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TEACHER VERSION
MALARIA CONTROL

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Abstract:

This project offers students a chance to make policy recommendations based on the analysis of models using both linear (exponential decay) and non-linear (logistic growth) differential equations. The scenario is based on the deployment of the United States Army's 62nd Engineer Battalion to West Africa in the fall of 2014. During this deployment the primary medical threat to Soldiers was malaria. It is up to the student to model and evaluate two methods of malaria prevention, malaria chemoprophylaxis and mosquito population control, and make recommendations to their commander.

SCENARIO DESCRIPTION

Background

Each year it is estimated that nearly 200 million people worldwide contract malaria, resulting in the deaths of approximately 584,000 people. Since 2005 more than 800 US service members have been diagnosed with malaria during overseas deployments. In 2014 a total of 44 service members, including 30 soldiers, contracted malaria [1]. Clearly, malaria is a continuing threat to soldiers operating overseas.

Malaria is a disease caused by a parasite that infects red blood cells. The parasite is transmitted from person to person through the bite of mosquitoes. Avoiding mosquito bites is the only sure method to prevent malaria infection. However, there are a number of medicines available to minimize the chance of contracting the illness in the event a mosquito bite occurs [3].

You are the Battalion Medical Service Officer for the 62nd Engineer Battalion. Your unit has just been notified that you will deploy to Liberia within the next 45 days to assist the Liberian military in its construction of medical treatment facilities. Your commander is aware of the malaria threat in the region and has asked you to analyze malaria preventive measures for the soldiers in your unit.

Part I: Numerical Methods and Pharmacokinetics of Malaria Chemoprophylaxis

Your first task is to analyze the anti-malarial drug dosing regimen for the battalion. Your commander's primary concerns are how soon to start treatment before the battalion arrives in Liberia and the potential risks if soldiers miss one or two of their scheduled doses. These questions require an understanding of pharmacokinetics.

A complete understanding of the pharmacokinetics of a drug requires information on the processes of absorption, distribution, metabolization, and excretion of the drug from the body. In order to simplify this problem we will assume that the anti-malarial medication is immediately absorbed into the blood stream and that all soldiers begin treatment with zero anti-malarial medication in their body. After the drug is absorbed into the blood, the rate of elimination of the drug from the body is proportional to the amount of drug currently in the blood. In other words, the more of the drug in the blood stream, the faster it is removed from the body. We will also assume that the rate of excretion of the drug is the same for all soldiers in the battalion.

In 2011 United States Africa Command (AFRICOM) issued a policy change recommending Malarone as the malaria chemoprophylaxis option for all US military operating in high malaria transmission areas of Africa [2]. Malarone is a pill taken at the same time each day that consists of two separate drugs, atovaquone and proguanil. A standard adult pill of Malarone contains 250mg of atovaquone and 100mg of proguanil. An individual must maintain at least 300mg of atovaquone and 30mg of proguanil in their blood at all times in order to prevent contracting malaria. A typical soldier's body eliminates atovaquone at a rate that corresponds to a half-life (time to eliminate one half of the original dose) of 48 hours. The half-life of proguanil is 12 hours [4].

Pharmacokinetics is the study of what the body does to a drug. Specifically, it refers to the movement of the drug into, through, and out of the body. Understanding the pharmacokinetics of a drug allows medical professionals to develop appropriate drug dosing regimens for their patients.

Requirements:

a) At $t = 0$ a typical soldier ingests one pill of Malarone. Write an initial value problem (IVP) that models the mass (mg) of the drug proguanil in the soldier's blood for $t \geq 0$. Solve this IVP analytically. After a soldier takes his first pill of Malarone, if he takes no further medication, for how many hours can he expect to have enough *proguanil* in his blood to prevent contracting malaria?

b) Approximate the solution to the IVP you developed in part (a) over the next seven days (168 hours) by implementing Euler's method in Excel with two step sizes: $h = 6$ hours and $h = 1$ hour. Compute the Sum of Squared Error (SSE) for both step sizes by comparing your estimate to the analytic solution (see the Numerical Methods Supplement for a discussion on SSE).

c) Approximate the solution to the IVP over the next seven days by implementing Improved Euler's method in Excel with step size: $h = 1$ hour. Compute the SSE using your analytic solution.

