

Mathematical insight of Methanol Toxicity Management using Charcoal and Folinic Acid

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Abstract. Methanol poisoning is a relatively uncommon yet highly perilous form of intoxication, leading to central nervous system depression, vision impairment, metabolic disruption, and even more deadly consequences if not quickly and effectively addressed. Keeping this in mind, this work primarily studies activated charcoal as first aid for methanol-intoxicated persons. In this research article, we initially develop a mathematical model for methanol-enzyme interaction, along with the effects of folate therapy. We consider a unique form of the Dubinin-Astakhov (DA) equation that characterizes the adsorption of methanol on activated charcoal. The impulsive differential equation which we formulate, based on the DA equation, examines the efficacy of activated charcoal in treating methanol toxicity. We also verify all our analytical results using numerical simulations.

Keywords: Methanol poisoning · Activated charcoal · Folinic acid · Impulsive differential equation.

1 Introduction

Over the years the issue of methanol poisoning has remained a significant concern for mankind. The majority of methanol poisoning incidents occur in low income areas and remote regions, where proper management protocols, primary treatments and antidotes are unavailable. This makes it more difficult to deal with this poisoning. In the past two decades in India, 23 methanol poisoning incidents have resulted in nearly 1,500 deaths [10], illustrating the severity of the issue. In this scenario, the use of activated charcoal and folate therapy as initial treatment can reduce mortality and organ damage from methanol poisoning.

Activated charcoal has a longstanding history as a universal antidote for poisoning [6,11]. It is highly porous and has a large surface area and contains binding sites with attractive forces that attract and hold toxins and chemicals. Upon oral administration of activated charcoal, it passes through the digestive pathway without entering the bloodstream [12]. Attractive forces on its surface adsorb toxins, preventing or reducing their absorption into the bloodstream.

The bound toxins are then eliminated from the body through normal bowel movements [6,12].

When methanol is consumed it passes through the digestive system and absorbs rapidly within 30-60 minutes [1,7]. Once absorbed it starts to break down, and shows toxic effects. In order to prevent the adsorption of methanol, activated charcoal needs to be administered very quickly. After being administered, charcoal binds to methanol and it is eliminated from the body through excretion.

Even with the administration of charcoal a small quantity of methanol may still be absorbed through the digestive system, and its metabolism in the liver produces toxic by-products, notably formaldehyde and formic acid. This sequential metabolism, primarily facilitated by alcohol dehydrogenase (ADH) and formaldehyde dehydrogenase (FLDH) enzymes, leads to the accumulation of formic acid, which causes central nervous system depression, neurological complications, and potentially fatal outcomes. Folinic acid breaks down formic acid into carbon dioxide and water, speeding up the removal of formate [1,7].

Numerous experimental studies have been conducted on the use of activated charcoal in the treatment of methanol poisoning, and ongoing research in this area is still in progress. Mathangi et al. did some experimental work in vivo and have shown that the mortality has been significantly reduced by the administration of activated charcoal [5]. In their study, Olson et al. explored the effectiveness of activated charcoal in the management of acute poisoning [6]. Ghosh and Peters [4] have done mathematical work on charcoal therapy for methanol poisoning, but they did not consider folinic acid as a supportive therapy. They also considered treatment with ethanol. In their study, Ghosh and Roy [13] performed a mathematical analysis after formulating an enzymatic model for methanol poisoning using ethanol as an antidote. They considered sodium bicarbonate as a supportive therapy and no activated charcoal therapy. They additionally looked at treatment with fomezipole, which is an alternative antidote.

Hence the use of activated charcoal to treat methanol poisoning is a very important potential therapy for methanol poisoning. The study in this paper is novel because it is the first mathematical study done on the application of folate and activated charcoal therapy for the treatment of methanol poisoning. This research can assist clinical researchers in designing and conducting further trials on charcoal dosing, and determining its optimal effectiveness for treating methanol toxicity.

In this research article, first we discuss the formulation of the mathematical model along with the necessary assumptions. In the following section, we derive some basic model properties such as non-negativity and boundedness. The selection of the adsorption function is discussed in section 4. Then, utilizing the absorption function, we formulate an impulsive differential equation for methanol concentration. In the next section, we present a variety of numerical simulations depicting the behaviour of the system with and without therapy over different time frames. At the end, we discuss the consequences of the analytical and numerical results and make some final remarks for our mathematical system.

