**Optimizing dose and frequency between doses of the oral antibiotic amoxicillin**

**Abstract** (/100 words)

*Summarize problem. Motivation. Approach and Results.*

**1 Introduction**

1.2 Motivation

*Why our problem is interesting and important. Give background.*

Everyone gets sick at some point in their life, whether it is a cold, flu, or infection. Medicine allows us to recover from illnesses and resume our lives. A specific class of antibiotics, called amoxicillin, is used to treat pneumonia as well as infections of the urinary treat, skin, ears, nose, and throat ([Akhavan et al., 2023](https://www.ncbi.nlm.nih.gov/books/NBK482250/)). It works by killing bacteria responsible for these infections. The dose or amount of medication that should be taken, as well as the frequency of doses, dictate how effective the medication is at treating the illness it is designed to treat. If the dose is too low, not all of the bacteria will be eliminated. If the dose is or frequency of medication intake is too high, side effects of taking the medicine may manifest. The side effects of overdose of amoxicillin range from mild ones including headaches and nausea, to severe symptoms including wheezing and renal failure (MedlinePlus; [Levison et al., 2009](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3675903/)). If the frequency is too low, bacteria populations may have a chance to re-establish themselves in-between doses, rendering the medication ineffective. In this study, we build a model of pharmacokinetics of amoxicillin (absorption, distribution, and elimination of amoxicillin in the human body), as well as a model of bacteria population in the human body to explore the impact of dose and frequency of doses of amoxicillin on the effective treatment of the common lower respiratory tract infection, pneumonia.

Antibiotics are highly prone to the buildup of bacteria resistance. This phenomenon occurs when medication is not taken for the full recommendation duration by healthcare professionals, thereby allowing some remnant bacteria to survive and reproduce rapidly, and select for individuals with antibiotic-resistance genes. It can also happen when antibiotics are overprescribed, or taking wrongfully (e.g. to treat a flu). The world is running out of antibiotics: the sheer rate at which antibiotics have been misused has resulted in ampicillin and amoxicillin becoming the only two remaining aminopenicillins on the US market. Due to the severity of the antibiotic resistance issue, we will also explore this phenomenon in our model.

1.3 Objectives

Using mathematical models, we describe how drug concentration in the bloodstream and bacteria abundance in the human body change over time upon administration of the first dose. We are modelling the intake of amoxicillin tablets (500 mg) and its impact on Streptococcus pneumoniae, the most common cause of pneumonia in the US. This is to achieve our two main objectives:

1. Objective 1: Determine how dose of amoxicillin impacts bacterial population dynamics.
2. Objective 2: Determine how frequency of amoxicillin impacts bacterial population dynamics.

**2 The Model**

*Deriving and describing the model. Present equation(s) and algorithm. State assumptions and rationale.*

**2.1 System of Equations and Variables**

The time-dependent equations that represent concentration of amoxicillin in the bloodstream and bacteria abundance are presented below. The time-dependent equation for drug concentration is (Equation 1):

(Equation 1)

D(t) represents the concentration of amoxicillin in the bloodstream and has units of ‘μg/mL’. The recommended adult dose is a 500 mg amoxicillin tablet every eight hours for lower respiratory tract infections ([FDA, 2008](https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050542s24,050754s11,050760s10,050761s10lbl.pdf)). After a dose of amoxicillin is taken orally, it is rapidly absorbed, with peak blood levels of (25.5-7.5) μg/mL typically reached within one to two hours for a 500 mg dose, and (3.5-5.0) ug/mL for 250 mg dose (Levison et al., 2009). A represents the scaling factor, and A = 20.65 for peak plasma concentration of 6.5 μg/mL and A = 15.09 for peak plasma concentration of 4.75 ug/mL (derived empirically). The absorption half-life is 43.2 minutes (τabsorb). Upon administration, amoxicillin is also rapidly processed by our kidneys; the half-life of amoxicillin in the bloodstream is roughly one hour (τelim = 61.3 minutes). After 8 hours, levels of amoxicillin in the bloodstream will be practically undetectable on average. However, the elimination half-life of amoxicillin may vary with age and bodily condition (please see Section 2.3 for sensitivity analyses pertaining to this parameter). We know the absorption and elimination processes of amoxicillin follow exponential behavior because “half-life” term is a parameter characteristic of exponential functions. Finally, f represents the interaction between drug and bacteria population; it represents how much drug is used up per unit bacteria. B(t) represents the abundance of bacteria in units of ‘individuals’.

