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Prediction of Drug Concentration in Human Bloodstream using Adams-Bashforth-Moulton Method

Farah Liyana Azizan[1,2], Saratha Sathasivam[1,*], Muraly Velavan[3], Nur Rusyidah Azri[1], Nur Iffah Rafhanah Abdul Manaf[1]

[1] School of Mathematical Sciences, Universiti Sains Malaysia, Penang, 11800, USM, Malaysia
[2] Centre for Pre-University Studies, Universiti Malaysia Sarawak, 94300, Kota Samarahan, Sarawak, Malaysia
[3] School of General Foundation and Studies, AIMST University, 08100, Bedong, Kedah, Malaysia

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ABSTRACT

Pharmaceutical drugs are chemicals that are intended to avoid, assess, heal, or cure a disease. It is also commonly referred to as medication. When medicine is taken, it gets absorbed into the bloodstream and spreads throughout the body and achieves its maximum concentration. Following this, the medication level gradually decreases as it is removed from the body. The concentration of the drug according to the time can be predicted by using mathematical concepts and pharmacokinetic models. The compartmental model is a fundamental type of model used in pharmacokinetics. The number of compartments required to describe the drug's action in the body is one-compartment, two-compartment, and multicompartment. These models can be used to forecast medication concentrations in the body over time. In this paper, we will be focussing on the one-compartment model and Adams Bashforth-Moulton method. Adams Method is one of the linear multistep techniques that is applied to solve numerical ordinary differential equations that contain the predictor method (Adams Bashforth) and corrector method (Adams Moulton). The integrated development environment used for the computation and graphing is MATLAB. The expected result of this report is that we will be able to predict the concentration of the chosen drugs over time and how long a certain person needs to wait before donating blood safely.

1. Introduction

The circulation of medications entering, across, and then away from the bloodstream is described as pharmacokinetics [1]. The type of reaction a person gets from a medication is defined by the material's essential pharmacological characteristics at the location of the action. The amount and expanse of absorption of the medication after its administration, the amount and expanse of transmission of the drug to different tissues and the rate of drug removal from the area are all factors that affect the beginning, strength, and length of the reaction. Drugs such as Phenobarbitone, Vancomycin, Aminoglycosides, Methotrexate, Carbamazepine, Tacrolimus, Phenytoin, Valproic Acid,

* *Corresponding author.*
E-mail address: saratha@usm.com

Digoxin, and Theophylline are frequently monitored in Malaysia [2]. In this research, we will only look at three different drugs which are Aminoglycosides, Vancomycin, and Valproic Acid.

Aminoglycosides are antibiotics that are mostly used to treat aerobic gram-negative bacilli infections and other bacteria such as Staphylococci and Mycobacterium tuberculosis [3]. Severe infections of the abdomen and urinary tract, bacteremia, and endocarditis are treated using Aminoglycosides. It is also a recognized medication to cure infections caused by aerobic Gram-negative bacilli [4]. Aminoglycosides that are mostly used in Malaysia are Gentamicin and Amikacin. The next drug that we will focus on is Valproic acid. The various types of seizures can be treated with Valproic acid. It is also able to treat mania in bipolar disorder patients and prevent migraine headaches. Valproic acid belongs to the anticonvulsant medicine class. It raises the concentration of a natural chemical in the brain. Valproic acid is usually used as a prescription for emotional state stabilizer as well as behavioral and emotions dysregulation [5]. The drug is also used for COVID-19 patients with serious mental illness to help them calm while undergoing therapy [6]. The third type of drug that we will focus on is Vancomycin. The microorganisms Amycolatopsis orientalis originated from the Borneo tropical forest and was the source of the first Vancomycin isolation in 1957 [7]. Vancomycin is used to treat intestine inflammation caused by certain bacteria that can occur after antibiotic therapy and is also movement resistant to enterococcal biofilms [8]. Infections of the urinary system, wounds, the dysbiotic gastrointestinal tract, and endocarditis all exhibit enterococcal biofilms [9].

Medications that have the ability to degrade the blood's quality or produce ill effects in the receiver have been discovered in the blood of medication-addicted donors [10]. One of the conditions for becoming a blood donor in Malaysia is not to be on any long-term medications. The majority of drugs do not restrict a person from giving blood. Common drugs, such as blood pressure meds, birth control pills, and over-the-counter pharmaceuticals, do not affect eligibility to give blood. A person who wants to donate platelets must stop taking aspirin or any aspirin-containing medicine at least 48 hours before the appointment. Patients who are on antibiotics should finish them before donating. Regardless of the sort of drug used, the person will usually be requested to wait one week before giving blood. This duration, however, is not always ideal for some people. As a result, donated blood or platelets may include medicines that are hazardous to the recipient. Unless they are utilizing teratogenic or platelet aggregation-inhibiting medicines, most blood banks ignore these cases and do not postpone blood donation [11]. The duration for the drug to leave the bloodstream is different depending on the type of drug and the health of the person. People who take the same dose of medication can have different durations to eliminate the medication from the bloodstream. Some factors that affect this are age, height, weight, genetics, and metabolism.

The connection involving medication usage and its concentration at the specified location via different components in biological processes is regarded as a critical topic. The dosage, as well as medication input and output in the working areas, have positive and negative impacts on the human body. Pharmacokinetics researchers explored the activity of a given medicine or chemical in numerous divisions of an individual. It aids in the awareness of the links between medication administration, dispersion, and excretion rates throughout the body, as well as the establishment of the intended therapeutic response. In this research, we want to find out how long certain drugs stay in the bloodstream so that we can know exactly when the potential donor can donate their blood safely for both the blood donor and the blood receiver. The reason we chose this problem is that certain drugs in the blood that are donated have poor quality and may harm the recipient. By finding out the exact concentration of the medicine in the bloodstream before donating blood can raise the safety and quality of the blood as required by regulatory guidelines. Moreover, we are able to eliminate whoever that unable to donate due to medication effects [11].

Drug diffusion mathematical modelling is a powerful prediction technique for gaining a fundamental grasp of bio-transport processes [12]. Although the mathematical modelling is conceptual, when contrasted and confirmed empirically, the findings confirmed lead to realistic outcomes. In the lack of experiments, a huge number of analytical modelling and computational methods were performed with a high degree of efficiency. Due to regional activities in every area of the section, compartment modelling is important in pharmacokinetics. A compartment model is a mathematical depiction of the body or a portion of the body that is used to investigate physical or pharmacologic dynamic features. Depending on the method or conveyance of material, the area is depicted as a number of compartments grouped either in series or in parallel. By using the Adams-Bashforth-Moulton method, we want to check whether the usual duration which is one week is enough. In this report, we will only look at three different drugs which are Aminoglycosides, Vancomycin, and Valproic Acid. These three medications are chosen because they fit the one-compartment model and are very harmful if exist in the donated blood. The Adams-Bashforth-Moulton is a technique for solving differential equations numerically. It is also called the Adams-Predictor-Corrector method, in which the Adams-Bashforth technique is a predictor meanwhile the Adams-Moulton process is the corrector [13]. In the prediction step, a predictor-corrector technique calculates a rough approximation overtly, then simplifies the first estimation indirectly in the corrector step. As a result, it is more precise in anticipating solutions and provides greater stability. To generate the four beginning requirements for the Adams-Bashforth-Moulton method, we will use the fourth-order Runge-Kutta (RK4) process. Other numerical approaches, including the Euler method, yield less accurate findings and are numerically unstable, hence the RK4 method is preferred. The objectives of this research are to investigate what kind of drugs (medicine) are frequently monitored in Malaysia, to create a differential equation based on the mixing problem which is a drug (substance) dissolved in the human body and finally to estimate the concentration of drug in the bloodstream by an arbitrary time by using the Adams-Bashforth-Moulton technique and creating a code by MATLAB. This article is written out as follows. The first section is an introduction, followed by a description of the technique in Section 2. The outcomes are discussed in the next section. The fourth section is devoted to discussions. The conclusion is found in Section 5.

