Drug Level Modelling with Difference and Differential Equations

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Abstract. In the current study, drug level in the human body is studied using mathematical modelling, where the difference equations have been used as a means of analyzing the dosage over a prescribed time, reduction in dose half-life, and the total amount of residual drug in the bloodstream for a given time-period. Further, the differential equations approach is investigated for data fitting using Mathematica to extend the application adhering to the continuous nature of the inherent function. The perspective helps to preserve critical resources and render comparative results. In this approach, zero-order, first-order, and fractional order kinetics are explored and compared.

1. Introduction
In the study, a recent real-world problem is selected to observe the given data, comprehend the pattern, and then model the situation. COVID-19 is an infectious disease caused by the most recently discovered coronavirus. The new virus and disease were unknown before the outbreak began in Wuhan, China, in December 2019. COVID-19 is now a pandemic affecting many countries globally. Various drugs are being developed for the COVID-19 pandemic, and mathematical modelling is proving a supportive tool. Bringing some relief for COVID-19 patients, even as the country was reporting its all-time high on each upcoming day of new coronavirus cases, the drugs/vaccines for COVID-19 are now being made available in medical stores/hospitals. Glenmark Pharmaceuticals on 20 June 2020 launched the antiviral drug Fabiflu, under the brand name Fabiflu, for the treatment of patients with mild to moderate COVID-19. The Mumbai-based drug firm had received manufacturing and marketing approval from the Drugs Controller General of India. According to the company [1], Fabiflu demonstrated promising clinical evidence, with positive results in mild to moderate COVID-19 cases [2]. Clinical improvement was observed in age groups of 20 to > 90 years. The drug claimed to provide a rapid decrease in viral load within four days, along with quicker symptomatic and radiological improvement. Fabiflu demonstrated up to 88 percent of clinical improvement in patients with mild to moderate COVID-19 [1]. It is a prescription-based medication with recommended dose being 1,800 mg twice daily on day one, followed by 800 mg twice daily up to day 14 [2]. Glenmark declared that mild to moderate COVID-19 patients with co-morbid conditions such as diabetes and heart disease can also use the drug [3]. At the same time, Remdesivir, intravenously administered in hospitals, has been the first treatment to show improvement in COVID-19 trials. It has been approved for emergency use in severely ill patients in the United States, India, and South Korea and received full approval in Japan [1]. Pharma major Cipla Ltd announced the launch of its generic version of antiviral drug Remdesivir for emergency use in the treatment of COVID-19 patients. The new drug was to be sold under the brand name Cipremi. According to a preliminary report from the ACTT-1 (Adaptive COVID-19 Treatment
Trial 1), a randomized clinical trial conducted with Remdesivir in 1063 patients over 60 centers across the US, Europe, and Asia demonstrated a faster time to clinical recovery in hospitalized patients as compared to placebo.

Most of these patients were on oxygen therapy of which some were receiving high flow oxygen or non-invasive ventilation, and some were on a mechanical ventilator. The mortality rates in the study were 7.1 percent in those given Remdesivir and 11.9 percent in those who were given a placebo [2].

In recent years, more costs of drug development and less productivity is a concern for new drug development [4]. To overcome the threat, different approaches like the use of adaptive trial design [5], ample use of biomarkers [6], starting personalized medicines, and the utilization of pharmacokinetics/pharmacodynamics (PK/PD) modelling and simulation [4] have been adopted. From the early phase of drug development to the last stage, PK/PD modelling is proven to be a good buy [7, 8, 9].

As per the existing literature, the drugs of high half-life and slow-release rate can be better dealt with fractional calculus. The study and analysis of the dosage of the two drugs are investigated and resolved.

2. Modelling of dosage of Fabiflu

Analogous to the study in [10], Table 1 is studied for finding how much amount of Fabiflu should be given to the patients per day, the total amount of absorbed dose of Fabiflu, and such related questions. On Day 1, 1800 mg of dose were given at both times of the day while from the subsequent days 800 mg was administered as in [2]. The pattern of drug absorption is observed, and it is attempted to get a recurrence relation for fitting the data. The recurrence relation is solved for the term identified in it. The relation helped estimate the level of dose in the human body at prescribed day, also the day by which a pre-decided level of the dose is absorbed by the patient.

The 1st dose is represented by \( a_0 \), amount of Fabiflu in the body after the first dose is given. \( a_1 \) represented the amount of Fabiflu in the body after the second dose. Similarly, \( a_n \) represents the amount of Fabiflu in the body after dose \((n + 1)\). A steady increase in the amount of dose by 800mg from day 2-14 is observed between the intervals. Pattern development is presented in Table 2. The next value of the dose could thus be predicted having known the previous value. It gives rise to (1).