2 Formulation of Mathematical Model

Upon ingestion of methanol (M), it undergoes interaction with the ADH enzyme (N_1) with rate constant r_1 , forming methanol-enzyme complex (X_1). This complex then decomposes into formaldehyde (T_1) and enzyme (N_1) at a rate r_3 . Concurrently the complex (X_1) reverts back to the initial reactants at the rate r_2 . In a similar fashion, formaldehyde (T_1) reacts with the FLDH enzyme (N_2), leading to the creation of a formaldehyde-enzyme complex (X_2) with rate constant r_4 . This complex subsequently breaks down into formic acid (T_2), liberating free enzyme (N_2) at a rate r_6 . Additionally the complex (X_2) undergoes reversal into formaldehyde and FLDH at a rate r_5 . After the intravenous administration of folinic acid (at strictly positive rate F_c), it catalyzes the breakdown of formate (denoted C) into CO_2 and H_2O with rate constant r_7 .

$$\frac{dN_1}{dt} = -r_1N_1M + r_2X_1 + r_3X_1, \quad (1a)$$

$$\frac{dM}{dt} = -r_1N_1M + r_2X_1, \quad (1b)$$

$$\frac{dX_1}{dt} = r_1N_1M - r_2X_1 - r_3X_1, \quad (1c)$$

$$\frac{dT_1}{dt} = r_3X_1 - r_4N_2T_1 + r_5X_2, \quad (1d)$$

$$\frac{dN_2}{dt} = -r_4T_1N_2 + r_5X_2 + r_6X_2, \quad (1e)$$

$$\frac{dX_2}{dt} = r_4N_2T_1 - r_5X_2 - r_6X_2, \quad (1f)$$

$$\frac{dT_2}{dt} = r_6X_2 - r_7FT_2, \quad (1g)$$

$$\frac{dF}{dt} = F_c - r_7FT_2, \quad (1h)$$

$$\frac{dC}{dt} = r_7FT_2, \quad (1i)$$

with the initial values: $N_1(0) = N_{10}$, $M(0) = M_0$, $N_2(0) = N_{20}$, $X_1(0) = 0$, $X_2(0) = 0$, $T_1(0) = 0$, $T_2(0) = 0$, $F(0) = 0$ and $C(0) = 0$, where N_{10} , N_{20} and M_0 , are strictly positive constants. In Equations (1a) - (1h) the quantity M denotes concentration of methanol measured in grams per kilogram of H_2O . As one litre of H_2O weighs one kilogram these units are equivalent to grams per litre of H_2O . Similarly the quantities N_1 , X_1 , T_1 , N_2 , X_2 , T_2 , F and C are also measured in grams per kilogram of H_2O . The rate F_c is measured in grams per kilogram of H_2O per unit time.

As C does not appear in Equations (1a)-(1h), Equation (1i) of the system (1) can be decoupled from the others. The total enzyme concentration, free enzyme plus combined enzyme, is constant. Hence

$$\frac{dN_1}{dt} + \frac{dX_1}{dt} = 0.$$

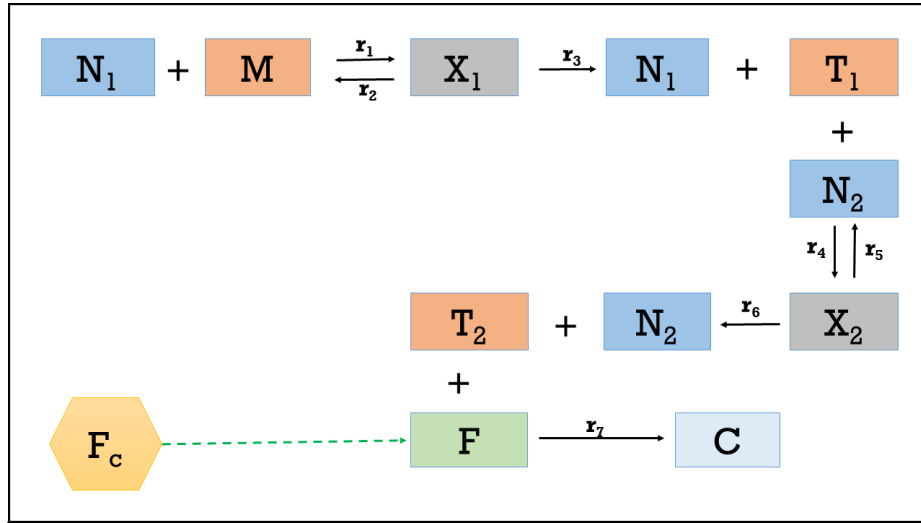


Fig. 1. Schematic diagram of the enzymatic reaction.