2. Methodology

2.1 Differential Equation for Drugs

We use the simplest pharmacokinetics model to generate a differential equation for the rate of drug concentration. Figure 1 [14] depicts a compartment model that describes the transport of a material into and out of the compartment. The rate of change in the amount of the substance in the compartment equals the difference between the rates at which it enters and exits the compartment. The Balance Law states that 'we cannot generate or destroy any stuff within the compartment' [14]. Expressing the mathematical relationship in words, we get

$$\text{Change in amount of substance in compartment} = \text{Transfer in} - \text{Transfer Out} \tag{1}$$

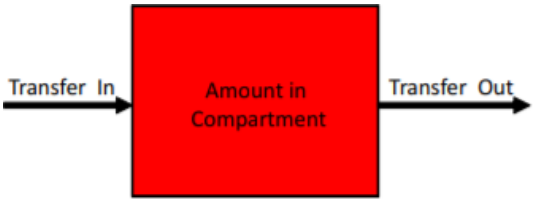


Fig. 1. One compartment model

First, we look at the single injection model (Figure 2), which assumes that just one injection is provided. The injection is represented by the model's initial conditions. Let $b(t)$ be the quantity of medication in the bloodstream at any time t, measured in hours. Let α be the rate of metabolization of the medication. The amount of medication in the bloodstream determines the rate at which it leaves the bloodstream.

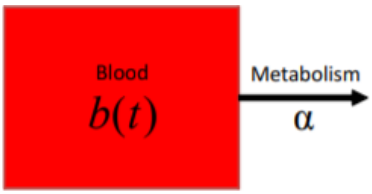


Fig. 2. Single injection model

Thus, by Eq. (1), it implies

$$\frac{db}{dt} = -\alpha b(t) \tag{2}$$

2.2 Aminoglycosides

Next, to get the value of α for Aminoglycosides, we have to find the estimated creatinine clearance (CrCl) and estimate Aminogycoside clearance (CLamg) [2].

$$\mathrm{CrCL(ml/min)} = \frac{(140-\mathrm{age})\times \mathrm{Body\ Weight(kg)}\times 1.04(\mathrm{Female})@1.23(\mathrm{Male})}{\mathrm{Serum\ creatinine\ level(\mu mol/ml)}} \tag{3}$$

$$\mathrm{CLamg(l/hr)} = 0.06 \times \mathrm{CrCL(ml/min)} \tag{4}$$

Substituting Eq. (3) into (4), we obtain

$$\mathrm{CLamg(l/hr)} = \frac{0.06\times(140-\mathrm{age})\times \mathrm{Body\ Weight(kg)}\times 1.04(\mathrm{Female})@1.23(\mathrm{Male})}{\mathrm{Serum\ creatinine\ level(\mu mol/ml)}} \tag{5}$$

We calculate for

$$\alpha(\mathrm{hr}^{-1}) = \frac{\mathrm{CLamg}}{\mathrm{Vd}} \tag{6}$$

where the volume distribution (Vd) for Aminoglycosides

$$\mathrm{Vd\ (l)} = 0.26 \times \mathrm{Body\ Weight\ (kg)} \tag{7}$$

Hence, we get

$$\alpha(\mathrm{hr}^{-1}) = \frac{0.06\times(140-\mathrm{age})\times 1.04(\mathrm{Female})@1.23(\mathrm{Male})}{0.26\times \mathrm{Serum\ creatinine\ level(\mu mol/ml)}} \tag{8}$$

2.3 Valproic Acid

Next, the formula for Clearance (CL) of Valproic Acid is

$$\mathrm{CL(l/hr)} = \frac{\mathrm{CL((ml/kg)/hr)} \times \mathrm{BodyWeight(kg)}}{1000\mathrm{ml}} \tag{9}$$

where the value for CL(ml/kg/hr) is shown below [2].

Table 1
The Clearance value for Valproic Acid

	Monotherapy	Polytherapy
Children	10 – 20ml/kg/hr	20 -30ml/kg/hr
Adult	Adult 7 – 12ml/kg/hr	15 -18ml/kg/hr

The value of α is obtained by using the formula

$$\alpha(\mathrm{hr}^{-1}) = \frac{\mathrm{CL(l/hr)}}{\mathrm{Vd(l)}} \tag{10}$$

where the volume distribution (Vd) for Valproic Acid

$$\mathrm{Vd\ (l)} = \mathrm{Vd(l/kg)} \times \mathrm{Body\ Weight\ (kg)} \tag{11}$$

Note that, Vd(l/kg) for adults is 0.15 L/kg for adults and 0.2 L/kg for children under 12 years of age. Then,

$$\mathrm{Vd\ (l)} = 0.15(\mathrm{Adults})@0.2(\mathrm{Children}) \times \mathrm{Body\ Weight\ (kg)} \tag{12}$$

Substituting the Eq. (9) and (12) into (10), we get,

$$\alpha(\mathrm{hr}^{-1}) = \frac{\mathrm{CL((ml/kg)/hr)}}{1000\mathrm{ml} \times 0.15(\mathrm{Adults})@0.2(\mathrm{Children})} \tag{13}$$

where we assume the CL(ml/kg/hr) value is the median for monotherapy based on Table 1. Therefore, for adults, $\alpha(\mathrm{hr}^{-1}) = \frac{19}{300}$ whereas $\alpha(\mathrm{hr}^{-1}) = \frac{3}{40}$ for children.

