REVSTAT – Statistical Journal
Volume 18, Number 5, October 2020, 565–574

# ENDEMIC-EPIDEMIC FRAMEWORK USED IN COVID-19 MODELLING

## (*Discussion on the paper by Nunes, Caetano, Antunes and Dias*)

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Abstract:

- Nunes *et al.* ([54]) provide an overview of mathematical models used to analyse epidemics and techniques for conducting studies to obtain parameter estimates for such models. They discuss the SEIR model which has been used in much coronavirus disease 2019 (COVID-19) analysis. Our discussion presents a modelling framework based in time series analysis developed for the analysis of infectious disease surveillance data, as well as our use of the framework in analysing COVID-19. We believe many of the purposes of modelling infectious disease outlined by Nunes *et al.* ([54]) as well as the benefits of mathematical modelling highlighted can also be found in the statistical modelling techniques we use in our work.

## 1. ENDEMIC-EPIDEMIC MODELLING FRAMEWORK

Multiple epidemic data sources provide valuable information on different aspects of an infectious disease outbreak ([19]). Indeed, a recent simulation study by Colón-González *et al.* [18] indicates that use of multiple data streams arising from such surveillance activities can be a useful approach to disease detection. However, it is pertinent that appropriate statistical techniques be used in analysing such data sources to incorporate the associated uncertainties to avoid introducing bias and artificial precision in estimates of disease outcomes, impacts of disease control interventions, and real-time predictions ([9]). One such statistical technique is the endemic-epidemic (EE) modelling framework. The EE framework is a multivariate time series model created for analysis of infectious disease surveillance data ([30]). The simplest EE model is a spatio-temporal multivariate time-series model of disease incidence from surveillance data. The model additively decomposes incidence into endemic and epidemic components. The endemic component covers exogenous factors such as seasonality, sociodemography, and population while the epidemic component is autoregressive and is driven by previous case counts (“infectiousness”), i.e. the force of infection. We will discuss this modelling approach and its applicability to the current COVID-19 setting.

## 1.1. Applications

The EE framework has been applied to a multitude of infectious diseases classified as various types, e.g. diseases with other reservoirs than just humans, vaccine-preventable diseases, and vector-borne diseases, showcasing its versatility. See Table 1 for an overview of diseases analysed using the method. COVID-19 and SFTS are both currently considered emerging infectious diseases, showcasing the EE framework's flexibility and ability to consider both novel and established diseases. Since its introduction, the EE framework has been extended to cover many different aspects of disease modelling and statistical analysis ([58, 57, 33, 47, 32, 48, 62]). Recent extensions include the possibility to estimate the serial interval distribution ([13]) and methodology to adjust for underreporting ([12]).

**Table 1**: Applications of the EE framework.

| Disease | Reference(s) |
|---|---|
| Endemic porcine diseases | [3] |
| Leishmaniasis | [1, 52] |
| Dengue | [16, 75] |
| Invasive pneumococcal disease | [17] |
| Campylobacteriosis | [69] |
| Hand, foot and mouth disease | [6] |
| Measles | [30, 34, 50, 56] |
| Influenza | [58, 46, 47, 62] |
| Norovirus | [32, 31, 13] |
| Rotavirus | [13, 12] |
| Pertussis | [51] |
| Tuberculosis | [76] |
| Meningococcal disease | [58] |
| Severe fever with thrombocytopenia syndrome (SFTS) | [71] |
| Coronavirus disease 2019 (COVID-19) | see next section |

NB: A regularly updated table of use cases is maintained by Sebastian Meyer at `https://github.com/rforge/surveillance/blob/master/www/applications_EE.csv`.

The EE framework is considered state-of-the-art and is often used used as a benchmark model for comparison in infectious disease modelling and probabilistic forecasting ([7, 61, 64]). In model construction using the EE framework, it is possible to incorporate dependencies such as the spatial movements of a population under study; the effects of human movement can be examined statistically using gravity models ([14]). Gravity models examine the flow from one subpopulation to another taking into account locations on mobility networks rather than geographical distance. Such models have been used to examine measles epidemics ([72, 38]) and influenza pandemics ([68]). This is but one example of where the EE framework works well with other available modelling options. Finally, the EE framework is implemented in a readily available software package ([50]), and its extensions are included in a wider ecosystem of packages within the same software ([11, 49, 10]).

## 1.2. Comparison with mathematical modelling approaches

To provide further synergy with established methods, the EE framework can be motivated from the discrete-time SIR compartmental model ([36, 6, 67]) and can be adjusted to include natural depletion of susceptibles ([66]) as well as to incorporate potential future pharmaceutical countermeasures and vaccines ([34]). Co-occurrences and co-infections as well as the existence of multi-strain pathogens provide added levels of complexity to disease transmission. Specifically for multiple strains of a disease, Wakefield *et al.* [67] outline models that can be used for outbreak detection in settings — including the EE framework. Additionally, bivariate analysis of different diseases can be conducted, see e.g. the example of influenza and meningococcal disease by Paul *et al.* [58]. For this reason we believe the EE framework should conceivably be able to include 2020 influenza season in the northern hemisphere in a model for COVID-19. This is a co-occurrence and co-infection scenario being raised by policy makers as we enter the final months of 2020. We conceptualise one situation where full synergy between mathematical and statistical modelling may not be possible: consider the Anderson–May equation for calculating the basic reproductive rate of sexually transmitted infections. Mathematically it might make sense to consider the interplay between the five or so parameters but once we examine case count data, we may only really be able to estimate one parameter in place of the five. If the effects are not inseparable, additional data may be required to estimate them.

