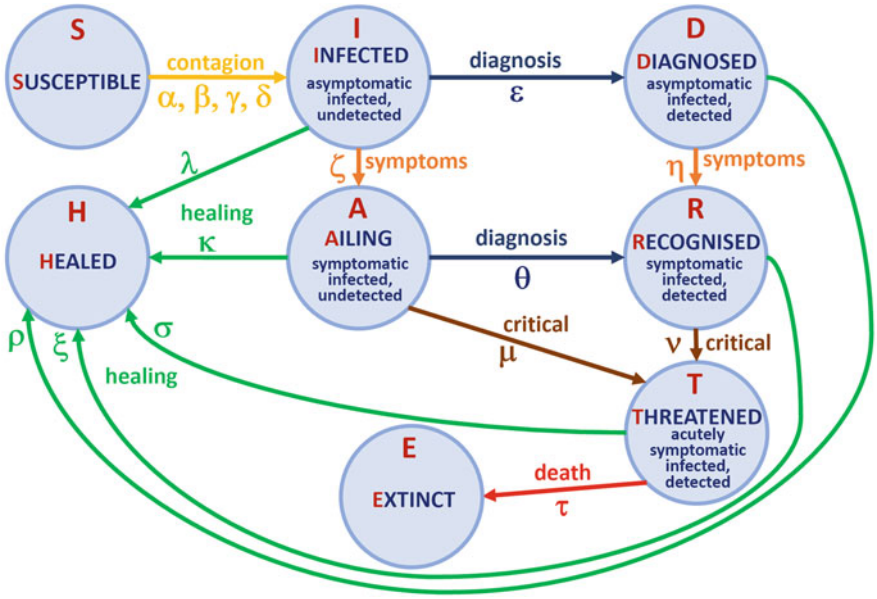
Several models of the COVID-19 pandemic started to appear in the early 2020. Stochastic transmission models were studied in Hellewell et al. (2020) and Kucharski et al. (2020) to analyze disease transmission and its control by isolation of cases. Also generalized compartmental models were considered: Lin (2020) extends a SEIR model considering perceived contagion risk and cumulative number of cases; Anastassopoulou et al. (2020) analyzes and forecasts the epidemic evolution in China based on a discrete-time SIR model explicitly accounting for dead individuals; and Wu et al. (2020) considers a meta-population SIR model, partitioning the population into age groups, to estimate the clinical severity of COVID-19 from transmission dynamics.

The compartmental SIDARTHE (Susceptible-Infected-Diagnosed-Ailing-Recognized-Threatened-Healed-Extinct; see Fig. 3) model is proposed in Giordano et al. (2020) to understand and predict the COVID-19 epidemic evolution, distinguishing between infected with different severity of illness and between detected and undetected cases of infection. The model highlights the parameters associated with the two main non-pharmaceutical interventions: social distancing and lockdown (which reduce the contagion parameters) and testing and contact tracing (which increase the diagnosis parameters, so that more infection cases are isolated). Different scenarios are explored to assess the effect of various interventions in the Italian case, and the results support the combination of social distancing with testing and contact tracing so as to rapidly end the epidemic.

A modified SIR model including both recovered and deceased, and taking into account that only a portion of infected individuals can be detected, is proposed in Calafiore et al. (2020). The model predicts the evolution of the contagion in Italy, and in each of its regions, so as to assess the effectiveness of containment and lockdown measures.

An extended SIR model that distinguishes between asymptomatic and symptomatic infected, as well as actual and confirmed cases, is used in Russo et al. (2020) to identify the estimated day zero of the COVID-19 outbreak in Lombardy (Italy).

A compartmental model that highlights the fraction of asymptomatic infectious individuals,



Modeling of Pandemics and Intervention Strategies: The COVID-19 Outbreak, Fig. 3 Graph representation of the mean-field compartmental epidemiological *SIDARTHE* (Susceptible-Infected-Diagnosed-Ailing-Recognised-Threatened-Healed-Extinct) model. (Reproduced from Giordano et al. 2020)

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considers the COVID-19 spread within and among regions in Italy, and assesses the impact of the adopted interventions is proposed in Di Giamberardino et al. (2020).

A feedback SIR model, with nonlinear transmission rates (Capasso and Serio 1978), is considered in Franco (2020) to study infection-based social distancing and its advantages (the infection peak is reduced, even in the presence of information delays) and disadvantages (extended duration of the epidemic).

The control-oriented SEIR model developed in Casella (2020) stresses the effect of delays and compares the outcomes of different containment policies, in China and in Lazio (Italy). It is shown that mitigation strategies (letting the epidemic run in a controlled way, typically aiming for herd immunity) are likely to fail because they aim at controlling fast unstable dynamics affected by time delays and uncertainties, while suppression strategies can be successful if they are prompt and drastic enough.

Fast multi-shot intermittent lockdown intervals with regular period are proposed in Bin et al. (2020) as an exit strategy from total lockdown to avoid second waves of infection. The suggested switching control strategy is open-loop and robust to delays and uncertainties in measurements, and the parameters of the mitigation strategy are tuned by a slow and robust outer supervisory feedback loop; the proposed approach is successfully tested on compartmental epidemic models ranging from the SIR to the SIDARTHE model (Giordano et al. 2020).

