INTRODUCTION TO THE POPULATION DYNAMICS OF INFECTIOUS DISEASES
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LAYOUT OF THE COURSE
This lecture course is divided into six sections. Apart from the first review section all other sections will have two parts. In the first part I’ll describe the basic mechanisms, concepts and results, in the second part we will focus our attention on the more applied literature to understand how these ideas are used in practice.

• Review Lectures 11 & 12
The basic models of infectious disease dynamics (the SIS and SIR models) are reviewed. Particular attention is paid to what biological understanding can be gained and the assumptions that underlie the models. The heterogeneities that arise when these assumptions are relaxed are also discussed.

• Age-Structure Lectures 13 & 14
We look at adding age-structure to the standard models, and consider why measles and whooping cough are childhood diseases. The implications of non-random mixing and the who acquires infection from whom matrix are discussed. We consider how the average age of infection can change and what effects this may have on disease severity. Finally, the idea of “endemic stability” is examined.

• Multi-Host / Multi-Strain Lectures 15 & 16
Diseases and hosts do not exist in isolation. Many diseases can infect multiple hosts, all hosts have many disease and strains of diseases that can infect them. Here we review the models necessary to understand such situations, concentrating primarily on the dynamics of strain structure.

• Stochasticity Lectures 17 & 18
The transmission of disease is inherently a stochastic process, with infection having an element of chance. The standard deterministic (clockwork) models have to be radically altered to mimic such random events. These models can then be used to predict the chance extinction of diseases when the level of incidence becomes low.

• Macro-parasites Lecture 19
So far we have only considered micro-parasites (diseases caused by viruses and bacteria). As the name suggests macro-parasites are much larger and generally have more complex life-cycles; this necessitates more complex models. In this lecture we review the basic elements of macro-parasite models.

• Complex models Lecture 20
In this final lecture we consider the formulation and behaviour of a complex model which includes spatial heterogeneity, stochasticity, multiple hosts, and time-varying parameters.

FINDING THE RIGHT MODEL.
First – “there are no right model, but there are certainly lots of wrong ones.”. Picking the right model for the job is a trade-off between simplicity, accuracy and generality. An inaccurate model is no good to anyone, we need a model that approximates what’s going on in the real world. A complex model might be more accurate (in general), but it may be too complex to understand
or parameterise. Finally, we need a model that is general enough that it can be adapted to suit our purposes. We can broadly classify models into three groups.

- **Simulations: complex but accurate** Such models include all the gory details. They attempt to describe every process and hence paint as accurate a picture as possible of the real system. The prime example of a simulation is the large computer models used for weather prediction - an example from the ecological literature is the forest competition model SORTIE and the ecosystem model ATLSS. Another large scale simulation comes from general circulation models for ocean productivity, here meteorological data and ocean flows are combined with plankton models to create detailed spatial predictions. Simulations such as these should only be used when an exact answer is required as they usually provide little intuitive understanding of the problem. However they may be used to perform ‘experiments’ which could not be attempted on the natural system.

- **Models: simple and general** Probably the most common way of analysing a biological system; they attempt to capture the main features and are parameterised with a specific problem in mind. In general they do not provide analytical solutions, but many of the standard mathematical techniques can be applied numerically.

- **Caricatures: simple** These types of model are highly generic (so the results hold for many biological systems) and they often give analytically tractable results. Caricatures are most commonly used to gain an intuitive understanding of an additional feature which is not commonly included, such as spatial heterogeneity, genetic variability or stochasticity.
Lectures 11 & 12: REVIEW

The Notation and Classification
Most diseases we shall be considering are caused by either viruses or bacteria. However, we shall ignore the dynamics within the human body (the interaction between diseases and the immune system is a growing field that is yet to be fully explored). Instead we classify individuals according to their status with respect to the disease,

- **Maternal Immunity** For around 6-12 months after birth, new-born infants may be protected by maternal immunity. For modelling purposes this is often ignored, individuals are only assumed to by “born” once maternal immunity has waned.
- **Susceptible** Individuals in this class can catch the disease if they are exposed to it. The number of susceptible individuals is usually labelled $S$.
- **Exposed** This class, usually labelled $E$, covers those people that have caught the disease, but that are not yet infectious. They are incubating the disease, with the number of viral particles or bacteria increasing rapidly.
- **Infectious** Infectious individuals, $I$, can spread the disease to any susceptibles that they come into contact with. (Note that Infected individuals are those that are either exposed or infectious)
- **Recovered** These people have recovered from the disease. Often (as is the case for measles) they maintain a life-long immunity after infection, although for other diseases with multiple strains (such as influenza) this is more complex. Not surprisingly these are labelled $R$.

Not all disease models will include all of these classes, and some models will include more. For example, there may be a vaccinated class, there may be waning immunity such that those individuals who have recovered steadily decay to a partially-susceptible class. We may also wish to sub-divide the classes further, such that the population is age-structured or sexually-structured. In the next few lectures we shall consider in detail a variety of models which use these classes in different combinations.

