The Effectiveness of Penicillin on the Treatment of Pneumonia: A model

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Abstract:

This article proposes a mathematical model that attempts to output the exact amount of time it will take for an individual to recover from varying severities of streptococcus pneumoniae. The model is denoted in discrete-time and is dependent on unit time, t. It takes into account the initial number of cells infected by streptococcus pneumoniae, the growth rate of those infected cells, the rate at which its antibiotic antagonist, penicillin, eliminates streptococcus pneumoniae, and the half-life of penicillin. When modelled, these factors yield realistic results that appear to be valid. It is not necessarily suggested that the model is ready for application in real-life scenarios but will instead serve as a steppingstone for future endeavours in scientific modelling. With the review of medical experts, the model could serve as a functional equation that can assist with predicting recovery times and as an indicator to pinpoint the exact quantities of antibiotics necessary for treatment.

Introduction:

Streptococcus Pneumoniae:

The first description of streptococcus pneumoniae dates back to 1874, when Austrian surgeon Theodor Billroth observed chains of 4-20 small organisms peculiarly arranged in pairs. Three years later, streptococcus pneumoniae was discovered and formally labelled by Louis Pastor. Pastor made his discovery through isolating bacteria from the uteruses and blood of women diagnosed with puerperal fever. It was quickly learned that streptococcus pneumoniae was a unique and lethal bacterial infection. Even today, streptococcus is renowned as a significant source of mortality, causing approximately 1 million deaths of children under the age of 5 and elderly seniors annually [4].

Pneumococcal infections spread via aerosol and droplets, colonizing and spreading internally causing pneumococcal disease. The bacteria enter through the nasal cavity and attach to nasopharyngeal epithelial cells. From there, the bacteria either remain in the nasal cavity or spreads further to organs such as the ears, sinuses, and lungs. Wherever the destination, the bacteria colonizes and spreads within the domain it resides. In the scenario this paper discusses, the bacteria can also spread throughout the bronchi in the lungs, penetrating the mucosal barrier to enter the bloodstream, causing the bacterial infection known as streptococcus pneumonia [4].

Symptoms of streptococcus pneumoniae include coughing, fever, shortness of breath, and stomach pain. If the infection progresses without treatment, additional symptoms include pleuritic chest pain, extreme laborious breathing, and shock [7]. The treatment of streptococcus pneumoniae includes a wide range of antibiotics. In this article, we discuss the efficacy of its most popular antagonist, penicillin.

Penicillin:

Penicillin was first discovered in 1928 by Sir Alexander Fleming, whose initial experimental objective was to find a treatment for the influenza virus. However, through the process, Fleming realized that penicillin was an effective treatment for more general bacterial infections. His discovery quickly became a drug that was globally renowned by medical professionals, as its wide range of effectiveness was recognized. Notably, penicillin was utilized in WWII. However, its widespread capabilities were not taken advantage of until later in the 20th century. Today, penicillin is regarded as one of the most effective and all-encompassing antibiotics in the medical market [3].

Penicillin belongs and functions similarly to drugs categorized as β-lactam drugs, which are characterized by their binding mechanisms that eliminate bacterial cells by inhibiting their replicating functions. A bacterial cell is protected by a cell wall, which is composed of peptidoglycan chains that cross-link to other peptidoglycan chains via the operator, DD-transpeptidase (also referred to as penicillin binding protein). Penicillin binds to the operator and inhibits cross-linking activity to prevent cell wall reformation, thus exposing the cell to external pressure causing it to collapse [1].

Penicillin is the primary antibiotic used in the treatment of streptococcus pneumoniae. Despite the abundance of biological, physiological, and chemical research that backs its effectiveness, few approaches have been made mathematically in addressing the efficacy of penicillin against streptococcus pneumoniae. This article proposes a model that attempts to output the exact time value that is required to eliminate an initial amount, $P(t)$, of streptococcus pneumoniae cells, given an initial dosage of penicillin, $\beta(t)$ that is re-administered when the drug has been fully consumed by the body. The details of the model are discussed below. This model serves as a steppingstone in scientific modelling, as it endeavours to predict recovery time based on multiple scientific variables.

