Block 1:
Basic methods and dynamics of infectious diseases

Practicals

Introduction to Infectious Disease Modelling and its Applications – 2018

Session 3: Setting up and interpreting simple models (Measles in Excel)

Practical

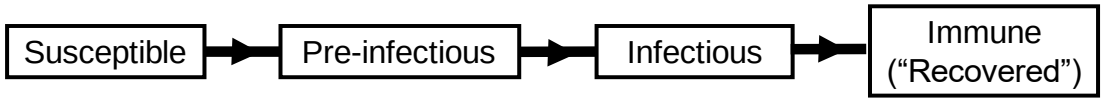
Objectives:

By the end of the practical you should:

- understand the mechanics of setting up simple models of immunizing infections using difference equations in Excel;
- understand the relationship between the key input parameters in the model.

Introduction

In the lecture, you saw that the following model of the transmission dynamics of measles in a closed population could be written using the difference equations below:



$$S_{t+1} = S_t - \lambda_t S_t \qquad \text{Equn 1}$$

$$E_{t+1} = E_t + \lambda_t S_t - fE_t \qquad \text{Equn 2}$$

$$I_{t+1} = I_t + f E_t - r I_t \qquad \text{Equn 3}$$

$$R_{t+1} = R_t + r I_t \qquad \text{Equn 4}$$

By assuming that individuals mix randomly, ie that $\lambda_t = \beta * I_t$, the first two equations can be rewritten as:

$$S_{t+1} = S_t - ß\, I_t S_t \qquad \text{Equn 1'}$$

$$E_{t+1} = E_t + ß\, I_t S_t - fE_t \qquad \text{Equn 2'}$$

where

- S_t , E_t , I_t and R_t are the number of susceptible, pre-infectious (infected, but not infectious), infectious and immune (recovered) individuals respectively at time *t*,
- λ_t is the risk a susceptible becomes infected between time *t* and *t*+1
- *ß* is the rate at which a specific infectious and susceptible individual come into effective contact per unit time,
- *f* is the proportion of pre-infectious individuals who become infectious between time t and *t*+1, and
- *r* is the proportion of infectious individuals who recover (become immune) between time *t* and *t*+1.

We will now set up this model in Excel.

Setting up difference equations in Excel

All models in the course can be found either in your H: drive or in the folder "U:\Download\Teach\scmodels"

1. Open up the spreadsheet *measles1.xls.*

The yellow cells (rows 3-8) show the key input parameters in the model, namely the total population size, R_0, the average pre-infectious and infectious periods – these have been assigned the names given in column G.

We begin by setting up the appropriate input parameters, which determine how many individuals are newly infected, become infectious and recover per unit time.

2. In the blue cells (located between rows 11 and 14), use the formulae given in the lecture (pages 8-11) to set up appropriate (Excel) formulae for:

a) the number of individuals effectively contacted by each person per day (ecr), in cell F11,
b) the rate at which 2 specific individuals come into effective contact per day (beta), in cell F12,
c) the average rate at which individuals become infectious per day (infous_rate), in cell F13
d) the average recovery rate per day (rec_rate), in cell F14.

in terms of the parameters provided in the yellow cells. Again, the contents of these blue cells have been assigned the names in column G.

The lilac or light purple cells (starting in row 43) will contain the number of individuals who are susceptible, pre-infectious, infectious and immune on day 0, 1, 2 etc. The number of individuals on day 0 are shown.

Q1 In the cells indicated, enter the (Excel) formulae for

*a) The number of susceptibles on **day 1**, in terms of beta and the number of individuals who are susceptible and infectious on **day 0** in B46.*

*b) The number of individuals who are pre-infectious on **day 1**, in terms of beta, infous_rate, and the number of individuals who are susceptible, pre-infectious and infectious on **day 0**, in C46.*

*c) The number of individuals who are infectious **on day 1**, in terms of infous_rate, rec_rate, and the number of individuals who are pre-infectious and infectious **on day 0**, in D46*

*d) The number of individuals who are immune on **day 1**, in terms of rec_rate and the number of individuals who are infectious and immune on **day 0**, in E46.*

3. Copy the expressions you have just set up down until the 200th day. Then, select columns H and P together, click with the right mouse button and select the unhide option. You should see a graph of the number of susceptible, infectious and immune individuals over time.

Q2 What do you notice? Why do no further new infectious persons occur in this population after a certain time? How long does it take before there are no infectious persons in the population?

Q3 How does the graph of the numbers of susceptible, infectious and immune individuals change if you change the pre-infectious period to be

a) 20 days
b) 5 days

Change the pre-infectious period back to be 8 days.

Q4 Which assumptions would you alter or add to the model to describe the transmission dynamics of measles in a large population (e.g. a town or country) over a period of years? (Note – you are not expected to make these changes just yet!)

To model the transmission dynamics of measles over longer time periods we will now change the model to incorporate births and deaths in the population. *NB. If the output from your model looks odd at this stage, you may like to check your equations against those in the file meas1a.xls, which contains the model which you should have developed so far.*

Incorporating births and deaths

1. If you have not already done so, change the durations of the pre-infectious and infectious periods to be 8 and 7 days (as assumed originally). Similarly, change the R_0 to be 13.

2. Select rows 8 and 10 together, click on your right mouse button and select the unhide option. Repeat the same for rows 14 and 19. You should now see cells for the life expectancy (currently set at 70 years), the average *per capita* mortality and birth rates and the number of births in this population per day.

3. Type in the appropriate formula for the average (daily) *per capita* mortality rate in cell F15 in terms of the life expectancy.

Q5 Assuming that the population size doesn't change over time (number of births= number deaths), what would be an appropriate expression for the daily per capita birth rate?

4. Set up the appropriate (Excel) formula in the cell for the *per capita* birth rate (in F16) and the number of births per day (in cell F17).

For now, we will assume that all individuals are born susceptible in this population.

Q6 Is this realistic? Is this a reasonable assumption to make? Why? What alternative assumptions might be appropriate?

Q7 How would you change equations 1-4 on page 1 to include the number of

a) births into the population in each time step?

b) deaths from the population in each time step?

Hint: you may find it helpful to first think about how you would change the model diagram on page 1 to deal with births and deaths.

5. Change the equations for the number of susceptible, pre-infectious, infectious and immune individuals at time t=1 to deal with new births and deaths into the population and then copy these formulae down to time t=200.

Q8 How does this change your answer to question Q2? How do you think your answer would change if you were to simulate the dynamics of measles for 10 years? For 50 years?

6. Copy the formulae in the cells for t=200 until t=18250 (ie 365*50 days = 50 years). Select rows 20 and 40 together, click with the right mouse button and select the unhide option. You should see a graph of the number of individuals who are susceptible and immune for the whole 50 year period. *NB. If the output from your model looks odd at this stage, you can check your equations against those in the file meas1b.xls, which contains the model which you should have developed so far.*

Q9 What do you notice? How are the changes in the number of susceptibles and immune related?

To extend the dynamics for an even longer time period (eg t=36500 days = 100 years), it would be possible to copy the formulae down still further. However, this would make the spreadsheet large (and possibly unmanageable, depending on the power of your computer).

One alternative is to take larger, e.g. 2, 3 day or longer time steps in the simulations. To do this, you need to convert the parameters currently used in the model into those appropriate for 2, 3 etc time steps. A method for doing this is illustrated below (optional). An alternative is to reformulate the equations using *differential equations* and to use a package specially designed to deal with this problem. We will be doing this in the next practical.

Changing the size of the time steps in the model

If you have time, follow the steps below to re-express the input parameters in terms of the size of the time step. Otherwise, open up the file *measlfin.xls*, which already has these expressions set up and check that you understand their logic.

Note that to convert a **daily** transition rate into that for a different-sized time step, you just need to multiply it by the size of the time step, e.g. if 5% of pre-infectious individuals become infectious each day, then roughly $3 \times 5 = 15\%$ of them should become infectious by the third day.

The size of the time step has been assigned the name “t_step”.

1. Amend the equations for the following parameters (by multiplying by 't_step' if necessary) to be in terms of t_step:
    a) the number of individuals effectively contacted per time step
    b) the rate at which two specific individuals come into effective contact per time step
    c) the average rate at which individuals become infectious,
    d) the average recovery rate,
    e) the mortality rate

Q10 Does taking a time step of 2 days influence the predicted cycles in the numbers of infectious persons? What happens when you change the time step to 3, 4 and 5 days? Why?

Q11 Would it be reasonable to take time steps of 10 days? Why?

In the next practical, we illustrate how the same model can be set up using differential equations.

Further exercises

If you have finished the practical early or if you wish to consolidate your understanding of the concepts covered in this session, please try the following exercises:

1. Exercises accompanying models 2.1 of the recommended course text[1] (see www.anintroductiontoinfectiousdiseasemodelling.com)
2. The paper and pen exercises at the end of chapter 2 of the recommended course text[1]. Solutions are available from the book's website.
3. Supplementary exercises (see the supplementary questions folder on Moodle or in the folder containing the model files on the network).

References

1. Vynnycky E, White RG. An Introduction to Infectious Disease Modelling". Oxford University Press, Oxford 2010

Introduction to Infectious Disease Modelling and its Applications – 2018

Session 4: Setting up and interpreting simple models in Berkeley Madonna

Practical

Overview and Objectives

In this session, you will learn how to set up a simple model of the transmission of an immunizing infection in a modelling package, Berkeley Madonna.

Berkeley Madonna provides two methods for setting up models:

1. **The flowchart approach:** this involves drawing a flowchart of the model and provides a quick way of setting up models without thinking too much about the equations. The models set up in this way provide a visual summary of all the equations and the components which are linked.
2. **The equation editor approach:** this method requires users to type in the differential equations.

The two methods are equivalent and give identical results. It is useful to know both methods: if a model that is set up using one approach gives unexpected results, its findings can be checked against those obtained from a model that is set up using the other approach. The practicals in this course are set up using both approaches and you will usually be able to select which approach you use.

