# Identification Problem in Pharmacokinetic Model for the Treatment of Type II Diabetes Mellitus Using Metformin

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## Abstract

Type II diabetes mellitus is a metabolic disorder in which a person has highly elevated blood glucose levels resulting from bodily tissues being resistant to the insulin that is produced in the pancreas. Metformin is an anti-hyperglycemic drug that is widely used for treating type II diabetes mellitus. Metformin works to reduce blood glucose levels by decreasing the rate of hepatic glucose output, decreasing the rate of intestinal glucose absorption, and increasing the rate of glucose uptake by

muscle cells and fat tissue. In this work, an identification problem was investigated using an existing pharmacokinetic compartmental model for type II diabetes mellitus where the effects of oral administration of metformin are considered. The parameters of the model were estimated.

**Mathematics Subject Classification:** 45Q05

**Keywords:** Parameter estimation, Pharmacokinetic model, Optimal parameters, Type II Diabetes Mellitus, Laplace transform

# 1  Introduction

It was estimated in 2011 that, worldwide, 347 million people have diabetes [1] and of these people, 90% are estimated to have type II diabetes [2]. Type II diabetes mellitus is sometimes referred to as adult-onset diabetes or non-insulin dependent diabetes.

Normally, when blood glucose levels rise too high, insulin that is produced in the pancreas will work to lower blood glucose levels back down to within a normal range. In type II diabetics, insulin is produced normally by the pancreas, however, the cells in their bodies do not use the insulin properly or they have become resistant to it entirely. This leads to highly elevated blood glucose levels, a condition called hyperglycemia. As a result of this, type II diabetics need to take anti-hyperglycemic drugs to help keep their blood glucose levels within a normal range.

Metformin is the drug of choice for type II diabetes. It has been used as an effective glucose-lowering agent in type II diabetes mellitus for over forty years [3]. Metformin works to lower blood glucose levels by decreasing intestinal glucose absorption [4], decreasing hepatic glucose output, and increasing the rate of absorption of glucose by muscle cells and fat tissue [5].

In most cases metformin is administered orally in the form of a 500-mg or 850-mg tablet, and due to the fact that metformin is not completely absorbed in the intestine, some of the oral dosage can be recovered from feces [6]. Metformin is not metabolized and as a result it is eliminated unchanged through the urinary system [7].

Metformin does not work to increase insulin concentrations and it does not cause weight gain [8]. Besides minor gastrointestinal upset, the other potential side effect of taking metformin is lactic acidosis, which is usually the result of metformin being wrongfully prescribed to a patient [3].

This paper is organized as follows. In section 2, we introduce the pharmacokinetic model. The methods and solutions for solving the model analytically are presented in section 3. The methods and solutions for solving the model

numerically are presented in section 4. Conclusions of this work are presented in section 5.

# 2 Pharmacokinetic Model

In this study a compartmental model is used to model the kinetics of the distribution of metformin through different biological compartments in type II diabetes mellitus patients. For the purpose of studying the mechanism of action of a drug, and for predicting the effects of new dosage regimens, it is useful to use mechanism-based models [9]. The compartmental model that is employed in this study has been used in two previous works [10, 11]. The four main places where metformin exhibits some mechanism of action to lower blood glucose levels are the gastrointestinal system, the liver, muscle cells, and fat tissue. Based on this, the following model is constructed.
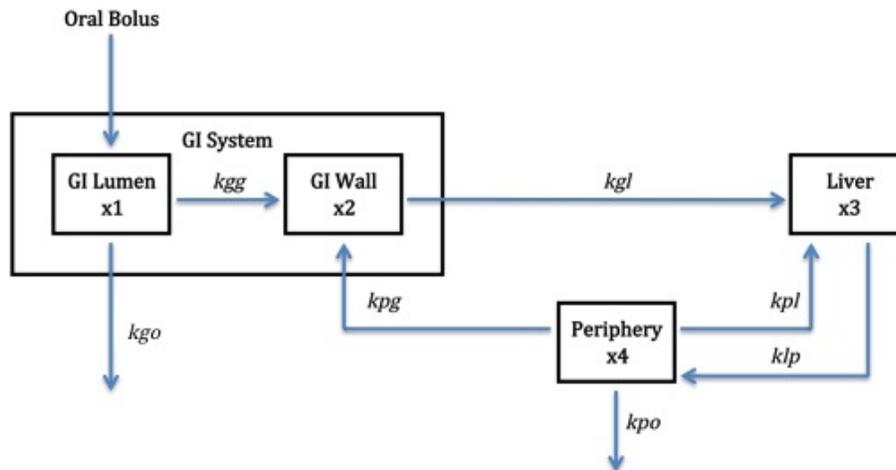