Model Construction:

Assumptions and Parameters:

The proposed model is one of discrete-time and is dependent on unit time, t, which is set to move state-to-state by a time step of 6 minutes (10% of an hour). All *variables* defined above the equation are taken into account, each encompassing its own range of mathematical assumptions. $P(t)$, which describes the number of infected cells, is assumed to commence with an initial value of $P(0) = 1000$. In the absence of its antagonist, penicillin, $P(t)$ would continue to grow at a rate of α. α denotes the *rate of infection* and is assumed to remain constant, doubling infected cells every 5 time steps (or equivalently, 30 minutes) [9]. The exponential nature of the growth rate is described as $\alpha = \ln(4)$. The derivation of this equation is displayed in the *Assigning Variables* section. $\beta(t)$, which denotes the *rate of restoration* is based on the assumption that 85% of infectious cells are eliminated every hour [2]. $\beta(t)$ is assumed to decrease at a constant rate in accordance to the half-life of penicillin, denoted as λ. As the drug is increasingly consumed in the body, its efficacy exponentially decreases. In addition, it is assumed that the amount of penicillin in the bloodstream is negligible after 5.5 half-

lives, which is equivalent to 77 time steps (7.7 hours) [5]. Consequently, it is assumed that a new dosage of penicillin is re-administered every 8 hours until the number of infected cells is reduced to approximately 0.

Furthermore, the model equation includes a set of strictly biological assumptions. Firstly, it is assumed that the model is most accurately applicable to a healthy male who is not subject to antibiotic resistance. Secondly, it is assumed that the subject is not allergic nor resistant to penicillin specifically. Thirdly, it is assumed that the method of administration does not play a significant role in altering the absorption rate and efficacy of penicillin. Lastly, the influence of varying metabolisms and other physiological properties are not taken into account in the model equation.

Variables:

- $\mathrm{P(t)}$ describes the number of cells infected by streptococcus pneumoniae at time t.
- $\beta(t)$ denotes the *rate of restoration* at time t, which is based on the efficacy of penicillin in eliminating streptococcus pneumoniae bacteria over a set amount of time. $\beta(t)$ changes in accordance to half-life and its efficacy decreases from the time of administration onwards, as the drug is consumed in the body. $\beta(t)$ also includes a component that re-administers a constant dosage of penicillin every 8 hours.
- α denotes the *rate of infection* which is based upon the growth rate of streptococcus pneumoniae bacteria.
- $\lambda(t)$ denotes the time value of the half-life of penicillin in the bloodstream.

Model Equation in Discrete-Time:

$$P(t+0.1) = P(t) + P(t)[\alpha + \beta(t)]$$
$$\beta(t+0.1) = \beta(t) + \lambda\beta(t)$$

Assigning Variables:

- The value for α was found using an exponential growth equation:

$$P(t) = P(0)e^{\alpha t}$$
$$4P(0) = P(0)e^{\alpha(1)}$$
$$\alpha = \ln(4)$$

- A similar process was used to find $\lambda = \frac{1}{1.4}\ln\left(\frac{1}{2}\right)$ and $\beta(0) = \ln(0.15)$.
- $P(0)$ is dependent on the initial severity of the case, our model assumes an initial infected cell value of 1000.

Results:

Taking into account the assumptions and parameters, the model equation outputs the following data:

In [1]:
```
from pylab import *
import numpy as np
```

In [2]:
```
a = np.log(4)
L = (1/1.4)*np.log(1/2)
h = 0.1

b_0 = np.log(0.15)
p_0 = 1000
t_0 = 0

T = 8 #time between doses
```

In [3]:
```
def one_dose(a, L, h, T, t0, p0, b0):
    N =  int(np.ceil(T)) + 1
    t = np.zeros(N)
    p = np.zeros(N)
    b = np.zeros(N)
    t[0] = t0
    p[0] = p0
    b[0] = b0
    for i in range(N-1):
        t[i+1] = t[i] + 1
        p[i+1] = p[i] + p[i]*(a + b[i])*h
        b[i+1] = b[i] + L*b[i]*h
    return t, p, b #t[1:], p[1:], b[1:]
```

In [4]:
```
res_one = one_dose(a, L, h, T, t_0, p_0, b_0)
```

In [5]:
```
res_one[0]
```

Out[5]:
```
array([0., 1., 2., 3., 4., 5., 6., 7., 8.])
```

Figure 1.1: Preliminary Code for *Single Administration*

```
In [6]: plot(res_one[0][:],res_one[1][:])
Out[6]: [<matplotlib.lines.Line2D at 0x7fed7ff646d8>]
```