This practical first illustrates the flowchart approach; the second approach is described on page 14. You will also have the chance to learn more about the equation editor approach later this week. If you are prefer to work immediately with the equation editor, please skip to page 14.

By the end of the practical you should

- understand the methods for setting up models using Berkeley Madonna
- understand the relationship between the different input parameters in the model

NB We will be using version 8.3.11 of Berkeley Madonna during this course.

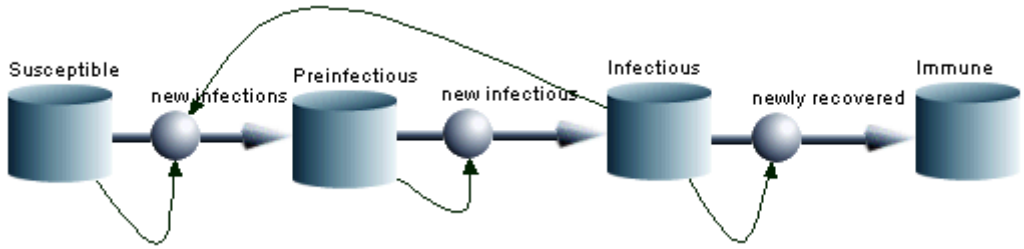
Part I: Setting up models using the flowchart editor

Overview of setting up models using flowcharts

To set up models using a flowchart in Berkeley Madonna you need to:

a) Draw a diagram of the model.
b) Define the parameters in the model.
c) Type in the equations for the numbers of individuals who move from one category to the next.
d) Run the model. i.e. Berkeley Madonna uses the model to calculate the number of people in each category over time.

The following shows the diagram which you might draw in Berkeley Madonna in order to set up a model describing the transmission of an immunizing infection:



Notice that there are two kinds of arrows, namely:

1. **The flow arrows (thick arrows with a circle in the middle)** which hold equations for the *number of individuals who move between categories per unit time*. e.g. the "*new infections*" arrow holds the number of individuals who are newly infected per unit time, which is given by the equation:

   β*No. of susceptible individuals * No. of infectious individuals

2. **The thin arrows (known as "arc" arrows in Berkeley Madonna):** these tell Berkeley Madonna which components depend on each other. For example, there is an arc arrow from the *Susceptible* compartment to the "*new infections*" arrow because the number of susceptible individuals is used in the equation in the "*new infections*" arrow. An analogous argument accounts for the arc arrow from the *Infectious* compartment to the "*new infections*" arrow.

The relationship between the equations in the flow arrows and the differential equations which you saw in the lecture is as follows:

$$\frac{dS(t)}{dt} = -\ \textbf{\textit{new infections}} \qquad =\beta S(t)I(t)$$

$$\frac{dE(t)}{dt} = \textbf{\textit{new infections}} - \textbf{\textit{new infectious}} \qquad =fE(t)$$

$$\frac{dI(t)}{dt} = \textbf{\textit{new infectious}} - \textbf{\textit{newly recovered}} \qquad =rI(t)$$

$$\frac{dR(t)}{dt} = \textbf{\textit{newly recovered}}$$

where

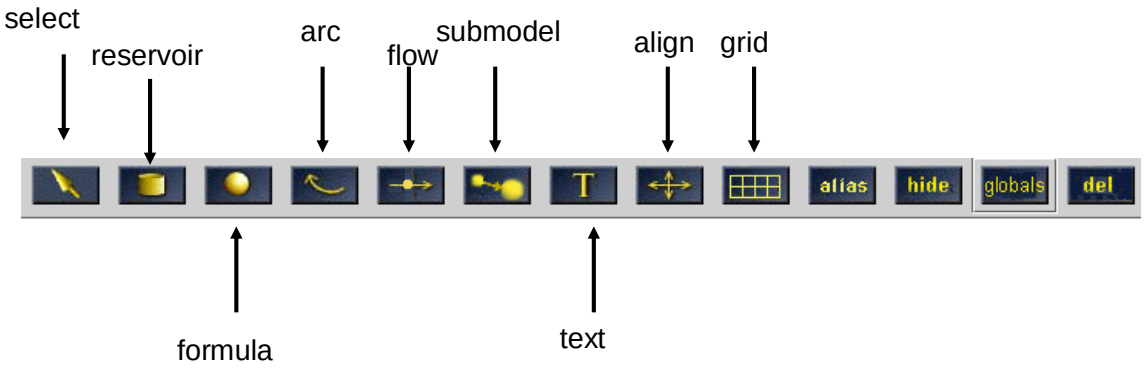
- *S(t), E(t), I(t)* and *R(t)* are the numbers of susceptible, pre-infectious, infectious and immune (recovered) individuals at time *t*
- ***β*** is the rate at which two specific individuals come into effective contact per unit time (and equal to **R_0/(total population size × duration of infectiousness)**.
- ***f*** is the rate at which pre-infectious individuals come infectious (and equal to **1/average pre-infectious period)**
- ***r*** is the rate at which individuals recover from being infectious (and equal to **1/infectious period**).

We will now set up the model.

1. Start up Berkeley-Madonna. This opens up a window (called "Untitled1 - Equations"); close this window by clicking on the x button on the top right hand corner of this window.

2. Choose the "File" option from the main menu and choose the "New Flowchart" option. If you see an error message, refer to the trouble-shooting section in the guide to Berkeley Madonna in section 5 (the "useful" section) of this manual.

You should now see a new window, called "Untitled2 – Flowchart" in which you develop your model. Familiarize yourselves with the names of different buttons on the toolbar:



Setting up compartments ("reservoirs")

We first set up four compartments which each hold the number of *susceptible, pre-infectious, infectious and immune* individuals at a given time. Note that Berkeley Madonna refers to these as "reservoirs".

1. Click on the reservoir button  on the toolbar, move the mouse to the middle of the window and click with the left mouse button to insert a reservoir. Repeat this three more times to insert three compartments. The model diagram should resemble the following:

NB If you ever need to delete a component from the flowchart window, click on it with your left mouse button to select it and then either click on the delete button on the toolbar or press the delete key on the keyboard whilst holding down the Ctrl key.

2. Rename the compartment labelled R1 to "*Susceptible*" by clicking or double clicking on the R1 label and then typing the word *Susceptible.* Click on OK to continue.

3. Similarly rename the R2 compartment to *Preinfectious*; likewise rename the R3 compartment to *Infectious* and the R4 compartment to *Immune.*

Specifying the transitions between categories

To specify that individuals can move from one category to the next, we first need to link the corresponding compartments with a "flow" arrow and a suitable "arc" arrow as follows.

1. Click on the flow button  on the tool bar. Click on the *Susceptible* box and, holding the left mouse button down, drag the mouse across to click on the *Preinfectious* box.

This sets up a flow arrow labelled J1, which links the *Susceptible* and *Preinfectious* boxes.

2. In the same way, specify that individuals can move from the *Preinfectious* to the *Infectious* category and from the *Infectious* to the *Immune* category. The model diagram should now resemble the following:

3. Rename the arrow labelled J1 to "*new infections*" by clicking or double clicking on the J1 label and typing *new infections*.

4. Similarly rename the J2 and J3 arrows to "*new infectious*" and "*newly recovered*" respectively.

We will now define the input parameters.

Specifying the input parameters

1. Click on the "globals" button. This opens up a window, in which you type your input parameters.

We will assume that the population comprises 100000 individuals. The infectious and pre-infectious periods for measles are 7 and 8 days respectively and the basic reproduction number is 13.

2. Type the following into this window, noting that you must have a space on either side of the equals sign, as otherwise, Berkeley Madonna will ignore the equations:

total_popn = 100000
preinfectious_period = 8
infectious_period = 7
R0 = 13

In Berkeley Madonna, parameters can be expressed in terms of other parameters. For example, to set up a parameter called "*infectious_rate*" which represents the rate at which individuals become infectious and equals 1/preinfectious_period, you can type the following in the "globals" window:

infectious_rate = 1/preinfectious_period

3. Set up the parameter *infectious_rate* as specified above and two further parameters:
   a) *rec_rate* (reflecting the rate at which infectious individuals recover to become immune)
   b) *beta* (reflecting the rate at which two specific individuals come into effective contact per unit time)

which are expressed in terms of the parameters *infectious_period*, *R0* and *total_popn.*

4. Type the values for the size of each of the compartments at the start:

Sus_0 = total_popn-1
Preinfectious_0 = 0
Infectious_0 = 1
Immune_0 = 0

5. Click on OK to close the globals window.

We are now ready to set up the equations in the flow arrows and compartments.

Setting up equations in the flow arrows

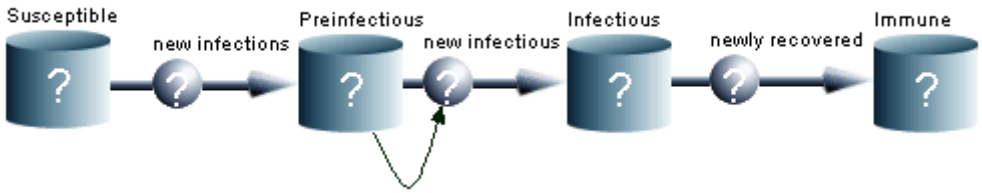
The flow arrows hold equations for the absolute number of individuals who move from one category to the next.

Considering the *new infectious* arrow, for example, we wish to set up the following equation:

*Preinfectious*infectious_rate*

As mentioned above, the flowchart provides a visual representation of the model equations and components which are linked. Berkeley Madonna only allows you to type in equations such as this if we have inserted a link (i.e. an arc arrow) between the *Preinfectious* compartment and the *new infectious* flow arrow.

