Using Spreadsheets to Visualize Virus Concentration

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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[1].

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

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[1]Problem taken from `Mathmodels.org` [2]

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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 $2, 3, 5, 9, 17, 33. \cdots$. 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 $1, 1, 1, 1, \cdots$. 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 $1.2, 1.4, 1.8 \cdots$ 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 $p = \frac{b}{1-a}$, 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:

$$x_{n+1} = 2x_n \quad (1)$$
$$x_0 = 1 \quad (2)$$

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,

$$x_{n+1} = 1.5x_n - 200,000 \quad (3)$$
$$x_0 = 1,048,576 \quad (4)$$

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:

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

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 modeling discrete dynamical systems, determining fixed points and their stability, and determining numerical solutions using 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 survey is provided in the Appendix.

4.1 Survey Results

Number of respondents = 12

Question number	% of correct responses
1	91.7
2	100
3	66.7
4	50
5	33.3

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 stability. More than half could visualize the dynamics of an abstract system with a stable fixed point (50-66.7%). However, only a third (33.3%) understood that if the initial condition (M_0) is a fixed point (even if it is unstable), then there is no change, and all iterates are the same as the initial condition ($M_t = M_0$ for all t).

Majority of the students (86.7%) recognized the use of piecewise 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 biological 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 useful but takes a lot of abstract thinking to understand", "if unfamiliar with math terminology it can be difficult to understand 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

[1] *Introduction to Mathematical Modeling Using Discrete Dynamical Systems*, F. Marotto

[2] http://www.mathmodels.org/problems/
Problem Number 20027: *Predicting the concentration of a Virus*

[3] PubMed http://www.ncbi.nlm.nih.gov/pubmedhealth/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 $M_{t+1} = 0.75M_t + 1$ is
   - $M^* = 0$
   - $M^* = 2.0$
   - $M^* = 4.0$
   - does not exist
2. The equilibrium value of the discrete dynamical system $M_{t+1} = 0.75M_t + 1$ is
   stable /unstable/ does not exist?
3. The equilibrium value of a discrete dynamical system is 3.5 and is known to be stable. If the initial condition is $M_0 = 5.0$ which of these can be M_1?
   - $M_1 = 3.5$
   - $M_1 = 4.0$
   - $M_1 = -4.25$
   - $M_1 = 7$
4. The equilibrium value of a discrete dynamical system is 9.0 and is known to be stable. If the initial condition is $M_0 = 5.0$ which of these can be M_1?
   - $M_1 = 6.0$
   - $M_1 = 4.0$
   - $M_1 = 5.0$
   - $M_1 = 0$
5. The equilibrium value of a discrete dynamical system is 4.0 and is known to be unstable. If the initial condition is $M_0 = 4.0$ which of these can be M_1?
   - $M_1 = 3.5$
   - $M_1 = 4.0$
   - $M_1 = -7$
   - $M_1 = 7$
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 biological phenomena.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly Disagree

8. Excel is a helpful tool for solving and visualizing solutions to discrete dynamical systems.
   - Strongly agree
   - Agree
   - Neutral
   - Disagree
   - Strongly Disagree
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.
   - Strongly agree
   - Agree
   - Neutral
   - Disagree
   - Strongly Disagree
10. **Any other comments:**

FIGURES

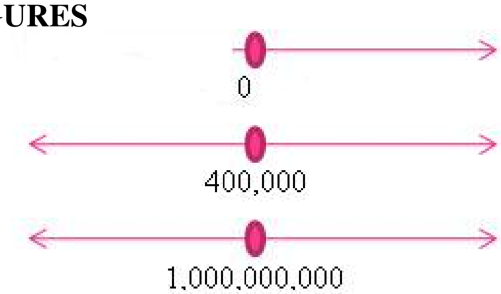

Figure 1: TOP: Phase line diagram for Phase 1, showing 0 **as an unstable equilibrium. MIDDLE: Phase line diagram for Phase 2, showing** $400,000$ **as an unstable equilibrium. BOTTOM: Phase line diagram for Phase 3, showing** $1,000,000,000$ **as an unstable equilibrium.**

n	X_n
0	1
1	2
2	4
3	8
4	16
5	32
6	64
7	128
8	256
9	512
10	1024
11	2048
12	4096
13	8192
14	16384
15	32768
16	65536
17	131072
18	262144
19	524288
20	1048576