2.4 Vancomycin

The formula of α for Aminoglycosides and Vancomycin are the same but have different values of Vd [2]. The volume distribution for Vancomycin is calculated by

$$\mathrm{Vd\ (l)} = 0.7 \times \mathrm{Body\ Weight\ (kg)} \tag{14}$$

Hence

$$\alpha(\mathrm{hr}^{-1}) = \frac{0.06 \times (140 - \mathrm{age}) \times 1.04(\mathrm{Female})@1.23(\mathrm{Male})}{0.7 \times \mathrm{Serumcreatininelevel(\mu mol/ml)}} \tag{15}$$

2.5 Calculate Initial Concentration for Drugs

The equation for the initial concentration of the drug is

$$b_0\,(\mathrm{mg/l}) = \frac{\text{Dose Administered (mg)}}{\text{Vd (l)}} \tag{16}$$

Then, the equation for Dose Administered is

$$\text{Dose Administered (mg)} = \text{Dosage (mg/kg)} \times \text{Body Weight (kg)} \tag{17}$$

Substituting Eq. (17) into (16), we get

$$b_0(\mathrm{mg/l}) = \frac{\text{Dosage(mg/kg)}\times\text{BodyWeight(kg)}}{\text{Vd (l)}} \tag{18}$$

2.6 Safe Level of Drug Concentration to Donate Blood

Aminoglycoside and Vancomycin are antibiotics. The person who took any antibiotic has to wait at least seven days after their last tablet. This is to make sure the person is free from any bacterial infection that could be transmitted through blood. The same conditions are valid for Valproic acid. Hence, the concentration for all three drugs must be zero (less than 0.002 is enough) before donation of blood is allowed.

2.7 The Adams-Bashforth-Moulton Method

The Adams-Bashforth-Moulton method is chosen to solve this problem. An algorithm that operates in two phases is known as a predictor-corrector approach [15]. Runge Kutta Forth Order formula is used to find the initial values. The prediction process is done by using the Adams Bashforth formula to calculate a rough approximation of the target quantity. Then, the corrector part is done by using the Adams Moulton formula that refines the initial estimate using a different method. It employs both an explicit and an implicit strategy for the predictor and corrector steps respectively.

Runge Kutta Forth Order Formula

$$\begin{aligned} K_1 &= hf(t_i, b_i) \\ K_2 &= hf\,Qt_i + \tfrac{h}{2}, b_i + \tfrac{K1}{2}S \\ K_3 &= hf\,Qt_i + \tfrac{h}{2}, b_i + \tfrac{K2}{2}S \\ K_4 &= hf(t_i + h, b_i + K_3) \end{aligned} \tag{19}$$

$$b_{i+1} = b_i + \tfrac{1}{6}(K_1 + 2K_2 + 2K_3 + K_4) \tag{20}$$

Forth Order Adams Bashforth Formula

$$y_{i+1} = y_i + \tfrac{h}{24}5(5f_i - 59f_{i-1} + 37f_{i-2} - 9f_{i-3}) \tag{21}$$

Forth Order Adams Moulton Formula

$$y_{i+1} = y_i + \frac{h}{24}(9f_{i+1} - 19f_i - 5f_{i-1} + f_{i-2}) \quad (22)$$

3. Implementation

By the proposed solution in the previous section, we can generate script files with MATLAB to make the computation easier and generate a graph for the rate of drug concentration. The main script file is drug_interface.m and the computational part is by Adam_Bashforth.m. We are using MATLAB as the programming IDE to generate the solution in this project. Table 2 explains each script file and their description.

Table 2
Description for each script file

Script File	Description
drug_interface.m	This is the main file that runs the whole program. It gives instruction/choice for the user and takes the input. Therefore, it acts as a user interface for the system.
Adam_Bashforth.m	This is the computational function that calculates the initial values by Runge-Kutta Fourth Order and then proceeds with Adam-Bashforth Predictor-Corrector. It will display two tables based on each method and generate a graph 'drug concentration vs time'.
Drug_A.m	This is a function type of script file, and it generates a differential equation and initial value condition for the Aminoglycosides. Then, it calls the computational function to generate the solution.
Drug_B.m	This is a function type of script file, and it generates a differential equation and initial value condition for the Valproic Acid. Then, it calls the computational function to generate the solution.
Drug_C.m	This is a function type of script file, and it generates a differential equation and initial value condition for the Vancomycin. Then, it calls the computational function to generate the solution.

3.1 Flowcharts

3.1.1 Flow chart for the main script file: drug_interface.m

Figure 3 below shows the flowchart for the main script file, acting as the interface for the coding system. At first, it will display the list of drugs and ask the user to select a drug to check its concentration. Then, the script file will check whether the choice for the drug exists. If the drug input is not in the system, the user will have a choice whether to try again or stop the system. Next, assume the drug input is in the list, and then it will ask for a few inputs based on the selected drug. It will ask for body weight in kg, age, dose of the drug in mg and the value for a time interval that we want to investigate the concentration for all types of drugs. In addition, if the drug is Aminoglycosides or Vancomycin, it will ask for more information which is the gender. Based on gender, it will set the constant value and serum creatinine level. Note that, the range the serum creatinine level for male is 60–110 micromoles per liter and for female is 45–90 mcmol/l. Therefore, in this coding, we take 90 mcmol/l for female and 65 mcmol/l. Lastly, this program will call the drug function based on the selected drug.