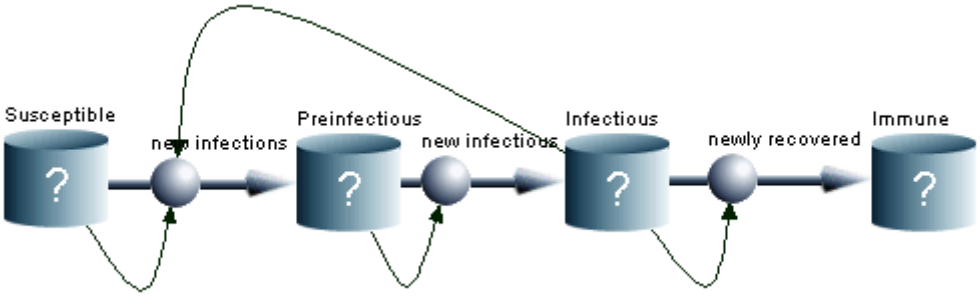
1. Click on the arc button  on the toolbar. Click on the *Preinfectious* compartment and, still holding down your left mouse button, drag the mouse across to click on the circle labelled "*new infectious*". Your model diagram should resemble the following:



2. Double click on the circle of the *new infectious* arrow and type in the appropriate expression in the box labeled "new infectious=". Click on OK to continue. By this stage, the question mark in the circle of the *new infectious* arrow should have disappeared.

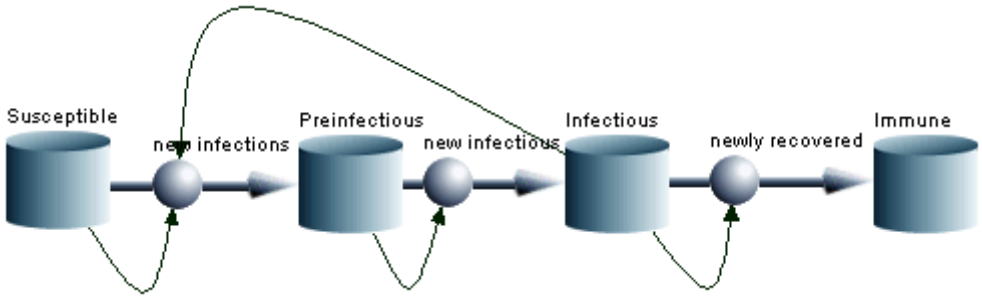
3. Repeat the above steps to insert appropriate links and equations for the *new infections* and "*newly recovered*" arrows (referring to page 2 of the practical for the equations if necessary!).

Your model diagram should now resemble the following:



4. Double click on the Susceptible compartment and specify that the number of susceptible individuals in the population at the start equals the value specified by *Sus_0* by typing in *Sus_0* in the INIT box. Click on OK to continue.

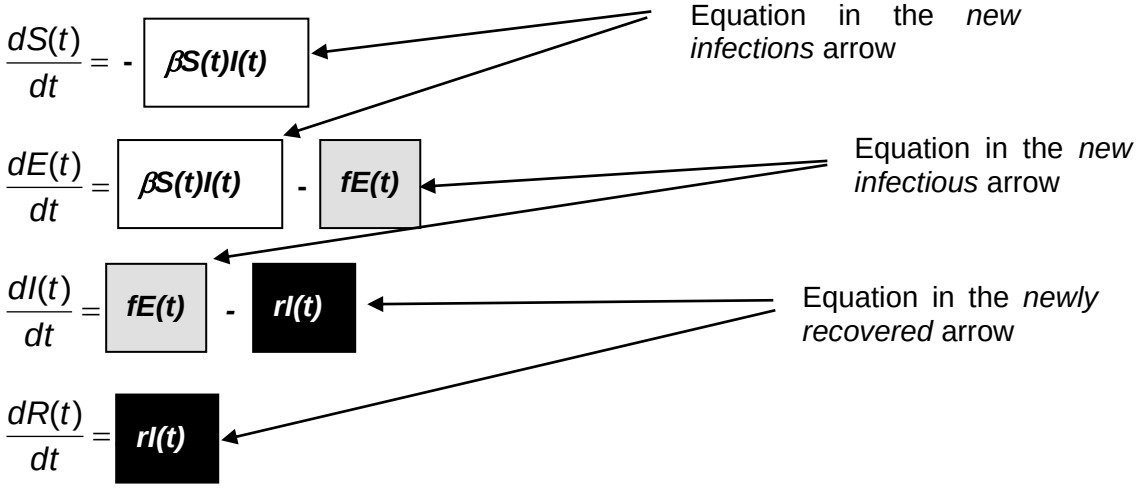
5. Similarly specify that the number of pre-infectious, infectious and immune individuals at the start equals the values of preinfectious_0, infectious_0 and immune_0. By this stage all the question marks in the model diagram should have disappeared and your model should resemble the following:



NB We could have typed in the actual value (e.g. 99,999 for the susceptible individuals) into the INIT boxes for each of the compartments; however, it is good practice to set up parameters for these values in the globals window, since this means that you then have a convenient record of these parameters in one place, and it becomes easy to change them later.

Berkeley Madonna summarizes the equations in the model in its “Equations” window. To see this, click on the model option in the menu and select the “Equations” option. The equations in this window cannot be edited at present – we will illustrate how you can edit them later in the practical.

To recap, the relationship between the equations in the flow arrows and the differential equations is as follows:



Notice that none of the equations in the flow arrows have a minus sign (i.e. they just reflect the **absolute** number of individuals who move from one category to the next). The direction of the flow arrow tells Berkeley Madonna whether individuals are exiting or entering the category.

We will now "run" the model (i.e. use it to make predictions).

Running the model

1. To run the model, select the parameters option from the main menu and choose the "Parameter window" option. This opens up a window, which lists, among other things:

a) The time period over which the model makes predictions (specified by the values of STARTTIME and STOPTIME, which are set to be 0 and 10 by default). *Note that the units of the start and stop time are determined by those of the parameters used in the flow arrows or, equivalently, the differential equations. If these are in units of per day, then the start and stop times are also in daily units.*

b) The number of individuals present in various compartments at the start (these are not always visible, depending on how the initial values have been set up).

c) The current values for all the parameters in the model, e.g. the R_0, the pre-infectious and infectious periods etc.

You can read about the other features in this window later (see Appendix).

We would like to run the model for 150 days.

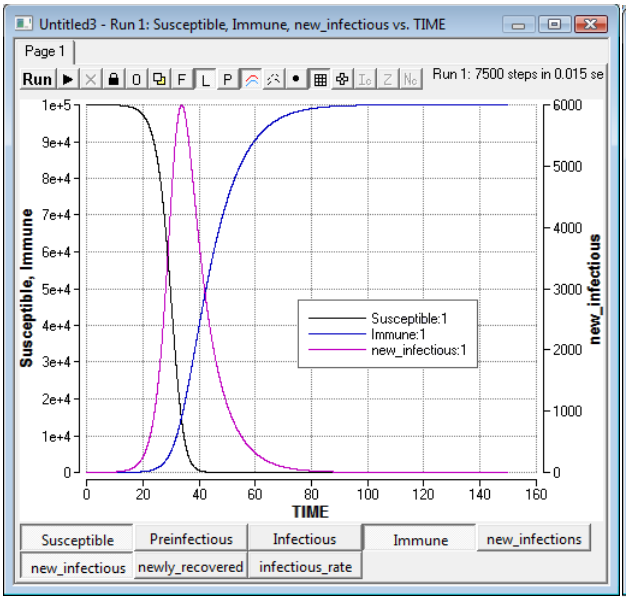
2. Click on the "STOPTIME" line and change it to equal 150 by typing 150 in the box alongside the reset button. Then click on the run button. *(NB. Do not press the reset button, as this resets the value of STOPTIME to 10 again!)*

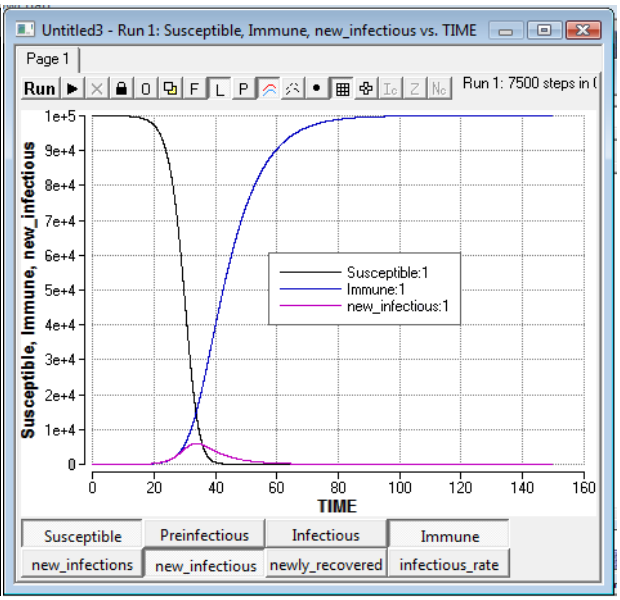
This opens up a window showing predictions of the numbers of susceptible and pre-

infectious individuals in the population over time.

3. To change this to plot the numbers of susceptible and immune individuals and new infectious persons over time, click on the button labelled "*Preinfectious*" at the bottom of this window to remove this plot from the figure and click on the "*Immune*" and "*new infectious*" buttons. By default, time (t) is plotted on the x-axis.

4. The buttons along the top of this window allow you to change the display (see Appendix for the definitions of these buttons). Click on the "Legend" button  to see the legend. Your graph should now resemble one of the following (depending on whether *new infectious* is plotted on the left or right y-axis):





If necessary, check your model against that in the file measles1a - flowchart.mmd, which contains the model which you should have developed by this stage of the practical.

Q1.1 What do you notice? According to the graph, how long does the epidemic last?
Note: To see the co-ordinates of a point, press on the "readout" button  *on the graph toolbar: a cross in a circle will appear, and the co-ordinates of this cross will appear on the top right hand corner of the window.*

The values of model parameters can be changed in the parameters window.

