A THREE COMPARTMENT MATHEMATICAL MODEL OF LIVER

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ABSTRACT
Mathematical modeling of pharmacokinetics is an important and growing field in drug development. Pharmacokinetics concerns with the distribution of drugs, chemicals or tracers by a fluid among the various compartment of human body. In this work we discuss the compartment mathematical model of liver function based on fundamental biological and pharmacological principles. Here we present behavior of thyroxin, iodine and bile over a period of time.

Keywords: liver, mathematical model, differential equations, pharmacokinetics, compartment model.

INTRODUCTION
Pharmacokinetics concerns with the distribution of drugs, chemicals or tracers by a fluid among the various compartment of human body [1]. The compartments could be fictitious spaces through which biomaterials pass through various locations (compartments of the body). The present investigation is on a three compartment model related to the liver in human body [2, 3, 4]. When a chemical, thyroxin is injected into the blood stream it is carried to the liver. The liver converts thyroxin to iodine, which is absorbed into the bile [5]. However, neither the conversion nor the absorption of which into the bile, would occur instantaneously. Some of the thyroxin (unconverted) reenters into the blood stream and gets recirculated. The Mathematical model is composed of three compartments: Compartment I, Compartment II and compartment III which represent blood vessels, liver and bile respectively as shown in the Figure-1.

![Figure-1. Mathematical model for liver.](image)

Notations adopted:
- \(x_1(t)\) = the quantity of thyroxin in the blood vessel at the instant time ‘t’
- \(x_2(t)\) = the quantity of iodine in the liver
- \(x_3(t)\) = the quantity of iodine absorbed in to the bile
- \(k_{12}\) = The rate of conversion of thyroxin into iodine
- \(k_{21}\) = The rate of the quantity of unabsorbed thyroxin sent out for recycling from Compartment II to compartment I
- \(k_{23}\) = rate of absorption of Iodine from compartment II into bile compartment III

\(x_{10}, x_{20}\) and \(x_{30}\) are initial the values of \(x_1, x_2, x_3\) respectively and the rate constants \(k_{12}, k_{21}\) and \(k_{23}\) are all positive.

It is assumed that the rate \(\dot{x}_1(t)\) at which thyroxin is converted to iodine as it transferred from compartment I to compartment II is proportional to concentration \(x_1(t)\) of thyroxin in the compartment I.

MODEL BLOCK - DIAGRAMS AND MODEL EQUATIONS

\[ \frac{dx_1}{dt} = -k_{12}x_1 + k_{21}x_2, \quad x_1(0) = x_{10} \]  
(1)
The rate of absorption of iodine in compartment II
\[ \dot{x}_2(t) = k_{12}x_1 - (k_{21} + k_{23})x_2, \quad x_2(0) = x_{20} \quad (2) \]

The rate of change of material in compartment III to compartment II
\[ \dot{x}_3(t) = -k_{32}x_3, \quad x_3(0) = x_{30} \quad (3) \]

The equations (1), (2), (3) can be put into the matrix form
\[
\frac{d}{dt} \begin{bmatrix} X \end{bmatrix} = AX
\]
where
\[
A = \begin{bmatrix}
-k_{12} & k_{21} & 0 \\
 0 & -k_{21} - (k_{23} + k_{23}) & 0 \\
 0 & k_{23} & 0
\end{bmatrix}
\quad \text{and} \quad
X = \begin{bmatrix} x_1 \\
x_2 \\
x_3
\end{bmatrix}
\]

Let \( X = X_0 e^{\lambda t} \) be a trial solution with initial conditions \( X(0) = [x_{10} \quad x_{20} \quad x_{30}]^T \)

The exponent \( \lambda \) satisfies the characteristic equation of \( A \):
\[
\det(A - \lambda I) = 0
\]
\[
i, e; \lambda \left[ \lambda^2 + (k_{12} + k_{21} + k_{23}) \lambda + k_{12}k_{23} \right] = 0
\]
the roots of which are \( \lambda = 0 \) and \( \lambda_2, \lambda_3 = -k \pm M \)

where
\[
k = \frac{k_{12} + k_{21} + k_{23}}{2}
\]
and
\[
M = \sqrt{k^2 - k_{12}k_{23}}
\]

Evidently \( M \) is real and less than \( k \). Hence \( \lambda_2 \) and \( \lambda_3 \) are both real and negative roots.

