Challenges and Future Directions in Pandemic Control

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Challenges and Future Directions in Pandemic Control

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Abstract— **In this letter, we describe some of the most important objectives and needs in pandemic control. We identify the main open problems in the different stages of the decision making process, as well as the most significant challenges to overcome them, leading to promising future research directions. We provide a concise review of the most recent literature describing such challenges, highlighting the main results, achievements and methodologies that can be employed to address them. In particular, we discuss some promising recent techniques that have been successfully applied to the Covid-19 pandemic and could be very valuable in the design of novel methodologies to face future pandemics.**

I. Introduction

In modern epidemiology, society is modelled as a highly complex spatially distributed network in which pathogens may spread. The emergence of a lethal infectious pathogen can lead to a pandemic, resulting in a serious global health emergency. For decision-makers, it is crucial to monitor and anticipate the epidemic evolution, so as to plan multi-pronged interventions aiming at reducing the diverse impacts of the pandemic. The challenges raised by a pandemic require the interplay between Epidemiology, Data Science and Control Theory. Epidemiology is crucial to understand the mechanisms that govern the spread of a disease. Data Science provides techniques, often in a Big Data context, to develop forecasting tools and spatio-temporal analysis. Finally, the results from the Control Theory community are used to design optimal mitigation and/or resource allocation strategies.

Many challenges, of disparate nature, must be addressed when monitoring, modelling and managing the evolution of a pandemic (see Figure 1). Here, we identify and discuss the most critical needs and objectives in the control of epidemics at different stages of the decision-making process, highlighting the main open problems and promising techniques.

Some of the most relevant challenges are:

1) Data accessibility and quality (e.g. lack of transparency, inconsistencies, different formats, reconciling monitoring and privacy).
2) Modelling issues (e.g. system complexity, non-identifiability issues, non-linearity, spatial distribution, time-varying and heterogeneous dynamics, the crucial role of delays, multiple pathogen strains, possible asymptomatic population).
3) Challenges in planning interventions and epidemic control (including physical distancing, non-pharmaceutical interventions, testing, contact tracing, drug distribution and vaccination campaigns), predicting their effectiveness, and choosing the most suitable criteria in the presence of multiple needs and limited resources.
4) Challenges in the design of implementable interventions, taking into account the complexity of human behaviour, logistic, administrative and political issues.

Our selection of fundamental challenges, promising approaches and relevant directions for future research is focused on how to take advantage of available data and advanced methodologies so as to better understand, predict and control a pandemic in a highly interconnected and technological society.

The letter is organized as follows. Section II analyses the main challenges and methods for real-time monitoring of pandemics. Section III addresses the problem of estimating the state of an epidemic, focusing on testing, contact tracing and observability/identifiability of mechanistic models. The potential of multi-scale integrated modelling and its open challenges are described in Section IV. The control objectives in the context of an epidemic are detailed in Section V. Section VI deals with control-oriented models, whereas VII analyses available epidemic control techniques and their limitations. Section VIII analyses the techniques for the optimal allocation of resources to fight pandemics. Finally, the main conclusions are summarised in Section IX.

II. Real Time Epidemiology

The vast amount of real-time data streams describing the evolution of epidemics in the 21st century offers many opportunities and challenges. Data sources are fundamental to achieve different goals [1]:

(i) Detecting a novel epidemic outbreak in a surveillance system.
(ii) Monitoring the epidemic incidence and the strain on the health-care system.
(iii) Assessing the socioeconomic impact of the epidemic, e.g. in terms of mobility, adherence of population to interventions and economic indicators.
(iv) Including fundamental auxiliary information (such as

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Difficulties					
MONITOR	Data transparency [1] Asymptomatic population [7] Observability issues [13] Privacy issues [4] Inconsistent data sets [1]	**MODEL**	Spatially distributed [10] Time-varying nature [8] Population heterogeneity [9] Complex human behaviour [18] Non-identifiability issues [13]	**MANAGE**	Uncertainty [8] Delays [2] Limited resources [10] Multicriteria nature [29] Global scale vaccine logistics [30]
Promising techniques and methods					
MONITOR	Contact-tracing [4] GIS and Big Data [5], [6] Spatial sentiment analysis [5] Pool testing [3] Structural observability and identifiability [13]	**MODEL**	In-Host modelling [19] Spatial epidemiology [5],[6],[10] Temporal network epidemiology [6] Social networks [10] Multiscale stochastic models [21] Uncertainty quantification [25],[26] Data-driven forecasting [24]	**MANAGE**	Trigger control [16], [27] Distributed MPC [29] Robust MPC [8] Structural system theory [28] Optimal resource allocation in networks [10]

Fig. 1. Difficulties, as well as promising techniques and methods, in the control of a pandemic.

demographics, weather and climate, air-transport connectivity) within predictive models.

