Deterministic Modeling Of Infectious Diseases: Theory And Methods
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Citation

Abstract
This study aims at providing an understanding of deterministic modeling as applied to the population dynamics of infectious diseases. Deterministic modeling is based on the nonlinear dynamics of infection spread in a population. The SEIR deterministic model can provide useful insights into the mechanic of many common childhood diseases such as measles. Simple deterministic models can help us identify the factors controlling the persistence and stability of transmitted viral and bacterial infections within large human communities. Deterministic models exhibit damped oscillations, show random variations (in chaotic regime), and predict the spread of infectious diseases. This paper provides an introduction to the theory and methods of deterministic modeling and will be followed by two other articles that will show how sensitivity analysis can be helpful for the forecast and control of common infectious diseases at the population scale.

INTRODUCTION
Traditional epidemiology studies disease with linear statistical (stochastic) models that consider individuals as though they were independent units of observation like balls in an urn. Further, these models are static and descriptive of epidemiologic phenomena that are thought to have attained a stable state(1). This traditional way of thinking disease processes is based on Newtonian physics; this means that, however complicated the disease mechanic may be, the relation of causes to effects is straightforward, that is, interactions are either ignored or considered second-order processes(2). Despite the pervasiveness of this well entrenched positivism, the complexity of natural processes has been recognized by the French mathematician Henri Poincaré for the first time at the start of the XXth century. Since then, the new paradigm of complexity has attempted to slowly find its way into epidemiology. Today, the study of complex systems involving nonlinear dynamics is investigated seriously(3-5). More recently, chaos theory has been developed that showed the importance of nonlinear phenomena in infectious disease processes(6). This new paradigm has elicited a conceptual upheaval because the fixed and static traditional approach is seen as inadequate to study the dynamic aspects of nonlinear phenomena(7). Complex systems change, evolve, adjust, and adapt their dynamics constantly. Nothing is static or invariant in complex systems, and everything has a historic background that constantly impinges on the particular pathway the system borrows. Epidemic phenomena are a case in point here. Propagation of infection in a population is complex as the system changes and adapts to exogenous (e.g., seasonal variation in the contact rate) as well as endogenous factors (e.g., herd immunity, prevalence of cases). Actors (individuals) in complex systems are interdependent and institute a dynamic that cannot be recognized by static or linear statistical models. Nonlinear deterministic modeling allows us to approach moderately complex systems and understand the interdependence between the individuals that constitute the system. This is a turning point in causal research as it allows to go beyond the traditional causality paradigm(5).

This paper aims at providing an understanding of how dynamic deterministic modeling can unveil the mechanic of the population dynamics of diseases. Infectious diseases at the population scale have been well studied with deterministic models(8,9). Also, this paper will provide a basic understanding of dynamic modeling as applied to infectious diseases in populations. This paper will later be followed by a second that will deal with an application of deterministic modeling to common childhood diseases; we will then show how dynamic modeling will allow us to modify the parameters of disease control as well as to forecast disease dynamic. Last, a third paper will describe how deterministic modeling can help figure out the interplay...
of AIDS and TB.

STOCHASTIC VERSUS DETERMINISTIC MODELS

Two types of model are useful in the study of infectious diseases at the population scale: these are stochastic and deterministic models.

Stochastic models rely on among-individual chance variation in risks of exposure, disease, and other factors. They are used when chance fluctuations or known heterogeneities are important as in small or isolated populations. Stochastic models have several advantages. More specifically, they allow follow-up of each individual in the population on a chance basis. Stochastic models, however, can be laborious to set up and need many simulations to yield useful predictions. Notwithstanding, incorporating chance variation into transmission processes provides a range of possible outcome-based probabilities(10). These models can become mathematically very complex and do not lend themselves to an explanation of the dynamic. We will not expand on stochastic models in this paper.

Deterministic models, also known as compartmental models, attempt to describe and explain what happens on the average at the population scale. They fit well large populations. These models categorize individuals into different subgroups (compartments). The SEIR model, for example, includes four compartments represented by the Susceptibles, Exposeds [infecteds], Infectious, and Recovereds [immunizeds]. Further, the models specify the transition rates between the compartments as susceptibles may become exposed, exposed infectious, and so on. The best known transition rate is the force of infection or attack rate that measures the rate at which susceptibles become infected.

Most models of infectious disease processes used until now are deterministic because they require less data, are relatively easy to set up, and because the computer softwares are widely available and user-friendly. The dynamics of the SEIR model are now well understood so that deterministic models are commonly used to explore whether a particular control strategy will be effective. Furthermore, many other more complex models exist that can incorporate stochastic elements, but we shall not be concerned with these models here.