## 2. COVID-19 CASE STUDIES

We feel the EE framework is particularly well-suited to being adapted to examine COVID-19. The EE framework was developed in surveillance situations of weekly case counts of established diseases, both in terms of biology as well as available information capturing infrastructure of their associated surveillance systems, meaning no new data gathering approaches were required. The EE framework offers increased flexibility and robustness compared to more standard epidemic models which may need to be constructed on a disease-by-disease basis. The framework allows us to incorporate available evidence at various levels of detail and examine intervention measures and other explanatory variables, e.g. meteorological ([6]) with all unknown parameters being estimated with likelihood techniques from the available data. Spatio-temporal spread can be captured by suitably parametrised power laws ([47]) and gravity models ([72]), and long term predictions can be produced ([32]). Importantly, the spatio-temporal formulation of the EE model can be extended to include age-dependent contact information ([48]), which is often considered a proxy of transmission events for respiratory disease such as COVID-19. The EE model has also been extended to include higher order lags in the epidemic component, allowing for the inclusion of infectiousness from the entire serial interval in the analysis of daily COVID-19 counts ([13]). This allows us to consider data at a finer temporal resolution than weekly, and analyse the near-real-time daily COVID-19 case information. We are aware that the EE framework has been used in the epidemiologic and economic studies of COVID-19 listed in Table 2.

**Table 2**: EE models focusing on COVID-19.

| **Author** | **Area of focus** |
|---|---|
| Dickson *et al.* [20] | Italy |
| Giuliani *et al.* [28] | Italy |
| Alipour *et al.* [4] | Germany |
| Berlamann and Haustein [8] | Germany |
| Fritz and Kauermann [23] | Germany |
| Fronterre *et al.* [24] | England |
| Ssentongo *et al.* [63] | African continent |
| **SUSPend** | Switzerland and surrounding |

### 2.1. Introduction of the SUSPend project

We have been using EE modelling approaches in the *SUSPend: Impact of Social distancing policies and Underreporting on the SPatio-temporal spread of COVID-19* project. This project is funded by the Swiss national science foundation's emergency support for research into coronaviruses as project number 196247. A description of the project can be found at `https://data.snf.ch/covid-19/snsf/196247`. Within the SUSPend project we are working on two subprojects, both concern the introduction of time-varying transmission weights in the model. The first subproject incorporates a contact matrix which changes over time. In particular, we are considering a synthetic contact matrix for Switzerland ([25]). The benefit to using the synthetic contact matrix for Switzerland rather than the single empirical one which exists ([35]) is that the sampling approach for the synthetic matrix is well-designed and the sample size is sufficiently large. The Swiss contact matrix considers contacts in various settings and we have adjusted these to reflect social distancing measures put in place, similar to other approaches seen in COVID-19 modelling ([70, 60, 55, 21]). The obvious alternative to adjusting contact matrices would be to consider instead contact surveys conducted during the COVID-19 outbreak as part of the EpiPose project (`https://cordis.europa.eu/project/id/101003688`), whose contact survey work has recently expanded to cover additional countries, including Switzerland [personal communication]. Such information has mainly been gathered in the United Kingdom, an island nation in northern Europe, which may be very different to landlocked Switzerland. Additional contact surveys conducted during the 2020 COVID-19 outbreak have been done by Feehan and Mahmud [22] in a north American setting and Latsuzbaia *et al.* [45] in a central European setting, indicating there is an increasing awareness that understanding the evolution of contacts established during an ongoing outbreak is useful for informing future outbreak modelling efforts.

The second subproject we are working on uses time-varying adjacency matrices and focuses on spatial spread of COVID-19. We create time-varying adjacency matrices for the seven Swiss NUTS-2 regions and their immediate neighbouring regions. These matrices are adjusted from baseline adjacencies based on mobility data gathered from smartphone users available at subregional level. Such mobility data has been used in studies of COVID-19 in multiple countries, including: China ([63, 44, 42, 27, 2]), Taiwan ([15]), Japan ([43]), Italy

([59, 26]), France ([26]), the United Kingdom ([39, 5, 26]), the United States of America ([65, 40, 37, 74, 41]), and Brazil, Chile, Bolivia, Colombia, and Peru ([74]). Our first project concerns the first half of 2020 while the timescale considered in the second project is longer. The EE framework is suitably flexible to allow us to incorporate additional information as it is found to be important. Thus, considerations nested in both policy making and biological can be included in the model as they are identified.

An issue common to the COVID-19 pandemic, and thus both of our subprojects, is the presence of underreporting and reporting delays in case data ([53]). Simple multiplication factors can be applied to address the former. However, such multiplication factors need to be time-dependent to incorporate increased testing capacities and changes in testing strategies observed in some countries. Multiplication factors may also vary across age groups, which is particularly relevant for the subproject with time-varying contact matrices as this has an age focus. The usefulness of incorporating delays in disease surveillance models has been shown ([12]). Nowcasting allows us to predict the true number of case counts based on available data and can be used to address reporting delays. Within compartmental modelling, nowcasting is often referred to as “real-time modelling”. Nowcasting requires information both on test and reporting date on an individual basis. Unfortunately such information is rarely available in surveillance systems.

## ACKNOWLEDGMENTS

We thank Lucas H. Kook for fruitful discussion on the Anderson–May equation. Our suggestions of use of mobility data made available by software companies is not an endorsement of the entities who gathered it. Country designation used in this manuscript are without prejudice to positions on status of the Republic of China (Taiwan) under the terms of international law.

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