(v) Analysing the effectiveness of countermeasures and planning of suitable control strategies.

Inferring meaningful information from the present data deluge is very challenging. First of all, the available data sources exhibit important limitations [1, §4]: a wide variety of data formats and structures, variability in criteria for data collection and availability, lack of transparency related to the real impact of the pandemic, and unreliable information relative to low-to-middle-income countries, among others. Secondly, highly resource-consuming big-data techniques are required to process spatially distributed information from mobility data sources, social networks, etc. In this context, data curation is crucial to ensure active management of data over its life cycle, guaranteeing that it meets the necessary quality requirements for its practical usage. Data-driven methods to monitor, model and manage an epidemic require that data is trustworthy, accessible, reusable, and frequently updated.

When monitoring the epidemic, aspects that can heavily bias the estimated infection incidence, making it deviate from the actual one, are the limited availability of tests, the variety in reporting behaviours (e.g., the number of infected is underestimated when only people with serious symptoms seek for medical advice and get tested), and the delays in detecting and reporting new infections [2]. Strategies such as pool testing can help maximise the number of performed tests even with scarce resources [3]. Early detection of local outbreaks can be achieved by monitoring wastewater systems, as well as through digital surveillance [4], which however poses privacy issues.

Generating consolidated time series through pre-processing raw data, data reconciliation, data fusion, clustering methods, and time-series theory is a fundamental step in developing data-driven methodologies. The objectives are i) to correct possible inconsistencies and enhance the quality of the raw time-series; ii) to combine data from different sources; iii) to restructure data into clusters with similar characteristics.

Geographic Information Systems (GIS) and big data technologies are fundamental for the rapid aggregation of multi-source big data to synthesize mobility indexes, assess the adherence of population to interventions and determine the spatial segmentation of the epidemic risk [5]. At the technical level, spatio-temporal analysis methods for big data are emerging [5], [6]. Promising techniques in this field are spatio-temporal clustering, multilevel modelling for small area estimation, and Bayesian approaches to disease mapping; see the review in [6]. For the decision-making process, spatial sentiment analysis techniques [5] are emerging to monitor the social impact of an epidemic and to anticipate the potential effectiveness of a given intervention, taking the complex nature of human behaviour into account.

III. Estimating the State of the epidemic

Estimating the epidemic size plays an important role in assessing the clinical severity of the disease (e.g. case fatality rate), the attained population-level immunity (which can be estimated through seroepidemiological studies and sero-surveillance), and epidemic evolution. Real-time estimation of the epidemic incidence allows us to understand the most common transmission vectors (in-house, in-hospital, at-work, etc.) and identify the contexts or scenarios with the highest risk of contagion, as well as those geographical areas with high community transmission. It also plays an important role in the predictions of future epidemic waves, along with the time and magnitude of the associated peaks.

Efficient approaches for testing and contact tracing are required to assess the epidemic situation in real time, which is critical while containing the contagion. Since contact tracing can only be effective at low enough case numbers, it is an effective countermeasure jointly with other non-pharmaceutical interventions, like physical distancing [7], [8].

Powerful tools to estimate the state of an epidemic are offered by compartmental and mechanistic models that emulate how the disease spreads. The classical approach partitions a population into different compartments and employs mechanistic differential-equation models to describe the transitions between compartments. The simplest compartmental model (SIR) includes Susceptible, Infected and Recovered/Removed compartments, while SEIR models include an Exposed compartment to model the latent period after the infection; different extensions to these compartmental models include extra compartments to characterize asymptomatic but still contagious population, population in quarantine, or hospitalised patients, just to name a few [9]. Also, networked models are adopted to take spatial heterogeneity and individual interactions into account [10],[11]. All epidemiological models depend on myriads of parameters (such as the contact rate, the transmission probability, the average infectious period) that can be either constant or time-varying [12].

The state variables associated with some compartments are directly measurable, such as the number of hospitalised patients, while others, such as the number of asymptomatic infection cases, are impossible (or at least impractical) to measure. Asymptomatic transmission is a crucial issue for several pathogens, including SARS-CoV-2, Zika virus and HIV. Similar considerations can be made with respect to the model parameters. Therefore, estimating unmeasured state variables and parameters based on available measurements is key. Structural observability/identifiability [13] plays here a crucial role: for a given compartmental model and measurable outputs, it allows to determine which compartments and parameters can be respectively observed and identified. Thus, this kind of analysis provides excellent tools to choose among different models and estimation goals depending on the situation, and prevents the use of unreliable combinations of measurements, models, and estimation goals that can lead to poor predictions, conflicting conclusions, and distrust of epidemiological models.

