Chapter 11
Epidemiology

Arresting the spread of infectious diseases is a fundamental objective for the global health community. Decreasing the burden of infectious diseases benefits at-risk individuals and society as a whole. The eradication of smallpox through human intervention is a substantial historical achievement. Children are no longer subject to the potentially fatal disease; further, without the need to vaccinate children against smallpox, resources can be reallocated to other infectious diseases. Poliomyelitis, also known as polio, will likely join smallpox as the second human infectious disease eradicated, ridding the world of a devastating disease that paralyzes children. With the increase in data from advanced surveillance systems for disease, computational resources for modeling and analysis, and multibillion dollar intervention efforts for vaccines and vector-control programs, humanity is poised to make substantial gains against a number of infectious diseases. For example, the Bill and Melinda Gates Foundation is focused on supporting global health initiatives, such as the fight against polio, having provided nearly thirty-seven billion dollars in grants since inception [28]. In this chapter, we describe how to analyze infectious disease data with DMD and suggest how the method can support ongoing eradication efforts.

The spread of infectious disease can be a challenge to model due to the lack of a single set of governing equations derived from first principles. Further, the underlying disease system can be mathematically modeled with a large variety of methods, including deterministic ordinary differential equations, stochastic differential equations, and microsimulations via agent-based models [157]. The advantageous characteristics of DMD, namely the equation-free aspect of operating solely on data snapshots, can help in the analysis of infectious disease data. DMD is a powerful method that can help with the large number of measurements and the nonlinear dynamics within the data as well as identify important coherent spatiotemporal structures of disease spread [224]. We begin by describing how infectious disease data can be formulated for DMD. Two examples are presented that include data of actual infectious disease spread: flu in the United States and measles in the United Kingdom.

11.1 ▪ Modeling infectious disease spread

Mathematically modeling the spread of infectious disease has a rich history, going back to the early twentieth century with the seminal work of Kermack and McK-

Figure 11.1. *Images representing infectious disease spread. The left panel illustrates humans interacting around a common water source. The right panel indicates a common disease vector: the mosquito. A vector is any species that transmits a pathogen to another species. In the case of malaria, the mosquito acts as a vector for malaria spreading in human populations. Reprinted with permission from the Institute for Disease Modeling.*

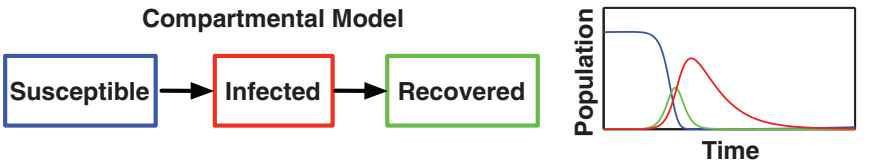

Figure 11.2. *The left panel illustrates a three-compartment dynamical model with three states: susceptible, infected, and recovered (SIR). The right panel shows an epidemic curve in time. The colors of the trajectories correspond to the compartment states.*

endrick [159]. One of the primary goals of computational epidemiology is to investigate how a population interacts with a pathogen in the context of a plethora of complex phenomena, such as the environment, heterogeneity in the population, and demographics. Figure 11.1 illustrates two complex disease interactions: people interacting at a local water source and the mosquito as an integral part of the transmission cycle of malaria. One of the early innovations in modeling was to abstract the population into groups according to their disease status. For example, people that are susceptible to acquiring a disease are grouped into a state called S. The population that is currently infected with the disease is grouped into the state I and the recovered in R. These states give rise to a model called SIR. Each individual in a population is thus grouped into one of three dynamical states or *compartments*, as in the left panel of Figure 11.2. This abstraction allows for a much lower dimensional dynamical model to be investigated versus modeling each individual in the population separately. An example of one such model is

$$\begin{aligned}\frac{dS_i}{dt} &= -\sum_{j=1}^{n}\beta_j S_i I_j,\\ \frac{dI_i}{dt} &= \sum_{j=1}^{n}\beta_j S_i I_j - \gamma I_i,\\ \frac{dR_i}{dt} &= \gamma I_i,\end{aligned} \tag{11.1}$$

where β is an infectious parameter and γ is the rate of recovery. These two parameters help define an important epidemiological characteristic: the basic reproduction number defined by $R_0 = \beta/\gamma$. If $R_0 > 1$, the disease-free solution of (11.1), where the entire population is contained in compartment S, is unstable. The introduction of a single infected individual would cause an epidemic. R_0 represents how many people are infected, on average, by a single infection into a naive population. Figure 11.2 shows an epidemic curve from a SIR-type model. A large number of models have been heuristically constructed to study different diseases and environmental situations; see [9, 157] for an extensive description of compartmental models both deterministic and stochastic, as well as agent-based models, where each individual is modeled independently.