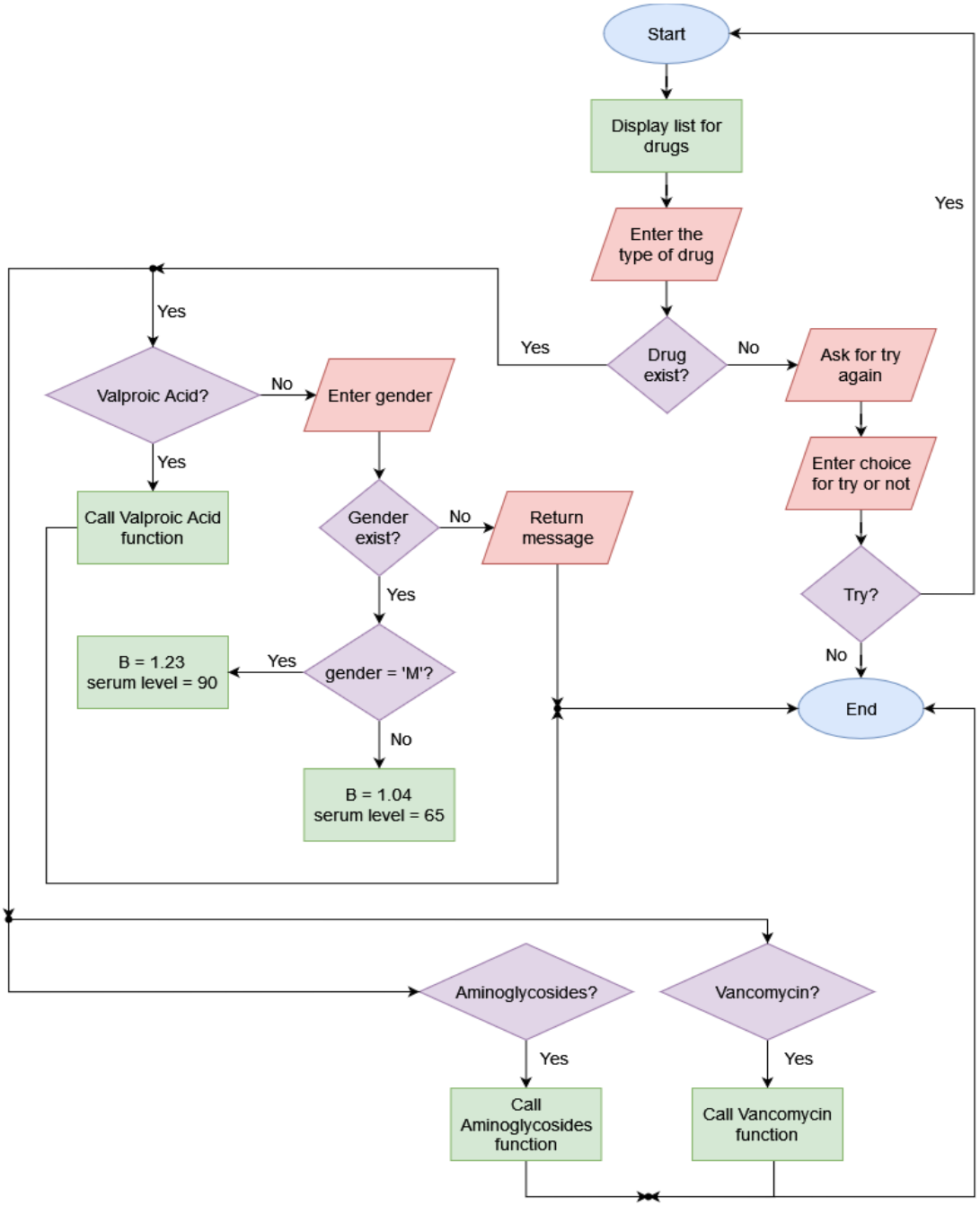


Fig. 3. Flow chart for the drug_interface.m

3.1.2 Flowchart for the computational script file: Adam_Bashforth.m

Adam_Bashforth.m is the computational script file for the coding as shown in Figure 4 below. It returns the values for the rate of drug concentration by the Adams-Bashforth-Moulton method and displays the graph for the drug concentration vs time. The script file will get the values for a differential equation, initial condition, and duration to investigate. Then, it will proceed with Runge-Kutta Fourth Order iteration will find 3 more initial values for the rate of drug concentration. Since it stated that i = 1:3, it means for i = 1, 2, 3. Thus, it will find values for t(2), t(3), t(4), b(2), b(3), and b(4). For each iteration, it will display the value and plot the graph based on the calculated values. Next, it will proceed with the Adams-Bashforth Predictor-Corrector Method for i = 4 and continue

until the last subinterval. b0 gives the value for the predictor and b1 gives the value for the corrector, based on Adams-Bashforth Predictor-Corrector formulas. For each iteration, it will display the value and plot the graph based on the calculated values. After all calculations and plotting have been done, it will display a graph for 'Drug Concentration vs Time by Adams-Bashforth Method'.

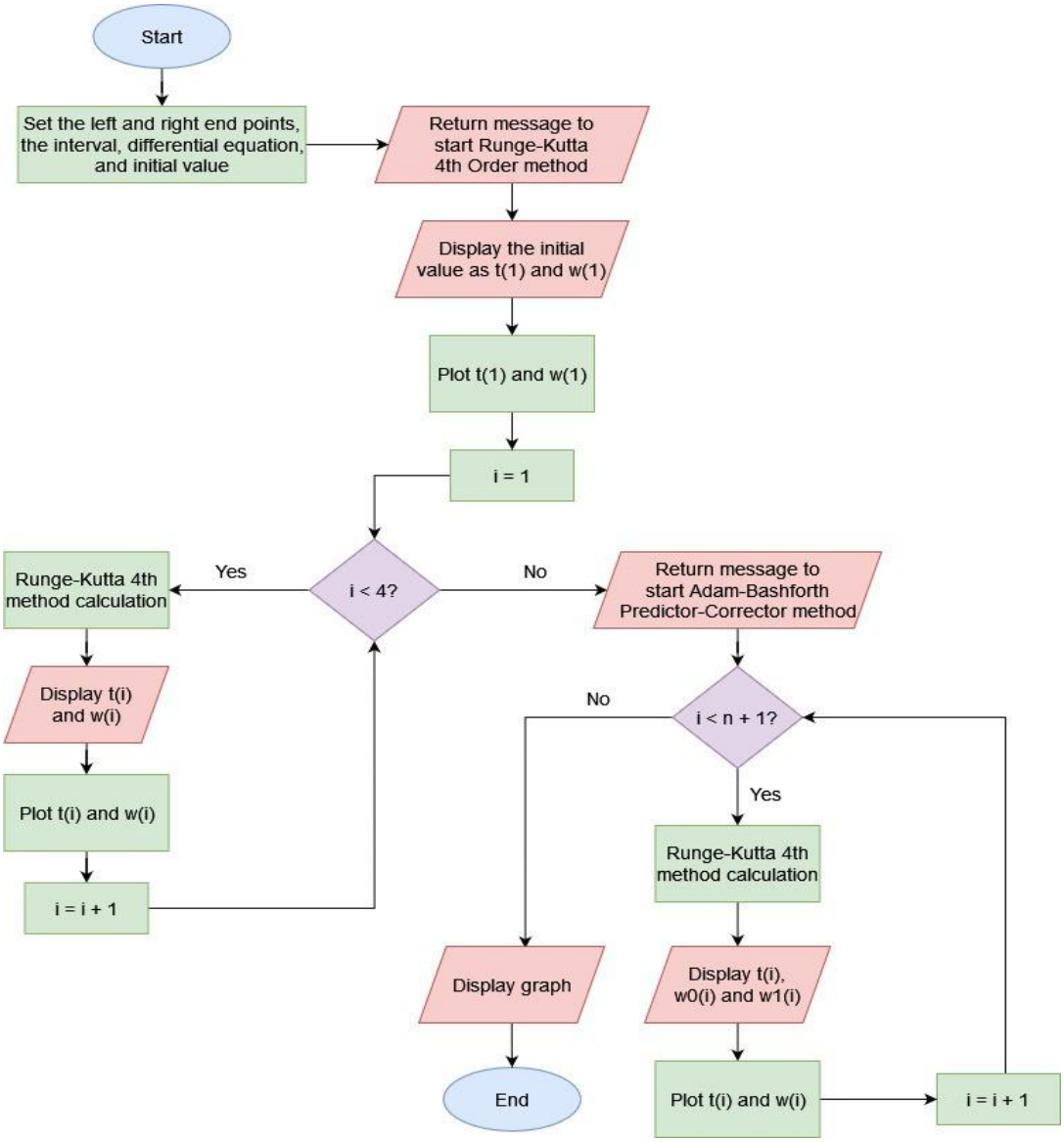


Fig. 4. Flow chart for the Adam_Bashforth.m

3.1.3 Flowchart for the function script file Aminoglycosides

Drug_A.m will generate the differential equation and initial value/condition for Aminoglycosides based on user input in the drug_interface.m as shown in Figure 5. The function Aminoglycosides will take the values of body weight in kg, age, drug dose in mg, duration in hours, constant B based on gender, Serum Creatinine level from the drug_interface.m. Then, it calculates the value for Vd, Cl, and alpha for Aminoglycoside's drug. Based on these, it will generate a differential equation and initial condition. Lastly, it will call the Adam_Bashforth function to generate the solution.