An additional challenge in state estimation arises where time delays are explicitly considered. Delays affect, among others, the process of detecting/reporting contagions [2] or the latency between infection and infectiousness. Delays are often incorporated in compartmental models, whose observability can be analysed resorting to the backward shift operator and rewriting the equations in differential form to determine whether strong, regular, or weak observability holds (see [14] for an application to the COVID-19 pandemic).

The most common situation in epidemic modelling is to have only partial information about the recovery and infection events (incomplete epidemic data). In this context, Markov Chain Monte Carlo methods (MCMC) and Expected Maximization (EM) algorithms are valuable methodologies to make Bayesian inferences about the missing data and the unknown parameters [12, §4].

Fitting the model parameters to the data available can be challenging even for medium-complexity models because of possible non-identifiability issues: different sets of parameters, yielding a similar fit to data, may provide a significantly different estimate of the main epidemic features, such as peak size or reproduction number [13], [8, §2.2]. This is critical, since very different control outputs could be proposed depending on the selected set of parameters. A promising approach to address this issue is to employ large-scale convex optimization to fit spatially distributed data in network modelling. The main idea is to use data reconciliation and regularization techniques, assuming that the spread of the disease is similar in locations with analogous characteristics [15]. In this way, the degrees of freedom in the identification process can be reduced to a level at which the obtained results are robust and consistent.

When both observability and identifiability analyses are correctly performed, the state estimation of the pandemic can provide essential information, such as e.g. the (possibly time-varying) rates of transmission and recovery, the latent period, and the fractions of asymptomatic population or exposed population.

IV. Multi-Scale Integrated Modelling

Modelling epidemics is challenging due to the complex nature of the spreading phenomena, which are intrinsically nonlinear and typically time-varying [9], [7], spatially distributed [10], [16] and large-scale, since they result from the interactions among myriads of agents. Delays (e.g. in symptom onset, in reporting infections) have a crucial role in the ensuing dynamics, which can be further complexified by the concurrent presence of multiple pathogen strains [17] and on-going mass vaccination. Other challenges are due to population heterogeneity, since the incidence and the clinical evolution of the disease can vary depending on demographic factors (such as age, gender, ethnicity), and to the need of accounting for unpredictable human behaviours [18].

To better understand, predict and control epidemics, we need multi-scale mathematical models that describe the interplay between the in-host and between-host evolution of infectious diseases. In-host dynamic captures the biological characteristics of the pathogen and its biochemical interactions with the host cells and immune system [19]. Between-host dynamic captures the spread of the disease in a population, describing the evolution of contagion both through aggregate compartmental models [9], [7] and through agent-based or networked models of the population [10].

To capture the spread of the disease considering the complex web of interactions between individuals, promising techniques are offered by spatial and network-based epidemiology [6], [10], often relying on big data [5], to infer realistic mobility/contact patterns, as well as temporal network epidemiology [6], [11]. Originating in statistical physics, percolation theory is a large branch of network theory concerned with the outcome of deleting nodes or edges from networks. It constitutes a powerful tool to understand the stochastic spread of an epidemic in a complex time-varying network [11, §6]. Another possibility to analyse the complex non-linear spatio-temporal spread is to resort to Dynamic Mode Decomposition and Koopman Operator Theory; preliminary results along these lines can be found in [20].

A holistic multi-scale perspective, embracing both in-host and between-host dynamics and taking into account the interactions between them, as well as including psychological, social and economic effects of the epidemic and the adopted countermeasures, is fundamental for a thorough understanding of the epidemic phenomenon as a whole. It also enables the design of optimal control interventions both at the patient level (pharmaceutical interventions, such as vaccines or targeted drugs) and at the population level (non-pharmaceutical interventions, such as lockdown, physical distancing, use of protective equipment, testing and contact tracing), which take into account the epidemiological and public-health perspective along with the impact on society at large. In this context, multi-scale stochastic models for epidemics have been recently put forth [21]. A fore-running attempt for multi-scale epidemic modelling that integrates epidemiology, immunology and economy is sketched in [22], but holistic multi-scale models are still in their infancy and constitute a promising direction for future interdisciplinary research.