5. Return to the parameters window, select the pre-infectious period, change it to be 5 days and run the model.

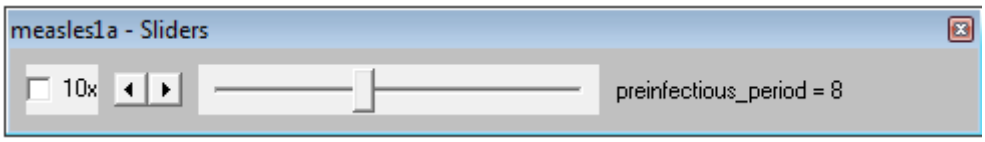
Q1.2 How does this change affect the graph of the number of new infectious persons, susceptible and immune individuals? (Note that Berkeley Madonna automatically changes the scale on the y-axis each time you run the model: to compare the output resulting from the two sets of assumptions, click on the overlay button  *on the graph toolbar before running the model. To view only the results from the most recent run of the model, deselect the overlay button before running the model.)*

The effect of changes in parameter values can also be explored using “sliders”, as follows:

6. Select the parameters option from the main menu and choose the “define sliders” option. This will open up a “Sliders” window.

7. Select *preinfectious_period* from the list of parameters in the left hand panel by double clicking on it. Specify that it should range between a minimum of 0 and a maximum of 20, with an increment of 0.2. Click on OK to continue.

You should now see the following slider:



8. Drag the slider to the right; you can also change the value by pressing the arrow keys on the keyboard if the slider has been selected.

Q1.3 What happens to the size of the epidemic (as reflected in the number of people who are immune at the end) as the pre-infectious period is increased? What happens as it is decreased?

9. Before continuing, return to the Parameters window and reset any parameters that you have changed (except for the STOPTIME) to their initial value (preinfectious_period=8 (days), infectious_period=7 (days), R0=13) by clicking on it and then clicking on the reset button. Note that any parameter that has changed since it was set up in the original model has an asterisk to the left of its value in the parameter list.

10. Please save your work before continuing.

We will now incorporate births and deaths in the population. If you are short of time, you can work through part II of the practical using the file “measles1b - flowchart.mmd” in which the final model has been set up. Alternatively, skip to the “final word” section and the summary.

Part II: Incorporating births and deaths into the model (optional)

1. Write down the expression for the number of births into the population per unit time, in terms of the *per capita* birth rate per unit time (*b_rate*) and *total_popn*.

2. Given a mortality rate of *m_rate* per unit time, write down the expressions for the number of susceptible, pre-infectious, infectious and immune individuals who die per unit time.

3. Given that the rate of change in the number of individuals in a given category is:
   + *the number who enter the category per unit time*
   - *the number who exit the category per unit time*

change the equations on page 2 of this practical to incorporate births into the population and deaths from the *Susceptible*, *Preinfectious*, *Infectious* and *Immune* categories.

We will now change our model accordingly.

4. Return to the Flowchart window *(Note. If this window, or any other window that you're interested in, is not visible, select the "Window" option from the main menu and select it from the list of available windows)*.

5. Click on the globals button and set up new parameters, called:

a) *life_expectancy_yrs*, which equals 70 years
b) *m_rate* for the **daily** mortality rate, corresponding to a life-expectancy of 70 **years**
c) *b_rate* which is equal to the value of *m_rate*.

Click on OK to continue.

If we assume that individuals are born susceptible, then we need to have a flow arrow entering the *Susceptible* compartment.

6. Click on the flow arrow. Move the mouse anywhere close to the *Susceptible* compartment (e.g. 1 cm to its left), click with the left mouse button and, holding it down, drag the mouse across to click on the Susceptible compartment. Rename this arrow to "births".

The methods for incorporating deaths is analogous, as follows:

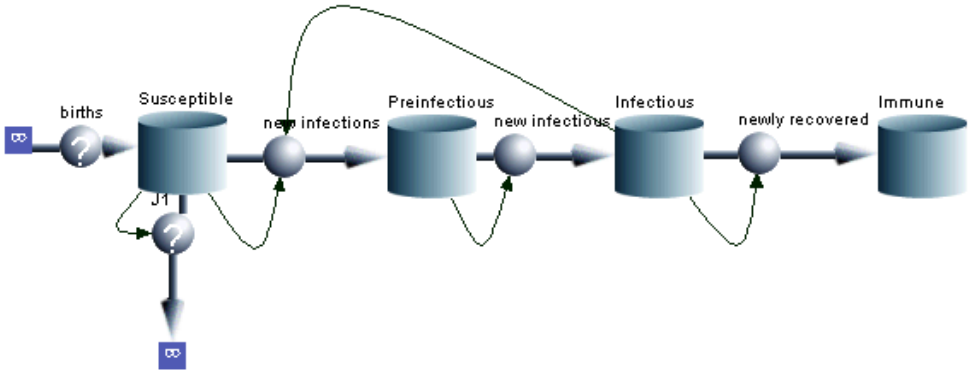
Considering the deaths from the susceptible compartment, since the equation for the number of susceptible individuals who die per unit time is

*Susceptible*m_rate*

we will need to have an arc arrow linking the Susceptible compartment to the flow arrow representing death from this category.

There is a short-cut for inserting flow and arc arrows simultaneously, as follows:

7. Click on the flow arrow using the left mouse button and then click on the *Susceptible* compartment. Holding down the ALT button and, holding down the left mouse button, drag the mouse down and release the left mouse button. You should see an arrow from the *Susceptible* compartment going to infinity (i.e. death!), together with an arc arrow as shown below:



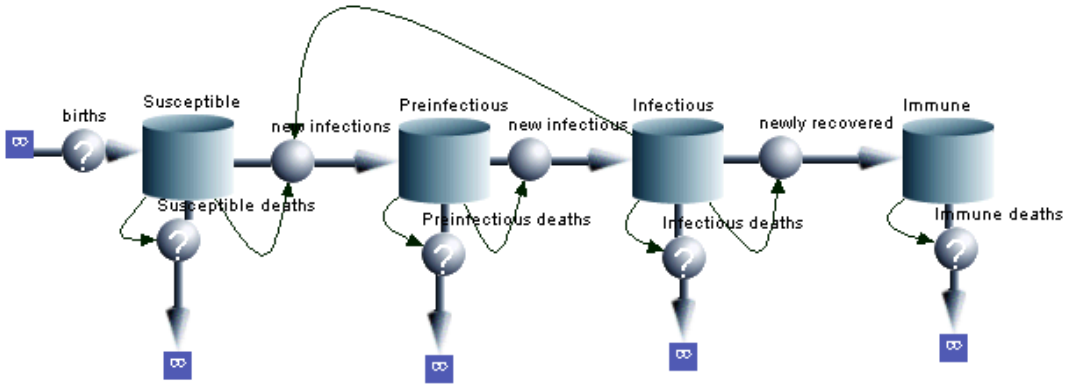
Note that we could have used this shortcut when setting up the flow arrows between

compartments in part 1. In fact, holding down the ALT key whilst you set up your flow arrows ensures that most of arc arrows in your model are in place when you need them…

8. Rename the J1 arrow to "*Susceptible deaths*".

9. Repeat the same steps to incorporate deaths from the *Preinfectious, Infectious* and *Immune* compartments.

Your diagram should resemble the following.



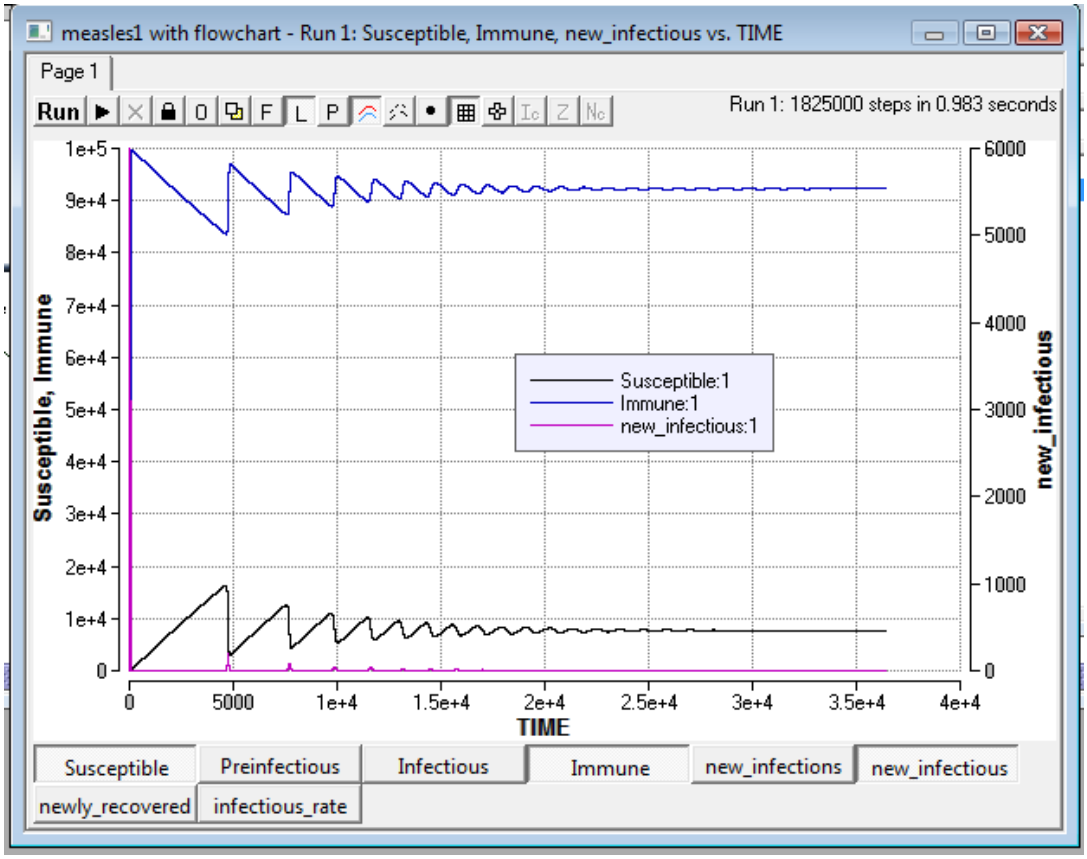
10. Set up appropriate equations in the *births*, *Susceptible deaths*, *Preinfectious deaths*, *Infectious deaths* and *Immune deaths* arrows.