The Basic Reproductive Ratio $R_0$
This is without doubt the most important quantity in the whole of epidemiology. It is defined as ....

The *average* number of secondary cases produced by an *average* infectious individual in a totally susceptible population.

As such it tells us whether a disease can invade a naive population. If $R_0 > 1$, then each infectious individual creates more than one new case and hence the disease spreads. When $R_0 < 1$ the disease dies out. Thus there is a relationship between $R_0$ and the stability of the disease-free state.

The following table shows the values of $R_0$ for a range of well-known diseases. Note the wide range of values, and the fact that $R_0$ depends on both the disease and the environment.

<table>
<thead>
<tr>
<th>Disease</th>
<th>$R_0$ (approx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small pox</td>
<td>4</td>
</tr>
<tr>
<td>Measles</td>
<td>17</td>
</tr>
<tr>
<td>Chicken pox</td>
<td>11</td>
</tr>
<tr>
<td>HIV (male homosexuals in England and Wales)</td>
<td>4</td>
</tr>
<tr>
<td>HIV (female prostitutes in Kenya)</td>
<td>11</td>
</tr>
<tr>
<td>Malaria</td>
<td>$\approx 100$</td>
</tr>
</tbody>
</table>
The S-I-S Model

The SIS model, showing the routes between the compartments.

The Susceptible-Infectious-Susceptible model is by far the simplest of all epidemiological models, but it serves to illustrate the main features of all disease models. It is commonly used in the study of sexually transmitted disease, where due to the vast number of strains there is no such thing as a recovered class. The dynamics of this model are described by,

\[
\begin{align*}
\frac{dS}{dt} &= BN - \beta SI/N + gI - dS \\
\frac{dI}{dt} &= \beta SI/N - gI - dI \\
\text{where } N &= S + I
\end{align*}
\]

Where \( B \) is the birth rate per individual, \( d \) is the natural death rate, \( g \) is the rate that infection is 'lost' or the recovery rate, and \( \beta \) is the so-called transmission or contact rate. We note that the term \(-gI\) means that infectious individuals decay back to being susceptible (cf radioactive decay and half-lives). The rate at which susceptibles catch the disease is termed the **force of infection**, \( \lambda \),

\[
\lambda = \frac{\beta I}{N}
\]

We note that the interaction between susceptibles \( S \) and infectious \( I \), is divided by the total population size \( N \). This is termed **pseudo mass-action**. True mass-action, which comes from thinking about randomly moving particles, would not be divided by \( N \). For true mass-action we would be envisaging a situation where as the population increased the individuals became more and more tightly packed and hence interacted more often. For most human populations, the density of individuals is fairly independent of population size – in fact it is the number of social contacts that is the determining factor. It appears that **pseudo mass-action** is the best description of human diseases – the evidence comes from the fact that the same parameters can be used to produce accurate models of measles and other diseases across a wide range of population sizes.

We can make this model even simpler by restricting our attention to a closed population without births or deaths \( (B = d = 0) \).

\[
\begin{align*}
\frac{dS}{dt} &= -\beta SI + gI \\
\frac{dI}{dt} &= \beta SI - gI
\end{align*}
\]

where \( S \) and \( I \) are now the proportion of susceptible and infectious individuals respectively. From this most basic of models we can calculate \( R_0 \).

\[
R_0 = \text{(rate at which secondary cases are produced)} \times \text{(average infectious period)} \\
= (\beta S) \times \left( \frac{1}{g} \right) = \frac{\beta}{g}
\]
So $R_0$ is increased by a long infectious period or a high rate of transmission.

We now want to look in more detail at the behaviour close to the fixed points. First we notice that we can simplify the dynamics by setting $S = 1 - I$, we then get the logistic growth model,

$$\frac{dI}{dt} = \beta(1 - I)I - gI = [\beta - g]I \left(1 - \frac{I\beta}{\beta - g}\right)$$

From this it should be obvious that the fixed points are $I^* = 0$ and $I^* = 1 - \frac{g}{\beta}$. Alternatively this could be written as $S^* = 1$ and $S^* = \frac{1}{R_0}$. This latter relationship is a classic result that we will show is generally true for a wide variety of models, the non-trivial level of susceptibles is the inverse of $R_0$.

The left-hand graph shows the typical dynamics of an SIS model ($\beta = 1.2, g = 1$), the right-hand graph shows how $S^*$ varies with $R_0$.

**THE S-I-R MODEL**

 SUSCEPTIBLE $\rightarrow$ INFECTIOUS $\rightarrow$ RECOVERED

The SIR model, showing the routes between the compartments.

The simple SIS model could be reduced to one-dimension (as $S$ and $I$ are related), as such its dynamics is trivial and cannot capture the behaviour of many real human diseases - although it can give a reasonable description of some STDs. We now study the SIR model – adding a recovered class which cannot catch the disease.