This implies that $N_1 + X_1$ is a constant. Using the initial condition we get $N_1 = N_{10} - X_1$. By employing the initial condition and carrying out analogous computations, we obtain

$$N_2 = N_{20} - X_2.$$

Using the above data, we reduced the model to get

$$\frac{dM}{dt} = -r_1(N_{10} - X_1)M + r_2X_1, \quad (2a)$$

$$\frac{dX_1}{dt} = r_1(N_{10} - X_1)M - r_2X_1 - r_3X_1, \quad (2b)$$

$$\frac{dT_1}{dt} = r_3X_1 - r_4(N_{20} - X_2)T_1 + r_5X_2, \quad (2c)$$

$$\frac{dX_2}{dt} = r_4(N_{20} - X_2)T_1 - r_5X_2 - r_6X_2, \quad (2d)$$

$$\frac{dT_2}{dt} = r_6X_2 - r_7FT_2, \quad (2e)$$

$$\frac{dF}{dt} = F_c - r_7FT_2. \quad (2f)$$

For further analysis we use this simplified model (2).

3 Model Properties

In this section, we will discuss the non-negativity and boundedness of our system (2).

3.1 Nonnegativity and Boundedness

Theorem 1. *All the solutions of the system (2) with initial conditions, are non-negative in \mathbb{R}^6 , for all time $t > 0$. M, X_1, T_1, X_2 and T_2 are all bounded, for all time $t > 0$.*

Proof. To show the positivity result we shall return to equations (1) and show that $N_1, M, X_1, T_1, N_2, X_2, T_2, F$ and C are strictly positive for $t > 0$. Let

$$t_0 = \sup\{\xi \geq 0 : N_1(u) > 0, M(u) > 0, X_1(u) > 0, T_1(u) > 0, N_2(u) > 0, X_2(u) > 0, T_2(u) > 0, F(u) > 0 \text{ and } C(u) > 0 \text{ for } u \in [0, \xi]\}.$$

Suppose that $t_0 < \infty$. Then for $t \in [0, t_0)$

$$\frac{dN_1}{dt} \geq -r_1 M N_1.$$

So
$$N_1(t) \geq N_{10} \exp\left(-r_1 \int_0^t M(u) du\right).$$

Hence letting $t \rightarrow t_0$,
$$N_1(t_0) \geq N_{10} \exp\left(-\int_0^{t_0} M(u) du\right) > 0.$$

Similarly $M(t_0) > 0$.

For X_1 by considering

$$\left. \frac{dX_1}{dt} \right|_{t=0},$$

it is straightforward to show that $X_1(\Delta t) > 0$ for Δt small and positive. Then by starting at $t = \Delta t$ rather than $t = 0$ it is straightforward to show similarly to above that $X_1(t_0) > 0$. For T_1 ,

$$\left. \frac{dT_1}{dt} \right|_{t=0} = 0, \text{ but } \left. \frac{d^2 T_1}{dt^2} \right|_{t=0} = r_3 r_1 N_{10} M_{10} > 0.$$

Hence again $T_1(\Delta t) > 0$ for Δt small and positive. So arguing as above $T_1(t_0) > 0$. A similar argument shows that each of $X_2(t_0), F(t_0), C(t_0), N_2(t_0)$ and $T_2(t_0) > 0$. This contradicts the definition of t_0 . Hence $t_0 = \infty$ which completes the proof of the positivity result.

Next we will show that M, X_1, T_1, X_2 and T_2 are bounded. Define a function Ψ as

$$\Psi = M + X_1 + T_1 + X_2 + T_2.$$

Therefore

$$\frac{d\Psi}{dt} = -r_7 F T_2 < 0.$$

So Ψ is monotone decreasing and $0 \leq \Psi \leq \Psi(0) < \infty$. So each of M, X_1, T_1, X_2 and T_2 are bounded. Therefore, for every solution of system (2) M, X_1, T_1, X_2 and T_2 are bounded.