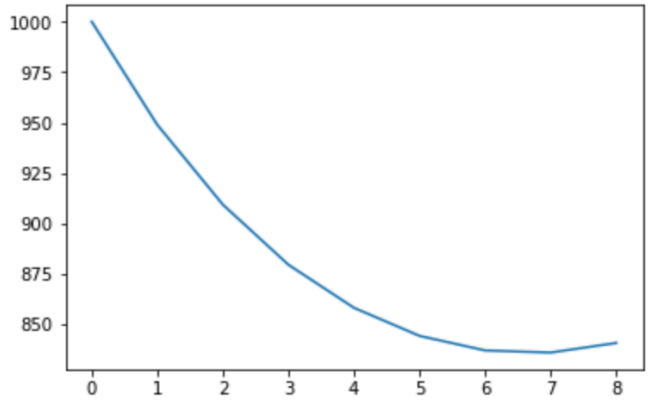

Figure 1.2: Elimination of Infected Cells, $P(t)$ Over *Single Administration*

```
In [7]: plot(res_one[0][:],res_one[2][:])
Out[7]: [<matplotlib.lines.Line2D at 0x7fed7feffef0>]
```

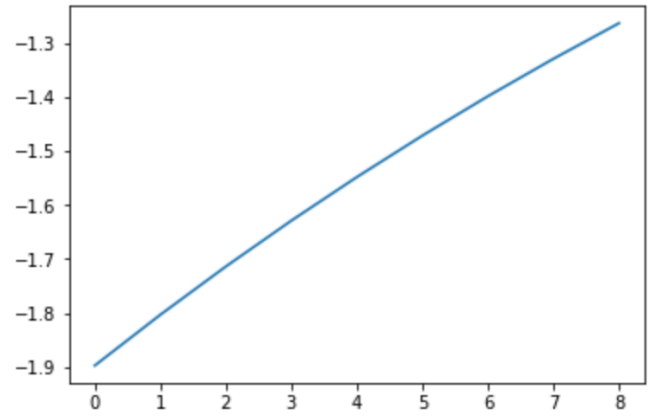

Figure 1.3: Decay of $\beta(t)$ Over *Single Administration*

```
In [8]: t = np.array([t_0])
        p = np.array([p_0])
        b = np.array([b_0])

        dosages = 0

        while p[-1] > 100:
            dosages = dosages + 1
            res = one_dose(a, L, h, T, t[0], p[-1], b[0])
            t = np.concatenate((t,t[-1]+res[0][1:]),axis=None)
            p = np.concatenate((p,res[1][1:]),axis=None)
            b = np.concatenate((b,res[2][1:]),axis=None)

In [9]: dosages

Out[9]: 14
```

Figure 2.1: Preliminary Code for *Until Extermination*

```
In [10]: plot(t[:],p[:])

Out[10]: [<matplotlib.lines.Line2D at 0x7fed7fe77278>]
```

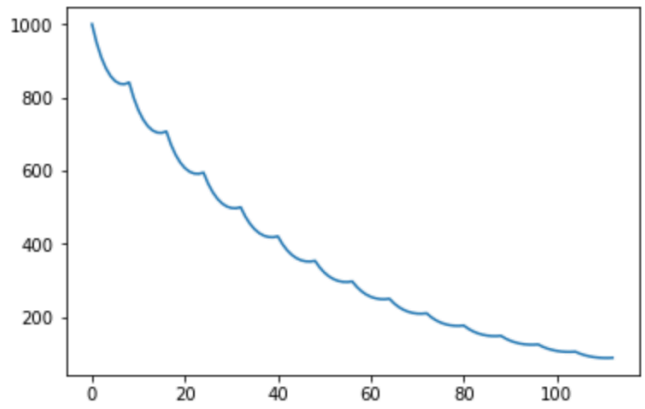

Figure 2.2: Elimination of Infected Cells, P(t) *Until Extermination*

```
In [11]: plot(t[:],b[:])
Out[11]: [<matplotlib.lines.Line2D at 0x7fed7fe49b00>]
```

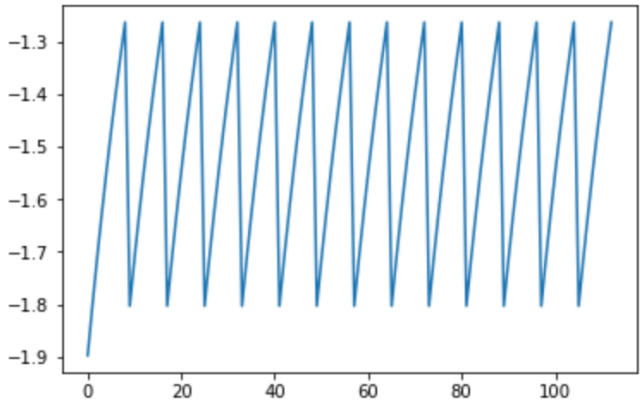

Figure 2.3: Decay of $\beta(t)$ *Until Extermination*

Analysis:
Displayed in Figure 1.2 is the effect of penicillin on the number of infected cells for a single administration. From this plot, we can see an accurate relationship that appears to be valid.