By this stage, all the question marks in your model diagram should have disappeared.

Before running the model, select the Equations window (either click on it or select it from the list under the Windows option on the main menu, or choose it from the list in the "Model" option on the main menu). Your equations should have now been updated to incorporate births and deaths into the population. Check that your answer to step 3 on page 9 is consistent with these equations.

10. To run the model, click on the parameters window, change the stop value to 36500 (i.e. the model will make predictions for 365*100 days = 100 years) and click on the run button.

You should now see the following figure (depending on whether *new infectious* is plotted on the left or right hand y-axis; if you wish to change the axis on which it's plotted, double click in the middle of the figure, choose the variable from the list on the right hand side by clicking on it and click on the "Right axis" box):



You can compare your model against that in the file “measles1b – flowchart.mmd”, if necessary.

Q1.4 How do the general patterns in the numbers of susceptible and immune individuals differ from those predicted using the difference equations in Excel during the last practical?

You should notice that, although the daily number of new infectious persons and the numbers of susceptible and immune individuals oscillates over time, these oscillations become weaker, and if the model is run for long enough, they seem to disappear entirely. This pattern is inconsistent with what happens in reality --- in many populations in which measles vaccination has not been introduced, measles epidemics occur every two years, which suggests that other factors help to sustain the epidemic cycles.

Q1.5 Suggest possible factors which might help to determine the regular patterns in measles cycles.

In the next practical, we will explore the factors determining these cycles in more detail.

11. Before continuing, please save your model.

If you have run out of time, please read the remainder of this practical before the next session.

Final word: approaches for setting up models in Berkeley Madonna

Berkeley Madonna's flowchart editor provides a quick way of setting up models without worrying too much about the equations. The models set up in this way provide a visual summary of all the equations and the components which are linked.

A disadvantage of setting up models with the flowchart editor is that the differential equations cannot be edited directly in the model, although, you can, of course, edit the equations in the flow arrows and the globals window. If you prefer to work with differential equations rather than with flowcharts, you have two options, namely:

i) Discard your flowchart once you have set it up. Once you do this, however, the flowchart cannot be recovered. Unless you have saved your model to another file beforehand, the model can only be developed further using the equations editor.

ii) Set up your model exclusively using the equation editor – see Appendix A1 (page 14) for the methods for doing so. The file "measles1a - equations.mmd" is an example of a model set up just by using the equation editor. This describes the transmission of measles in a population without accounting for births and deaths (i.e. the equation editor equivalent of the file "measles1a – flowchart.mmd" developed in Part I). The file "measles1b – equations.mmd" is the same model accounting for births and deaths. The equations in these files can be written in any text editor or word processing package and pasted in to the equations window. The disadvantage of models set up using the equation editor is that Berkeley Madonna does not provide a flowchart for it.

The approach that you use to set up models depends on personal preference: some users prefer to work only with differential equations; others prefer to work with flowcharts. The models that you develop using one or the other method will give identical results.

In the remaining practicals of this course, you can choose which approach you wish to use.

If you have time, try the supplementary questions (see the supplementary questions folder on Moodle or in the folder containing the model files on the network), where you can contrast the two approaches of setting up models using a model of hookworm.

Appendix

A.1 Setting up models using the equation editor

The following provides a quick overview of the steps for setting up models using Berkeley Madonna's equation editor from scratch. You may like to follow these steps either after you've explored the flowchart method of setting up models, or if you prefer to work with equations.

1. Select the "New" option from the File option in the menu. This will open up a new window with the following text:

   METHOD RK4

   STARTTIME = 0

   STOPTIME=10

   DT = 0.02

   You can change these as appropriate later.

2. Decide on the name of each compartment in your model and type in the differential equations for each compartment. The notation for the rate of change in the number of Susceptible individuals might be written as:

   d/dt (Susceptible) = -beta*Susceptible*Infectious

   Alternatively, the differential equations can be split up into two equations, in the same way as those which were automatically generated by Berkeley Madonna for models set up using the flowchart editor, i.e. by assigning a name and assigning appropriate equations to the number of individuals who move out of the Susceptible compartment per unit time as follows:

   d/dt (Susceptible) = - new_infections
   new_infections = beta*Susceptible*Infectious

3. Type in the initial values for each compartment. For example, if there are 100000 susceptible individuals at the start, then you would type:

   INIT Susceptible = 100000

   Alternatively, it is good practice to set up a parameter, such as Sus_0, to reflect the initial number of susceptible (or other) individuals as it then becomes easy to change this value in the Parameters window or using the sliders. The number of susceptibles would then be initialized as follows:

   INIT Susceptible = Sus_0
   Sus_0 = 100000

4. Type in the parameters for your model, for example, beta, the recovery rate, R_0 etc. Note that parameters can be expressed in terms of other parameters in the model. For example, you can type the following expression for beta, assuming that R0, total_popn and infectious_period have already been set up :

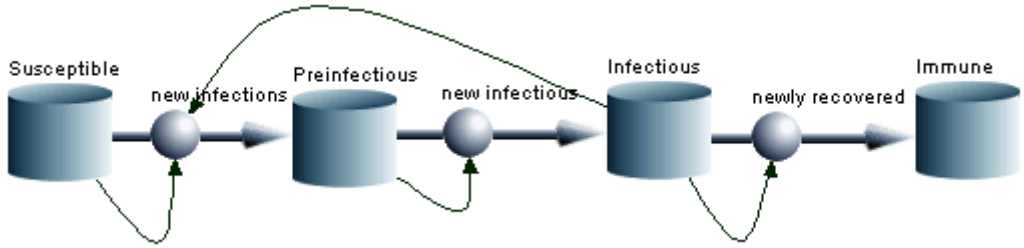
beta = R0/(total_popn*infectious_period)

See the section on specifying the input parameters (page 4) for the values that we are using in this practical.

5. Run the model (see page 7 for the steps for doing this) and follow the remaining steps in part 1 this practical if you are trying to complete this practical using the equation editor. Likewise adapt the steps in part 2 of this practical to deal with births and deaths.

A2. Setting up models using the flowchart editor

You would draw the following diagram in Berkeley Madonna to set up a model describing the transmission of an immunizing infection (without accounting for births and deaths):



The key features of the diagram are:

1. **The boxes (known as "reservoirs" in Berkeley Madonna)** represent the number of individuals in the given compartment e.g. the "Susceptible" reservoir represents the number of susceptible individuals, the "Preinfectious" reservoir represents the number of pre-infectious individuals etc.

2. **The flow arrows (thick arrows with a circle in the middle)** hold the equations for the *absolute number of individuals who move from one category to the next per unit time*. e.g. the "*new infections*" arrow holds the number of individuals who are newly infected per unit time, which is given by the equation:

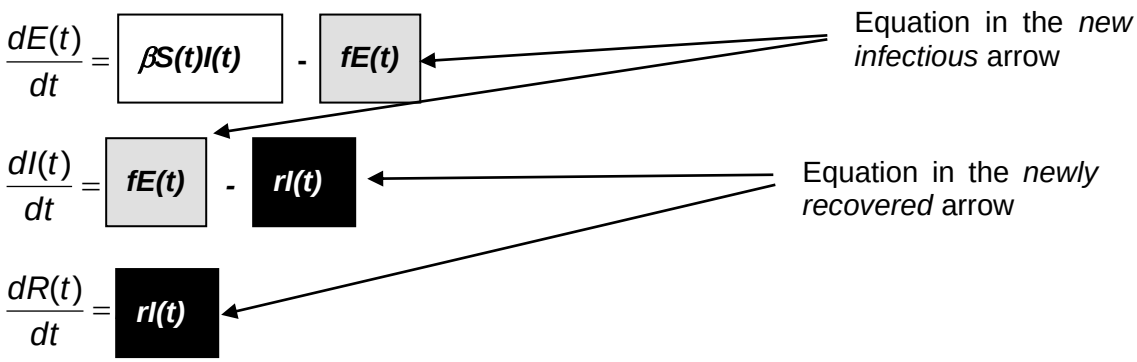
   β*No. of susceptible individuals * No. of infectious individuals

3. **The thin arrows (known as "arc" arrows in Berkeley Madonna):** these tell Berkeley Madonna which components depend on each other. For example there is an arc arrow from the Susceptible compartment to the "*new infections*" arrow because the number of susceptible individuals is used in the equation in the "*new infections*" arrow. An analogous argument accounts for the arc arrow from the Infectious compartment to the "new_infections" arrow.

The relationship between differential equations and the equations in the flow arrows is as follows:

$$\frac{dS(t)}{dt} = -\boxed{\beta S(t)I(t)}$$

Equation in the *new infections* arrow



When setting up the model recall that:

- None of the equations in the flow arrows have a minus sign (i.e. they just reflect the **absolute** number of individuals who move from one category to the next). The direction of the flow arrow tells Berkeley Madonna whether the individuals are exiting or entering the category.

- In most models, the equation in the flow arrow depends on the compartment from which it originates and you will almost always need to have an arc arrow from a given compartment into the flow arrow which goes out of it.

- You can either set up the flow arrow first and add the arc arrow later OR (more efficiently) set up the flow and arc arrows simultaneously by holding down the ALT key whilst you set up your flow arrow.

A3. Key features of Berkeley Madonna

The following provides a guide to particular features of Berkeley Madonna which are used in this practical. There is more detailed guide to Berkeley Madonna in the "useful" section (section 5) of the course manual.