Figure 1: Pharmacokinetic model showing the distribution of metformin

The gastrointestinal system makes up the first two compartments, the GI lumen and the GI wall. This is necessary for three reasons. First, it will show the rate of absorption of metformin after oral administration. Second, not all of the orally administered metformin is absorbed so it shows the amount that is excreted as feces. Third, it shows the accumulation of metformin in the GI wall, through both the GI lumen and arterial blood supply to the intestine [10].

The third compartment in this model is the liver and the fourth compartment is the periphery. The periphery consists of everything else in the body, most notably the kidneys and two of the sites of action of metformin: the muscle cells and fat tissue.

The oral bolus is the amount of metformin in the tablet that is being administered. The rate of absorption of metformin from the GI lumen into the GI wall is shown by the rate constant $k_{gg}$ whereas $k_{go}$ shows the rate of elimination of the unabsorbed metformin in the GI lumen. The following rate constants show transfer of metformin between two compartments: $k_{gl}$ is from the GI wall to the liver, $k_{lp}$ is from the liver to the periphery, $k_{pl}$ is from the periphery to the liver, and $k_{pg}$ is from the periphery to the GI wall. Lastly, the rate of elimination of metformin through the urinary system is shown by the rate constant $k_{po}$. This model accounts for unidirectional blood flow through the portal system because through the oral administration route, metformin will pass through both the GI wall and the liver before it reaches the periphery [11]. We assume that all changes are first order processes.

Based on the model, a system of linear ordinary differential equations can be constructed. Each equation relates the amount of metformin in each compartment to the amount of time that has elapsed since the administration of metformin.

$$\frac{dx_1}{dt} = -x_1 k_{gg} - x_1 k_{go} \tag{1}$$

$$\frac{dx_2}{dt} = x_1 k_{gg} - x_2 k_{gl} + x_4 k_{pg} \tag{2}$$

$$\frac{dx_3}{dt} = x_2 k_{gl} - x_3 k_{lp} + x_4 k_{pl} \tag{3}$$

$$\frac{dx_4}{dt} = x_3 k_{lp} - x_4 k_{pg} - x_4 k_{pl} - x_4 k_{po} \tag{4}$$

This system of equations is the same as for the model that has been used twice in the past [10, 11]. Concentrations of metformin in each compartment are not used because that would involve estimation of the volumes of each of the compartments. As a result, just the amounts (in mg) are used in our system of equations. Converting the system of linear ordinary differential equations into matrix form gives the following matrix.

$$\begin{bmatrix} x_1'(t) \\ x_2'(t) \\ x_3'(t) \\ x_4'(t) \end{bmatrix} = \begin{bmatrix} -(k_{gg} + k_{go}) & 0 & 0 & 0 \\ k_{gg} & -k_{gl} & 0 & k_{pg} \\ 0 & k_{gl} & -k_{lp} & k_{pl} \\ 0 & 0 & k_{lp} & -(k_{pg} + k_{pl} + k_{po}) \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \\ x_4(t) \end{bmatrix}$$

Which can then be shown in the following equation.

$$\vec{x}\,'(t) = A\,\vec{x}(t)$$

# 3 Analytical Solutions

The general overview for finding the analytical solutions for $x_1(t), x_2(t), x_3(t)$, and $x_4(t)$ first involved converting the system of linear ordinary differential equations into matrix form. To solve this, the Laplace transform was used to convert this from the time $(t)$ domain to the complex $(s)$ domain. Once in the complex domain, the solutions for $x_1(s), x_2(s), x_3(s)$, and $x_4(s)$ were found using Cramer's rule. After this the inverse Laplace transform was used to convert the analytical solutions in the complex $(s)$ domain back into the time $(t)$ domain.