d) Create a table summarizing the results of all numerical methods (parts c and d). This table should include columns for time, the actual mass of proguanil in the soldier's blood (from part b), and the approximate values of the solution for all methods and step sizes at $t = 0, 24, 48, ..., 168$ only. You should have a total of 5 columns. Include an additional entry at the bottom of each of the last 3 columns providing the SSE for that method and step size. Discuss your results. Your analysis should include a comparison of error for different step sizes and for different methods.

e) Write an IVP that models the mass (mg) of the drug *atovaquone* in a typical soldier's blood for $t \geq 0$ if a soldier ingests only one pill of Malarone at $t = 0$. Approximate the solution to this IVP using Improved Euler's method in Excel with step size: $h = 1$ hour.

f) Using your solutions to parts (c) and (e), if a soldier ingests one pill of Malarone at the same time each day, how long before your unit's departure to Liberia should soldiers begin taking their pills? In other words, how long until the soldiers will consistently have enough proguanil AND atovaquone in their blood to prevent contracting malaria? Illustrate your result using a chart or table.

g) Assume a typical soldier reaches a "steady state" level of proguanil and atovaquone in their body after their 8th dose of Malarone. If after reaching "steady state" a soldier misses one dose, are they at risk of contracting malaria? How about after missing two consecutive doses? Explain.

Part II: Mosquito Population Control

Unfortunately anti-malarial drugs are not 100% effective at preventing the spread of malaria. The only sure method to prevent contracting malaria is to avoid mosquito bites. In light of this, your commander has asked you to look at methods to control the mosquito population in the battalion area near the living quarters. His objective is to reduce the mosquito population in both the short (less than 6 months) and long (greater than 6 months) term while also minimizing the environmental impact and potential soldier health problems associated with the mosquito control measures that are implemented.

There are two typical approaches to mosquito control. The first approach is to directly kill mosquitoes using an insecticide spray. The effectiveness of this method depends on the frequency of spraying and the concentration of the insecticide. However, frequent spraying of insecticide has potential negative health effects on both humans and nearby wildlife. This method is also temporary as the mosquito population will recover once routine spraying has stopped. The second approach to mosquito population control is to eliminate the resources that support the mosquito population. This is done through the destruction of mosquito breeding grounds and involves everything from filling in small puddles to the draining of swamps and marshes. Keeping in consideration manpower and budget constraints, you must find the combination of these two approaches that best meets your commander's objectives over the next six months.

Studies on mosquito control indicate that the rate of change of the mosquito population, P, (measured in millions of mosquitoes) in Liberia can be accurately modeled using the following Initial Value Problem:

$$\frac{dP}{dt} = kP\left(1 - \frac{P}{M}\right) - EP, \qquad P(0) = P_0$$

where E is a constant that represents the effectiveness of insecticide spraying efforts, M is the local carrying capacity and is affected by efforts to reduce mosquito breeding grounds, k is the population growth constant, P_0 is the initial population, and time t is measured in months. Current estimates suggest that there are approximately 10 million mosquitoes living near your unit's base camp in Liberia. Data indicates that $M = 11$ million and $k = 1.2$ for this mosquito population.

Use the information provided and Improved Euler's method to evaluate the three mosquito population control courses of action (COA) that have been proposed by the battalion staff. Recommend a COA to your commander that you feel best supports his objectives and support your recommendation with mathematics. Be sure to include other considerations (not just what your mathematical model tells you) in your analysis. Tables, graphs, and other visual representations that summarize and support your analysis and recommendation are encouraged and should be included in an appendix.

COA A - In this COA the battalion would devote most of its available resources for mosquito control to the use of insecticide. Soldiers would spray highly concentrated and expensive insecticide in the soldier living areas daily. Due to the emphasis on the use of insecticide the battalion would be limited to destroying small mosquito breeding grounds only on the base camp. You estimate a value for E of E_A (see table below) and a new carrying capacity of M_A million mosquitoes that would be in effect immediately.

COA B - In this COA the battalion would devote most of its resources towards destroying mosquito breeding grounds. This COA would involve the permanent draining of a nearby marsh that is believed to be the primary breeding ground for mosquitoes at the base camp. Draining the marsh would take time to complete, delaying any impact on the mosquito population by two months, but would lower the carrying capacity to M_B million mosquitoes. The battalion would still spray insecticide but less frequently and with less potency than in COA A. It is estimated that spraying would immediately result in a value for E of E_B.