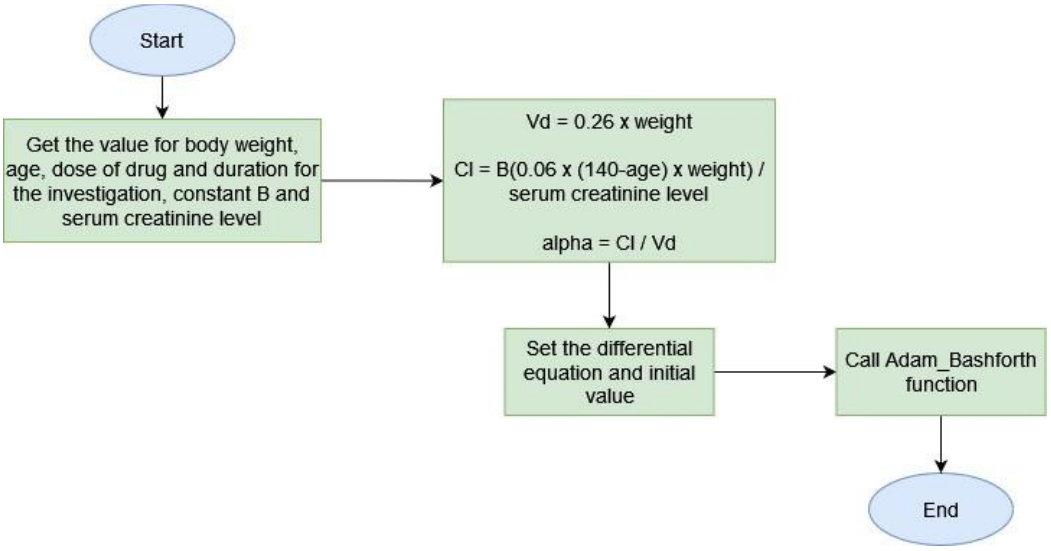


Fig 5. Flow chart for the Drug_A.m

3.1.4 Flowchart for the function script file for Valproic Acid

Figure 6 shows the flowchart for Drug_B.m that will generate the differential equation and initial value/condition for Valproic Acid based on user input in the drug_interface.m. This is a function script that will take all necessary values from the drug_interface.m such as body weight in kg, age, drug dose in mg, duration in hours. Then, based on age, it will classify whether the person is a child or an adult. If he/she is an adult, we will set the value for volume distribution (Vd) as 0.15 times body weight and the alpha is 19/300. Otherwise, the value for Vd is 0.2 times body weight and the alpha is 3/40. The value of alpha is used to generate the differential equation for the problem and Vd is used to find the initial value for the drug concentration for t=0. The differential equation and the initial value are for Valproic Acid only.

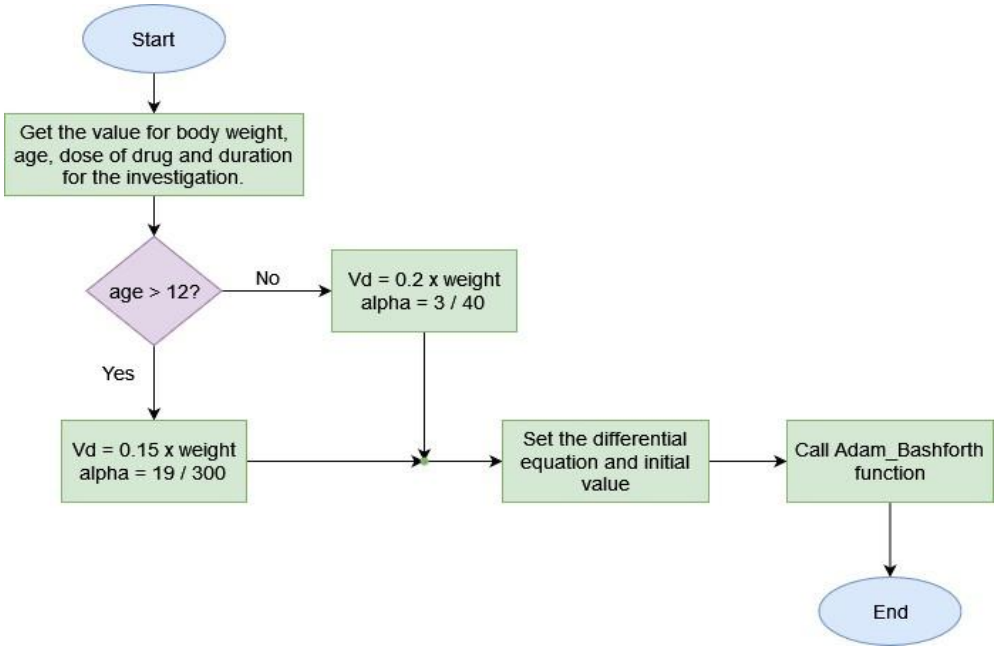


Fig. 6. Flow chart for the Drug_B.m

3.1.5 Flow chart for the function script file for Vancomycin

Drug_C.m will generate the differential equation and initial value/condition for Vancomycin based on user input in the drug_interface.m as shown in Figure 7. This script file a function to generate a differential equation and the initial value for the Vancomycin drug. Everything is the same as the Drug_A.m script file. The only difference is the formula for Vd.

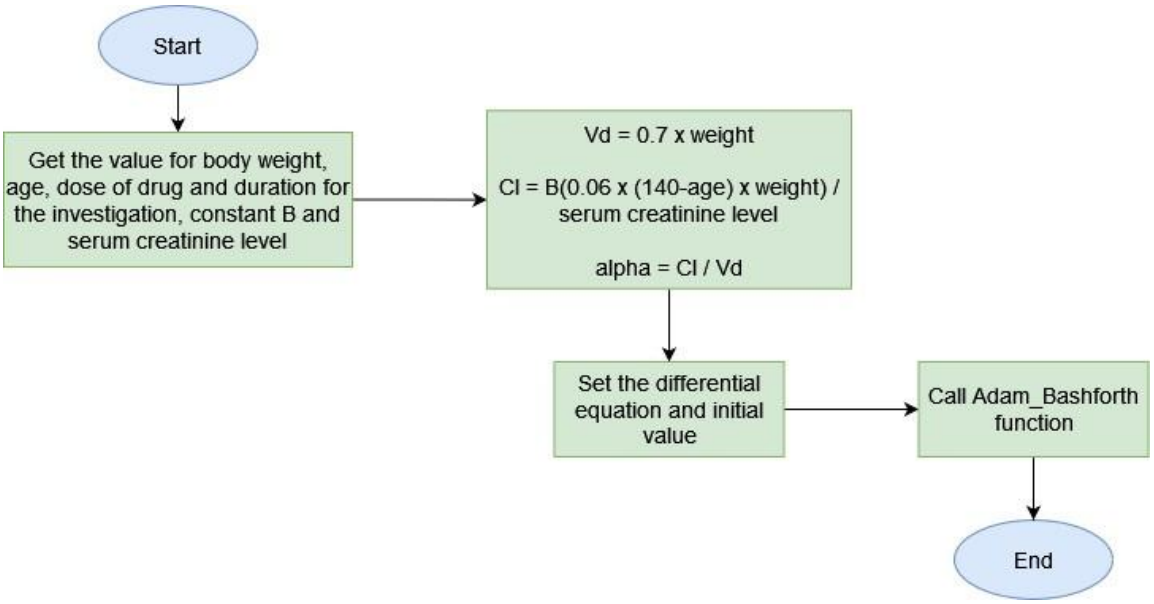


Fig. 7. Flow chart for the Drug_C.m

4. Results

In order to generate the result and compare these three drugs, we have to fix an assumption. Let the person be a female with 60kg and she is 30 years old. Assume she consumes the maximum dose for the drug. We want to see the estimated value and the graph for the next 18 hours after she consumes the drug.