**The Simple Epidemic**

Initially, we shall ignore all demography (births and deaths) by assuming that the progress of the disease is much more rapid than the natural birth and death rate. This model is called the
Simple Epidemic and may provide a good description of a ‘one-shot’ disease such as influenza.

\[
\begin{align*}
\frac{dS}{dt} &= -\beta SI \\
\frac{dI}{dt} &= \beta SI - gI \\
\frac{dR}{dt} &= gI
\end{align*}
\]

The initial condition for this system is \( S(0) = 1 - \varepsilon, I(0) = \varepsilon, R(0) = 0 \), with \( \varepsilon \ll 1 \). Hence we are again dealing with proportions of the population, and we have assumed that all individuals are initially susceptible and then introduce a very small quantity of infection. We can find a value for \( R_0 \), which again is \( \beta / g \). We note that there is still a simple relationship between \( S \) and \( R_0 \); when \( S > 1/R_0 \) the disease increases whereas when \( S < 1/R_0 \) the disease decreases. We note that the only fixed-point of the system is when there is no disease present \( I^* = 0 \).

The left-hand graph shows the typical dynamics of a simple-epidemic SIR model \((\beta = 1.2, g = 1)\), the right-hand graph shows how the final size of the epidemic varies with \( R_0 \).

For this simple-epidemic, the more interesting question is the final state of the system. It is clear that without births to replenish the number of susceptible individuals, the level of susceptibles must decrease through time. This in turn leads to a decrease in the amount of infection - the question is does the disease die out before all the susceptibles are exhausted. We now wish to determine the final size of the epidemic \((R_\infty)\),

\[
R_\infty = R(\infty) = 1 - S(\infty) = \text{total proportion infected}
\]

We calculate this value using an important trick developed by Kermack and McKendrick (1927):

\[
R_\infty = 1 - \exp \left( -R_0 R_\infty \right).
\]

Although this has no analytical solution we can easily calculate its value numerically, in which case we find that \( R_\infty \) rapidly approaches 1 as \( R_0 \) becomes significantly larger than one.

The full SIR model

In reality there is no single model that can be called the SIR model - many different slight variations exist. The version given below is one of the most used, and displays all the important
features common to this family of models.

\[
\begin{align*}
\frac{dS}{dt} &= B - \beta SI / N - dS \\
\frac{dI}{dt} &= \beta SI / N - gI - dI \\
\frac{dR}{dt} &= gI - dR \\
N &= S + I + R
\end{align*}
\]

In general this is a three-dimensional system, but to simplify matters we can set \( B = dN \) such that the population size remains constant, and then rescale so that we are again dealing with proportions. We now look at the fundamental parameters and dynamics of this model.

For the full SIR model, with births replenishing the level of susceptibles, there is a second fixed point in which the disease is present. From setting \( \frac{dI}{dt} = 0 \) we get,

\[
S^* = \frac{g + d}{\beta} = \frac{1}{R_0}
\]

which shouldn’t be too surprising. And from \( \frac{dS}{dt} = 0 \),

\[
I^* = \frac{B}{g + d} - \frac{d}{\beta}
\]

It should be clear that the number of infectious individuals is limited by the birth rate – clearly it is impossible to keep infecting more people than are being born.

Looking at the Jacobian for this fixed point provides a very important insight into the dynamics of real diseases,

\[
J = \begin{pmatrix} -\beta I - d & -\beta S \\ \beta I & \beta S - g - d \end{pmatrix} = \begin{pmatrix} -\frac{\beta B}{g + d} & -g - d \\ \frac{\beta B}{g + d} - d & 0 \end{pmatrix}
\]

Therefore the eigenvalues are,

\[
\lambda = -\beta d \pm \sqrt{\beta^2 B^2 + 4d(g + d)^3 - 4\beta B(g + d)^2} \frac{2(g + d)}{2(g + d)}
\]

and making the assumption that \( d = B \) is small compared to the other terms,

\[
\lambda = -\beta d \pm 2i \sqrt{d g^2 (\beta - g)} = -\frac{d R_0}{2} \pm i \sqrt{d(\beta - g)}
\]

So it is clear that if \( R_0 \) is greater than one then the fixed point will be stable, and we converge to this point with damped oscillations.

The SIR model displays damped oscillations spiralling in towards the equilibrium. The period \( T \) is given by:

\[
T = \frac{2\pi}{\sqrt{d(\beta - g)}} = 2\pi \sqrt{\frac{\text{Life expectancy \times Infectious Period}}{R_0 - 1}} = 2\pi \sqrt{\text{Average age of infection \times Infectious Period}}
\]
The dynamics of the full SIR model using the parameters for measles in England and Wales ($B = d = 5.5 \times 10^{-5}$ per day, $R_0 = 17$, $g^{-1} = 13$ days). Note the period of inter-epidemic oscillations, which is longer for large epidemics due to non-linearities far from the fixed point. The susceptibles decline during an epidemic, but are replaced by births in the troughs.

We note that this approximation only holds when the oscillations are small. For larger oscillations, the period between epidemic is longer.

