Using Spreadsheets to Visualize Virus Concentration

Jyoti Champanerkar*
Department of Mathematics
William Paterson University
Wayne, NJ 07470.
champanerkarj@wpunj.edu

Christina Dizzia
Department of Mathematics
William Paterson University
Wayne, NJ 07470.

ABSTRACT
In this paper, we model the growth of a virus in an infected person, taking into account the effect of antivirals and immunity of the person. We use discrete dynamical systems or difference equations to model the situation. Excel is then used to obtain and visualize numerical solutions.

Keywords
Difference Equation, Recurrence Relation, Virus Concentration, Discrete Dynamical Systems

1. INTRODUCTION
Hantavirus can cause life-threatening infection which is spread to humans by rodents. Early symptoms of hantavirus disease are similar to flu, including chills, fever and muscle aches [3]. A virus found at a construction site in Rwanda is similar in behavior to the hantavirus. The virus grows rapidly from just a single cell, doubling every hour, and remains undetected by the human body until it reaches one million copies. Once the immune system detects the virus, it raises the body temperature, lowers the virus replication rate to 150% per hour and can kill a maximum of 200,000 copies of the virus per hour. An hourly dose of antivirals and the immune system together can kill 500,000,000 copies of the virus per hour while keeping the replication rate at 150% per hour. If the number of virus cells reach one billion before the antivirals are prescribed, the virus cannot be stopped and the infected person will die when the number of copies reach one trillion §.

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We will model the phases of the disease using discrete dynamical systems, analyze them using phase line analysis and obtain numerical solutions using Excel.

2. DISCRETE DYNAMICAL SYSTEM

2.1 A Brief Background
A discrete dynamical system consists of a difference equation or a recurrence relation, along with an initial condition. A difference equation describes any \( n + 1 \)th term of a sequence using some of the previous \( n \) terms. For example, the difference equation \( x_{n+1} = 2x_n - 1 \) along with the initial condition \( x_0 = 2 \) describes the sequence \( 2, 3, 5, 9, 17, 33, \ldots \). The zeroth term of the sequence \( x_0 = 2 \) is given and each subsequent term is obtained by doubling the previous term and subtracting one from it. Thus we have \( x_1 = 2(2) - 1 = 3 \) and so on.

Observe that for the difference equation above, \( x_{n+1} = 2x_n - 1 \), if we started with an initial condition \( x_0 = 1 \), we would generate the constant sequence \( 1, 1, 1, \ldots \). Such a value, if it exists, is called an equilibrium or a fixed point. An equilibrium \( p \) of a difference equation is a value such that if the initial condition is \( p \), all subsequent terms in the generated sequence are also \( p \). If the initial condition is chosen close to an equilibrium value and subsequent terms generated eventually get closer and closer to the equilibrium, then we say that the equilibrium is stable otherwise it is unstable. In the example above, \( x_{n+1} = 2x_n - 1 \); if we choose \( x_0 = 1.1 \), the subsequent terms are 2.1, 4.1, 8.1, which are farther from \( p = 1 \) than even the initial condition. So \( p = 1 \) is an unstable equilibrium.

In general, for a difference equation \( x_{n+1} = ax_n + b \), the equilibrium is given by \( p = \frac{1}{1-a} \), which exists if \( a \neq 1 \) and any initial point is an equilibrium if \( a = 1 \) and \( b = 0 \). The equilibrium \( p = \frac{b}{1-a} \), if it exists, is stable when \( |a| < 1 \) and unstable when \( |a| > 1 \).

2.2 Modeling virus concentration
Let \( x_n \) denote the number of copies of the virus in the body at the end of \( n \) hours.

2.2.1 Initial Phase/ Phase 1
We assume that a single virus cell has infected a soldier. Hence, the initial condition is \( x_0 = 1 \). The virus doubles every hour. Hence at the end of \( n + 1 \) hours, there are double the number of virus copies of what were at the end of \( n \) hours. This gives the system:
\[ x_{n+1} = 2x_n \] (1)

\[ x_0 = 1 \] (2)

This system has the equilibrium point \( p = 0 \) and it is unstable (since \(|2| > 1\)). Which means that in the initial phase, even if a single copy of virus enters the body, the number of copies of the virus will increase (away from 0). See Figure 1.

We numerically solve this system using Excel and find that it would take, approximately, **20 hours** before the number of copies of the virus reaches one million, at which time the immune system begins to respond. See Figure 2.