Thus, the difference equation is

\[
a_n = a_{n-1} + 800
\]

except for \( n = 0,1 \) where \( a_0 = 1800, a_1 = 3600 \). The total amount of dose absorbed in the body can be calculated just by knowing the number of doses. Solving (1) using the substitution method, we get

\[
a_n = 2800 + 800n.
\]

Table 1. The total amount of Fabiflu absorbed by the body.

| Day | Time | Dose (mg) | Total absorbed (mg) | Dose (n) | Total dose given \((a_{n-1})\) | Pattern |
|-----|------|-----------|---------------------|---------|-------------------------------|---------|
| 1   | T1   | 1800      | 0                   | 1       | 1800                          |         |
|     | T2   | 1800      | 1800                | 2       | 3600 a1= a0+1800              |         |
| 2   | T1   | 800       | 3600                | 3       | 4400 a2= a1+800              |         |
|     | T2   | 800       | 4400                | 4       | 5200 a3= a2+800              |         |
| 3   | :    | :         | :                  | :       | :                            |         |
| 14  | T1   | 800       | :                  | n+1     | :                            |         |
|     | T2   | 800       | :                  | :       | :                            |         |

Table 2. Pattern development of Fabiflu dose.

| Time (Day 1) | Fabiflu | Cipremi |
|--------------|---------|---------|
| 08:00        | 1800    | 200     |
| 09:00        | 1566.99 | 193.19  |
| 10:00        | 1364.14 | 186.61  |
| 11:00        | 1187.56 | 180.25  |
| 12:00        | 1033.83 | 174.11  |
| 13:00        | 900     | 168.18  |

Table 3. Amount of Fabiflu/Cipremi (mg) in blood-stream over time.

Table 4. Reduction in Fabifu
Thus, after the first two doses, the sequence increased by the constant term which gives rise to a few uncertainties regarding the amount of drug increasing in the patient’s body, possible side-effects, and routes of elimination of the drug.

As per [1], Fabiflu (generic name of Fabiflu) is an antiviral drug licensed in Japan in 2014 for the treatment of influenza. The elimination half-life of Fabiflu is estimated to range from 2 to 5.5 hours [1]. Considering the half-life of the drug as 5 hours, the reduction in the amount of Fabiflu in the body over a period of time is analyzed from the data in Table 3.

It is observed that the amount of drug in the bloodstream reduced over a period was not constant. However, the pattern demonstrated a constant ratio in reduction. It is reducing at a rate of 87 percent. Mathematically, it can be demonstrated as in Table 4.

Thus, in general, one can write \( r = \left( \frac{1}{2} \right)^{\frac{1}{h}} \) where \( t \) is the time in hours and \( h \) is half-life of the drug.

The pattern seen in the reduction of the amount of drugs in Table 3 is summarized in Table 5. They have represented the initial amount of Fabiflu in the body by \( a_0 \), reduction in the amount of Fabiflu after one hour is represented by \( a_1 \), and so on. The amount of drug present in the body at the later hour is \( r = 0.870550563 \) times that of a formal hour and the difference equation for the same can be formulated as:

\[
a_n = 0.870550563 \cdot a_{n-1}.
\]

Thus, the difference equation formed as:

\[
a_n = r \cdot a_{n-1}.
\]

To check the relation between the amount of drug reduced at \( n^{th} \) hour with \( n^{th} \) hour, (4) is solved as

\[
a_n = \begin{cases} 
(r)^n \cdot 1800; & \text{day 1} \\
(r)^n \cdot 800; & \text{day 2 to day 14}
\end{cases}
\]

| Hour | Pattern for Fabiflu | Pattern for Cipremi |
|------|---------------------|---------------------|
| 0    | \( a_0 = 1800 \)    | \( a_0 = 200 \)     |
| 1    | \( a_1 \cdot 0.87055 \cdot a_0 \) | \( a_1 \cdot 0.96593 \cdot a_0 \) |
| 2    | \( a_2 \cdot 0.87055 \cdot a_1 \) | \( a_2 \cdot 0.96593 \cdot a_1 \) |
| 3    | \( a_3 \cdot 0.87055 \cdot a_2 \) | \( a_3 \cdot 0.96593 \cdot a_2 \) |
| 4    | \( a_4 \cdot 0.87055 \cdot a_3 \) | \( a_4 \cdot 0.96593 \cdot a_3 \) |
| 5    | \( a_5 \cdot 0.87055 \cdot a_4 \) | \( a_5 \cdot 0.96593 \cdot a_4 \) |
| \vdots | \( a_n \cdot 0.87055 \cdot a_{n-1} \) | \( a_n \cdot 0.96593 \cdot a_{n-1} \) |