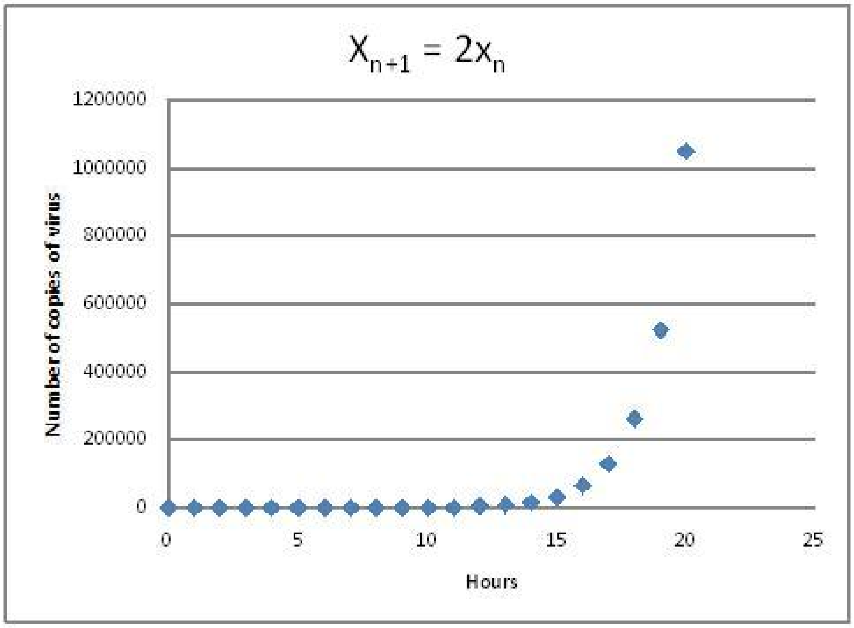

Figure 2: Initial phase of the infection: It takes about 20 hours for the virus to reach one million copies, at which time the immune system begins to respond.

1	n	xn
2	0	1048576
3	1	1372864
4	2	1859296
5	3	2588944
6	4	3683416
7	5	5325124
8	6	7787686
9	7	11481529
10	8	17022294
11	9	25333440
12	10	37800160
13	11	56500241
14	12	84550361
15	13	1.27E+08
16	14	1.9E+08
17	15	2.84E+08
18	16	4.26E+08
19	17	6.39E+08
20	18	9.59E+08
21	19	1.44E+09

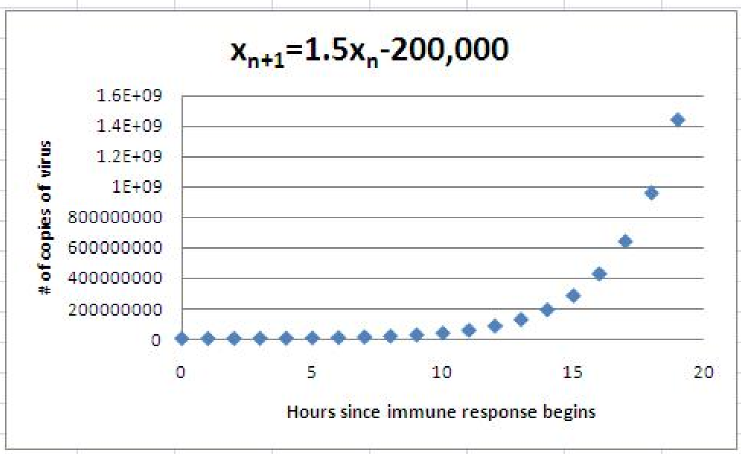

Figure 3: Response of the immune system: It takes about 19 hours after the immune response begins for the virus to reach one billion copies.

n	xn
0	1.44E+09
1	1.657E+09
2	1.986E+09
3	2.479E+09
4	3.218E+09
5	4.327E+09
6	5.991E+09
7	8.487E+09
8	1.223E+10
9	1.785E+10
10	2.627E+10
11	3.89E+10
12	5.785E+10
13	8.628E+10
14	1.289E+11
15	1.929E+11
16	2.888E+11
17	4.327E+11
18	6.486E+11
19	9.724E+11
20	1.458E+12