### 2.2.2 Response of the Immune System / Phase 2

When the immune system begins to respond, the temperature of the body rises, the replication rate of the virus reduces to 150% per hour and the immune system kills up to 200,000 copies of the virus per hour. Thus we have,

\[ x_{n+1} = 1.5x_n - 200,000 \] (3)

\[ x_0 = 1,048,576 \] (4)

This system has the equilibrium point \( p = 400,000 \) and it is unstable (since \(|1.5| > 1\)). See Figure 1. This means that if the immune system responded before the number of copies reached 400,000 \((x_0 < p)\), the virus would be cleaned out of the body, but if the immune system responds after the number of copies reached 400,000 \((x_0 > p)\), the number of copies of virus would continue to increase. However, since the immune system responds after the virus has reached one million copies, this virus cannot be cleaned out of the body by the immune system alone. We use the initial condition \(x_0 = 1,048,576\) instead of one million, since by the end of 20 hours the virus had reached 1,048,576 copies and between 19 and 20 hours, the virus had not crossed one million copies and to avoid fractional hours.

We numerically solve the system using Excel and find that it would take, approximately, 19 hours for the number of copies of virus to cross one billion. Thus, it would take 39 hours since the first copy of virus enters the body, for the virus to reach one billion copies. See Figure 3.

### 2.2.3 Administration of Antivirals / Phase 3

When hourly antivirals are administered, the immune system along with the antivirals kills 500,000,000 copies of the virus and replication stays at 150%. This gives the difference equation:

\[ x_{n+1} = 1.5x_n - 500,000,000 \] (5)

This system has an equilibrium \( p = 1,000,000,000 \), which is unstable. See Figure 1. We consider two different initial conditions.

If the antivirals are started after the virus had reached one billion copies, the initial condition is \( x_0 = 1,438,187,806 \), the number of copies reached at the end of Phase 2, that is 39 hours after being infected. In this case, the replication process cannot be stopped and the virus reaches one trillion copies in next 20 hours. This means the person will die in spite of hourly administration of antivirals. We illustrate this using Excel. See Figure 4.

If the antivirals are started before the virus has reached one billion copies, the initial condition is \( x_0 = 958,925,204 \), the number of copies reached an hour before the end of Phase 2. In this case, the virus can be eradicated from the body within 8 hours of administering antivirals. We illustrate this using Excel. See Figure 5.

Thus a person can be saved if antivirals are administered within 39 hours since the virus has entered the body. If it is 40 hours since the infection, it is too late. We once again emphasize that we consider only hourly increments in order to keep the model simple.

### 3. AN APPLICATION

Consider a soldier in the field getting infected by the virus studied in the previous section. At 0200 hours on Tuesday a soldier’s body temperature soared to 104 degrees. Thinking quickly back across his day, he realizes that he started feeling hot and achy at about 2000 hours the previous day. The soldier cannot receive medicine until 1400 hours the next day. Is it in time?

Using the model developed and numerical solution obtained using Excel in the previous sections, we come up with the following time line. Also see Figures 6 & 7.

- 0600 hours on Monday - Working backwards, since the immune system responds after about 20 hours, this is the approximate time that the soldier got infected by the virus.
- 2000 hours on Monday - soldier felt hot and achy at this time: The soldier has, 16,384 copies of the virus in his body at this time.
- 0200 hours on Tuesday - body temperature soars to 104 degrees : This is the time when immune system starts responding. At this time there are approximately 1,048,576 copies of virus in the soldier’s body.
- 2100 hours on Tuesday - This is 19 hours after the immune response has begun; the number of copies of the virus reaches one billion. Any time after that, the antivirals will be ineffective.
- 1400 hours on Wednesday - At this time, the number of copies of the virus reach one trillion and the soldier dies. Unfortunately, this is also the time that the medicine reaches the camp.

### 4. CLASSROOM EXPERIENCE

In Spring 2009, this work was first assigned as a project to an undergraduate math major. The student had prior knowledge of discrete dynamical systems, and spent several weeks...
on solving the entire problem. This student then presented
the results to other students and faculty in the mathematics
department.

In Fall 2011, based on the previous success, this project
was assigned to undergraduate biology majors enrolled in
a mathematical biology class, as an in-class project for 90
minutes. These students had some experience with mod-
eling discrete dynamical systems, determining fixed points
and their stability, and determining numerical solutions us-
ing Excel. At the end of this project, these 12 participants
were surveyed to assess their understanding of fixed points
and stability. The survey also gauged their impression of
whether this project showed them the role of mathematics
in understanding biological phenomenon. The complete sur-
vey is provided in the Appendix.

4.1 Survey Results

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The first five questions assessed their understanding of an
equilibrium point and its stability. Most of the students
(91.7%) could determine a fixed point of a simple difference
equation and all (100%) of them could determine its stabil-
ity. More than half could visualize the dynamics of an ab-
stract system with a stable fixed point (50-66.7%). However,
only a third (33.3%) understood that if the initial condition
(M0) is a fixed point (even if it is unstable), then there is no
change, and all iterates are the same as the initial condition
(Mt = M0 for all t).