The construction of a compartmental model to represent an infectious disease within a population requires a considerable number of modeling choices. The number of states within these models can be combinatorially large when considering a variety of heterogeneities within the population and/or pathogen. In (11.1), the index i could represent different age groups, where the infectiousness of the disease β_i is age dependent. Consider (11.1) with more indices representing different heterogeneities. To fit the parameters of this model, either extensive knowledge of the system or a significant amount of data is required. Instead of investigating the spread of infectious disease with models such as these, DMD is used to discover important dynamical characteristics solely from observational data.

11.2 ▪ Infectious disease data

DMD analyzes snapshots of infectious disease data from experiments, numerical simulations, or historical records to extract coherent spatiotemporal patterns. Data collected from separate spatial locations can be formed into vectors representing state snapshots that evolve in time. Figure 11.3 illustrates the collection of data and how to construct the DMD data matrices. In fluid dynamics, the measured state $\mathbf{x}_k$ is clearly related to the physics, for example, the velocity, vorticity, and stream functions at each discretized spatial grid point. For well-curated disease data, as found in the output of detailed numerical simulations, the choice of states $\mathbf{x}_k$ may be equally well defined, for example, the number of infections in a given spatial node. For data collected from the field, an aggregation step is required across both space and time. Often the data arrives in the form of individual patient records with a time and location information. To form the data matrices, the records have to be binned in space and time. Temporally resolving the individual records depends on the time scales involved in disease transmission. One natural choice for units of time is the average incubation period of the disease. In space, politically defined boundaries such as states, counties, or cities are often used. After deciding on the aggregation, each pair of state snapshots $\mathbf{x}_k$ and $\mathbf{x}_{k+1}$

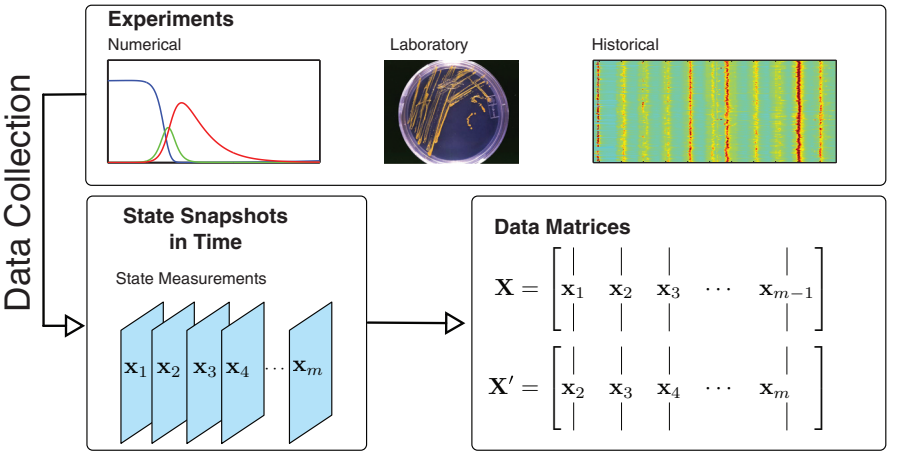

Figure 11.3. *An illustration regarding the collection of data from a variety of sources. Also, the snapshot data is collected into the data matrices for DMD. Reprinted with permission from Oxford University Press; figure adapted from* [224].