**Vaccination**

Successful vaccination moves individuals straight into the recovered class, so that they can no-longer catch or spread the infection. We can therefore introduce a model in which individuals are vaccinated at a rate $V$ (note that the vaccination of infected or recovered individuals is assumed to have no effect).

\[
\begin{align*}
\frac{dS}{dt} &= B - \beta SI - dS - VS \\
\frac{dI}{dt} &= \beta SI - gI - dI \\
\frac{dR}{dt} &= VS + gI - dR
\end{align*}
\]

If the disease remains endemic, we have the equilibrium solutions $S^* = 1/R_0$ (surprise surprise) and $I^* = \frac{d}{\beta + d} - \frac{V}{\beta}$. However, if the level of vaccination is sufficiently high we can eliminate the disease, in particular $V > d(R_0 - 1)$. Above this critical level $S^*$ is kept below $1/R_0$ even when the disease is absent, so the disease cannot re-invade. This leads us to the critical vaccination threshold — the proportion of the population that needs to be vaccinated if a disease is to be eradicated and prevented from returning.

\[V_C = 1 - \frac{1}{R_0}\]

Thus diseases with a low $R_0$, such as small-pox ($R_0 \approx 5 \Rightarrow V_C \approx 80\%$), can be easily eradicated by vaccination, whereas diseases with high $R_0$, such as measles ($R_0 \approx 17 \Rightarrow V_C \approx 94\%$) and malaria ($R_0 \approx 100 \Rightarrow V_C \approx 99\%$) are much more difficult.
SUMMARY

- For a disease to persist, the susceptibles need to be replaced either by new births (SIR), or recovering individuals (SIS).

- In general $R_0$ is approximately:

\[
\frac{\text{Transmission rate}}{\text{Recovery rate}} = \frac{\beta}{g}
\]

- When $S > 1/R_0$ the level of infection increases, when $S < 1/R_0$ the level of infection decreases. Hence at equilibrium $S^* = 1/R_0$.

- For the SIR model, the natural period of the epidemics can be related to measurable demographic factors. Many perturbations can excite regular epidemics close to this natural period.

- To eradicate a disease it is necessary to vaccinate a proportion $1 - 1/R_0$ of the population.
Lectures 13 & 14: AGE-STRUCTURE

A two-class age-structured model, showing the routes between the compartments.

There are many examples of diseases which tend to be age-specific. There are a host of childhood infections, such as measles, whooping cough, rubella, chickenpox and mumps, which before vaccination were usually first caught in early childhood. A simple model can explain what common factor meant that these diseases were contracted in childhood. These diseases can be studied using the SIR model. Consider a group of $C$ children that are all born susceptible, ignoring deaths we have:

$$\frac{dC}{dt} = -\beta I^* C \quad \Rightarrow \quad C(t) = C(0) \exp(-\beta I^* t) \approx C(0) \exp(-d[R_0 - 1]t)$$

So the number of susceptible children left decays exponentially as they get older, and the decay is faster the larger $R_0$ is. So what defines a childhood disease is simply a high $R_0$, so that you catch the disease before you become an adult.

However, the most important thing about childhood diseases, is that they affect children - and that children have very different mixing patterns to adults. We therefore consider how to model two different classes, children and adults, before developing a more general framework. We label children and adults by subscripts, such that $S_C$ and $S_A$ are the proportion of susceptible children and adults respectively. (It will be much easier if we assume that these proportions are a fraction of the entire population, and not the particular age-class. We also let $N_C$ be the proportion of the population that are children.) The dynamics of the childhood class can be broken into three components:

1) Birth, as before children are born susceptible.
2) Infection, susceptible individuals can be infected from two sources, either by infected adults or by infected children. Thus for the childhood class we need two transmission rates; transmission to children from adults $\beta_{CA}$ and transmission to children from children $\beta_{CC}$.
3) Finally, in the childhood class we shall ignore mortality, but we do lose children to the adult class due to natural ageing. We assume the childhood class is for ages zero to $A_C = 1/L$.

The equations for the childhood class are therefore

$$\frac{dS_C}{dt} = B - (\beta_{CA} I_A + \beta_{CC} I_C) S_C - L S_C$$

$$\frac{dI_C}{dt} = (\beta_{CA} I_A + \beta_{CC} I_C) S_C - g I_C - L I_C$$

Similarly we can formulate equations for the adult class, noting that there are no births but there are maturing children, and that the natural death rate must be increased to $\delta = \frac{dL}{L-d}$ as
the population is older.

\[
\frac{dS_A}{dt} = LS_C - (\beta_{AA}I_A + \beta_{AC}I_C) S_A - \delta S_A
\]

\[
\frac{dI_A}{dt} = LI_C + (\beta_{AA}I_A + \beta_{AC}I_C) S_A - gI_A - \delta I_A
\]

The main difference between this model and the standard SIR model is that the transmission rate has been replaced by a matrix of values representing the mixing between the two age classes – this matrix is called the Who Acquires Infection From Whom (WAIFW) matrix. There are other bits of accountancy due to individuals getting older and moving between classes. In general, we can write down equations for a model with \( n \) age classes:

\[
\frac{dS_n}{dt} = B_n + L_{n-1}S_{n-1} - \sum_m \beta_{nm}I_mS_n - L_nS_n - d_nS_n
\]

\[
\frac{dI_n}{dt} = L_{n-1}I_{n-1} + \sum_m \beta_{nm}I_mS_n - L_nI_n - d_nI_n
\]

So \( B_0 \) is the birth rate (and all other \( B_n \) are zero), \( L_n \) is the rate at which individuals mature and leave the \( n \) class (\( 1/L_n \) equals the age-span in class \( n \)), \( d_n \) is the natural death rate in class \( n \) and \( \beta_{mn} \) is the rate of transmission from class \( m \) to class \( n \).