Majority of the students (86.7%) recognized the use of piece-
wise functions in the project (question 6), and all of them
(100%) agreed (or strongly agreed) that discrete dynamical
systems (question 7) and using Excel to solve discrete
dynamical systems (question 8) were useful in modeling bi-
ological phenomena. More than half (58.8%) could relate
the stability of an equilibrium point to the stability of the
underlying system (question 9).

Only three comments (question 10) were received: “very use-
ful but takes a lot of abstract thinking to understand”, “if unfa-
familiar with math terminology it can be difficult to un-
derstand what solution is being asked for”, and “Good lab
and interesting [application]”.

The problem of predicting the concentration of a virus is a
straight forward application of discrete dynamical systems.
It can easily be done in one or two lab-periods with guidance
from an instructor or over several weeks by students working
independently.

5. REFERENCES

Dynamical Systems, F. Marotto

Problem Number 20027: Predicting the concentration of
a Virus

/PMH0002358/

APPENDIX

Survey Questions

The following questions were asked on the survey given to
students enrolled in a mathematical biology class after they
were done working on the virus concentration project (Fall
2011).

Circle the best option for questions 1 - 9.

1. The equilibrium value of the discrete dynamical system

   Mt+1 = 0.75Mt + 1 is

   • M* = 0
   • M* = 2.0
   • M* = 4.0
   • does not exist

2. The equilibrium value of the discrete dynamical system

   Mt+1 = 0.75Mt + 1 is

   stable /unstable/ does not exist?

3. The equilibrium value of a discrete dynamical system

   Mt = 5 and is known to be stable. If the initial condition

   is M0 = 5.0 which of these can be Mt?

   • Mt = 3.5
   • Mt = 4.0
   • Mt = -4.25
   • Mt = 7

4. The equilibrium value of a discrete dynamical system

   Mt = 9.0 and is known to be stable. If the initial condition

   is M0 = 5.0 which of these can be Mt?

   • Mt = 6.0
   • Mt = 4.0
   • Mt = 5.0
   • Mt = 0

5. The equilibrium value of a discrete dynamical system is

   4.0 and is known to be unstable. If the initial condition

   is M0 = 4.0 which of these can be Mt?

   • Mt = 3.5
   • Mt = 4.0
   • Mt = -7
   • Mt = 7

6. The virus concentration problem was solved by using

   piecewise defined functions since an updating function

   was defined for each phase.

   • Strongly agree
   • Agree
   • Neutral
   • Disagree
   • Strongly Disagree

7. Discrete dynamical systems are useful in modeling bi-

   ological phenomena.
8. Excel is a helpful tool for solving and visualizing solutions to discrete dynamical systems.

9. Stability of an equilibrium point for a discrete dynamical system corresponds to stabilizing of the system towards the equilibrium in the long run, for reasonable initial conditions.

10. Any other comments:

FIGURES

Figure 1: TOP: Phase line diagram for Phase 1, showing 0 as an unstable equilibrium. MIDDLE: Phase line diagram for Phase 2, showing 400,000 as an unstable equilibrium. BOTTOM: Phase line diagram for Phase 3, showing 1,000,000,000 as an unstable equilibrium.
Figure 2: Initial phase of the infection: It takes about 20 hours for the virus to reach one million copies, at which time the immune system begins to respond.

Figure 3: Response of the immune system: It takes about 19 hours after the immune response begins for the virus to reach one billion copies.
Figure 4: Administration of antivirals not helpful: If antivirals are administered after the virus has reached one billion copies, it takes about 20 more hours, for the virus to reach one trillion copies, at which time the infected person will die.

Figure 5: Administration of antivirals is helpful: If antivirals are administered an hour before the virus reaches one billion copies, it takes about 8 hours, for the virus to be eradicated from the body.
Figure 6: This table shows the number of copies of the virus in the soldiers body, obtained using MS Excel. The discrete dynamical systems used are described in phases I and II in the paper. Given that the immune system responds on Tuesday 0200 hours (in the case described in the paper), we work backwards and estimate that the infection began on Monday at 0600 hours.

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Figure 7: This graph shows the virus concentration on a log scale. The bend in the graph, is where the immune system begins to respond, which occurs on Tuesday at 0200 hours for the case described in the paper. The soldier dies, right as the antivirals arrive at the camp on Wednesday, at 1400 hours. The antivirals would have been ineffective anytime after Tuesday, 1900 hours.