To see that F is not always bounded consider the solution with $X_1(0) = T_1(0) = X_2(0) = T_2(0) = F(0) = 0$ when $F = F_c t$ is clearly unbounded.

4 Adsorption function

There are several equations that describe adsorption, including the Langmuir equation, the Freundlich equation, the Dubinin-Astakhov (DA) equation, and the Dubinin-Raduskevich equation [2,3,8]. Here, we consider a specific form of the DA equation, which describes the physical adsorption of methanol on charcoal, which is

$$M^* = M_0 \exp\left(-K \left(T \ln \frac{P_0}{P}\right)^n\right), \quad (3)$$

where M^* represents the concentration of methanol adsorbed at pressure P , M_0 is the adsorption capacity of charcoal, n is the characteristic parameter of the adsorbent adsorbate pair and P_0 represents the saturation pressure. The adsorption parameter K depends on the specific pair of adsorbents and adsorbate and it remains constant for that particular combination. T is the adsorption temperature.

This equation involves three parameters: concentration, pressure, and temperature. However, when considering the adsorption of methanol by charcoal in our body, the temperature is assumed to remain constant. This function will assist in determining the change in methanol concentration during the adsorption on charcoal.

In poisoning cases, pressure initially rises and stabilizes over time, so pressure can be expressed as a function of time, and we define it as [4]:

$$P = \frac{e^t}{1 + e^t}. \quad (4)$$

5 Effect of impulsive dosing of folinic acid on the system

This section focuses on analyzing the impact of charcoal dosing for methanol adsorption through a one-dimensional impulsive system. The rate of methanol adsorption onto charcoal can be determined by differentiating the function (3) with respect to time (t), and using the equation (4)

$$\begin{aligned} \frac{dM^*}{dt} &= n \sqrt[n]{K} T M^* \left(\ln \frac{M_0}{M^*}\right)^{\frac{n-1}{n}} \left(1 - P_0 \exp\left(-\frac{1}{T \sqrt[n]{K}} \left(\ln \frac{M_0}{M^*}\right)^{\frac{1}{n}}\right)\right), \quad (5) \\ &= G(M^*). \end{aligned}$$

Parameter	Assigned Value	Reference
r_1	$(0.2 - 2.5) (\text{gm/Kg})^{-1}(\text{hour})^{-1}$	[4,13]
r_2	$(0.02 - 0.25) (\text{hour})^{-1}$	[4,13]
r_3	$(0.2 - 3) (\text{hour})^{-1}$	[4,13]
r_4	$(0.1 - 2) (\text{gm/Kg})^{-1}(\text{hour})^{-1}$	[4,13]
r_5	$(0.02 - 0.25) (\text{hour})^{-1}$	[4,13]
r_6	$(1 - 2.5) (\text{hour})^{-1}$	[4,13]
r_7	$10 (\text{gm/Kg})^{-1}(\text{hour})^{-1}$	Estimated

Table 1. Parameter values.

Here $G(M^*)$ represents the rate of change of methanol concentration for each charcoal dosing due to adsorption.

We define the impulsive differential equation as follows:

$$\begin{aligned} \frac{dM}{dt} &= -r_1(N_{10} - X_1)M + r_2X_1, \quad t \neq t_r, \\ \Delta M &= -G(M^*), \quad t = t_r, \end{aligned} \quad (6)$$

where $\Delta M = M(t_r^+) - M(t_r^-)$, and $M(t_r^+)$ and $M(t_r^-)$ are the concentrations of methanol just after, and just before, the r^{th} impulse.

6 Numerical Simulations

In this section we will study the behaviour of our system numerically. All numerical results presented in this section were generated using Matlab 2016a. The parameter values utilized in these simulations are outlined in Table 1. To administer activated charcoal therapy after an individual has been poisoned, a solution of activated charcoal must be given, either as a drink by mouth for those patients who are conscious, or through a naso-gastric tube for unconscious patients [4]. Ghosh and Peters [4] discuss administering activated charcoal with a 12 minute interdose interval as an example. Based on this, we discuss administering doses at intervals of 10, 15 and 20 minutes as realistic possibilities. Note also that Ghosh and Roy [13] discuss periodically administering ethanol but with a longer interdose interval of 1 hour.