4.1 Output for Aminoglycosides (Drug A)

There are 2 types of Aminoglycosides and have different doses based on weight,

i. Amikacin: 5.0–7.5 mg/kg
ii. Gentamicin Tobramycin: 1.5–2.0 mg/kg

Since Amikacin has a higher dose than Gentamicin Tobramycin, we chose Amikacin as the consumed drug. Therefore, the dose is 7.5 x 60 = 450mg. The result for Amikacin (Aminoglycosides) are as follow:

```
Command Window
  Type of drug (medicine)
  A: Aminoglycosides
  B: Valproic Acid
  C: Vancomycin

  Enter type of drug: A
  Enter body weight (in kg): 60
  Enter age: 30
  Enter drug dose (in mg): 450
  Enter duration (in hours): 12
  Enter M for male and F for female.
  Enter gender: F


  By Runge-Kutta Forth Order, the initial values are:

     t          b
  --------------------
  0.0000  28.84615385
  1.0000  19.22001572
  2.0000  12.80617881
  3.0000   8.53267854
```

Fig. 8. The input and the initial values for Aminoglycosides

```
Hence, by Adam-Bashforth Predictor-Corrector Method, we have:

    t      Predictor     Corrector
--------------------------------
4.0000   5.73600526   5.67379443
5.0000   3.82107062   3.77274878
6.0000   2.53396587   2.50941357
7.0000   1.68759755   1.66872103
8.0000   1.12292115   1.10962198
9.0000   0.74631345   0.73789903
10.0000   0.49632709   0.49069288
11.0000   0.33009982   0.32629889
12.0000   0.21949353   0.21698334
13.0000   0.14595729   0.14429031
14.0000   0.09706184   0.09595031
15.0000   0.06454391   0.06380521
16.0000   0.04292028   0.04242933
17.0000   0.02854134   0.02821473
18.0000   0.01897947   0.01876228
```

Fig. 9. The predictor and corrector value for Aminoglycosides 450mg for 18 hours

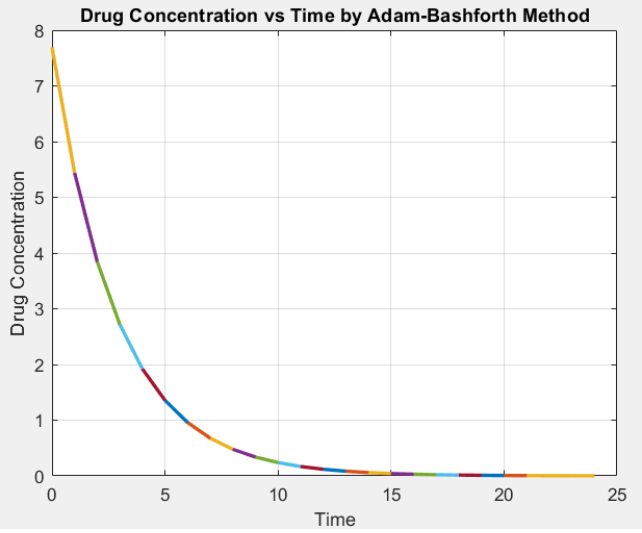


Fig. 10. Drug concentration vs time for Aminoglycosides (18 hours)

Figure 8 is the input and the initial values for Aminoglycosides. Based on Figure 9 and Figure 10, we can see that the concentration of the drug is flushed out from the body before 18 hours.

4.2 Output for Valproic Acid (Drug B)

The starting dose for Valproic Acid is 250mg and a person can take at most 500mg of Valproic Acid. By assuming the dose taken is 500mg, we can generate the following result:

```
Command Window
  Type of drug (medicine)
  A: Aminoglycosides
  B: Valproic Acid
  C: Vancomycin

  Enter type of drug: B
  Enter body weight (in kg): 60
  Enter age: 30
  Enter drug dose (in mg): 500
  Enter duration (in hours): 12


  By Runge-Kutta Forth Order, the initial values are:

     t          b
  --------------------
  0.0000   55.55555556
  1.0000   52.14614184
  2.0000   48.94596196
  3.0000   45.94217534
```

Fig. 11. The input and the initial values for Valproic Acid

```
Hence, by Adam-Bashforth Predictor-Corrector Method, we have:

   t      Predictor     Corrector
  ---------------------------------
  4.0000   43.12274651   43.12272739
  5.0000   40.47632564   40.47630754
  6.0000   37.99231397   37.99229713
  7.0000   35.66074503   35.66072918
  8.0000   33.47226325   33.47224837
  9.0000   31.41808747   31.41807351
  10.0000   29.48997542   29.48996231
  11.0000   27.68019063   27.68017832
  12.0000   25.98147141   25.98145986
  13.0000   24.38700172   24.38699088
  14.0000   22.89038383   22.89037365
  15.0000   21.48561261   21.48560306
  16.0000   20.16705149   20.16704253
  17.0000   18.92940980   18.92940138
  18.0000   17.76772154   17.76771365
```

Fig. 12. The predictor and corrector value for Valproic Acid 500mg for 18 hours

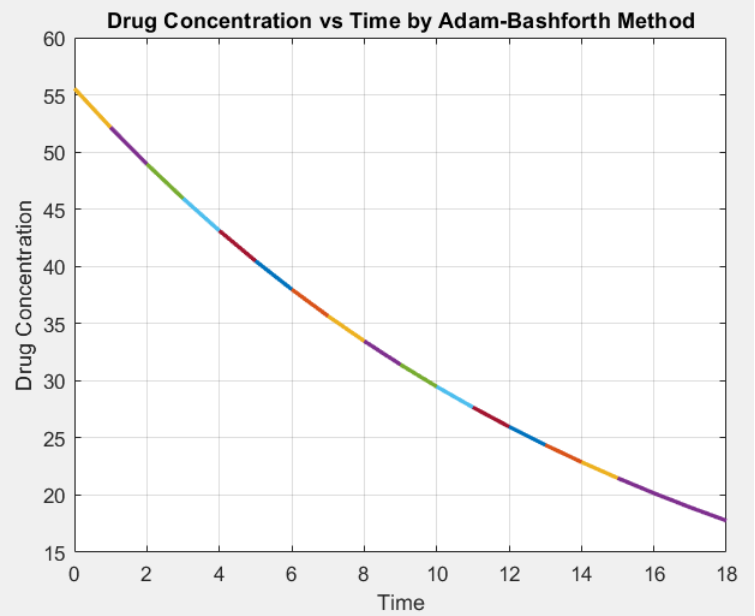


Fig. 13. Drug concentration vs time for Valproic Acid (18 hours)

Figure 11 is the input and the initial values for Valproic Acid. Based on Figure 12 and Figure 13, we can see that the concentration of the drug still remains high in the body even after 18 hours.