| Hour | Fabiflu level | Cipremi level |
|------|--------------|---------------|
| 0    | \( a_0 = 1800 \) | \( a_0 = 200 \) |
| 1    | \( a_1 \cdot r \cdot 1800 \) | \( a_1 \cdot r \cdot 200 \) |
| 2    | \( a_2 \cdot r \cdot 1800 \) | \( a_2 \cdot r \cdot 200 + 100 \) |
| 3    | \( a_3 \cdot r \cdot 1800 \) | \( a_3 \cdot r \cdot 200 + 100 \) |
| 4    | \( a_4 \cdot r \cdot 1800 \) | \( a_4 \cdot r \cdot 200 + 100 \) |
| 5    | \( a_5 \cdot r \cdot 1800 \) | \( a_5 \cdot r \cdot 200 + 100 \) |
| \vdots | \( a_n \cdot r \cdot 1800 \) | \( a_n \cdot r \cdot 200 + 100 \) |
| 48   | \( a_{48} \cdot r^{24} \cdot 1800 + 800 \) | \( a_{48} \cdot r^{24} \cdot 200 + 100 \) |

Table 5. Day 1 Pattern Development

Table 6. Total amount of Fabiflu/Cipremi in bloodstream.
The graph of the reduced amount of drugs over a period of time is plotted in Figure 1.

![Figure 1](image)

**Figure 1.** Reduced amount of Fabiflu/Cipremi

The amount of Fabiflu in the body after a certain period won’t be the same as (5) as it reveals only the reduced amount of drug. To find the total amount of drugs in the body, Table 6 is tabulated. Continuing in this way, a geometric series is obtained. The series for the sum of first \( n \) terms to find \( a_n \) indicates the total amount of drug in the body over a certain time \( n \).

\[
a_n = \begin{cases} 
  r^n * 1800; & 0 \leq n < 12 \\
  r^n \left[ 1000 \left( 1 + \frac{1}{r^{12}} \right) + 800 \left( \frac{1 - r^{(n+12)}}{1 - r^{12}} \right) \right]; & n_1 \leq n < n_1 + 12, \text{ for } n_1 = 12k \text{ where } 1 \leq k < 28 \\
  r^n \left[ 1000 \left( 1 + \frac{1}{r^{12}} \right) + 800 \left( \frac{1 - r^{336}}{1 - r^{12}} \right) \right]; & n \geq 336
\end{cases}
\]

(6)

The total amount of the drug is shown graphically in Figure 2.

![Figure 2](image)

**Figure 2.** Fabiflu amount for prescribed regular and incremental dosage for missed dosage

On successful completion of the model, the solution of the difference equation is found to be useful in determining the total amount of drug level in the blood-stream for the given time. In the event of a missed dosage an incremental half dose or an incremental quarter dose as shown in Figure 2 is helpful to reinstate the level of the drug in the blood-stream. In the latter case, the drug level is restored gradually with relatively minor upshoot.

2.1 Differential equation model development:

An alternative method to the difference equation approach, indicates a possibility of modelling the data through differential calculus using Mathematica to extend the application adhering to the continuous nature of the inherent function. Noyes-Whitney Law [11] for drug release evaluation is given as

\[
\frac{dC}{dt} = k \left( C_s - C_t \right)
\]

where \( \frac{dC}{dt} \) dissolution rate, \( k \) dissolution rate constant, \( C_s \) drug
concentration in stagnant layer and \( C_t \) drug concentration in the solution bulk at a time as per the Laws in the kinetics of drug release. Fick’s law of diffusion [12] diffusion of drug molecule takes place from higher concentration region to lower concentration and diffusion rate is directly proportional to the concentration gradient. Various mathematical models [13] have been used in literature to study drug release profiles, drug diffusion, and drug elimination. In the current study, two such models viz, zero-order model and first-order model are fitted to the reduction (elimination) data of one of the COVID-19 drugs i.e. Fabiflu. The zero-order model defines the process of constant drug levels in the blood throughout the conveyance. In kinetics of zero-order with constant change rate in mass per unit time given as [11]:

\[
\frac{dC}{dt} = k. \tag{7}
\]

The solution of (7) as a function of time with the initial condition \( C(0) = c_0 \) is linearly expressed as:

\[
C = kt + c_0. \tag{8}
\]

The first-order model defines the process where the rate is directly proportional to the drug concentration at any time \( t \) [14].