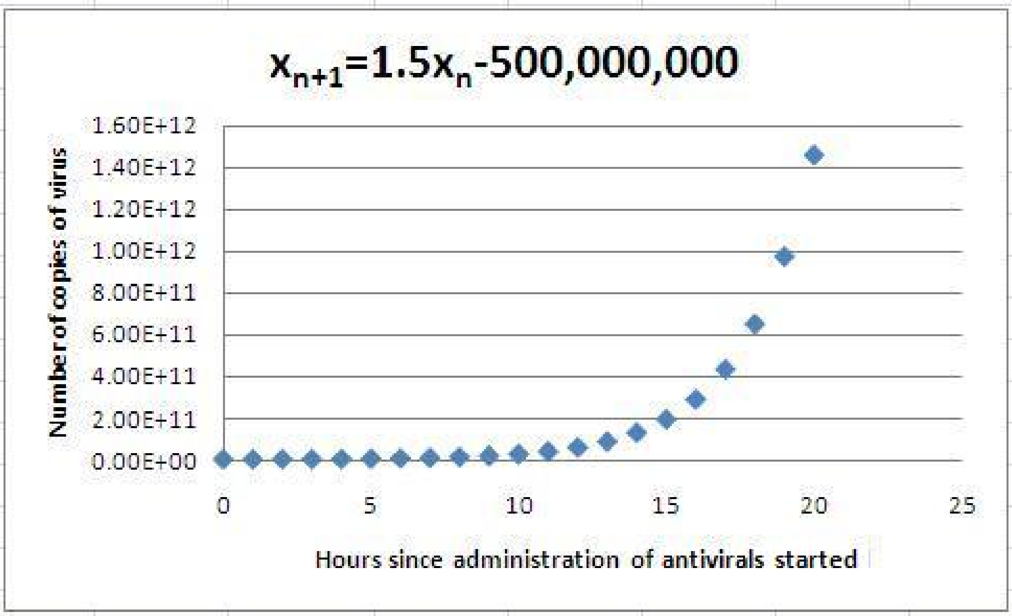

Figure 4: Administration of antivirals not helpful: If antivirals are administered after the virus has reached one billion copies, it takes about 20 more hours, for the virus to reach one trillion copies, at which time the infected person will die.

n	xn
0	9.59E+08
1	9.38E+08
2	9.08E+08
3	8.61E+08
4	7.92E+08
5	6.88E+08
6	5.32E+08
7	2.98E+08
8	-5.3E+07

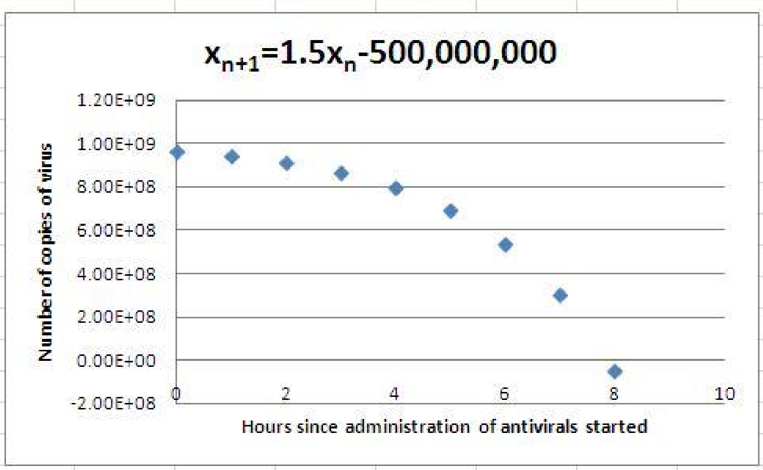

Figure 5: Administration of antivirals is helpful: If antivirals are administered an hour before the virus reaches one billion copies, it takes about 8 hours, for the virus to be eradicated from the body.

Day	Hours	X_n	Day	Hours	X_n	Day	Hours	X_n
Monday	0000		Tuesday	0000	262144	Wednesday	0000	4.853E+09
				0100	524288		0100	7.279E+09
				0200	1048576			1.092E+10
					1372864			1.638E+10
					1859296			2.457E+10
					2588944			3.685E+10
Monday	0600	1			3683416			5.527E+10
		2			5325124			8.291E+10
		4			7787686			1.244E+11
		8			11481529			1.865E+11
		16			17022294			2.798E+11
		32			25333440			4.197E+11
	1200	64		1200	37800160		1200	6.296E+11
		128		1300	56500241		1300	9.444E+11
		256			84550361		1400	1.417E+12
		512			1.27E+08			
		1024			1.9E+08			
		2048			2.84E+08			
		4096			4.26E+08			
		8192			6.39E+08			
	2000	16384			9.59E+08			
		32768		2100	1.44E+09			
		65536			2.16E+09			
	2300	131072		2300	3.24E+09			

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.