4.3 Output for Vancomycin (Drug C)

The dose of Vancomycin for an adult is 15 to 20 mg/kg. Therefore, the dose chosen for Vancomycin is 1200mg.

```
Command Window
  Type of drug (medicine)
  A: Aminoglycosides
  B: Valproic Acid
  C: Vancomycin

  Enter type of drug: C
  Enter body weight (in kg): 60
  Enter age: 30
  Enter drug dose (in mg): 1200
  Enter duration (in hours): 12
  Enter M for male and F for female.
  Enter gender: F


  By Runge-Kutta Forth Order, the initial values are:

     t          b
  --------------------
  0.0000   28.57142857
  1.0000   24.57060508
  2.0000   21.13001219
  3.0000   18.17120148
```

Fig. 14. The input and the initial values for Vancomycin

Hence, by Adam-Bashforth Predictor-Corrector Method, we have:

t	Predictor	Corrector
4.0000	15.62727929	15.62662562
5.0000	13.43895488	13.43837686
6.0000	11.55703642	11.55655618
7.0000	9.93867184	9.93825281
8.0000	8.54692628	8.54656590
9.0000	7.35007141	7.34976158
10.0000	6.32081625	6.32054979
11.0000	5.43569113	5.43546198
12.0000	4.67451305	4.67431599
13.0000	4.01992529	4.01975582
14.0000	3.45700166	3.45685592
15.0000	2.97290611	2.97278078
16.0000	2.55660008	2.55649230
17.0000	2.19859079	2.19849810
18.0000	1.89071474	1.89063503

Fig. 15. The predictor and corrector value for Vancomycin 1200mg for 18 hours

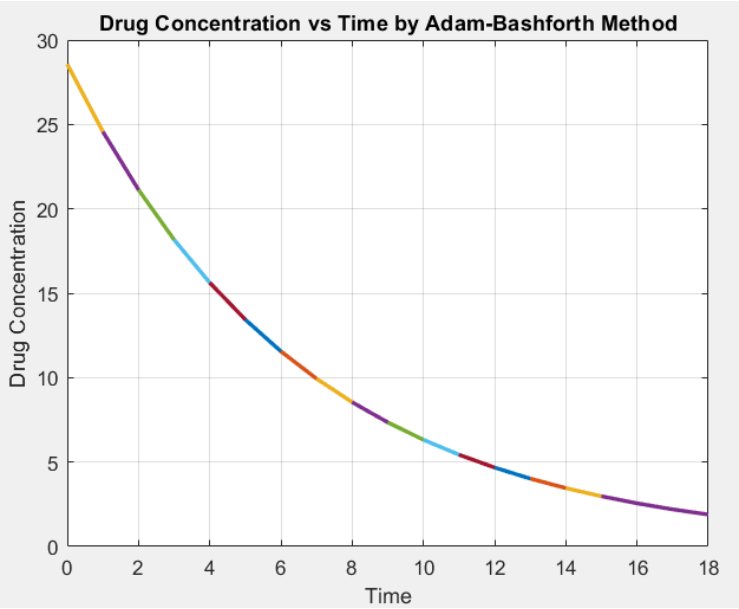


Fig. 16. Drug concentration vs time for Valproic Acid (18 hours)

The input and starting values for Vancomycin are shown in Figure 14. Figures 15 and 16 show that even after 18 hours, the drug concentration is still present in the body.

4.4 Output If Error Occur

The error will occur when the user enters an input that does not allow the system to proceed or an irrational value. For instance, the system already gives a list of drugs for the user to select but the user enters a value out of the list.

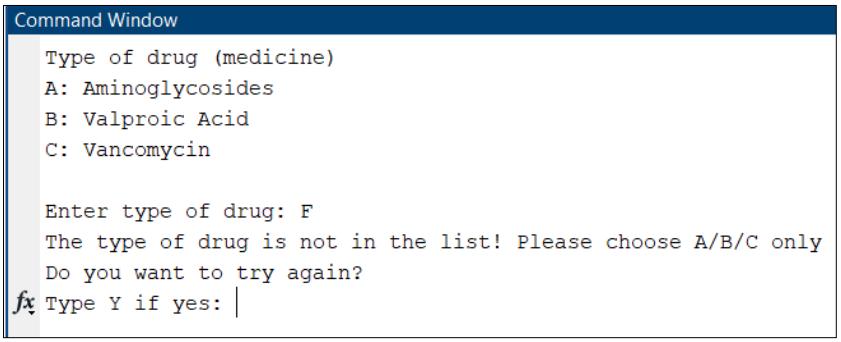


Fig. 17. The drug type is not exist

Therefore, based on Figure 17, the system will give the user another chance to try again the system. Next, from Figure 18, the user also may enter a different value for the gender even though it is already stated that M is for male and F for female. Then, the system will stop running.

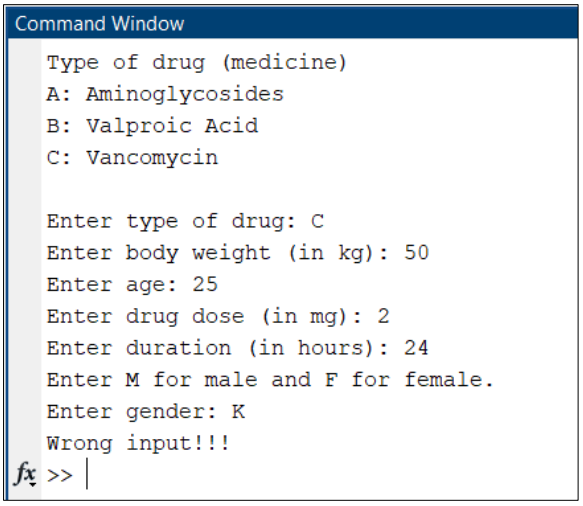


Fig. 18. User enters other values for gender

Other than that, the user also may

- Enter a negative value for body weight
- Enter a body weight in other units such as g or lbs.
- Enter a negative value for age
- Enter a negative duration
- Enter the duration in other units such as minutes

Even though the error occurs because the value is irrational/illogical, the system will still proceed to calculate and generate a solution for the problem.

5. Discussions

We realized that it would be easier if we combined all these outputs into one table and a graph only. However, it is more readable if we separate them into their function and only show the values for the drug that we want. Also, we can add more drugs easily to investigate them, without changing the whole code. Moreover, each type of drug will have a different dose based on the consumer and

the consumer also has a different body type and gender. Hence, it is impossible to have the output in one table/graph. However, we gather all the information that we achieve in this section. Refer to Table 3 to see the comparison of these drugs for the same assumption.