In Figure 2, the absorption of methanol (M) against pressure (P) for various values of n have been depicted. Plots were generated for $n=1.7$, $n=2.6$, $n=3$, $n=3.2$, $n=3.33$ and $n=3.4$. It is interesting to note that starting from $n=1.7$, the graph of methanol adsorption increases with increments of n , but starts to decrease after increasing n from 3.2 to 3.4. Therefore, it is observed that the optimal value is attained at $n=3.2$.

Figure 3 illustrates a comparison between the trajectories of reactants in the absence of any treatment and with impulsive dosing of charcoal therapy at 10

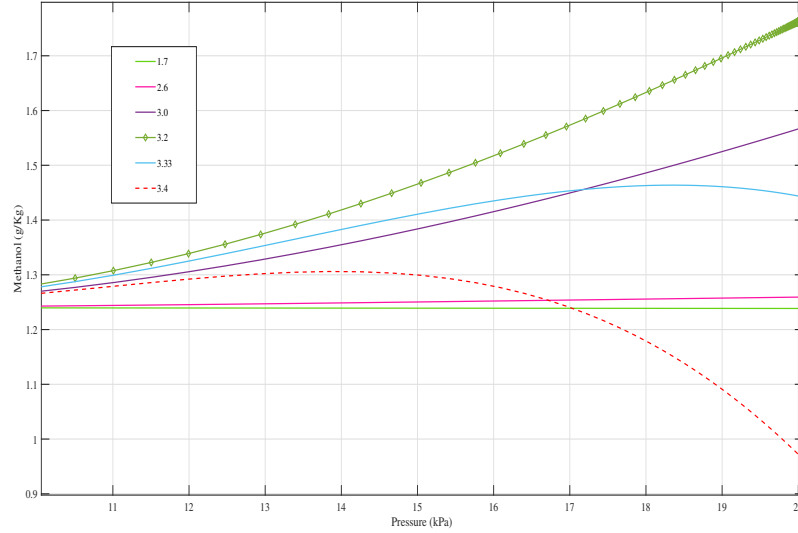


Fig. 2. Methanol adsorption against pressure for various values of the characteristic parameter n . The values of the parameters are chosen as: $M_0 = 0.96$ g/Kg, $K = 3.01 \times 10^{-6}$ ($^{\circ}C$) $^{-n}$, $T = 35^{\circ}C$ and $P_0 = 5.5$ kPa.

minute intervals and folate therapy given 30 minutes after methanol ingestion. This clearly indicates that the concentrations of toxic methanol, formaldehyde and formic acid are significantly reduced. From a biological standpoint this signifies that activated charcoal starts adsorbing methanol, while folic acid actively removes the accumulated formic acid.

In Figure 4 we investigate the kinetics of methanol during impulsive activated charcoal dosing for different intervals (10 minutes, 15 minutes and 20 minutes). Figure 4 illustrates that a 10 minute interval, 15 minute and 20 minute interdose interval take respectively 2.5 hours, 3.2 hours and 4 hours to effectively excrete methanol from the body.

7 Discussion and Conclusion

Our study focuses on lowering the deaths resulting from methanol intoxication through first aid using activated charcoal and folate administration, instead of halting the methanol-enzyme reaction by introducing an enzyme inhibitor (such as ethanol or fomepizole) into the system due to the complex administration procedure and the lack of well-equipped medical centres in remote areas.

Initially, we developed a nonlinear mathematical model for methanol-enzyme reactions incorporating folic acid therapy. We also explored a distinctive form