Our equation matches the classic behavior of antibiotics in the human bloodstream, which involves steep increase to maximum achievable concentration, then decay once elimination rate exceeds absorption rate (Figure 1).

<insert side-by-side figures>

The time-dependent equation for bacteria abundance is (Equation 2):

(Equation 2)

where k is doubling rate of bacteria, B represents 2kt or the dependent bacteria growth function, and g represents how many bacteria are destroy yed per unit amoxicillin.

Bacteria grow exponentially, and their doubling time can be just 20 minutes in length when resources are plentiful (food, space; [UTexas Calculus](https://web.ma.utexas.edu/users/m408n/m408c/CurrentWeb/LM1-5-5.php#:~:text=The%20population%20of%20a%20colony,the%20time%2C%20measured%20in%20minutes.)). Thus, k = 1/20 min-1.

Taking the derivatives of Equation 1 and Equation 2 respectively gives us the system of equations we want to solve for:

(Equation 3)

(Equation 4)

The doubling time (k) is multiplied with the bacteria growth function because the derivative of an exponential function is equal to the growth rate multiplied by the original exponential function.

2.2 Assumptions and Justifications

Here is a list of our assumptions and justifications for these assumptions:

* We assumed bacteria have doubling rate of (1/100 min); literature says bacteria can double every 20 minutes in an absolutely non-competitive, plentiful resource environment. 1/100 min seems like reasonable number that is realistic.
* We assumed bacteria have no carrying capacity, and this is justified because the human body has abundant resources for the bacterium
* We assume drug is not used up (retains its integrity) upon interaction with bacteria because how it works is it destroys bacteria by competing against it for an enzyme that assembles bacterial cell walls. So this assumption is reasonable
* Molar mass of amoxicillin is 365.4 g/mol, so for 500 mg dose, that is equal to 182.7 mol of amoxicillin released into bloodstream. This is equal to 6.022 \* 1023 \* 182.7 molecules of amoxicillin ingested per dose. But for our model, we are using scaled-down versions of amoxicillin molecules and bacteria (50 molecules and 100 bacteria respectively) to make the numbers easier to work with, to allow us to see their interactions more clearly, and to prevent bacteria numbers from going out of control too quickly. This also allows us to plot amoxicillin and bacterial counts on the same axes
* For simplicity, we assumed drug is not used up upon reaction with bacteria
* We assume peak plasma concentration of amoxicillin is reached almost instantaneously upon intravenous injection, thereby omitting a delay for blood concentrations to spike, to make calculations simpler
* Due to uncertainty around how many individual amoxicillin molecules there are within a given concentration, we assume a large number of amoxicillin (e.g. 500 molecules) for the smallest peak plasma concentration, then increase the count for the other doses proportionately with respect to the difference between the peak plasma concentrations (i.e. from 6.5 to 8.5 ug/mL, which is a factor of X, so we multiplied the molecule count by the same factor)
* We assume for every ‘g’ bacterial cells are destroyed per minute, or ‘1/g’ units of drug were used up. This is called the drug efficacy, in other words how effective is it at killing bacteria. This parameter can reflect of the person previously developed antibiotic resistance (lower g) versus they have not misused antibiotics before (higher g)

2.3 Sensitivity Analysis

We wanted to assess the sensitivity of the model to doses, frequency of doses, and efficacy of drug (antibiotic resistance). The values we chose to explore for these parameters are:

* dose: 4.75, 6.5, and 8.5 ug/mL peak plasma concentrations, which we assumed to be an order-of-magnitude estimate of 50, 100, and 200 million amoxicillin molecules (a large number)
* frequency of doses: 5 hours, 8 hours (recommended), 12 hours to see its effect on patient health
* efficacy of drug: this is the ‘g’ coefficient in front of the B(t) term which represents bacterial population (Equation 2 and 4). If a person has previous buildup of antibiotic resistance already, this ‘g’ coefficient will be smaller. We varied this coefficient to explore how antibiotic resistance affects treatment. Furthermore, in the current model, if bacterial population is allowed to reach carrying capacity (1010 cells) before the full 10-day period, then we decrease g accordingly to reflect real-time development of antibiotic resistance. We considered values of 500, 1000, 2000 for this term

**3 Results and Analyses**

3.1 Solving the Equations

We assigned the parameters to the model and used ode45 solver in Matlab to integrate the time-dependent different equations Equation 3 and 4. To mimic a person taking a dose of amoxicillin every 8 hours, we solved the system of equations for 8 hours, then ran the ode45 solver again, this time with the drug abundance and bacteria population at the end of the previous 8-hour simulation. We did this for a total of 21 times, as there are 21 8-hour periods in two weeks, and we wanted to follow a person taking medication for 10+ days, as is recommended by healthcare professionals (cite).

We also tried 5 hours as period in-between doses, with initial drug concentration of 5000 amoxicillin molecules per mL, ratio of 10 bacteria:1 molecule of amoxicillin (g = 10), carrying capacity of 1010 bacteria, initial bacterial population of 106 cells. We ran the simulation for 15 hours (3\* 5 hour periods)… It is recommended that there be at least 10 days’ treatment for any infection caused by Streptococcus pyogenes to prevent the occurrence of acute rheumatic fever.

ode45 solver does not work if bacteria population approaches infinity. This is when drug stops killing bacteria and bacteria have a chance to rebound.