Another open challenge is to devise novel integrated model-based and data-based approaches that are tailored to nonlinear spreading dynamics. Through an integrated model-and-data framework [12], we could both leverage insights provided by first-principle knowledge about the epidemic phenomena and the current availability of huge amounts of data, which are, however, often inaccurate, incomplete or uncertain, and from which further knowledge can be extracted through learning approaches.

V. Control Objectives

In order to contain the spread of an epidemic, it is necessary to decide on the most effective timing and stringency of interventions, and the optimal distribution of available resources. This is a multifaceted problem that, in most cases, can be stated as a constrained optimization problem [23], [10]. Taking a holistic perspective, the objective function should account for health, social and financial impacts of the pandemic. From a public health viewpoint, the goal is to minimize the total number of deaths due to the disease, or the total number of infections (or of proxy variables, such as the reproduction number). From a financial perspective, the aim is to minimize the impact of the disease on both the economy and financial agents; the economic consequences of an epidemic can be measured through indexes related to wealth creation and job destruction. The temporal persistence of the disease is a major factor in this direction; in fact, it impacts the three facets mentioned above: health, social, and finance. Hence, the optimization problem should not only minimize the total number of deaths (or of infections), but it should do so in the shortest possible time.

To achieve these objectives, decision makers have at their disposal a wide array of tools. At the earliest stage of a new epidemic, pharmaceutical interventions are often not available and the main mechanism to contain the disease is movement restrictions within a region, traffic control across regions, and social distancing measures, which come at a social and economic cost. In this scenario, a decision maker needs current estimates of the epidemic state and predictive models of the disease to assess the situation and the risks, and implement movement restrictions aimed at creating firewalls around areas with high prevalence, as well as social distancing measures to reduce the spread of infections. As mentioned above, these complex decisions can be made aided by optimization tools, intended for reducing the total number of infections/deaths while minimizing the socioeconomic costs of the implemented measures [10]. To formulate a suitable optimization problem, we need reliable and robust models able to predict the impact of different countermeasures on the future epidemic evolution [7], [8]. We also need appropriate cost functions accounting for the socioeconomic costs of these countermeasures. The optimization problem can then be formulated in three closely related ways: (1) finding a point in a Pareto boundary by choosing the relative importance of health, social, and economic factors; (2) setting mathematical bounds on the levels of acceptable social/economic costs and then determining the optimal resource distribution to minimise the impact on health; (3) setting bounds on the healthcare system strain (such as bounds on the number of occupied ward or intensive-care-unit beds in hospitals) and minimise the socioeconomic impact.

VI. Control-oriented Predictive Models

Prior to developing a control strategy, it is important to implement predictive models to assess the impact of interventions on the spread of the pathogen, the healthcare system, the mortality rate, and so on. In this regard, it is important to have access not only to the data corresponding to epidemiological variables, but also to keep track of the implemented non-pharmaceutical interventions [1, §8.2].

Both the time-varying and stochastic nature of the epidemic phenomenon require not only the design of forecasting tools [24, §4], but also the quantification of the uncertainty related to the obtained predictions [25]. The accuracy limitations of the predictive models are due to different factors, like gaps in our mechanistic understanding of disease transmission, low quality data, and fundamental limits to the predictability of complex epidemic processes [25]. Another relevant source of uncertainty is the interplay between disease and human behaviour, which can lead to outcomes that are difficult to predict [18]. This is fueled by social media, fear-reinforcing 24/7 news, and political polarization.

Sensitivity analysis, Monte Carlo methods, generalized polynomial chaos are examples of uncertain quantification techniques [26] that are often used in epidemiology. An emerging technology in epidemic modelling is the use of positive systems theory: since populations in a compartmental model are non-negative, it is possible to develop guaranteed interval predictions that account for all the range of variability of the uncertain parameters [8, §5].

In order to develop control strategies, it is of paramount importance to develop predictive models well-suited for the implementation of effective decision making in the context of an epidemic outbreak. There is a trade-off between highly complex models and oversimplified ones. For example, not considering the asymptomatic population in the Covid-19 pandemic can result in an excessive oversimplification, while too complex networked models might hinder the numerical solution of the optimization problems that arise in an optimal control formulation. Medium-complexity compartmental models have been often used as predictive models for control in the Covid-19 pandemic (e.g. the SIDARTHE model [7] in the model predictive control formulation proposed in [8] and the switching approach in [27]). The focus is on the robust achievement of various epidemic objectives, and not on the development of a precise model.

VII. Control Techniques

In a control setting, an epidemic is a time-varying uncertain process in which adaptive feedback strategies are required to compensate for uncertainty, model mismatch and time-varying nature.