## 3.1 Process Used to Find Analytical Solutions

The following equation represents the system of linear ordinary differential equations in matrix form.

$$\vec{x}\,'(t) = A\,\vec{x}(t)$$

Then the Laplace transform was used to convert this system from the time $(t)$ domain into the complex $(s)$ domain. Using the Laplace transform on both sides of the equation yielded the following.

$$[s - A]\,\vec{x}(s) = \vec{x}(0)$$

In the above equation, $\vec{x}(0)$ is the initial conditions. This is where we account for the amount of metformin that is in the body at the time of administration. For example, if there are 10 mg of metformin in the liver at the time of administration, 10 would be the value of $x_3^\circ$. This equation is then converted to matrix form.

$$\begin{bmatrix} s + k_{gg} + k_{go} & 0 & 0 & 0 \\ -k_{gg} & s + k_{gl} & 0 & -k_{pg} \\ 0 & -k_{gl} & s + k_{lp} & -k_{pl} \\ 0 & 0 & -k_{lp} & s + k_{pg} + k_{pl} + k_{po} \end{bmatrix} \begin{bmatrix} x_1(s) \\ x_2(s) \\ x_3(s) \\ x_4(s) \end{bmatrix} = \begin{bmatrix} x_1^\circ \\ x_2^\circ \\ x_3^\circ \\ x_4^\circ \end{bmatrix}$$

The matrix $[s - A]$ is the identity matrix $I_4$ times $s$, minus the constant coefficient matrix $A$. To solve this matrix, Cramer's rule was used. First, the

determinant of the $[s - A]$ matrix was found.

$$det([s - A]) = (s + kgg + kgo)(s + kgl)(s + klp)(s + kpg + kpl + kpo)$$

This determinant was then used in finding the analytical solutions for each of the four compartments.

To find the analytical solution in the complex domain for $x_1(s)$, the first column in the $[s - A]$ matrix was replaced with the initial conditions and the determinant of the resulting $[s - A]_1$ matrix was found.

$$det([s - A]_1) = (\mathrm{x}_1^\circ)(s + kgl)(s + klp)(s + kpg + kpl + kpo)$$

$$x_1(s) = \frac{det([s-A]_1)}{det([s-A])} = \frac{(x_1^\circ)}{(s+kgg+kgo)}$$

Then the inverse Laplace transform was used to convert the analytical solution from the complex domain back to the time domain. Using the inverse Laplace transform on both sides of the equation yielded the following.

$$x_1(t) = x_1^\circ \, e^{-(kgg+kgo)t}$$

Then using the same method, the analytical solutions in the time domain were found for the remaining three compartments.

For $x_2(t)$, the GI wall
$$x_2(t) = C_1 \, e^{-(kgg+kgo)t} + C_2 \, e^{-(kgl)t} + C_3 \, e^{-(klp)t} + C_4 \, e^{-(kpg+kpl+kpo)t}$$

For $x_3(t)$, the liver
$$x_3(t) = x_3^\circ \, e^{-(klp)t}$$

And for $x_4(t)$, the periphery
$$x_4(t) = C_5 \, e^{-(kgg+kgo)t} + C_5 \, e^{-(kgl)t} + C_7 \, e^{-(klp)t} + C_8 \, e^{-(kpg+kpl+kpo)t}$$

The analytical solutions are shown in matrix form as follows

$$
\begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \\ x_4(t) \end{bmatrix} =
\begin{bmatrix} x_1^\circ & 0 & 0 & 0 \\ C_1 & C_2 & C_3 & C_4 \\ 0 & 0 & x_3^\circ & 0 \\ C_5 & C_6 & C_7 & C_8 \end{bmatrix}
\begin{bmatrix} e^{-(kgg+kgo)t} \\ e^{-(kgl)t} \\ e^{-(klp)t} \\ e^{-(kpg+kpl+kpo)t} \end{bmatrix}
$$

where,

$$C_1 = \frac{(-kpl)(-klp)(-kgg)(x_1^\circ)}{(kgg+kgo-kgl)(kgg+kgo-klp)(kgg+kgo-kpg-kpl-kpo)} \;,$$

$$C_2 = x_2^\circ - \frac{(-kpg)(x_4^\circ)}{(-kgl+kpg+kpl+kpo)} - \frac{(-kpl)(-klp)(-kgg)(x_1^\circ)}{(kgl-klp)(kgg+kgo-kgl)(kgl-kpg-kpl-kpo)} \;,$$