is collected and formed into the DMD data matrices:

$$\mathbf{X} = \begin{bmatrix} | & | & & | \\ \mathbf{x}_1 & \mathbf{x}_2 & \cdots & \mathbf{x}_{m-1} \\ | & | & & | \end{bmatrix}, \quad \mathbf{X}' = \begin{bmatrix} | & | & & | \\ \mathbf{x}_2 & \mathbf{x}_3 & \cdots & \mathbf{x}_m \\ | & | & & | \end{bmatrix},$$

where each column represents a different snapshot in time. Each row describes a specific state of the system, for example, the number of new disease cases involving children, at a given spatial location. DMD does not require sequential time-series data, where $\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_m$ are measured from a single trajectory in phase space. The data can be of the form

$$\mathbf{X} = \begin{bmatrix} | & | & & | \\ \mathbf{x}_1 & \mathbf{x}_2 & \cdots & \mathbf{x}_{m-1} \\ | & | & & | \end{bmatrix}, \quad \mathbf{X}' = \begin{bmatrix} | & | & & | \\ \mathbf{x}'_1 & \mathbf{x}'_2 & \cdots & \mathbf{x}'_{m-1} \\ | & | & & | \end{bmatrix},$$

where the dynamics relate $\mathbf{x}_k$ to $\mathbf{x}'_k$, but $\mathbf{x}_1, \mathbf{x}_2, \ldots$ may be nonsequential. This is an important distinction, especially if DMD is being applied to data collected from numerical simulations. In this case, the simulation can be executed with a variety of initial conditions representing different areas of phase space.

11.3 ▪ DMD for infectious disease data

Figure 11.4 illustrates the DMD computation for infectious disease data. The collection of eigenvalues and their respective dynamic modes represent the spatiotemporal patterns discovered within the dataset. The eigenvalues offer dynamic characteristics such as growth/decay and oscillatory behavior of each dynamic mode. In Figure 11.4, two pairs of complex eigenvalues are represented with red and blue open circles. The eigenvalues are plotted in the complex plane for a discrete dynamical system. Note

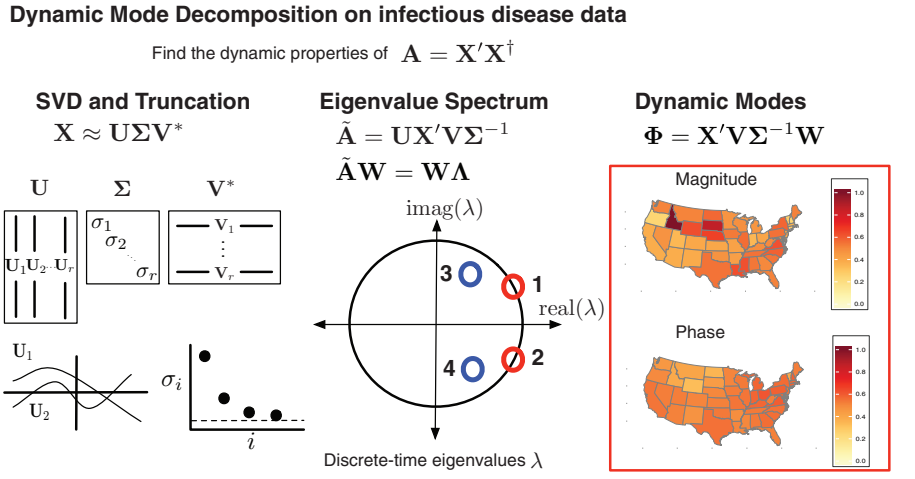

Figure 11.4. *A depiction of the DMD algorithm for infectious disease data. Reprinted with permission from Oxford University Press; figure adapted from* [224].

that if the eigenvalues are within the unit circle, they are stable. If outside, the eigenvalues are unstable. One pair of eigenvalues is on the complex unit circle, representing a purely oscillatory mode. Interpreting the oscillatory frequency in the complex plane for a given Δt can be difficult. Instead, the discrete eigenvalue can be converted in a continuous oscillatory frequency by the relationship

$$\text{frequency}_j = \frac{\text{imag}(\ln(\lambda_j))}{2\pi\Delta t}. \tag{11.2}$$

The relationship between discrete- and continuous-time eigenvalues was discussed in Chapter 1. In this chapter, we often refer to the continuous-time frequencies $\omega = \ln(\lambda)/\Delta t$ for interpretability. For example, examining continuous frequencies with units of (1/year) can be more convenient than with their discrete eigenvalue counterparts.

The dynamic modes offer a rich set of information about the disease system. For each mode, two important pieces of information are included for each element of the mode vector. The absolute value of the element provides a measure of the spatial location's participation for that mode. If the element is complex valued, the angle between the real and imaginary components is a description of the phase of that element relative to the others oscillating at the frequency associated with that mode. Figure 11.4 shows a single dynamic mode plotted in terms of magnitude and phase, where each element of the dynamic mode is a location on the map of the contiguous United States.