There are several complications with studying this model compared to the standard SIR models.

1) \( \beta \) is now a matrix of values.

Previously, for a one class model we generally knew the average infectious period, the level of seroprevalence in the population (\( 1 - S^* \)), and the life expectancy. This allowed us to calculate the single parameter \( \beta \). In simple terms the information about one age class allows us to estimate one \( \beta \) parameter. However, for age structured models, we have \( n \) age-classes (and hopefully \( n \) levels of seroprevalence) but \( n^2 \) terms in the \( \beta \) matrix and hence \( n^2 \) parameters to estimate – this is impossible. We therefore seek a simpler from of the matrix (with just \( n \) parameters) so that we can successfully estimate all the terms.

2) How to find \( R_0 \).

In theory we could calculate an \( R_0 \) value for each age class, telling us how many secondary cases would be produced. For class \( n \), ignoring demography

\[
R_0^n = \sum_m \beta_{nm}N_m.
\]

However, we really want a single value such that we can tell if a disease will invade and how quickly it will spread. The simplest solution would seem to be to average all the \( R_0 \)'s for each age group – however the answer from this is not what we're looking for and almost always underestimates \( R_0 \). We need to weight the \( R_0 \)'s according to the level of infection that is expected in that class in the early stages of the epidemic. The easiest way to solve this is as an eigenvalue; in particular \( R_0 = (1 + \lambda)/g \), where \( \lambda \) is the dominant eigenvalue of the matrix \( \beta \).

\[
\hat{\beta}_{mn} = \beta_{mn}N_m
\]

As expected, when this value of \( R_0 \) is greater than one the disease can invade and persist within the population, otherwise it is doomed to extinction. Note that depending on initial conditions a disease may grow or decay in the early generations independent of \( R_0 - R_0 \) tells us about the
eventual growth rate.

However it is no-longer true that $S^* = 1/R_0$, nor is it true that $S_n^* = 1/R_0^n$. These simple relations have been lost when the extra heterogeneity was added.

3) Simple Relationships

Once this additional structure is added to the equations all of the simple results relating $R_0$, the equilibrium levels and the final size of the epidemic. Many of these now become complex matrix equations, however the results for vaccination are worth considering.

Firstly, if we vaccinate at random then the classic threshold result still applies $V_C = 1 - 1/R_0$. Disappointingly, this level of vaccination is often much larger than would be predicted if we (foolishly) ignored the age-structure. We can however use the heterogeneities to target our vaccination campaign, focusing on the core-groups that are most responsible for the spread of infection. Often, we can do better than the standard (non-structured) models would predict.

The critical level of vaccination needed to eradicate a STD, as a percentage of the entire population, as the coverage in the high-risk group increases. In this example, the transmission matrix is $\beta = \begin{pmatrix} 10 & 1 \\ 1 & 2 \end{pmatrix}$, with $N_H = 0.2$, $N_L = 0.8$ and $g = 1$ as before.

<table>
<thead>
<tr>
<th>SUMMARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>• When a population has some structure, we need to use a vector and eigenvalue approach.</td>
</tr>
<tr>
<td>• It is often difficult to estimate all of the rapidly growing number of parameters.</td>
</tr>
<tr>
<td>• The inclusion of structure means that $R_0$ is larger than if we simply average.</td>
</tr>
<tr>
<td>• We can use the structure to get improved vaccination results.</td>
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<tr>
<td>• Similar methods can be applied to other heterogeneities, most commonly the number of sexual partners.</td>
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</tbody>
</table>
Lectures 15 & 16: Multi-Host & Multi-Strain

Multi-Host Diseases If a disease can infect multiple hosts, then the models that can be applied are the same as those for age-structure. We can qualify this with a simple example of the spread of foot-and-mouth between buffalo (B) and domestic cattle (C).

\[
\begin{align*}
\frac{dS_B}{dt} &= B_B - (\beta_{BB} I_B + \beta_{BC} I_C) S_B - d_B S_B \\
\frac{dI_B}{dt} &= (\beta_{BB} I_B + \beta_{BC} I_C) S_B - g_B I_B - d_B I_B \\
\frac{dS_C}{dt} &= B_C - (\beta_{CB} I_B + \beta_{CC} I_C) S_C - d_C S_C \\
\frac{dI_C}{dt} &= (\beta_{CB} I_B + \beta_{CC} I_C) S_C - g_C I_C - d_C I_C
\end{align*}
\]

For this example, we would expect the matrix \( \beta \) to be dominated by the diagonal terms, and from field observations \( g_B < g_C \).