$$C_3 = \frac{-(-kpl)(-klp)(-kgg)(x_1^\circ)}{(klp-kgl)(kgg+kgo-klp)(klp-kpg-kpl-kpo)} \;,$$

$$C_4 = \frac{-(-kpg)(x_4^\circ)}{(kgl-kpg-kpl-kpo)} - \frac{(-kpl)(-klp)(-kgg)(x_1^\circ)}{(-kgl+kpg+kpl+kpo)(-klp+kpg+kpl+kpo)(kgg+kgo-kpg-kpl-kpo)}$$

$$C_5 = \frac{-(-kgg)(-kgl)(-klp)(x_1^\circ)}{(kgg+kgo-kgl)(kgg+kgo-klp)(kgg+kgo-kpg-kpl-kpo)} \;,$$

$$C_6 = \frac{(-kgg)(-kgl)(-klp)(x_1^\circ)}{(kgl-klp)(kgg+kgo-kgl)(kgl-kpg-kpl-kpo)} \;,$$

$$C_7 = \frac{(-kgg)(-kgl)(-klp)(x_1^\circ)}{(klp-kgl)(kgg+kgo-klp)(klp-kpg-kpl-kpo)} \;,$$

$$C_8 = x_4^\circ + \frac{(-kgg)(-kgl)(-klp)(x_1^\circ)}{(-kgl+kpg+kpl+kpo)(-klp+kpg+kpl+kpo)(kgg+kgo-kpg-kpl-kpo)}$$

# 4  Numerical Results

Matlab generated data were used to estimate parameters associated in the pharmacokinetic model introduced in section 2. Values between 0 and 1 were arbitrarily assigned to each of the seven rate constants. The initial conditions that were chosen were [500 0 0 0], where 500 implies that a 500-mg pill is being administered. These initial conditions can be changed as necessary. For example, if there are 40 mg of metformin in the liver at the time of administration, then the initial conditions would be [500 0 40 0].

From the generated data, measurements were taken at 100 time intervals. A multiplier of 200 was used, which means that between each time interval there are 200 data points, yielding a total of 20,000 data points. In order for the Matlab generated data to provide a more realistic representation of real biological data small amounts of deviation were introduced into the data.
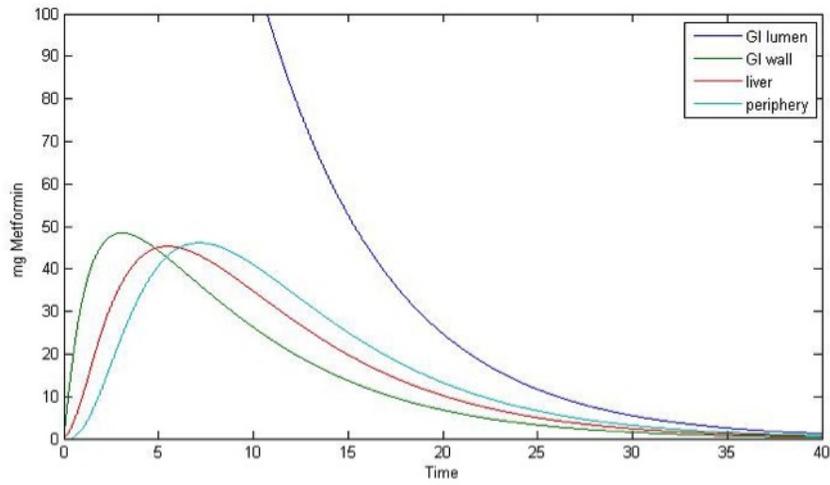
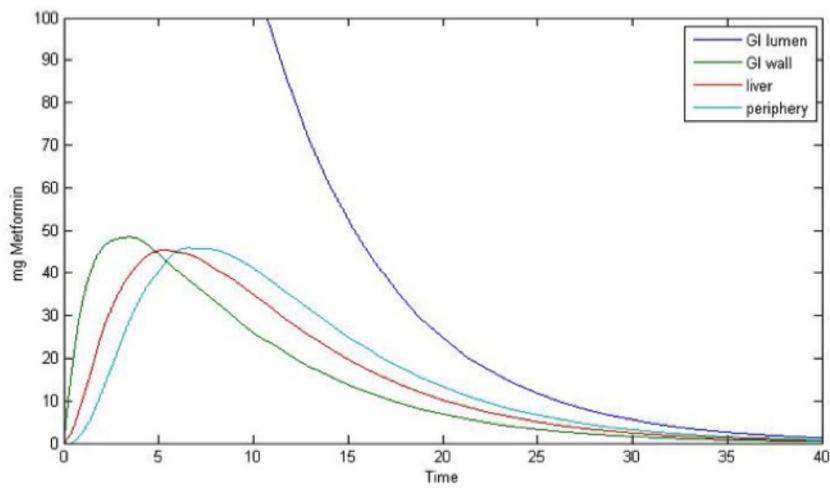Figure 2: Plot of Matlab generated data with 0% deviation in the data