Table 3
Comparison of these drugs

Drug	Aminoglycosides	Valproic Acid	Vancomycin
Dose range (for adult)	Amikacin: 5.0–7.5 mg/kg Gentamicin Tobramycin: 1.5–2.0 mg/kg	250mg to 500mg	15 to 20 mg/kg
Assumption	A woman who is 30 years old and her weight is 60kg. She consumes the maximum dose of the drug.		
Dose	Amikacin: 450mg	500mg	1200mg
Initial drug concentration	28.84615	55.55556	28.57143
Drug concentration at time = 18 hours	0.01876	17.76771	1.89064
Drug concentration at time = 48 hours	0.00000009	2.65748933	0.02046708
Drug concentration at time = 168 hours	0	0.00132994	0

Since aspirin interferes with platelet function, it should be stopped before platelet donation. However, after 48 hours, the drug concentration level is already too low for all these three drugs. So, it is safe to donate blood. Note that a week has 168 hours, and all these drugs take less than that to achieve a concentration of less than 0.002. Therefore, we can conclude that the drug will completely flush from our bodies in less than a week.

Based on this report, we know that every type of drug has a different differential equation. Thus, we need to generate the differential equation based on the assumption. By using MATLAB, it is easier to generate the differential equation and the solution. Without MATLAB, it is time-killing to calculate each iteration for the Adams-Bashforth Predictor Corrector method.

Table 3 shows that Valproic acid has the highest initial drug concentration. Note that bipolar disorder, epilepsy, and migraine are treated with valproic acid. Hence, it needs long-term effects on the human body to cure/assess the pain. Whereas Aminoglycosides and Vancomycin have a lower initial concentration and are easy to eliminate from the human body.

6. Conclusions

The report was designed to estimate the concentration of drugs over time for three particular drugs which are Aminoglycosides, Valproic Acid and Vancomycin as well as find out how long each person has to wait before donating blood. The duration for the drug concentration to be zero in the bloodstream for each person is different. However, the differences are very small, and we can conclude that the maximum duration for all three drugs will be eliminated from the bloodstream is one week. This method can also be applied to other drugs that fit the one-compartment model like Theophylline, Ethosuximide and Procainamide. The only distinction will be in the computation for Vd and α. Moreover, the coding that was created can also be used to detect rare cases where the drug concentration for a certain person is not zero by a week. Then, we can use this finding to defer that person from donating temporarily. It will assist blood banks in determining whether a blood donor on medication should be rejected or not. Hence, the safety of the donor and the receiver can be ensured and prevent things like transmission of the drug during the donation process which can cause very harmful effects to the health of the person receiving the blood.

References

[1] D. Waller and A. Sampson, *Pharmacokinetics*. 2018. https://doi.org/10.1016/B978-0-7020-7167-6.00002-6
[2] Pharmaceutical Services Division Ministry of Health Malaysia, *Clinical Pharmacokinetics Pharmacy Handbook*. 2019.
[3] Dabrowski, Maciej, Zuzanna Bukowy-Bieryllo, Claire L. Jackson, and Ewa Zietkiewicz. "Properties of non-aminoglycoside compounds used to stimulate translational readthrough of PTC mutations in primary ciliary dyskinesia." *International journal of molecular sciences* 22, no. 9 (2021): 4923. https://doi.org/10.3390/ijms22094923
[4] Nagel-Wolfrum, Kerstin, Fabian Möller, Inessa Penner, Timor Baasov, and Uwe Wolfrum. "Targeting nonsense mutations in diseases with translational read-through-inducing drugs (TRIDs)." *BioDrugs* 30, no. 2 (2016): 49-74. https://doi.org/10.1007/s40259-016-0157-6
[5] Nasreddine, Wassim, and Ahmad Beydoun. "Valproate-induced thrombocytopenia: a prospective monotherapy study." *Epilepsia* 49, no. 3 (2008): 438-445. https://doi.org/10.1111/j.1528-1167.2007.01429.x
[6] Syed, Saba, Michael Couse, and Rashi Ojha. "Management challenges in patients with comorbid COVID-19 associated delirium and serious mental illness–A case series." *The International Journal of Psychiatry in Medicine* 56, no. 4 (2021): 255-265. https://doi.org/10.1177/0091217420985979
[7] Kayode, O. Stephanie, and Krzysztof Rutkowski. "Vancomycin hypersensitivity: it is not always what it seems." *The Journal of Allergy and Clinical Immunology: In Practice* 9, no. 2 (2021): 913-915. https://doi.org/10.1016/j.jaip.2020.10.040
[8] Sandoe, Jonathan AT, Joanne Wysome, Andrew P. West, John Heritage, and Mark H. Wilcox. "Measurement of ampicillin, vancomycin, linezolid and gentamicin activity against enterococcal biofilms." *Journal of antimicrobial chemotherapy* 57, no. 4 (2006): 767-770. https://doi.org/10.1093/jac/dkl013
[9] Ch'ng, Jun-Hong, Kelvin KL Chong, Ling Ning Lam, Jun Jie Wong, and Kimberly A. Kline. "Biofilm-associated infection by enterococci." *Nature Reviews Microbiology* 17, no. 2 (2019): 82-94. https://doi.org/10.1038/s41579-018-0107-z
[10] Mahnovski, V., M. H. Cheng, A. I. Lipsey, and K. Keyomarsi. "Drugs in blood donors." *Clinical chemistry* 33, no. 1 (1987): 189-189. https://doi.org/10.1093/clinchem/33.1.189
[11] Becker, Christian DK, Dirk O. Stichtenoth, Michael G. Wichmann, Christof Schaefer, and Ladislaus Szinicz. "Blood donors on medication–an approach to minimize drug burden for recipients of blood products and to limit deferral of donors." *Transfusion Medicine and Hemotherapy* 36, no. 2 (2009): 107-113. https://doi.org/10.1159/000203355
[12] Khanday, M. A., Aasma Rafiq, and Khalid Nazir. "Mathematical models for drug diffusion through the compartments of blood and tissue medium." *Alexandria Journal of Medicine* 53, no. 3 (2017): 245-249. https://doi.org/10.1016/j.ajme.2016.03.005
[13] Gu, Yajing, and Yuanguo Zhu. "Adams predictor–corrector method for solving uncertain differential equation." *Computational and Applied Mathematics* 40 (2021): 1-20. https://doi.org/10.1007/s40314-021-01461-2
[14] Koch-Noble, G. A. "Drugs in the classroom: Using pharmacokinetics to introduce biomathematical modeling." *Mathematical Modelling of Natural Phenomena* 6, no. 6 (2011): 227-244. https://doi.org/10.1051/mmnp/20116612
[15] Ascher, Uri M., and Linda R. Petzold. *Computer methods for ordinary differential equations and differential-algebraic equations*. Vol. 61. Siam, 1998. https://doi.org/10.1137/1.9781611971392