A more complex set of dynamics can occur when there are obligate hosts involved in the transmission process. Such a scenario exists for the spread of malaria (where the parasite is transmitted from person to person via mosquitoes), or bubonic plague (where the bacterium are transmitted from rodent to rodent via infected fleas and occasionally to humans). For malaria, the following would be a plausible model of mosquitoes (M) and humans (H).

\[
\begin{align*}
\frac{dS_H}{dt} &= B_H - \beta_{HM} I_M S_H - d_H S_H \\
\frac{dI_H}{dt} &= \beta_{HM} I_M S_H - m_H I_H - d_H I_H \\
\frac{dS_M}{dt} &= B_M - \beta_{MH} I_H S_M - d_M S_M \\
\frac{dI_M}{dt} &= \beta_{MH} I_H S_M - d_M I_M
\end{align*}
\]

For this model it might be more sensible to let \( S_M \) and \( I_M \) refer to the density of mosquitoes (rather than proportion) as we would expect bite-rate and hence transmission to increase with density.

Multi-Strain Diseases We wish to consider two strains of disease that are interacting. The simplest model is to assume that the two strains are completely cross-reactive, such that immunity to one strain automatically confers immunity to the other. Following the basic SIR model, we now have two \( I \) classes dependent on the infecting strain.

\[
\begin{align*}
\frac{dS}{dt} &= B - \beta_1 I_1 S - \beta_2 I_2 S - d S \\
\frac{dI_1}{dt} &= \beta_1 I_1 S - g_1 I_1 - d I_1 \\
\frac{dI_2}{dt} &= \beta_2 I_2 S - g_2 I_2 - d I_2 \\
\frac{dR}{dt} &= g_1 I_1 + g_2 I_2 - d R
\end{align*}
\]

From this simple model we see that one strain ALWAYS dominates. This is clear if we look at the ratios of the two strains,

\[
\frac{d}{dt} \frac{I_1}{I_1 + I_2} = \frac{I_1 I_2}{(I_1 + I_2)^2} \left[ (\beta_1 S - g_1) - (\beta_2 S - g_2) \right]
\]
From which we find that the strain with the largest $R_0$ always dominates.

Much more complex dynamics are obtainable when two strains only confer partial immunity.

A two-strain model, showing the routes to complete immunity.

This model has eight compartments, and a variety of different transmission parameters (which measure the extent of cross-immunity). The most difficult part of working with such models is developing an intuitive notation. A common example, which can be extended to model any number of strains is to have a string of subscripts; thus $N_{SI}$ is the number of individuals that are susceptible to strain 1 and infected with strain 2. The dynamics of each subscript can then be written down as before: e.g.

$$\frac{dN_{SS}}{dt} = B_{SS} - \beta_1^{SS} \sum_x N_{IX} N_{SS} - \beta_2^{SS} \sum_x N_{XI} N_{SS} - d_{SS} N_{SS}$$

$$\frac{dN_{SI}}{dt} = \beta_2^{SS} \sum_x N_{XI} N_{SS} - \beta_1^{SI} \sum_x N_{IX} N_{SI} - g_2 N_{SI} - d_{SI} N_{SI}$$

$$\frac{dN_{SR}}{dt} = g_2 N_{SI} - \beta_1^{SR} \sum_x N_{IX} N_{SR} - d_{SR} N_{SR}$$

This sort of dynamics is used to understand the evolutionary dynamic of diseases, such as influenza where antigenic changes occur on a yearly basis driven by increasing resistance to the commonest strains.

**SUMMARY**

- Multiple strains or multiple hosts increases the number of compartments.
- With complete cross-immunity the strain with the largest $R_0$ wins.
- With partial cross-immunity a rich pattern of dynamics can be observed.
Lectures 17 & 18: STOCHASTICITY AND EXTINCTIONS

Stochasticity can be a major driving force in the behaviour of epidemics, and yet it is one of the most difficult concepts to deal with mathematically. Most of the results shown therefore come from computer simulations of stochastic populations. There are three main forms of stochasticity, environmental, additive and demographic.

Environmental
Environmental stochasticity, as its name suggests, comes from sources external to the disease population. This is generally modelled as random noise added to the parameters; most commonly we set $\beta = \beta_0 + \beta_1 \xi$, where $\xi$ is some type of noise term. Such a form of stochasticity can be easily studied mathematically, but neglects the individual nature of the population.

Additive
Additive stochasticity, or noise, is random perturbations applied to the basic variables (usually the number of infecteds). The better models assume that the noise scales in some non-linear way with the level of infection. Thus our equation becomes:

$$\frac{dI}{dt} = \beta IS - gI + f(I)\xi$$

where $\xi$ is again some appropriate noise term. Although this type of model can be very effective, it again ignores the individual nature of the population.

Demographic
This type of stochasticity arises because the population is composed of whole individuals, so events occur at random and make whole number changes. The following “program” performs demographic iterations.