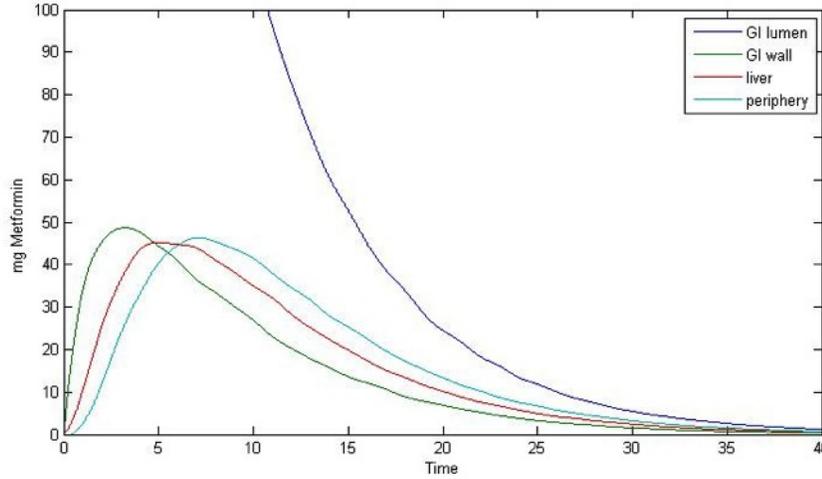Figure 3: Plot of Matlab generated data with 5% deviation in the data

Figure 4: Plot of Matlab generated data with 10% deviation in the data

The numerical solutions for the Matlab generated data were found using two Matlab functions. The first was fitfun which was used to define the change in the amount of metformin in a compartment. The second one was fminsearch which uses a simplex method to find the values of the rate constants, for example, $k_{gg}$, $k_{pg}$ and $k_{gl}$ that minimize the difference between $\Delta x_2(t)$ and $\Delta x_2(t)''$

$$\Delta x_2(t) = x_2(t) - x_2(t-1)$$

$$\Delta x_2(t)'' = x_1(t-1)\frac{k_{gg}}{m} + x_4(t-1)\frac{k_{pg}}{m} - x_2(t-1)\frac{k_{gl}}{m}$$

Table 1: Numerical solutions for the rate constants that were calculated using Matlab

| Rate Constants | Assigned Values | 0% Deviation | 5% Deviation | 10% Deviation |
|:---:|:---:|:---:|:---:|:---:|
| $k_{gg}$ | 0.100000 | 0.100094 | 0.099602 | 0.098593 |
| $k_{go}$ | 0.050000 | 0.050050 | 0.044991 | 0.051675 |
| $k_{gl}$ | 0.700000 | 0.699310 | 0.688405 | 0.657787 |
| $k_{lp}$ | 0.800000 | 0.798980 | 0.741137 | 0.608021 |
| $k_{pg}$ | 0.100000 | 0.098263 | 0.090720 | 0.072913 |
| $k_{pl}$ | 0.150000 | 0.149254 | 0.103234 | 0.004873 |
| $k_{po}$ | 0.500000 | 0.500598 | 0.499026 | 0.489011 |

# 5    Conclusions

We established a pharmacokinetic model associated with several parameters. Analytical and numerical solutions were established. Matlab functions fitfun and fminsearch were used to estimate the parameters. Based on our results we can conclude that the model does work to accurately find the numerical solutions for the values of the rate constants. This was also true when we introduced various amounts of deviation into the data.

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