In kinetics of First order, the proportionality of change rate to the existing value \( (C) \) is considered [11]:

\[
\frac{dC}{dt} = -kC. \tag{9}
\]

Classically, the equation of exponential relaxation helps derive the solution considering an initial condition of \( C(0) = c_0 \):

\[
C = c_0 e^{-kt}. \tag{10}
\]

As in [15, 16], some diffusional processes do not follow Fick’s law. Super-division and sub-division are observed to follow mean-square displacement as non-integer power of time. The fractional calculus approach suits best describe such processes. Classical calculus is a special case of fractional calculus for \( \alpha = 1 \).

The first-order equation can be converted into fractional terms replacing a derivative of order 1 by a fractional order \( \alpha \) and written as [15]:

\[
\frac{d^\alpha C}{dC^\alpha} = -kC. \tag{11}
\]

The solution for (11) is given by:

\[
C = c_0 E_{\alpha} \left(-kt^\alpha\right). \tag{12}
\]

For \( \alpha = 1 \), implies a special case of fractional order resulting in first order. Parameters estimated while applying (7) and (9) to the dataset is depicted in Table 7. \( R^2 \), as a measure of goodness of fit, indicates that (9) is better data-fit as shown in Figure 4 than (7) shown in Figure 3.
In the difference equation model demonstrated above, a time interval of one hour is considered. However, the level of drug in the blood-stream is a continuous process for which differential equation is advantageous. On application of differential equation model, we can estimate the continuous data function and obtain satisfactory goodness of fit.

Table 7. Parameter estimation (Figure 1).

| Parameter | Estimate | Standard-error | $R^2$ |
|-----------|----------|----------------|-------|
| $k$       | -124.53  | 8.25059        | 0.95  |
| $c_0$     | 1624.11  | 53.5759        |       |
| $k$       | 0.13863  | 2.6447*10^{-7} |       |
| $c_0$     | 1800     | 0.00181664     |       |

Table 8. Total amount of Cipremi absorbed by body.

| Day | Dose (mg) | Total absorbed (mg) |
|-----|-----------|---------------------|
| 1   | 200       | 0                   |
| 2   | 100       | 200                 |
| 10  | 100       | .                   |

3. Modelling for dosage of Cipremi by difference equation

To gain understanding about increasing and decreasing sequence, modelling into difference equation and solving it for $n^{th}$ term, other drugs are taken up for study. For Cipremi, clinical trials used a regimen of 200mg once daily on the first day, followed by 100mg once daily for another 9 days as in [2]. Early data suggested that some patients could benefit from only 5 days of treatment. Table 8 shows the total amount of Cipremi absorbed by the body. From the Table 8, the difference equation is formed as:

$$ a_n = a_{n-1} + 100 \quad (13) $$

for $n = 1, 2, \ldots, 9$ where $a_0 = 200$.

Solving (13) using the substitution method, we get

$$ a_n = 200 + 100n. \quad (14) $$

Remdesivir (generic name of Cipremi) is a prodrug that is converted in the body into GS-441524 [17]. It is an antiviral drug developed by Gilead Sciences. It is the main metabolite of the antiviral prodrug remdesivir, which the latter is converted into inside the body. GS-441524 is then phosphorylated to the active nucleotide triphosphate form. A 10mg/kg intravenous dose in non-human primates has a plasma half-life of 0.39 hours. The nucleoside triphosphate metabolite has a half-life of 14 hours in non-human primates. The nucleoside triphosphate metabolite has a half-life of approximately 20 hours in humans [18]. The
calculated ratio is \( r = 0.97 \). Using the half-life, amount of Cipremi is calculated in Table 3. The pattern can be displayed as in Table 5. Thus, the difference equation is formed as

\[
a_n = 0.965936328 \times a_{n-1}.
\]

Solving (15) using the substitution method, we get

\[
a_n = \begin{cases}
(0.965936328)^n \times 200; & \text{day 1} \\
(0.965936328)^n \times 100; & \text{day 2 to day 10}
\end{cases}
\]

The graph of the reduced amount of drugs over a period of time is plotted in Figure 1. To find the total amount of Cipremi in the patient’s body Table 6 is prepared. A geometric series is obtained. The series for the sum of first \( n \) terms to find \( a_n \) is solved which indicated the total amount of drug in the body over a certain time \( n \).

\[
a_n = \begin{cases}
200; & 0 \leq n < 24 \\
\left[100 + 100 \frac{1 - r^{-(n_{i+24})}}{1 - r^{-24}}\right]; & n_i \leq n < n_i + 24 \text{ for } n_i = 24k \text{ where } 1 \leq k < 9 \\
\left[100 + 100 \frac{1 - r^{-240}}{1 - r^{-24}}\right]; & n \geq 216
\end{cases}
\]

Results are plotted graphically in Figure 5.