The "Parameters" window

The parameters window for most models typically lists the following:

a) The method which Berkeley Madonna uses to convert the differential equations to difference equations and to adjust for errors in this conversion. This is normally set to be "Runge-Kutta 4" which we will be using in most of the models. For some exceptional models (see later sessions in the course), this method doesn't work and in this instance, we use the "Euler" method using a small step size. This method is equivalent to setting up the same difference equations in Excel.

b) The time step which Berkeley Madonna uses in solving the difference equations (specified by the value of DT which is set to be 0.02 time units by default).

c) The time period over which the model makes predictions of the number of people in each compartment (specified by the values of STARTTIME and STOPTIME, which

are set to be 0 and 10 by default). Note that the units of your stoptime are determined by the units of the parameters in the flow arrows or the differential equations: if these are in units of per day, then STOPTIME is in daily units.

d) DTOUT, which specifies the number of output steps generated in each model run. The default (0) means that the output is generated for each time step i.e. every 0.02 days if DT is set to be 0.02 days.

e) The number of individuals present in each compartment at the start (specified by the values INIT Susceptible, INIT Preinfectious, etc)

f) The current values for all the parameters in the model e.g. the R0, the pre-infectious and infectious periods etc.

The figures or graph window

The following table summarizes the functions of the buttons which are usually available on the graphical toolbar:

	Definition	**Description**
Run	Run	Runs the model.
▶	New page	Inserts another page of graphs.
✕	Delete	Deletes the current page of graphs.
🔒	Lock	Locks the current page of figures: the figures will remain unchanged if you re-run your model with other parameter values.
0	Overlay plots	If this button is pressed down, then the results of further runs of your model will be added to the current figure.
	Table	Presents the values for the series being plotted. To export these values e.g. to Excel, click on the "Save Table as" option from the File option on the main menu. You can then import the resulting file into Excel or other programs.
F	Fast Fourier transform	Carries out a Fast Fourier transform of the model output – consult the manual for Berkeley Madonna for further details.
L	Legend	Adds the legend to the figure.
P	Parameters	Adds the parameter values to the figure.
	Colours	Changes the colour scheme from colour to black and white.
	Dashed lines	Changes the lines from being solid to dashed.
•	Data points	Presents the series plotted as individual data points rather than as a continuous line.
	Grid	Adds gridlines to the figure.
	Readout	When this is pressed, a cross in a circle appears; the co-ordinates of this cross are shown on the top right hand corner of the window. Clicking anywhere in the window will move this cross to that location.
Z	Zoom out	Note that you can zoom in on a portion of the graph by clicking with the left mouse button anywhere on the graph when the pointer is a solid black cross and, holding the left mouse button down, dragging across to the point that you're interested in. Clicking on the zoom out button will return the view of the figure to normal.

Introduction to Infectious Disease Modelling and its Applications – 2018

Session 5: Analysing the dynamics of infectious diseases

Practical

Overview and Objectives:

This practical revises the relationship between the basic and net reproduction numbers, the herd immunity threshold and the trend in number of new infectious persons, and explores how the size of the basic reproduction number affects the inter-epidemic period.

By the end of this practical, you should understand the relationship between:

- the basic and net reproduction numbers and the herd immunity threshold;
- the peaks in the number of new infectious persons of an immunizing infection and the prevalence of susceptible and immune individuals in the population;
- the basic reproduction number and the inter-epidemic period.

Part I: The relationship between the basic and net reproduction numbers and the herd immunity threshold

The relationship between the net reproduction number and trends in the number of new infectious persons/unit time

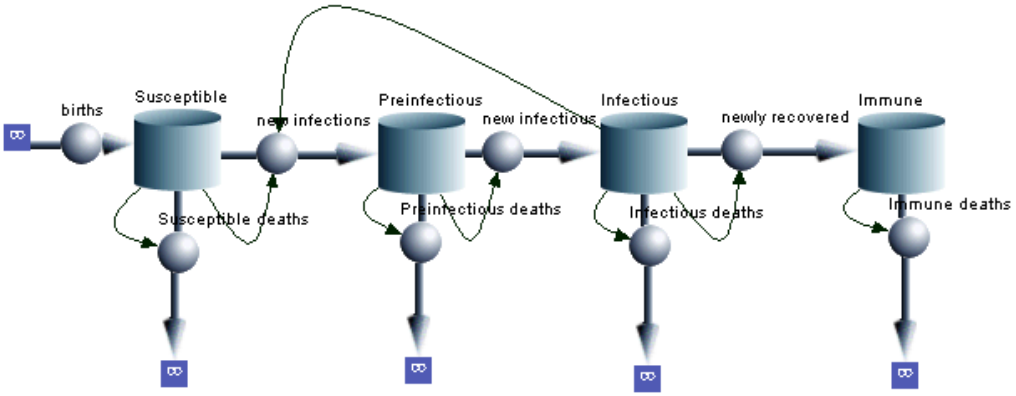
We first focus on how the net reproduction number changes during the epidemic cycles for a simple immunizing infection. You may remember from previous studies that the net reproduction number, R_n is given by the following expression:

$$R_n = R_0 * \textit{proportion susceptible}$$

1. Open up the file “measles2 – flowchart.mmd”. Alternatively, if you prefer to work without the flowchart, open up the file “measles2 – equations.mmd”. Unless otherwise stated, the instructions for this practical are identical for both files.

The model in these files is closely related to the model which you created in the last session, except that it has 2 new variables *prop_sus and prop_imm.* You can see these by clicking on the globals button in the flowchart window (for those using “measles2 – flowchart”) or by viewing the equations window (for those using “measles2 – equations”).

The R_0 is currently 13. The model diagram is on the next page.



Before continuing, check that you understand what *prop_sus* and *prop_imm* represent.

2. If you're using "measles2 – flowchart", set up a new variable called *Rn* in the globals window, representing the net reproduction number, using an appropriate expression. If you're using "measles2 – equations", set up *Rn* in the equation editor.

3. Open up the parameters window and run the model, which has been set to run for 73000 days.

We first focus on the relationship between *Rn* and the daily number of new infectious persons over time.

4. Set up a new figure (page 2) by clicking on the "New Page" button on the toolbar of the figures page.

The easiest way to add another variable (i.e. *Rn*) to the plot is to select the button for that variable at the bottom of this window. Berkeley Madonna automatically includes buttons for the first few variables in the model; buttons for other variables (e.g. the *Rn*) can be added manually, using the steps below.

5. Double click in the middle of the figures window. This opens up a new window called "Choose variables".

6. Double click on *Rn* in the variables list in the left hand side of this window, so that *Rn* appears in the list under the "Y Axes" section. This section lists the components for which buttons will be set up at the bottom of the figures window.

7. Click on OK to continue and re-run the model to add *Rn* to the plot (it should appear on the left-hand y-axis).

8. Change the scale on the axis for the *Rn* to go from 0 to 1.5. *NB To change the scale on the axes, double click on either the x or y-axis. In the window which then appears, click on the "Scales" tab, deselect the auto button for the axis that you're interested in and change the minimum and maximum values. You can ignore the value of #Div – this just specifies how many gridlines are provided for the given axis.*

9. We are interested in how the net reproduction number changes during an epidemic cycle, e.g. over a 10 year period, so, in a similar way, change the x-axis scale to go from time t=14600 (i.e. the 40th year) to time t=18250 (the 50th year).

Q1.1 How does the net reproduction number change over time? What is the value of the net reproduction number when the daily number of new infectious persons peaks? What is its value when the daily number of new infectious persons reaches a trough?

Q1.2 What is the trend in the daily number of new infectious persons when $R_n<1$? What is its trend when

a) $R_n>1$ and

b) $R_n=1$?

Is this reasonable?

10. Copy the figure (to page 3) by clicking on the "New Page" button  , add *prop_sus* to this new plot on the left-hand y-axis and remove *Rn* from the plot.

Q1.3 What proportion of the population is susceptible to infection when the daily number of new infectious persons peaks or troughs? (You may need to change the left-hand y-axis scale to go from 0 to 0.15.) Is this consistent with what you expect and why?

The relationship between the herd immunity threshold and trends in the number of new infectious persons

You may recall from previous studies that for transmission of an infection to cease, the proportion of the population which is immune must be kept above the "Herd immunity threshold" (*H*), which is given by:

$$H= 1- 1/R_0$$

Q1.4 Using this expression, calculate the herd immunity threshold in this population.

1. Copy the figure to a new page (page 4), add *prop_imm* to the new plot on the left-hand y-axis, and remove *prop_sus* from the plot. Change the left-hand y-axis scale to go from 0.8 to 1.0 to see the line for *prop_imm*.

Q1.5 What is the value of prop_imm when the number of new infectious persons per day peaks or troughs? What do you notice about the value of prop_imm when the daily number of new infectious persons is declining? What is its value when the the daily number of new infectious persons is increasing? How does this relate to your estimate of the herd immunity threshold?

2. Return to page 1 of the figures window.

Q1.6 (optional) What is the long-term equilibrium value for the proportion of the population which is susceptible or immune? How do these values relate to the herd immunity threshold which you have just calculated and why?

We will now change the model to explore how vaccinating a fixed proportion of the population at close to the herd immunity threshold affects transmission.

Before continuing, deselect *prop_imm* and *prop_sus* from the figure in page 1.

The relationship between the herd immunity threshold and impact of vaccination

1. Set up a new parameter (in the Globals window if you're using "measles2 – flowchart.mmd", or in the equation window otherwise) called prop_vacc, reflecting the vaccination coverage in the population. Set it to equal 0.75.

We will assume that vaccination is introduced sometime (e.g. 50 years) after the infection has been circulating in the population.

2. Add the following text to your model immediately after your definition of prop_vacc:

eff_cov = if (time>18250) then prop_vacc else 0

According to this line of text, the parameter eff_cov, which we will take to reflect the proportion of newborns which are effectively vaccinated, takes the value of prop_vacc 18250 days (i.e. 50 years) after the start of the simulations and is zero otherwise.