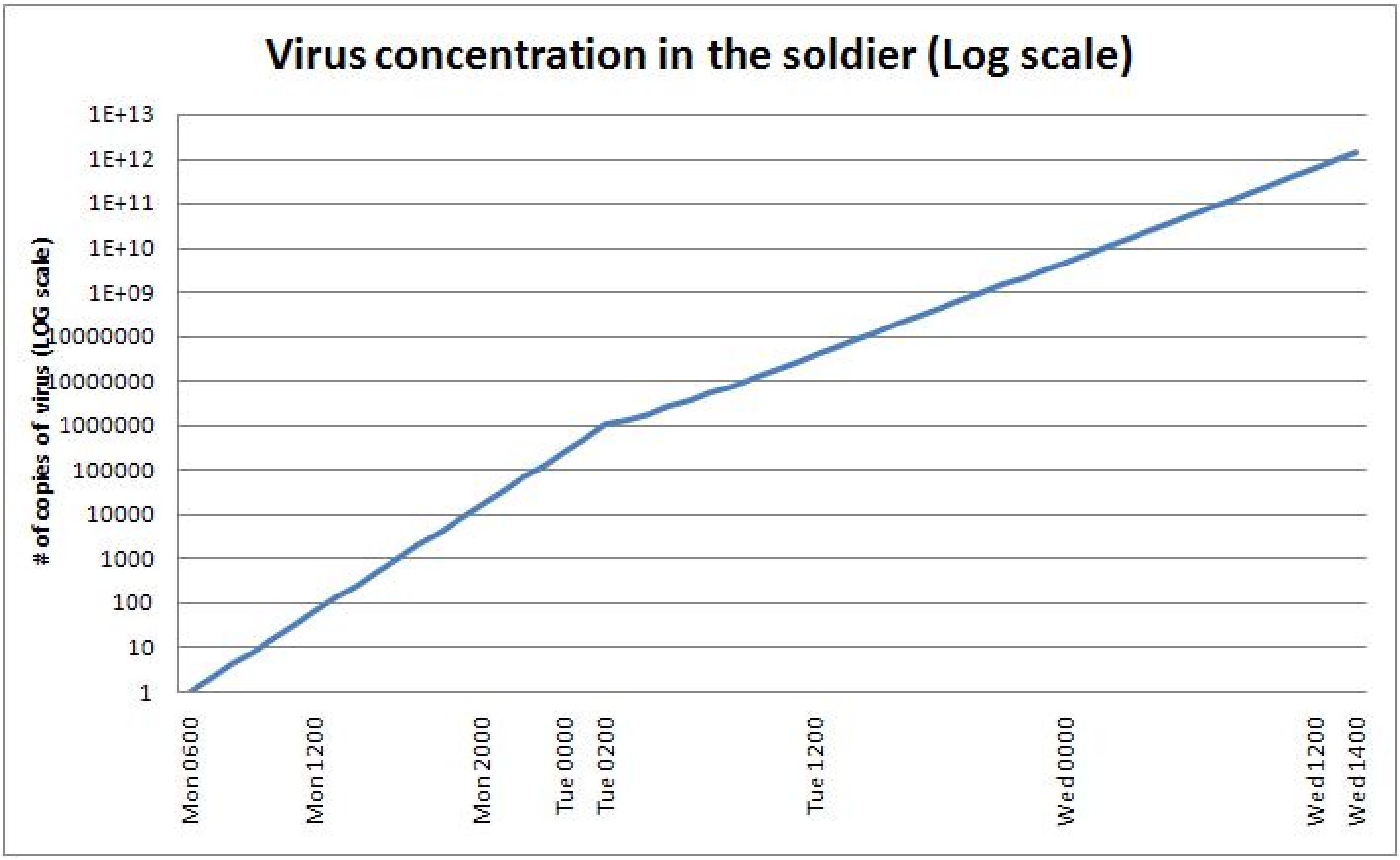

Figure 7: This graph shows the virus concentration on a log scale. The bend in the graph, is where the immune system begins to respond, which occurs on Tuesday at 0200 hours for the case described in the paper. The soldier dies, right as the antivirals arrive at the camp on Wednesday, at 1400 hours.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