In Figure 1.3, we see the constant decay rate of the efficacy of penicillin, denoted $\beta(t)$ in the model equation. As the *rate of restoration* decreases exponentially with time, we can see the slope in Figure 1.2 gradually increase until it reaches a tangent around 7.7 hours. From there, 5.5 half-lives have passed and the amount of penicillin within the bloodstream is negligible. When no penicillin is present, as the Figure 1.2 shows, the infected cells begin to multiply with respect to the growth rate of the bacteria, α.

In Figure 2.2, we see the relationship between infected cells and penicillin where the drug is re-administered every 8 hours. As seen in Figure 1.2, the number of infected cells, $P(t)$, is quickly reduced at the beginning of administration. But as the efficacy of penicillin diminishes with time, the bacteria are eliminated at a slower rate. When the amount of penicillin in the body is negligible, the bacteria begins to multiply again. However, in contrast to initial analyses, Figure 2.2 depicts the number of administrations and exact time value required to fully exterminate the infected cells. Here, we can see 14 peaks along the scalloping slope, inferring that 14 full administrations are required in 8 hour successions to eliminate an initial amount, $P(0)$, of 1000 infected cells. Over the course of these administrations, 107.8 hours or equivalently, 4.5 days, are passed. Figure 2.3, similar to Figure 1.3, depicts the decay rate of penicillin for the 14 administrations.

Conclusion:

The model equation proposed appears to yield valid results. The analysis conducted using the variables defined show that the model is sound. With respect to the half-life of penicillin, an initial amount of 1000 infected cells, $P(0)$, could be exterminated over 14 administrations of the drug. Correspondingly, this would take approximately 4.5 days. This amount of time and re-administration interval is supported by medical research [8].

However, the model is not without its assumptions and parameters that which require careful consideration. The equation was modelled in accordance to the biological and physiological properties of an otherwise healthy male who was not allergic nor immune to penicillin. Furthermore, other important factors such as metabolic rate, method of administration, and cell absorption rate were not taken into account [6]. These variables would result in large degrees of variance in the equation output. Thus, although the model serves as a steppingstone in scientific modelling, it is not yet applicable in real-life scenarios. This is especially true when considering the deadly potential of streptococcus pneumoniae.

That being said, with some professional advancement and expert advice, the proposed model could yield useful results for medical professionals in the future. The analysis shows that the model has the potential to predict recovery rates for individuals infected by streptococcus. Such information has high utility for patients and doctors in a clinical setting. Furthermore, the model is useful for penicillin buyers and suppliers, as it indicates the amount of penicillin required to treat varying severities of streptococcus pneumoniae infections.

The proposed model opens many doors to pursue further accuracy. Firstly, addressing the model's assumptions and parameters. The model can achieve more generalizability if it included the efficacy of penicillin across several modes of administration, for example, orally or injection. Subsequently, the model can consider individual subject variables, such as varying metabolism and cell absorption rate. Furthermore, demographic data can be included that takes into account allergies, gender, age, and relative health prior to contracting pneumonia [6]. Secondly, to achieve more applicability, the model must consider the pressing issue of antibiotic resistance and tolerance. Infected cells previously exposed to an antibiotic can become resistant to it and take longer to repair. There are even cases where infected cells can develop immunity. A serious reduction in efficacy may result from antibiotic resistance and thus, is another factor the model must consider to increase its generalizability [10]. Also, since antibiotic resistance is mainly caused by over prescription, our model will come in use to doctors to prevent them from over-prescribing antibiotics, thereby preventing antibiotic resistance. Thirdly and lastly, the proposed model may serve as a template for other models that would aim to evaluate the efficacy of an antibiotic on a target bacterial infection. In other contexts involving fewer assumptions, the model might yield results that are meaningful and applicable in real-life.

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