3. Change the model (in the Flowchart editor, if you're using the file "measles2 – flowchart" or in the equations editor if you're using "measles2 – equations") so that:

a) a proportion eff_cov of newborn individuals are effectively vaccinated (i.e. enter the immune compartment) after they are born
b) the remainder (1-eff_cov) enter the susceptible compartment.

If you're unsure of how to do this, you can refer to the files measles2 +vacc – flowchart.mmd or measles2+vacc – equations.mmd for a hint.

4. Run the model for values of *prop_vacc* which are either above or below the herd immunity threshold, either by setting up (and using!) the sliders or by changing the value in the parameter window. If you are using the sliders, set the increment for *prop_vacc* to equal 0.01.

Q1.7 What happens to the number of new infectious persons per day (see page 1 of the figures window) if the proportion of the population which is effectively vaccinated is below the herd immunity threshold? What happens to the number of new infectious persons per day if this proportion is above the herd immunity threshold?

Note: You can check your model against that in the files "measles2+vacc – flowchart.mmd" or "measles2+vacc – equations.mmd", if necessary.

If you have time, try part 2 of this practical in which we explore how R_0 and other factors (e.g. the vaccination coverage, the birth rate in the population) affect the epidemic cycles.

Part II: The effect of the basic reproduction number and other factors on the inter-epidemic period (optional)

1. Reset the proportion of the population which is vaccinated to be zero and re-run the model.

Q2.1 What is the inter-epidemic period 50-100 years after the introduction of one infectious case into this population? (Hint: How many cycles in the number of new infectious persons per day occur in each 10 year period?)
Note: If you wish to change the x-axis scale to use annual, rather than daily time units, set up a variable called "year" which equals time/365, double click anywhere in the middle of the figures window, select "year" from the list under "X-axis", choose OK and re-run the model.

Anderson and May (1991) provide a formula for estimating the inter-epidemic period for immunizing infections:

$$T = 2\pi\sqrt{\frac{L(D+D')}{R_0 - 1}}$$

where D' is the average duration of the pre-infectious period, D is the average duration of infectiousness, L is the life expectancy and π is the universal constant (3.14…).

Q2.2 Are your results from the previous question consistent with this formula? (Note that the life expectancy currently equals 70 years).

2. Run the model for values of R_0 of 5 and 18. To put these values into perspective, the R_0 for measles was estimated to be about 5-6 in Kansas 1918-9, 13-14 in Cirencester (UK) in 1947-50 and 18 in England and Wales in 1950-68.

Q2.3 How does the inter-epidemic period resulting from an R_0 of 18 compare against that resulting from an R_0 of 5? Why might this occur?

Q2.4 How might you expect the introduction of vaccination to affect the inter-epidemic period? Check your hypothesis by changing the value of prop_vacc.

Q2.5 How might the birth rate in the population influence the inter-epidemic period? Test your hypothesis by changing the birth rate assuming that the population size remains constant over time.

Q2.6 Would you expect the inter-epidemic period for measles to be shorter than that for chickenpox? mumps? rubella? Why?

3. Change the parameters to be those for influenza (pre-infectious and infectious periods of 2 days and a basic reproduction number of 2), reset the birth rate to be that in the original model (i.e. corresponding to a life expectancy of 70 years) and, making sure that no-one is vaccinated in the population, run the model.

Q2.7 Why might you be cautious about using predictions of the inter-epidemic period for influenza from this model?

If you have time, try the following:

1. The supplementary questions for this session (see the supplementary questions folder on Moodle or in the folder containing the model files on the network), which illustrate Berkeley Madonna's parameter plot facility and discuss how the pre-infectious and infectious periods and "seasonal transmission" (e.g. resulting from school closures during the holidays) affect the inter-epidemic period.

2. The exercises associated with the model files for chapter 4 of recommended course text[1] (see www.anintroductiontoinfectiousdiseasemodelling.com).

References

1. Vynnycky E and White RG. An introduction to infectious disease modelling. Oxford University Press. Oxford, 2010.

Introduction to Infectious Disease Modelling and its Applications – 2018

Session 7: Revision of Berkeley Madonna - Did country ξ adequately prepare for the influenza pandemic?

Practical

Overview

The aims of this exercise are to:

1. Give you practice in designing your own models and setting them up in Berkeley Madonna;
2. Illustrate questions which could be solved using the techniques you have covered during the course;
3. Help consolidate the material which you've learnt so far;
4. Introduce you to methods for analysing data using Berkeley Madonna.

To improve your learning experience, you are asked to work in pairs.

Context

It is April 20xy and you belong to one of the leading team of modellers in your country, **ξ** (pronounced Xsi). A few months ago, your country experienced the first wave of an influenza pandemic with approximately 60,000 individuals (~15% of the population) reported to have experienced symptoms.

Before the pandemic, it had successfully vaccinated 50% of individuals with a poor quality influenza vaccine, as it was logistically impossible to achieve an overall coverage exceeding 50%. Your Minister of Public Health is currently reviewing its handling of the influenza pandemic and has asked each team to answer the following questions:

1. How many cases (among children, adults and overall) would have been reported in the first pandemic wave if no one had been vaccinated?
2. Would vaccination have had a bigger impact on the size of the first wave of the pandemic if the government had vaccinated only
    i. children or
    ii. adults
3. What further information does it need to answer these questions?

In this session, you are asked to work in pairs to:

i) discuss the available data and produce a model which describes influenza transmission between different age groups in country ξ;
ii) use the model to answer the above questions
iii) think about the limitations of the model and what further data or information you need.

Model specifications

The model should be set up in Berkeley Madonna (in your spare time, you can set it up in Excel). The model should be as simple as possible and **in this session, you should assume that individuals mix randomly**. You will be able to refine this assumption later in the course, should you wish to do so.

You should start by developing a model which aims to reproduce the numbers of cases reported during the first pandemic wave (see below), stratified for children and adults, using the available information. You may like to read the suggested steps for hints about how to approach setting up the model.

Try to use both the flowchart and the equation editor approaches. Pages 4-7 of this handout provide a summary of working with both approaches and dealing with Figures in Berkeley Madonna. **You should adapt the flowchart or equation editor versions of the "measles closed.mmd" model, which describes the transmission of measles in a closed population and is very similar to the model that you developed during the first Berkeley Madonna practical.**

The Department of Health has very generously released the following information about *HxNy* and the population…

Data

Demography:

The population currently comprises 400,000 individuals with 131,950 children and 268050 adults.

Characteristics of the HxNy strain:

Newly infected individuals typically became infectious after an average period of 2 days and shed virus for an average of 2 days thereafter. According to a study conducted at the end of the pandemic wave, of those who had not been vaccinated and had serological signs of infection, approximately 65% experienced clinical symptoms (e.g. fever, cough). The infectiousness of individuals who experienced influenza infection but did not have any clinical symptoms is not known. However, it is plausible that they were as infectious as those who had clinical symptoms.

The mortality rate associated with *HxNy* is thought to be very low and, as the population is remarkably healthy, very few people died of other causes during the pandemic wave. Few individuals were known to have experienced disease more than once during the first pandemic.

The basic reproduction number for the influenza pandemics which occurred during the 20th century was about 2.

According to a serological study carried out at the end of the first wave, 40% of all individuals who showed serological signs of having been infected (and who had not been vaccinated) visited their GP and were reported during the pandemic.

Vaccination

The vaccine used before the first pandemic wave had an efficacy of about 30%.

Suggested steps

The following are some suggested steps that you may like to follow. There is no "right" order in following the steps, and you will find that you end up revisiting the steps several times.

Setting up the model

1. Think about the general structure (SEIR, SIR, SEIRS etc). Does the model need to be age-stratified? If the model needs to be age-stratified, you can refer to the steps later in this document to work out how to copy model diagrams, if you're using the flowchart editor.

2. Think about the equations for the number of new infections over time and change the current equations if necessary. If you're using the flowchart editor, change any other flow equations, if necessary; if you're using the equation editor, change any differential equations, as required.

3. Incorporate the parameters that you do know into the model (e.g. the pre-infectious period, infectious period etc), and make assumptions for others. For example, if you don't know the value for R_0, just set up a parameter called "R0" and assign it some plausible value. You will be able to infer unknown parameters from the available data later.

4. Think about the initial conditions in the model, i.e. how many persons are in each of the compartments at the start? Then set up parameters in the model (in the globals window for flowchart models) or in the equations editor (equation editor) which hold the number of individuals in each compartment at the start. If you're using the flowchart editor, you may need to update the equations in the initial values box (seen when clicking on the compartment) to refer to the initial numbers that you've set up in the globals window.

5. Think about what output you would like the model to produce and, if that variable doesn't yet exist in the model, set up a variable which produces this output. The output that you need should be comparable to the data that you have available. For example, if you only have data on the final epidemic size, you need to have a variable which calculates the final epidemic size in the model. See the comments about setting up variables later in these notes.

6. At this point, you should try running the model. However, Berkeley Madonna may come up with error messages; if this is the case, you need to check over your equations to identify the error. You may also need to think about other issues, such the size of STOPTIME (i.e. the duration over which the model runs).

After the model runs and produces sensible output...

1. Once you reach this stage, you should now think about what parameter you need for the model output to change to match the data that you have available. You can change the parameter by trial and error by using the sliders or parameter window.

You can also use the parameter plot feature, which plots the outcome of interest for values of the given parameter in a certain range.

2. Once you have identified the value of the parameter which results in model predictions which matching the observed data, you are ready to answer the questions described above. PLEASE DO NOT WORRY IF YOU DO NOT REACH THIS STAGE.... THE MAIN AIM OF THIS EXERCISE IS TO GAIN PRACTICE IN SETTING UP MODELS IN BERKELEY MADONNA.

Technicalities of working with Berkeley Madonna

Tips for keeping in reasonable control of your model

The following are some common-sense guidelines – you may come up with others!