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| **Parameters**  half-life of elimination (τe)  doubling time (1/k)  cells of bacteria killed per unit drug per minute (g)  initial dose of amoxicillin (D1)  initial bacteria population (B1)  time interval (tr) | **Plots** | **Discussion**  When is drug almost used up, and bacteria rebounds (i.e. to determine optimal dose frequency)? |
| τe = 61.3 min  1/k = 100 min  g = 1/20  D1= 50 molecules of amoxicillin  B1 = 100 bacterial cells  tr = 480 min or 8 h |  | Bacteria rebounds before drug is used up (D(t) = 0) because exponential growth term outweighs destruction by drug. Under these conditions, optimal dose must be < 8 hours |
| Sensitivity analysis for ‘drug efficacy’ term: if g is too small, bacteria will reproduce too quickly and overwhelm system | Within 8 hours, we are already a sick (probably dead) person. |  |
| If we increase g, the drug efficacy, from  g = 1/20 to g= 1/10 |  | Here, the bacteria and drug concentrations are of similar magnitude so that they can be plotted on the same axes. Just before the drug decayed to zero, it killed off enough bacteria to reach a fixed point (dB/dt = 0, at t = 259 minutes, B = 7.7414 cells). However, this fixed point is unstable because soon the bacteria starts multiplying again as the drug concentration tends toward zero |
| If we consider multiple doses of the same drug every 8 hours | Amoxicillin count never reaches past 51 molecules because most of it is used up in the 8 hours. | We need X doses before bacteria population finally drops to 0. It seems as long as there is B > 0, the war is not over yet!  dose 1: fixed point = 257 min, then rebounds  dose 2: fixed point at time = 914 min (sign on dB/dt) changes from negative to positive  dose 3: no fixed point, dBdt always < 0  dose 4: < 0  so after dose 2, bacteria just keeps decreasing and decreasing.  at the end of 5 doses, bacteria population = 4.45 \* 10-5 cells. Matlab never completely goes to zero, so need to define “death”, set our own threshold for death. Define death of bacteria population to be when cell count falls below 1 cell, which happens after 559 minutes. |
| Can we achieve the same effect with less time between doses (greater frequency)? To help people get better faster. Try:  tr = 4 h. Similar to dose argument, this is not ideal for the patient, but here we are just exploring |  | Then bacteria reaches magnitude on the order of 10-5 also after 5 doses (25 hours). Bacterial cell count falls below 1 after 308 minutes, for administration of a dose every 4 hours.  Concentration of drug never exceeds 52 molecules of amoxicillin. Hard to reach toxic levels, or is dose just not frequent enough? |
| What if we try setting period between doses to be 1 hr? See what happens  Interestingly for dose = 100 molecules, tr = 4 hr or less, no fixed points. dB/dt consistently negative throughout entire run. This means if treatment is potent enough, bacteria do not have a chance to rebound before next dose. Their behavior is: as time -> infinity, bacteria population -> 0. dB/dt also gets closer to zero over time, becomes less negative over time. But dB/dt sign does not change, no fixed points. |  | Bacterial cell counts fall below 1 cell after 127 minutes. Maximum drug concentration reached is 80.24 (80 molecules).  As frequency of dose increases, bacteria population falls to zero more quickly. However, this results in toxic amounts of amoxicillin in your bloodstream. |
| Can we kill bacteria faster with greater dose? But limit is when dose becomes too toxic for humans (i.e. more than just some minor symptoms)  Do not take > 2000 mg/day, which is 500 mg/8 hours. We are using 50 molecules to tackle 20 bacteria, but the reality is these numbers both need to be multiplied by 106 to represent reality (we are working with a scaled down model). Assuming 50 molecules = 500 mg dose, we should not exceed this. But can explore this hypothetical situation, i.e. assume humans do not develop severe symptoms from amoxicillin overdose; try:  D1 = 100; | Define toxicity as substantially > 50 molecules of amoxicillin in the human body. 51, 52 – that is okay. But 70, 80 is not okay. | Bacterial cell count falls below 1 after only 92 minutes! However, peak concentrations of amoxicillin reach 100.4 (100 molecules), which is a lot more than the recommended dose of 50 molecules (representing 500 mg/8 hour). Severe symptoms of amoxicillin overdose include development of a rash, vomiting, diarrhea, and difficulty breathing. |
| What happens when dose < 500 mg?  D1 = 25; |  | Matlab ode solver fails when bacteria population grows out of control. After 317 minutes, output stopped. Infection went out of control, person falls sick and is in danger of dying.  It reaches a fixed point at time = 92 minutes with population = 57 cells, but this is an unstable fixed point. Very quickly the bacterial population rebounds after the small dose is used up. |

3.2 Results of Sensitivity Analysis

*Plot d(drug)/dt over time as well as d(bacteria)/dt over time. Sensitivity analysis.*

**4 Discussion of Results**

4.1 Optimal Dose and Dose Frequency

4.2 Shortcomings of Analysis

* We did not consider carrying capacity for bacteria, although in the human body they may be restricted by space.
* The relationship between peak plasma concentration and dose was assumed to be proportional to one another, so if I increase dose, I obtain the same amount of increase in peak plasma concentration. This makes model easier to parameterize (in terms of dose).
* Assumed 500 mg dose of amoxicillin results in 50 molecules in our scaled-down model. Bacteria is also scaled down to prevent ode45 solver from crashing.

*Sources of Uncertainty. Other limitations.*

4.3 Future Research Directions

Describe what the plot shows. Present fixed points, what do they mean. Describe what the sensitivity analysis tells us. Unknowns, sources of uncertainty, future research directions.

5 Conclusion

Summarize everything from motivation to discussion.

Statements of Contribution

Alice… Finn… Avi… Matthew…

CRediT Taxonomy: Conceptualization; Methodology; Software; Validation; Formal analysis; Investigation; Resources; Data Curation; Writing – Original Draft; Writing – Editing & Review; Visualization; Supervision; Project administration; Funding acquisition