COA C - This COA seeks to balance the insecticide and breeding ground destruction approaches. In this COA the battalion would use the same, more potent, insecticide as COA A but spray less frequently. This would free up manpower to destroy small mosquito breeding grounds in both the base camp and in the areas surrounding the base camp. You estimate a new value for E of E_C and a new carrying capacity of M_C million mosquitoes that would be in effect immediately.

	COA A		**COA B**		**COA C**	
	M_A	E_A	M_B	E_B	M_C	E_C
Set 1	10.5	0.55	6.0	0.10	9.0	0.40
Set 2	10.0	0.60	5.5	0.10	8.5	0.45
Set 3	10.5	0.50	6.5	0.10	9.0	0.40

Hardcopy Submission Requirements and Guidance:

Your submission should follow this general format:

1. Cover Sheet
2. Executive Summary - The executive summary consists of a single spaced 1 page paper formatted with Times New Roman, 12 point font, and documented in accordance with the MLA style. The executive summary should summarize your work for Part II in such a way that the reader can rapidly become acquainted with the material. It should contain a brief description of the problem, important background information, a discussion of pertinent assumptions, a short description of your methodology, concise analysis, and your main conclusions. Assume the reader is familiar with the basics of calculus and differential equations, so there is no need to walk through every step of your solution process or include equations. However, you should still describe the processes and mathematical techniques you used to reach your conclusions and explain why you used them. To assist the reader, be sure to present your Bottom Line Up Front (BLUF). Refer to appendices as necessary.
3. Appendices - Appendices should be neatly formatted and present information in a logical manner. Do NOT simply print out Mathematica code or a long Excel spreadsheet. Consolidate your results and provide a short explanation of what it is the reader is seeing while also highlighting key pieces of information in the appendix.
   (a) Appendix A - Answers and analysis for Part I
   (b) Appendix B - Provide a table that summarizes the results of your analysis for all three COAs in Part II. Also include a copy of all work you used to analyze your recommended COA.
   (c) Additional Appendices - Include additional appendices as necessary.
4. Works Cited

Appendix A: Numerical Methods Supplement [5]

Many differential equations cannot be solved analytically. When presented with a differential equation that cannot be solved explicitly we can turn to numerical methods to provide a near approximation of the solution. This is similar to a situation in calculus: if we cannot find an antiderivative in terms of elementary functions, we turn to a numerical method such as area estimation using endpoints or midpoints to evaluate a definite integral.

With numerical methods, as with qualitative methods, we obtain information about the solution - quantitative and qualitative respectively - without the use of a solution formula.

Euler's Method

The simplest numerical solution method was developed by Euler and is based on the tangent line approximation to a function. Given the initial value $y(t_0) = y_0$, we define t_n and y_n recursively by the following:

$$n = 0, 1, 2, \ldots$$

$$t_{n+1} = t_n + h$$

$$y_{n+1} = y_n + hf(t_n, y_n)$$

where $f(t_n, y_n) = y'_n$ and $h = t_{n+1} - t_n$. The approximations y_{n+1} become better as h (step size) is reduced.

Example 1 Consider the initial value problem:

$$\frac{dy}{dt} = \frac{t}{y} \qquad y(0) = 1.$$

We wish to approximate $y(0.3)$ using Euler's method with step size $h = 0.1$. After three steps we find $y(0.3) = 1.0298$. See Figure 1.

	A	B	C	D	E	F	G	H	I	J
1	Euler's Method for dy/dt = t/y , y(0) = 1									
2	t0 =	0								
3	y0=	1								
4	h =	0.1								
5										
6	Euler's Method, h = 0.1						Accepted Solution			Squared Error
7	n	t_n	y_n	f(t_n,y_n)	y_(n+1)		t	ya(t)		(ya(t)-y_n)^2
8	0	0	1.0000	0.0000	1.0000		0	1		0
9	1	0.1	1.0000	0.1000	1.0100		0.1	1.00499		2.49001E-05
10	2	0.2	1.0100	0.1980	1.0298		0.2	1.0198		9.604E-05
11	3	0.3	1.0298				0.3	1.04403		0.000202437
12									SSE =	0.000323377

Figure 1. Using Euler's method with step size $h = 0.1$ to approximate $y(0.3)$ with three steps.