1) Make a list of all possible events, $E$, and the rate at which they occur, $R_E$.
2) The rate at which any event occurs is $R_{total} = \sum_E R_E$.
3) Pick a random number, $RAN D_1$; the time until the next event is $\delta T = -1/R_{total} \log(RAN D_2)$
4) Pick another random number, $RAN D_2$; find event $i$ such that

$$\sum_{E<i} R_E < RAN D_2 < \sum_{E \leq i} R_E$$

5) Perform event $i$, increase the time by $\delta T$, and return to 1.

This process is then repeated time and time again, as the computer program moves forward one small increment after another. Note that as the population size increases, so the rate at which events occur decreases and the average step size gets smaller – thus (unlike the deterministic models) stochastic models get slower as the population considered gets larger.

The following are a set of common observations for all models with demographic stochasticity.

**Individuals.** The population is composed of whole individuals, so changes must occur in integer multiples. We must therefore think about probabilistic rates and not differential rates. We are best to deal with numbers and not proportions.

**Population Size.** The most obvious factor is that larger populations suffer less from stochasticity than smaller ones. Basically this is because one individual in a small population is worth more than one individual in a large population. Thus a populations become very large (and it’s not clear how large this should be) their behaviour approximates the deterministic model.
**Transients.** The behaviour of stochastic models is a trade-off between two competing forces, the deterministic part pulls the orbits back towards the equilibrium (or any other attractor) while the stochastic part pushes trajectories away. Thus how the transient dynamics of trajectories return to the equilibrium dominates the dynamics. Stochasticity (of any form) is known to excite oscillations at the natural frequency of the epidemic.

**Extinctions.** In general we are interested in situations where $R_0 > 1$. However, even under these conditions chance events can drive a population to extinction. This leads to the idea of a *critical community size* as the smallest population that does not suffer from frequent stochastic extinctions. This is obviously very important when considering eradication by vaccination.

**Failure to Invade.** When a single infection invades a population, there is always a chance that it will recover before spreading the infection any further. The spread is defined as a *branching process* and fails to generate a large epidemic with probability $1/R_0$.

### SUMMARY

- Stochasticity comes from many different sources. Demographic stochasticity, due to the individual nature of populations, is probably the most important.

- Random fluctuations cause transient behaviour to dominate, and can cause extinctions.

- Smaller populations suffer more from stochasticity.

- Few mathematical results are possible, instead we rely on computer simulation.
Lectures 19: MACRO-PARASITES

Whereas the study of micro-parasites concentrates on bacterial and viral diseases, the study of macro-parasites considers infection by larger organisms, such as protozoa, helminths and arthropods. Protozoa are single celled organisms including Amoebae, Flagellates (diseases include Sleeping Sickness), Ciliates and Sporozoa (diseases include Malaria). As these simple creatures reproduce very quickly within the host, the mathematical models which describe these infections are comparable with standard micro-parasite disease models. Arthropods Most arthropods which attack humans are blood feeders, examples include mosquitoes, ticks and fleas which can act as vectors for other infectious agents, transporting the disease from one host to the next. Helminths are parasitic worms, including tapeworms, flukes and roundworms. In this lecture we shall concentrate on the study of this type of macro-parasite.

What differentiates the study of helminth infections from standard disease models is the variability in worm burden and the complexity of the parasite lifecycle. Although for most micro-parasitic diseases hosts can either be classified as susceptible, infected or recovered, for helminth infections we must also track the number of worms (or burden) within each host. Many helminths spend some part of their reproductive cycle out side the host, often inside a host of a different species.

The left-hand figure shows a generalisation of the life-cycle of macro-parasitic worms. The right-hand figure is the life-cycle of schistosomes or blood flukes, which involves reproduction within humans and snails as well as free-swimming stages. Schistosomiasis causes extensive damage to the blood vessels surrounding the lungs and liver.

For macro-parasite systems we need to modify the definition of the basic reproductive ratio \( R_0 \),

\[
R_0 = \text{average number of offspring produced by a mature parasite that themselves survive to reproductive maturity in the absence of density-dependent effect.}
\]
That is, $R_0$ is the number of offspring expected to complete a full reproductive cycle, when there is no intraspecific competition.

Some general features of macro-parasite systems which influence the construction of models are,
- The time the parasite spends within the human host is often much longer than the rest of its life cycle. Therefore, researchers often just consider the dynamics within the human population and assume that the rest rapidly achieve equilibrium.
- In general, it is found that a mass-action type formulation is the most accurate, where,

$$\text{The rate of infection } \propto \text{density of host } \times \text{density of infective stages}$$

- There is frequently a delay been the infection of a human host and the onset of reproductive maturity - this leads to the formulation of delayed differential equations. (Time-delayed differential equations frequently arise in population biology where they most often have a destabilising effect)
- Macro-parasite distributions are highly aggregated. The distribution is often termed over-dispersed which states that the variance is greater than the mean. The best fit to the distribution of worm burdens is a negative binomial,

$$P(n|M) = \frac{(k + n - 1)!}{n!(k - 1)!} \left( \frac{M}{k} \right)^n \left( 1 + \frac{M}{k} \right)^{-k-n}$$

where $M$ is the mean worm burden and $k$ measures the degree of aggregation.