11.4 ▪ Examples

In this section, DMD is applied to two infectious disease examples. For each of these examples, a discussion is included examining both the data and the output of DMD. DMD identifies relevant spatiotemporal modes for each example.

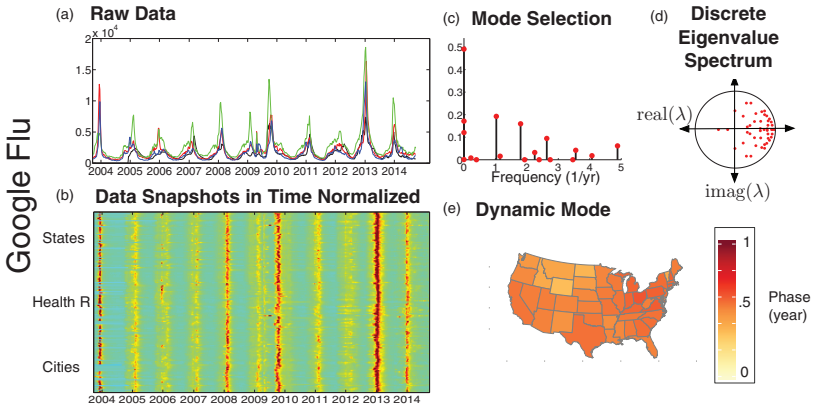

Figure 11.5. *An illustration showing the data from the Google Flu Trend tool and the output of DMD.* (a) *shows the raw data of four states' timeseries.* (b) *shows all of the locations; each timeseries has been normalized.* (c) *shows the mode selection plot.* (d) *illustrates the discrete eigenvalue distribution.* (e) *shows the phase of each element of a dynamic mode associated with the yearly frequency. Reprinted with permission from Oxford University Press; figure adapted from* [224].

11.4.1 ▪ Google Flu Trend

Google has analyzed how flu-related search terms are indicators for predicting the spread of flu within the United States. The output of the analysis has been publicly distributed as the Google Flu Trend tool, providing spatiotemporal data of flu in the United States [113]. Despite recent scientific investigations casting doubt on the validity of the Google Flu predictions [171], the dataset can be used as an example for applying DMD. In this example, we focus on the data from the United States.

The data provided by the tool comes in the form of a two-dimensional array with state, city, and health-human-service region on the location axis and time in seven-day increments on the other axis. Figure 11.5(a) shows four traces of raw data from Alaska (black), California (red), Texas (green), and New York (blue). All of the spatial locations' time series can be visualized by a heat map in (b) after normalizing each time trace by its own mean and setting the variance to one. This normalization helps to account for larger population centers; see [158] for a similar normalization. Figure 11.5 illustrates the clear seasonality of flu in the United States. In this example, we take data from June 2007 to July 2014 and focus solely on the state information to visualize the dynamic modes as a map of the contiguous United States.

The output of DMD is illustrated in Figure 11.5(c). The eigenvalue structure indicates a number of modes that are well within the unit circle. These eigenvalues will quickly decay and not contribute to longer time-scale behavior. The mode selection plot suggests the data contains a yearly frequency. The mode and frequency from DMD align with the striking seasonally varying profile in Figure 11.5(d). The phase of the dynamic mode associated with this yearly frequency is plotted in Figure 11.5(e). The phase is plotted between 0 and 1, representing the time of the year. The dynamic mode plotted on the map shows a number of interesting features. One such feature is the smooth transition of phase traveling north from California to Washington on the west coast. The phase information for this yearly seasonal flu dynamic mode offers