Next use $h = 0.05$ and six steps. Notice that $y(0.3) = 1.036982$. See Figure 2.

In this example, cutting the step size in half had the effect of cutting the error approximately in half. As expected the global error in the Euler's method is proportional to h.

The squared error in the tables above were determined by squaring the difference between the exact value y_a and the experimentally determined value y_n from Euler's method.

$$\text{SquaredError} = (y_a(t) - y_n)^2$$

The Sum of Squared Error (SSE) was determined by adding up the squared error values,

$$SSE = \sum_{i=0}^{n-1} (y_a(t) - y_n)^2 .$$

	A	B	C	D	E	F	G	H	I	J
13	h =	0.05								
14										
15	Euler's Method, h = 0.05						Accepted Solution			Squared Error
16	n	t_n	y_n	f(t_n,y_n)	y_(n+1)		t	ya(t)		(ya(t)-y_n)^2
17	0	0	1	0	1		0	1		0
18	1	0.05	1	0.05	1.0025		0.05	1.00125		1.5625E-06
19	2	0.1	1.0025	0.099751	1.007488		0.1	1.00499		6.2001E-06
20	3	0.15	1.007488	0.148885	1.014932		0.15	1.01119		1.37083E-05
21	4	0.2	1.014932	0.197058	1.024785		0.2	1.0198		2.36994E-05
22	5	0.25	1.024785	0.243954	1.036982		0.25	1.03078		3.5944E-05
23	6	0.3	1.036982				0.3	1.04403		4.96693E-05
24									SSE =	0.000130784

Figure 2. Using Euler's method with step size $h = 0.05$ to approximate $y(0.3)$ with six steps.

Improved Euler's Method or Huen's Method

We again start with the tangent line approximation using Euler's method; however, we now replace the slope $y'(t_n)$ by the average of the two slopes $y'(t_n)$ and $y'(t_{n+1})$, such that:

$$n = 0, 1, 2, \ldots$$

$$t_{n+1} = t_n + h$$

$$y_{n+1} = y_n + h\frac{(f(t_n, y_n) + f(t_{n+1}, y^*_{n+1}))}{2},$$

where $f(t_n, y_n) = y'_n$, and $f(t_{n+1}, y^*_{n+1}) = y'_{n+1}$, given the initial value $y(t_0) = y_0$. Notice that y'_{n+1} requires y^*_{n+1}. Therefore we first compute one Euler's method step to approximate y^*_{n+1}, such that $y^*_{n+1} = y_n + hf(t_n, y_n)$. We will call this solution a "predictor" for y_{n+1}. We then "correct" this solution using what is referred to as the improved Euler's method or Huen's Method[6], which simplifies to:

$$y_{n+1} = y_n + h\frac{(f(t_n, y_n) + f(t_{n+1}, y_n + hf(t_n, y_n)))}{2},$$

Example 2 We again consider the initial value problem from Example 1 and find an approximation to $y(0.3)$ with $h = 0.1$. We obtain $y(0.3) = 1.0441$. See Figure 3.

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	h=	0.1											
2													
3	(Improved Euler: RK2), h = 0.1									Accepted Solution			Squared Error
4	n	t_n	y_n	f(t_n,y_n)	t_(n+1)	y*_(n+1)	f(t_(n+1),y*_(n+1))	y_(n+1)		t	ya(t)		(ya(t)-y_n)^2
5	0	0	1.0000	0	0.1	1	0.1	1.005		0	1		0
6	1	0.1	1.0050	0.0995	0.2	1.01495	0.197053994	1.01983		0.1	1.00499		1E-10
7	2	0.2	1.0198	0.19611	0.3	1.03944	0.288617231	1.04406		0.2	1.0198		7.74179E-10
8	3	0.3	1.0441							0.3	1.04403		1.17391E-09
9												SSE =	2.04809E-09

Figure 3. Using Improved Euler's method with step size $h = 0.1$ to approximate $y(0.3)$.

Notice that the SSE in the improved Euler method with $h = 0.1$ is considerably less than the SSE in the Euler method with $h = 0.05$. The global error in the improved Euler method is proportional to h^2.

REFERENCES

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