To make decisions in such a highly uncertain context, where exact parameter values are hardly known, it would be important to identify scale-invariant and parameter-independent features of epidemiological models, based on which robust decisions could be safely enforced even with poor knowledge of the system parameters; to this aim, structural approaches tailored to biological and epidemiological models, such as those surveyed in [28], could be exploited.

The need to enforce restrictions during an epidemic, combined with behavioural fatigue due to their socioeconomic consequences, is likely to trigger intermittent containment measures, with the alternation between higher-transmission and lower-transmission phases. Promising techniques for the design of intermittent restrictions (trigger control) are outlined in [27], [16]. In this setting, as commented before, the control goals are often stated in terms of a multi-objective formulation. Trigger control of an epidemic can be addressed by means of oracle-based approaches: given a particular epidemiological situation, the oracle answers yes or no to the question whether a given intervention should be adopted (see e.g. [8, §3.1.2]). In this context, the decision problem can be viewed as a classification problem (supervised learning), for which many approaches from machine learning exist (support vector machines, random forest, neuronal networks, etc.). In this case, interpretable classification techniques are preferable, because they not only provide an answer, but also motivate it.

Model Predictive Control (MPC) formulations are particularly flexible, because they can explicitly consider constraints (e.g. bounds to prevent the saturation of the healthcare system) and support decisions by identifying the optimal timing and intensity of interventions [29], [8].

The output of a model predictive controller is adaptive, in the sense that it takes into account the latest available information on the epidemic state; MPC schemes can cope with model uncertainty and/or disturbances. Moreover, some MPC formulations explicitly consider the uncertainty affecting the parameters of the epidemic model [8]. Because of the spatially clustered distribution of an epidemic [10], specific control techniques from the field of distributed model predictive control can be applied, as in [29].

VIII. Optimal Resource Allocation: Testing and Vaccination

At the early stage of a pandemic, the optimal distribution of medical tests is of the utmost importance. Since the adopted policies are decided based on the available estimates of the epidemic state, it is of critical importance to design an efficient strategy to distribute tests throughout the population. This problem can be posed as an optimization program where the objective is to maximize the amount of collected information about the state of the disease, while satisfying constraints on the number of available tests [3]. An appropriate distribution of tests not only better informs health agencies about the state of the disease, but can also be used as a tool for early detection of new outbreaks. Since outbreaks tend to grow exponentially at the early stages, an effective system for early detection of outbreaks can drastically reduce both social and economic impacts.

The production and distribution of vaccines is another essential pillar in the suppression of an epidemic, especially for a pandemic that demands global-scale vaccine logistics [30]. The distribution of vaccines should be strategically designed to minimize the total number of deaths at the end of the vaccination campaign. To this aim, not only fabrication and distribution limits should be taken into account, but also an allocation strategy should be carefully designed to decide which subpopulations should be vaccinated first. Obviously, those with a higher mortality rate should have a priority in the vaccination process; however, to face an infectious disease, the optimal strategy might be to also vaccinate potential superspreaders, such as frontline workers, at an early stage. Furthermore, the optimal distribution of different types of vaccines, each with a different price, efficacy, and fabrication/distribution limits, requires the solution of a large optimization program. Another challenge in this scenario is the emergence of different pathogen strains during the vaccination roll-out, as in the Covid-19 pandemic, against which different available vaccines may be differently effective.

IX. Concluding Discussion

We have selected the main objectives and challenges when addressing epidemics, and pandemics, from a systems-and-control perspective. Adopting a holistic approach, we have described and discussed the main tasks required for data-driven management of an epidemic: i) monitoring the disease spread, ii) developing control-oriented predictive models, iii) making optimal decisions for planning both interventions and allocation of resources. We have highlighted the most promising emerging methodologies to address the different challenges raised by present and future epidemics of the 21st century. The general methodologies proposed in our references, although often applied to the topical case study of Covid-19, could be adopted as well to deal with other infectious diseases. Useful tools for an improved management of pandemics from a systems-and-control perspective can be inspired by the theory of the robust control of positive systems, structural approaches to assess properties of systems even in highly uncertain settings, polynomial chaos techniques for uncertainty quantification, percolation theory to effectively assess the evolution of epidemics through complex network-based models, approaches for large-scale optimization suitably tailored to exploit the specific features of epidemiological models. Promising avenues for future interdisciplinary research are opened by the need of holistic, integrated models that bridge multiple resolution scales and incorporate the multi-faceted impact of epidemics on healthcare as well as the social, psychological, economic consequences of the contagion and of the necessary countermeasures to stop its spread.

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