**Figure 5.** Amount of nucleoside triphosphate in the blood-stream

Thus, the model is developed for the second dosage too. The methodology of difference equations has been used for both medicines. Like Fabiflu, the differential equation approach can be used for fitting data further resulting in analogous inferences.

4. Conclusion

The difference equation to calculate the concentration of drug in the bloodstream was derived in the study by identifying geometric series. It was solved and results were presented graphically to visualize the pattern and estimate the drug level. This model may be useful for recommending remedial actions to restore requisite drug level in cases of possible discrepancies occurring due to missing a dose or overdose. The half-life of the drug was considered as the factor of estimation. The differential equation approach was explored through zero-order and first-order equations to investigate continuous form of the pattern. The data fitting in the study revealed that, the first order kinetics demonstrated better results.
5. References

[1] Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M and Barkate H 2021 Role of favipiravir in the treatment of COVID-19 International Journal of Infectious Diseases 102 501-508.

[2] Parasher A 2021 COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment Postgraduate Medical Journal 97(1147) 312-320.

[3] Khan S and Al-Balushi K 2021 Combating COVID-19: The role of drug repurposing and medicinal plants Journal of infection and public health 14(4) 495-503.

[4] Rajman I 2008 PK/PD modelling and simulations: utility in drug development Drug discovery today 13(7-8) 341-346.

[5] Chang M, Chow S and Pong A 2006 Adaptive design in clinical research: issues, opportunities, and recommendations Journal of biopharmaceutical statistics 16(3) 299-309.

[6] Biomarkers Definitions Working Group Biomarkers and surrogate endpoints in clinical trials: proposed definitions and conceptual framework Clin. pharmacol.Ther. 69 89–95.

[7] Chaikin P, Rhodes G, Bruno R, Rohatagi S and Natarajan C 2000 Pharmacokinetics/pharmacodynamics in drug development: an industrial perspective The Journal of Clinical Pharmacology 40(12) 1428-1438.

[8] Gieschke R and Steimer J 2000 Pharmacometrics: modelling and simulation tools to improve decision making in clinical drug development European journal of drug metabolism and pharmacokinetics 25(1) 49-58.

[9] Colburn W and Lee J 2003 Biomarkers, validation and pharmacokinetic-pharmacodynamic modelling Clinical pharmacokinetics 42(12) 997-1022.

[10] Acker K 2004 Drug Levels and Difference Equations The Mathematics Teacher 98(4) 266-273.

[11] Gouda R, Baishya H and Qing Z 2017 Application of mathematical models in drug release kinetics of carbidopa and levodopa ER Tablets J. Dev. Drugs 6(02) 1-8.

[12] Brahankar D and Jaiswal S 2009 Biopharmaceutics and Pharmacokinetics: A treatise Vallabh Prakashan.

[13] Thakkar V, Shah P, Soni T, Parmar M, Gohel M and Gandhi T 2009 Goodness-of-fit model-dependent approach for release kinetics of levofloxacin hemihydrates floating Tablet Dissolution Technologies 16(1) 35-39.

[14] Dash S, Murthy P, Nath L and Chowdhury P 2010 Kinetic modeling on drug release from controlled drug delivery systems Acta Pol Pharm 67(3) 217-223.

[15] Dokoumetzidis A and Macheras P 2009 Fractional kinetics in drug absorption and disposition processes Journal of pharmacokinetics and pharmacodynamics 36(2) 165-178.

[16] Popović J, Atanačković M, Pilipović A, Rapać M, Pilipović S and Atanačković T 2010 A new approach to the compartmental analysis in pharmacokinetics: fractional time evolution of diclofenac Journal of pharmacokinetics and pharmacodynamics 37(2) 119-134.

[17] Bhagat D, Suryawanshi M and Suryawanshi I 2020 A Systematic Review of Antiviral Drugs for the Treatment of the COVID-19 Pandemic Manipal Journal of Pharmaceutical Sciences 6(2) 109-113.

[18] www.drugbank.ca/drugs