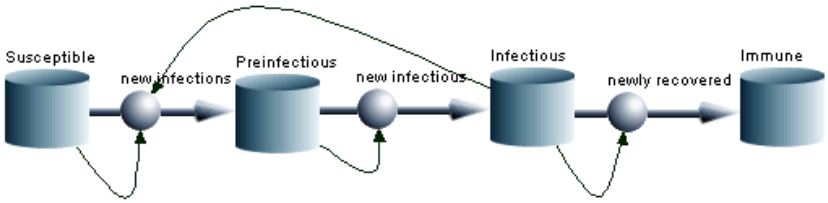
1. Try to use parameter and compartment names which are meaningful to anyone.
2. Include comments to yourself about what each parameter or variable means or why you included it. You can add comments to the equations in the global window (flowchart option) and the equations window (equation editor option). Anything enclosed in curly brackets { } is a comment and is ignored by Berkeley Madonna. Also, any text which occurs on the same line after a semicolon (;) is ignored by Berkeley Madonna.
3. If the force of infection depends on more than one compartment, set up an expression for this in your model and use this in the differential equation or flowchart.
4. Try to keep the code neatly laid out as it then becomes easier to spot mistakes.
5. Delete code that you do not need.
6. Keep definitions of similar parameters or variables grouped together. For example, keep the demographic variables together and separate from the parameters on the natural history of the infection.
7. Always check that the model is producing the output that you expect. For example, is the proportion of individuals who are immune at the end greater than the proportion at the start? If you're unsure, check your output against that generated using the same model set up in Excel or using the flowchart editor (if you're using the equation editor) and the equation editor (if you're using the flowchart editor).

Setting up models using flowcharts

Setting up new models

The following summarizes the stages and some of the key considerations for setting up models using Berkeley Madonna's flowchart facility.

1. Draw a diagram of the model. The following is the flowchart diagram of the transmission dynamics of measles which you set in the first Berkeley Madonna practical:



2. Define the parameters in the model. These are defined in the globals window, which is accessed from the globals button 

on the toolbar of the flowchart window. Note that parameters can be expressed in terms of other parameters in the model. For example, you can type the following expression for beta, assuming that R0, total_popn and infous_period have already been set up :

beta = R0/(total_popn*infous_period)

You should always remember that Berkeley Madonna needs a space to be inserted on either side of the equals sign for equations in the globals window.

3. Set up parameters for the initial values of the compartments in the globals window, e.g. include the following if there are 100,000 and 0 susceptible and pre-infectious indiviudals at the start respectively:

   Sus_0 = 100000
   Preinfectious_0 = 0

4. Type in the equations in the flow arrows for the number of individuals who move from one category to the next.

5. Type in the initial values for all the compartments using the parameters set up in step 3.

6. Run the model.

Copying flow diagrams

Note that is possible to copy either part or all of a model diagram. The method is similar to the method that you would use in Word or any other Windows package:

1. Select the elements in the diagram that you need using your mouse (e.g. by clicking with the left mouse button and, still holding down the left mouse button, dragging across the parts that you need).
2. Click on the copy  button or press the “Ctrl” and “C” button simultaneously.
3. Click on the paste  button or press the “Ctrl” and “V” button simultaneously. Berkeley Madonna will then superimpose the copied diagram onto the current diagram in pink.
4. Click on one of the pink elements and drag it away from the original diagram so that you can see it. This will move all the parts that have been selected (i.e. in pink) away from the original diagram.

Creating variables in models set up using the flowchart editor

Variables that depend on any other variable or compartment in the model can be set up in the globals window. To set up a variable for the proportion immune, you need to use the name that you’ve assigned to the number of immune individuals in the model diagram and the name of the variable describing the total population size. For example, if you have assigned the name “Imm” to the immune compartment in the model diagram, and you have assigned the name “total_popn” to the population size, you would type the following for the equation for the proportion immune in the globals window:

prop_imm = Imm/total_popn

In general, the name of a variable set up in the globals window is not allowed to have any spaces – Berkeley Madonna would come up with a compiler error if you were to type the following in the globals window:

prop imm = Imm/total_popn

Also, if you wish to refer to a compartment or flow arrow whose name has space in the model diagram, you must replace the space with an underscore when referring to that compartment or variable in an equation. For example, if the number of immune young individuals has the name “Imm y” in the model diagram, you would need to use the name “Imm_y” when referring to them in equations set up in the globals window.

See below for a guide to figures and changing parameter values.

Setting up models using the equation editor

To set up models using Berkeley Madonna’s equation editor from scratch, you need to follow the following steps:

1. Select the “New” option from the File option in the menu. This will open up a new window with the following text:

   ```
   METHOD RK4

   STARTTIME = 0
   STOPTIME=10
   DT = 0.02
   ```

   You can change these as appropriate later.

2. Decide on the name of each compartment in the model and type in the differential equations for each compartment. The notation for the rate of change in the number of Susceptible individuals might be written down as:

   d/dt (Susceptible) = -beta*Susceptible*Infectious

   Alternatively, the differential equations can be split up into two equations, in the same way as those which were automatically generated by Berkeley Madonna for models set up using the flowchart editor, i.e. by assigning a name and assigning appropriate equations to the number of individuals who move out of the Susceptible compartment per unit time as follows:

   d/dt (Susceptible) = - new_infections
   new_infections = beta*Susceptible*Infectious

3. Type in the initial values for each compartment. For example, if there are 100000 susceptible individuals at the start, then you would type:

   ```
   INIT Susceptible = 100000
   ```

   Alternatively, it is good practice to set up a parameter, such as Sus_0, to reflect the initial number of susceptible (or other) individuals, as it then becomes easy to change this value in the Parameters window or using the sliders. The number of susceptibles would then be initialized as follows:

   ```
   INIT Susceptible = Sus_0
   Sus_0 = 100000
   ```

4. Type in the parameters for your model, for example, beta, the recovery rate, R_0 etc. Note that parameters can be expressed in terms of other parameters in the model. For example, you can type the following expression for beta, assuming that R0, total_popn and infous_period have already been set up :

   beta = R0/(total_popn*infous_period)

5. Run the model.

See below for a guide to figures and changing parameter values.

Changing parameter values

- Once you've set up your model, you can change the values of parameters either by:
  - changing the value in the "Parameters window" (see above) or
  - by defining sliders for that parameter (see above)
- Any parameter which has changed since it was originally set up in the globals window has an asterisk alongside it. To reset that parameter value to its initial value, select that parameter in the Parameters window and click on the reset button.
- Any changes to parameter values which are made in the globals window are usually not recognized by Berkeley Madonna unless the model is recompiled. If you are unsure as to whether the change has been implemented, try changing the value of the parameter in the Parameters window.

Setting up figures

The figures or graph window

Berkeley Madonna automatically generates a figure each time that you run your model; the first time that you run your model, Berkeley Madonna decides the axes on which the variables are plotted and you will then need to edit your figure. The following table summarizes the functions of the buttons which are usually available on the graphical toolbar:

	Definition	Description
Run	Run	Runs the model.
▶	New page	Inserts another page of graphs.
✕	Delete	Deletes the current page of graphs.
🔒	Lock	Locks the current page of figures: the figures will remain unchanged if you re-run your model with other parameter values.
0	Overlay plots	If this button is pressed down, then the results of further runs of your model will be added to the current figure.
	Table	Presents the values for the series being plotted. To export these values e.g. to Excel, click on the "Save Table as" option from the File option on the main menu. You can then import the resulting file into Excel or other programs.
F	Fast Fourier transform	Carries out a Fast Fourier transform of the model output – consult the manual for Berkeley Madonna for further details.
L	Legend	Adds the legend to the figure.
P	Parameters	Adds the parameter values to the figure.
	Colours	Changes the colour scheme from colour to black and white.
	Dashed lines	Changes the lines from being solid to dashed.
•	Data points	Presents the series plotted as individual data points rather than as a continuous line.
	Grid	Adds gridlines to the figure.
	Readout	When this is pressed, a cross in a circle appears; the co-ordinates of this cross are shown on the top right hand corner of the window. Clicking anywhere in the window will move this cross to that location.
Z	Zoom out	Note that you can zoom in on a portion of the graph by clicking with the left mouse button anywhere on the graph when the pointer is a solid black cross and, holding the left mouse button down, dragging across to the point that you're interested in. Clicking on the zoom out button will return the view of the figure to normal.

Changing scales on the axes

You can change the scale on the axes, by double clicking on either the x or y-axis, clicking on the "Scales" tab, deselecting the auto button for the axis that you're interested in and changing the values for the minimum, maximum accordingly. The number of divisions (the final column, labelled #Div at the bottom) specifies the number of tick marks on the axes. e.g. If your x-axis goes from 0 to 10 and you specify that you have 5 divisions, then you will have tick marks at 2, 4, 6, 8 and 10.

Adding variables to your plot

The easiest way of adding another component to the plot is to select the button corresponding to that component at the bottom of this window. Berkeley Madonna automatically includes buttons for the first few variables in the model at the bottom of the figures window. If the variable that you would to plot is not represented by a button, you can add further buttons as follows:

Double click in the middle of the figures window. This will open up a new window called "Choose variables". The variable that you're interested in should appear in the list of variables in the left hand side of this window; double click on this variable so that it appears in the list under the "Y Axes" section. This section lists the components for which buttons will be set up at the bottom of the figures window. Click on OK to continue. Note that once you've added a new button in this way, you will need to re-run the model before the output for that component will appear.

Changing the units on the axis scale

If you prefer to change e.g. the x-axis scale to use annual, rather than daily time units, set up a new variable called "year" (equalling time/365) in globals window (if you're using the flowchart facility) or in the equations editor if you're using the equations editor. After running the model, double click anywhere in the middle of figures window and choose "year" from the pull-down menu under "X-axis". Click on OK to continue.

Changing the axis on which a variable is plotted

Double click in the middle of the figure, choose the variable from the list on the right hand side by clicking on it and click on the "Right axis" box.