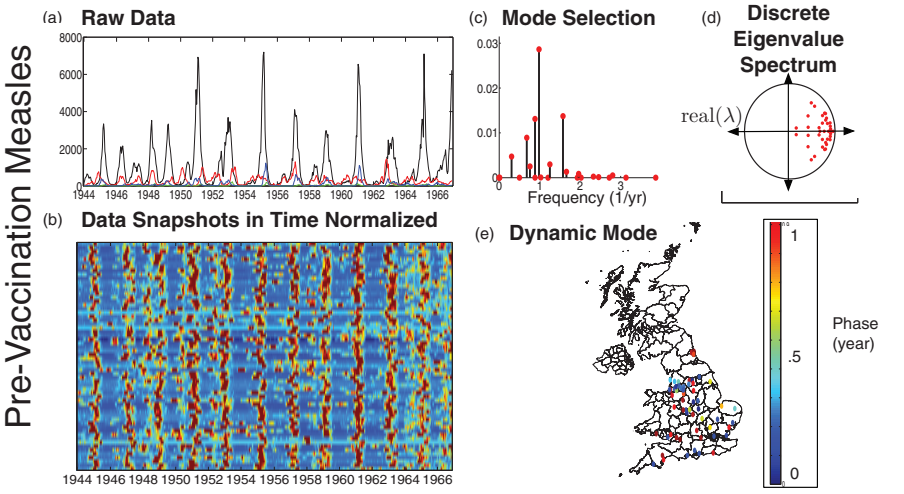

Figure 11.6. *An illustration showing the data from prevaccination measles in the United Kingdom and the output of DMD.* (a) *shows the raw data of four cities' time series.* (b) *shows all of the locations; each time series has been normalized.* (c) *shows the mode selection plot.* (d) *illustrates the discrete eigenvalue distribution.* (e) *shows the phase of each element of a dynamic mode associated with the yearly frequency. Reprinted with permission from Oxford University Press; figure adapted from* [224].

insight for public service campaigns against flu and timing of vaccination campaigns.

11.4.2 ▪ Prevaccination measles in the United Kingdom

DMD is now applied to data describing cases of measles from the prevaccination era of the United Kingdom over a 22-year period. The measles cases are reported every two weeks from 60 cities. Other traditional time-series analysis methods, like the Fourier decomposition, have been previously applied to this dataset [158]. Figure 11.6(a) illustrates four time traces of the raw data from four cities, London (black), Liverpool (red), Colchester (green), and Cardiff (blue). Similar to the first example, each location's time series is normalized in mean and variance, allowing for visual comparison. The normalization allows for places with large populations, like London, to be compared to smaller towns.

Similar to the Google Flu data, a clear seasonality is visually apparent in Figure 11.6 for the measles dataset. A notable distinction in the United Kingdom data, compared to the flu, is the wider diversity of peak measles times by year and city. DMD identifies the seasonal mode and finds the phase difference across different cities. Figure 11.6(d) shows the eigenvalue distribution. The phase of the dynamic mode associated with the yearly cycle (computed at ≈ 0.98 per year) is illustrated in Figure 11.6(e). Groupings of cities near London share similar phase whereas a number of cities in western United Kingdom are more than four months out of phase.

11.5 ▪ The epidemiological interpretation of DMD modes

The dynamic modes discovered by DMD allow for a number of interesting and relevant epidemiological interpretations of the large-scale dynamic patterns of infectious disease spread. DMD automatically identifies the frequency content of the time series. In addition to identifying oscillations, the eigenvalues of the DMD output can also have a decay or growth component. The dynamic modes associated with these eigenvalues describe the relative phase of oscillation by examining the angle of each element in the dynamic mode, as shown in both the flu and measles data examples. The phase information alone is useful for allocating vaccine resources for the year, sending surveillance teams to monitor the disease, and timing the interventions to leverage natural disease dynamics.

The dynamic modes offer insight into the epidemiological connectedness of spatial locations. Most disease monitoring is reported along political boundaries. The dynamic modes help connect politically defined areas into groupings of spatial locations that are evolving with similar dynamics. Within each dynamic mode, the magnitude of the element provides a measure of the contribution of that location to the mode. In the examples, similar phase information indicates well-connected areas, such as the Montana, Washington, Idaho, and Wyoming grouping or the states in New England for flu. Its important to note that the areas do not necessarily need to be physically connected to each other to be epidemiologically connected. Different modes of transportation, such as air travel, might connect areas that are separated by great distances, such as Los Angeles and New York City.

For infectious diseases like poliomyelitis, supplementary immunization activities (SIAs) are conducted in portions of countries that are believed to still be endemic. These SIAs are focused, short-term immunization campaigns. The dynamic modes can help with campaign planning by identifying the epidemiologically linked areas and directing resources according to their dynamics. Further, surveillance teams can be deployed according to expected cases given the underlying dynamics. This helps minimize redundant measurements. The dynamic modes and their respective frequencies offer a number of exciting avenues for helping with ongoing eradication campaigns and the general control of the spread of infectious disease. The methodological extension of DMD to include inputs, described in Chapter 6, will also help with planning eradication campaigns. DMDc identifies how the inputs drive the system, which could substantially benefit intervention efforts.