A robust and optimal control strategy for the COVID-19 outbreak is proposed in Köhler et al. (2020) based on model predictive control approaches that dynamically adapt social distancing measures, using the SIDARTHE model (Giordano et al. 2020).

An extended SIR model with specific compartments for socially distanced susceptible and infected (either asymptomatic or symptomatic) individuals is introduced in Gevertz et al. (2020). The analysis of time-varying social distancing strategies reveals that they are effective only if enacted quickly enough, and there is a critical intervention delay after which they have little effect; moreover, periodic relaxation strategies can be effective but are extremely fragile to small

errors in timing or parameters, while gradual relaxation substantially improves the epidemic situation, but the rate of relaxation needs to be carefully chosen to prevent a second outbreak.

Economists modeled the epidemic resorting to a SIR model that incorporates the optimizing behavior of rational agents, incentives influencing the transitions, and externalities representing restrictive government interventions (Garibaldi et al. 2020): agent-based rational decision-making, leading to a decentralized epidemic equilibrium, yields outcomes consistent with the original model in Kermack and McKendrick (1927).

The work in Gatto et al. (2020) analyzes the local-global effect of containment measures by studying a meta-population SEIR-like model that interconnects the epidemics in different Italian provinces to model the spatial spreading of the outbreak; the resolution that models the disease spread at the appropriate geographical scale allows for both spatial and temporal design of containment measures and makes it possible to forecast the medical resources and infrastructures needed. The same spatially explicit approach is adopted in Bertuzzo et al. (2020) to suggest appropriate relaxations of the containment measures adopted in Italy, discussing possible options such as tracing and testing, stop-and-go lockdown enforcement, and delayed lockdown relaxations.

A networked meta-population SIR model is proposed in Della Rossa et al. (2020) to describe the Italian epidemics by looking at the country as a network of regions, each with different epidemic parameters; this reveals the different regional effects of the adopted countermeasures, as well as the important impact of regional heterogeneity on the outbreak evolution, and suggests that differentiated (but coordinated) feedback interventions enforced at a regional level could be particularly beneficial.

A meta-population networked model is also proposed in Zino et al. (2020), focused on the role of activity and mobility in the COVID-19 outbreak in Italy: the model considers the reduction in activity (to study the effect of "stay at home" policies) and mobility within and between provinces (to study the effect of mobility limitations, travel bans, and isolation of red zones), as well as isolation (to study the effect of quarantine and testing).

A different methodology is proposed in Fanti et al. (2020), where a multi-criteria approach is adopted for COVID-19 risk assessment in different lockdown scenarios, focusing on urban district lockdowns in Puglia (Italy).

Several epidemic scenarios with different testing policies and mobility restrictions are outlined in Dahleh et al. (2020), where a network SIR-like model is used to explore control approaches based on testing, distancing, and quarantining.

The challenges of forecasting the spread of COVID-19 using different models (exponential, SIR, and Hawkes self-exciting branching process) are discussed in Bertozzi et al. (2020).

Model accuracy and validation The proposed models were tested against official epidemiological data provided by local and national governments. In spite of the large noise and uncertainty affecting the available data on the COVID-19 epidemic evolution, the proposed models, with the parameters fit based on real data, proved to be able to accurately reproduce and predict the outbreak dynamics.

Summary and Future Directions

We provided an overview of dynamic models, both compartmental and network-based, to describe, predict, and control the evolution of epidemics, with a special focus on the models and intervention strategies tailored to the ongoing COVID-19 pandemic.

Models proved to be a precious tool not only to forecast epidemic phenomena but also to assess and predict the effectiveness of different policies and countermeasures. Non-pharmaceutical strategies are lockdown and social distancing (including the widespread use of personal protective equipment), population-scale testing, and contact tracing. Each strategy has some fragilities. The impact of lockdown on the economy, as well as on mental health (Torales et al. 2020),

needs to be taken into account, while the effectiveness and correct use of personal protective equipment has been long debated. Testing strategies need to cope with a limited availability of tests; this problem is studied in Drakopoulos and Randhawa (2020) using a resource allocation approach, and it is shown that it may prove efficient to release less accurate tests when the epidemic is picking up and then more accurate tests as they become available. Contact tracing requires the adoption of individual tracking and monitoring via apps that generate privacy concerns.

In this complex situation, outlining different scenarios and predictions based on the available data and on solid mathematical modeling can inform and guide policymakers deciding how to handle the ongoing pandemic. Therefore, we are convinced that the contribution of the systems-and-control community will be valuable to contain the COVID-19 outbreak, as well as future pandemics. At the same time, the peculiar characteristics of epidemiological models pose important theoretical challenges that are pushing out the frontiers of the methodological tools developed by our community.

Cross-References

- ▸ Control in Intensive Care Units
- ▸ Controlling Collective Behavior in Complex Systems
- ▸ Dynamical Social Networks
- ▸ Robustness Analysis of Biological Models

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