![Histograms showing the distribution of the negative binomial](image)

Figures showing how the distribution of the negative binomial changes with $k$. From left to right the level of aggregation is $k = 0.4$, $k = 1$ and $k = 5$; throughout $M = 20$.

As $k \to \infty$ the distribution tends to Poisson, and the variance is minimised. In general, it is found that $k$ lies between 0.1 and 1.0 (Anderson and May 1985). Notice that from the negative binomial distribution, we can find the prevalence of the macro-parasite. The prevalence is defined as the proportion of hosts that are infected, i.e. the proportion with a non-zero worm burden.

$$\text{prevalence} = 1 - P(0) = 1 - \left( \frac{k}{M + k} \right)^{-k}$$

Prevalence levels for schistosomes in humans range from between 0.3% to 70%, depending upon location and species. It has often been observed that many humans are predisposed to having a high or low worm
burden, although this may be partially attributed to life-style or nutrition, it is believed that much of this heterogeneity is due to differing levels of genetic resistance to infection.

Although many authors have devised complex, biologically realistic, mechanisms which produce a negative binomial distribution of worms, this distribution can also be formed from a much simpler basis. Assuming random infection at rate \( \lambda \), a within host death rate of \( d \), and a self-infection (or within host reproduction) rate of \( r < d \), we obtain

\[
\frac{dP(n)}{dt} = [\lambda + r(n-1)]P(n-1) + [d(n+1)]P(n+1) - [\lambda + (d + r)n]P(n)
\]

The equilibrium distribution of this system is a negative binomial with,

\[ M = \frac{\lambda}{d-r} \quad k = \frac{\lambda}{r} \]

Hence, a simple birth-death model can also generate the observed levels of worm burden.

- Species of worm such as Schistosoma can produce between one hundred and three thousand eggs per female per day. However, density-dependence or crowding effects usually act to limit parasite survival and fecundity in those hosts with a high worm burden. In fact it has been observed that the number of cercariae emerging from a snail is independent of worm burden. Therefore snails can be considered as either susceptible or infected, and their precise burden ignored.

- Although most worm species reproduce asexually within the intermediate host (eg schistosomes reproduce asexually within the snail) the majority of parasites reproduce sexually within humans. This introduces the concept of a mating function \( \phi \). Where \( \phi(n) \) is the probability that a female worm is mated given that the worm-burden with the host is \( n \). Note that in general \( \phi(1) = 0 \). Let us consider two cases where males and females are randomly distributed.

**Polygamous**

\[
\phi(n) = \sum_{f=0}^{n-1} \frac{f}{2^n} \frac{n!}{(n-f)!f!} \left( \frac{1}{2} \right)^f \left( \frac{1}{2} \right)^{n-f}
\]

\[
= 1 - \frac{1}{2^{n-1}}
\]

**Monogamous**

\[
\phi(n) = \sum_{f=0}^{n} \frac{\min(f, n-f)}{2^n} \frac{n!}{(n-f)!f!} \left( \frac{1}{2} \right)^f \left( \frac{1}{2} \right)^{n-f}
\]

\[
\phi(2n) = \phi(2n + 1) = 1 - \frac{1}{2^{2n}} \frac{(2n)!}{n!n!}
\]

[Exercise: Check the above calculation from polygamous and monogamous worms]. To calculate the rate of egg production, we need to sum the mating function and density dependent fecundity over the distribution of worms.
The differential equations for the mean number of adult worms per host and larvae is,

\[
\frac{dM}{dt} = \int_{t}^{t+\tau} \beta L(t - \tau_L) dt - \sum_{n} nd(n) \mathcal{P}(n|M) - \sum_{n} nm(n) \mathcal{P}(n|M)
\]

\[
\frac{dL}{dt} = N \sum_{n} E(n) \mathcal{P}(n|M(t - \tau_M)) - DL - N\beta L
\]

where \(N\) is the total number of potential hosts. This form of model has been used by many authors to study the dynamics of schistosome parasites and other helminths. Under the simplifying assumptions that \(m\) and \(d\) are independent of \(n\), that \(E\) is proportional to \(n\) and that \(\tau_L\) and \(\tau_M\) are small, the equations reduce to,

\[
\frac{dM}{dt} = \beta L - dM - mM
\]

\[
\frac{dL}{dt} = NEM - DL - N\beta L
\]

Hence, we can calculate \(R_0\) for this system,

\[
R_0 = \frac{NE}{d + m} \frac{\beta}{D + \beta N}
\]

From this we observe that hosts must be above some critical density for the parasite to persist,

\[
N > \frac{D(d + m)}{\beta E - \beta(d + m)}
\]

If we allow the use of more general functions for \(m\), \(d\) and \(E\), then usually the system is no-longer analytic and we have to resort to numerical calculations.

**SUMMARY**

- Macro-parasitic infections have far more complex life-cycles than micro-parasites.
- We are often interested in the number of parasites within a host (burden).
- Macro-parasites often have secondary obligate hosts.