INFECTIOUS DISEASES DYNAMICS

Before going on with deterministic modeling, it is important to understand how epidemics set up in a population. For diseases conferring long-lasting immunity following infection (e.g., measles), the number of susceptibles decreases with time. Before the outbreak of a first measles case, the proportion of susceptibles (S) is 100% in the population because everyone is susceptible; therefore, the proportion of exposed (E), infectious (I), and immune (R) is 0. When an epidemic starts to spread, S decreases, and I and R increase until every infected gets immunized. Chart 1 displays an example of a measles epidemic situation for a population of 100 000 persons.

Figure 1
Chart 1: The dynamic of measles epidemic

The potential of infection in a population depends on the basic reproduction number (Ro) that is defined as the average number of persons directly infected by an infectious case during his entire infectious period when he enters a totally susceptible population(11). The development and size of an epidemic are determined by Ro that relies on:

- the attack rate (risk of transmission per contact),
- the number of potentially infectious contacts that the average person in a population has per unit time,
- and the duration of the infectivity period(11).

If, at any time, Ro gets smaller than 1, the disease eventually disappears from the population because, on average, each infected cannot insure transmission of the infectious agent to one susceptible; this results in new waves of infection being of lesser amplitude than preceding ones and, finally, to disease elimination. On the other hand, if Ro equals 1 the disease remains endemic as one infectious transmits the infectious agent to one susceptible on the average. Last, if Ro gets greater than 1 an epidemic builds up. This threshold theorem has been established by Kermack and McKendric(12) and explains why the introduction of
infectious individuals into a community of susceptibles does not automatically give rise to an epidemic outbreak.

**DETERMINISTIC MODELING**

The first step of deterministic modeling consists in having a complete and realistic picture of the biology of the disease (e.g., the duration of the period of infectivity, incubation period, immune status after infection). The second step is to collect data on the demographic, epidemiologic, and biologic characteristics of the infection (transition rates) and the population (birth and death rates). Third, a parsimonious model is selected.

**Chart 2: Common models of infectious diseases**

Chart 2 shows some of the more common models used in infectious disease modeling. For example, the SEIR model (most appropriate for measles) takes care of the infecteds (E). This means that the model (and the available data) accounts for the latent period of the disease; this model is needed when infected individuals (exposed) go through a latent period before being infectious. The latent period of measles is well known (about 8 days), and this information has to be translated in an appropriate model. If, on the other hand, one deals with an infectious agent with no latent period (individuals are infectious as soon as infected) then SIR would offer a relevant alternate model. Further, one may notice that the SEIR model postulates long-lasting immunity after infection since there is no transition from the recovereds to the susceptibles. The SIRS and SEIRS models rather posit that the recovereds become susceptibles as their immunity dies away.

The rate-limiting step in epidemics is Ro. This is a measure of the force of infection, i.e., the rate at which susceptibles become infected. Ro implies that susceptibles get in contact with infectious and that the contact can lead (with a probability b) to effective transmission of the infectious agent (this takes account of the type of contact and the duration of the period of infectivity). A mass action principle (everyone can contact anyone in the population) is involved in determining the frequency of infections that denies heterogeneity in the contact rate. The SEIR model thus remains simple because no population age-structure is considered, random mixing is posited whatever the geographic distance and social organization characterizing the S and I compartments (mass action principle), no seasonal variation of the contact rate is involved (such as one would like to postulate for measles), and the force of infection is age/time-independent. Further, the population birth and death rates, which could alter the dynamics of the disease, are considered stable so that population growth or dampening is denied by hypothesis. As it stands, therefore, the SEIR model can be used for short-term forecasts only. Of course, the neglected quantities of the SEIR model can be allowed for if data are available, but this would make for a more complex model. It has however been shown that the SEIR model as is can indeed capture the mechanic of disease infection in the population and allow for meaningful predictions.

**DETERMINISTIC MODELING USING DIFFERENCE EQUATIONS**

Deterministic models may be analyzed with either difference or differential equations. Difference equations describe the transitions between the different disease compartments using discrete time steps and by expressing the number of cases at a given time \(t+1\) in terms of that at the preceding time \(t\). For the SEIR model, this would mean that:

**Figure 3**

\[
\begin{align*}
S_t & \xrightarrow{l} E_t \xrightarrow{f} I_t & I_t \xrightarrow{r} R_t
\end{align*}
\]

where:
- \(R_t\) = number of immunes at time \(t\)
- \(S_t\) = number of susceptibles at time \(t\)
- \(E_t\) = number of infected but not yet infectious at time \(t\)
- \(I_t\) = number of infectious at time \(t\)
l = is the risk of a susceptible individual becoming infected or the average rate of infection per susceptible per unit time (l = b*I with b being the effective contact probability between infectious and susceptibles). Consult Philippe(13) for a difference between a risk and a rate.

f = is the risk of an infected individual becoming infectious per unit time

r = is the risk of an infectious individual of recovering (immune) per unit time.