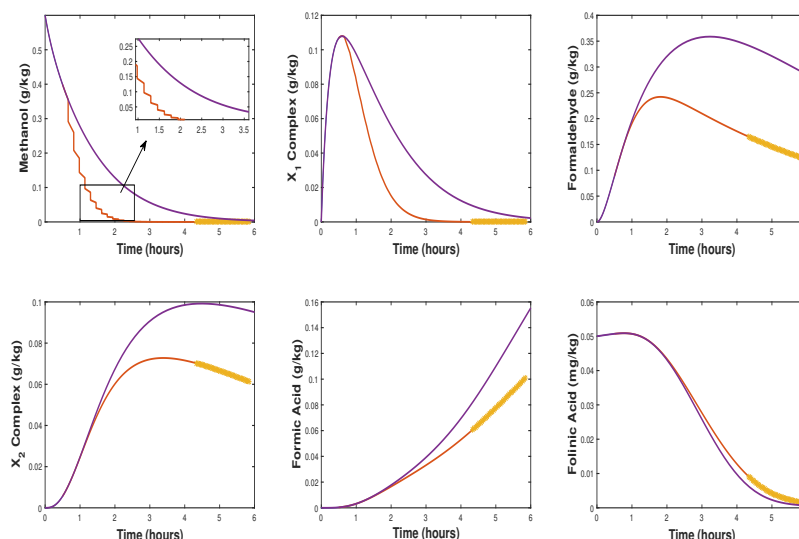


Fig. 3. Comparison of each reactant in the absence of activated charcoal and with impulsive dosing of activated charcoal at intervals of 10 minutes, all the parameter values are taken from Table 1.

of the Dubinin-Astakhov (DA) equation, that characterizes the adsorption kinetics of methanol on activated charcoal. Next we established a one dimensional impulsive differential equation system utilizing the DA equation to estimate the approximate duration of methanol excretion from the body.

We have studied the adsorption function for various values of the characteristic parameter n , and our numerical findings indicate that $n = 3.2$ provides optimal performance for the adsorption function. We have utilised this value of n in the impulsive differential equation. Based on Figures 3 and 4, we can conclude that a 10 minute interdose interval for impulsive activated charcoal dosing yields superior results compared to intervals of 15 and 20 minutes. This charcoal therapy with a 10 minute interdose interval, initiated 30 minutes after methanol ingestion, takes 2.5 hours to effectively eliminate methanol from the body through excretion.

Clinical trials on charcoal therapy for methanol poisoning are very limited and have not yet been conducted with humans, with current research still in progress on animals. Due to the lack of real life experiments on humans we cannot compare our results with real world findings. We are predicting the potential effects and the time required for charcoal to remove methanol. Clinical researchers can use our results for future human trials.

Thus a limitation of this study is the lack of real life experiments to compare our results with clinical data. Moreover while most model parameters originate

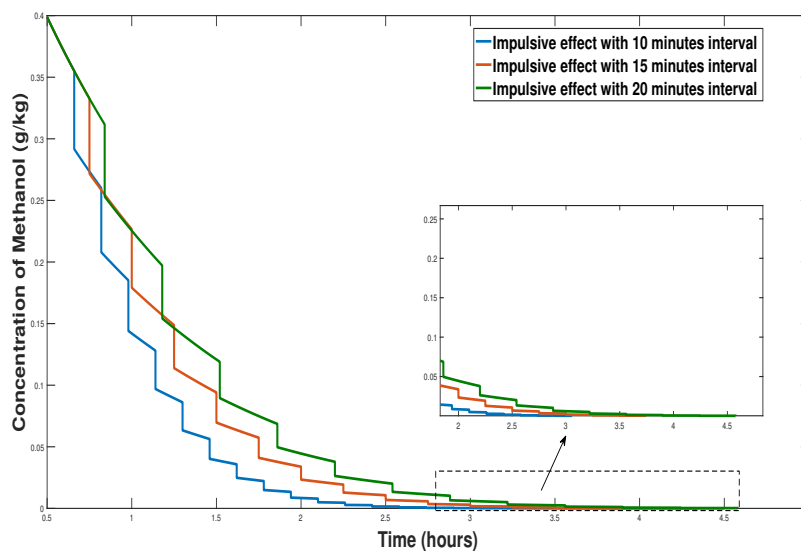


Fig. 4. Comparison of the dynamics of methanol for impulsive dosing of activated charcoal at intervals of 10, 15 and 20 minutes, parameter values are given in Table 1.

from experiments, some are assigned hypothetically due to lack of real clinical data. If proper clinical data were available it would be possible to predict the results more accurately and realistically. Additionally methanol is rapidly absorbed into the bloodstream within 30-90 minutes. A further limitation of this study is that charcoal administration will not be effective if methanol consumption is detected too late.

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