The number of Susceptibles, Exposeds (infecteds), Infectious, and Recovereds (immunizeds) at time t+1 is therefore given by the following difference (recurrence) equations:

\[ S_{t+1} = S_t - \beta S_t I_t \] (or: \[ S_{t+1} = S_t - lS_t \])

\[ E_{t+1} = E_t + \beta S_t I_t - fE_t \]

\[ I_{t+1} = I_t + fE_t - rI_t \]

\[ R_{t+1} = R_t + rI_t \]

Modeling with difference equations can easily be implemented using “Excel” software (Microsoft Office). Information is required on the contact parameter (β) and transitions parameters (f and r). Technically, the transition parameters are supposed to be transition risks, but if the rate remains small (< 0.10) the risk is approximately equal to the rate(13). The reliability of models based on difference equations depends on the size of the time step used. The most accurate description of the transmission dynamics are obtained using time steps which are as small as possible. When the time step is too large, for example 5 days, the output of the model is nonsense as the dynamic of infection is not a matter of weeks but days or hours. This occurs because the transition rates (assumed to be continuous in time) are at variance with the time step used. Time steps should therefore match the epidemiology of the disease process to model. Thus, differential equations (rather than difference equations) have to be used to describe the transmission dynamics of an infection.

DETERMINISTIC MODELING USING DIFFERENTIAL EQUATIONS

To highlight the fact that we consider the transitions for continuous rather than discrete time intervals, we use the symbols S(t), E(t), I(t) and R(t).

\[ \frac{dS}{dt} = -lS(t) \]
\[ \frac{dE}{dt} = lS(t) - fE(t) \]
\[ \frac{dI}{dt} = fE(t) - rI(t) \]
\[ \frac{dR}{dt} = rI(t), \]

where \[ dS/dt \] means «change in S per (small) unit time dt». More explicitly, \[ dS/dt = -lS(t) \] means that the compartment of susceptibles depletes itself of the quantity lS(t) as susceptibles become infected (E) during the time interval dt. The number of newly infected \[ lS(t) \] is added to the exposed (E) compartment (second equation) which is, itself, reduced by a quantity \( fE(t) \) on behalf of the infectious compartment (third equation), and so on.

Modeling with differential equations can be undertaken with specialized softwares like “Stella” (High Performance Systems) or “ModelMaker” (Family Genetix). These softwares allow the user to sketch models and estimate the impact of transition parameters and their change on the epidemic situation. This aspect of modeling (sensitivity analysis) will be the topic of the second paper in this series.

The models presented in Chart 2 are quite simple. They assume that individuals mix at random (mass action
principle), they do not stratify individuals according to age and sex, the population size is assumed constant over time (no birth or death rates are taken into account), and the transition rates are expected to remain invariant in time. Some of these assumptions may be unrealistic, but the model can nevertheless reproduce the commonly observed short-term seasonal cycles of infections observed in many populations.

**DISCUSSION**

The major problem with all infectious disease models is that the contact pattern in the population is often unknown, and somewhat difficult to measure. Further, the $I_S(t)$ or $bS(t)I(t)$ equation component is a source of important nonlinearity of the SEIR model. It can make the difference between regular cyclic variations of incidence and chaos. Notwithstanding, the models with their current limitations can be used to better the understanding of the nonlinear dynamics of infection spread in a population. This is because one must distinguish between predictive modeling and explanatory modeling. Predictive modeling uses complex models in the hope to mimic observation as closely as possible. Explanatory modeling is rather concerned with capturing the main features of a dynamic given some assumptions. Explanatory modeling thus aims at understanding the dynamics. Explanatory modeling can, therefore, help interpret observed epidemiological trends, guide the collection of data towards further understanding, and design programs for the control of infectious diseases. In fact, simple deterministic models can help us gain insight into the factor controlling the persistence and stability of transmitted viral and bacterial infections within large human communities. On the whole, explanatory deterministic models exhibit damped oscillations, show random variations (in chaotic regime), and predict the spread of infectious diseases.

The next paper in this series will show how changes in the transition rates or varying the assumptions of the models can alter the profile of an epidemic. This step of data analysis will provide us with a powerful mean not only to understand how epidemics evolve, but also how they can be controlled.

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**References**

1. Philippe P. and Mansi O: Nonlinearity in the epidemiology of complex health and disease
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