The solutions of equations (1), (2), (3) can be written as
\[
x_1(t) = A + Be^{\lambda_2 t} + Ce^{\lambda_3 t} \quad (9)
\]
\[
x_2(t) = \frac{1}{k_{21}} \left[ Ak_{12} + B(\lambda_2 + k_{12})e^{\lambda_2 t} + C(\lambda_3 + k_{12})e^{\lambda_3 t} \right] \quad (10)
\]
\[
x_3(t) = \frac{k_{23}}{k_{21}} \left[ Ak_{12} + B(\lambda_2 + k_{12})e^{\lambda_2 t} + C(\lambda_3 + k_{12})e^{\lambda_3 t} \right] + E \quad (11)
\]

where \( A, B, C \) and \( E \) are arbitrary constants. Using the initial conditions, we get the values of the constants
\[
A = 0 \quad (12)
\]
\[
B = \frac{x_{10} (k_{12} + \lambda_3) - k_{21}x_{20}}{\lambda_3 - \lambda_2} \quad (13)
\]
\[
C = \frac{k_{21}x_{20} - (k_{12} + \lambda_2)x_{10}}{\lambda_3 - \lambda_2} \quad (14)
\]
and
\[
E = \frac{k_{23}}{k_{21}} (x_{10} + x_{20} + x_{30}) \quad (15)
\]

Substituting these values in (1.1), (1.2), (1.3) we get after some simplification
\[
x_1(t) = \frac{x_{10} (k_{12} + \lambda_3) - k_{21}x_{20}e^{\lambda_2 t}}{\lambda_3 - \lambda_2} + \frac{k_{23}x_{20} - (k_{12} + \lambda_2)x_{10}e^{\lambda_3 t}}{\lambda_3 - \lambda_2} + \frac{e^{\lambda_3 t}}{M} \left[ (k_{23}x_{20} - x_{10} (k_{12} + \lambda_3))sinhMt + (Mx_{10})coshMt \right] \quad (16)
\]
\[ x_2(t) = \frac{1}{k_{21}} \left[ \frac{x_{10}(k_{12} + \lambda_1) - k_{21} x_{20}}{\lambda_3 - \lambda_2} (\lambda_2 + k_{12}) e^{\lambda_2 t} + \frac{k_{21} x_{20} - x_{10}(k_{12} + \lambda_2)}{\lambda_3 - \lambda_2} (\lambda_3 + k_{12}) e^{\lambda_3 t} \right] \]

\[ = \frac{e^{-k_1 t}}{M} \left[ (2x_{10}k_{12} - k_{21}x_{20}) \sinh Mt + (Mx_{20}) \cosh Mt \right] \]  

(17)

\[ x_3(t) = \frac{k_{32}}{k_{21}} \left[ \frac{x_{10}(k_{12} + \lambda_2)}{\lambda_3 - \lambda_2} (\lambda_2 + k_{12}) e^{\lambda_2 t} + \frac{k_{21} x_{20} - x_{10}(k_{12} + \lambda_2)}{\lambda_3 - \lambda_2} (\lambda_3 + k_{12}) e^{\lambda_3 t} \right] + (x_{10} + x_{20} + x_{30}) \]

\[ = \frac{e^{-k_2 t}}{M} \left[ k_{32} x_{20} - k(x_{10} + x_{20}) \right] \sinh Mt - M(x_{10} + x_{20}) \cosh Mt \]  

(18)

The variations of \( x_1(t), x_2(t) \) and \( x_3(t) \) vs 't' are illustrated for a select range of values of \( k_{12}, k_{21}, k_{23} \) (vide Figure-2 to Figure-5) and for the initial values \( x_{10} = 150, x_{20} = 125 \) and \( x_{30} = 65 \) of thyroxin, iodine and bile, respectively.

**Figure-2.** Variation of thyroxin, iodine, bile for the transfer coefficients \( k_{12} = 0.185, k_{21} = 0.056 \) and \( k_{23} = 0.006 \).

**Figure-3.** Variation of thyroxin, iodine, bile for the transfer coefficients \( k_{12} = 0.185, k_{21} = 0.0511 \) and \( k_{32} = 0.0001 \).

**Figure-4.** Variation of thyroxin, iodine, bile for the transfer coefficients \( k_{12} = 0.185, k_{21} = 0.0511 \) and \( k_{32} = 0.0001 \).
Figure-5. Variation of thyroxin, iodine, bile for the transfer coefficients $k_{12}=0.185$, $k_{21}=0.055$ and $k_{23}=0.0005$.

CONCLUSIONS

Thyroxin monotonically decreases reaching zero level. Iodine initially rises to reach a maximum and falls asymptotically to approach to zero as is the case with thyroxin. The bile increase monotonically approaches asymptotic level.

Incipient variations of $x_1(t)$, $x_2(t)$ and $x_3(t)$ (i.e.; variations for small range time $t'$)

It is known

$$\cosh Mt = 1 + \frac{(kt)^2}{2!} + O(t^3)$$

and

$$\sinh Mt = kt + O(t^3)$$

Neglecting term of $O(t^3)$, we get

$$x_1 = x_{10} + (k_{23} x_{20} - k_{12} x_{10}) t + \frac{1}{2} \left[(k_{12} + k_{23}) (x_{10} - x_{20} - k_{12} x_{20})\right] t^2$$

(19)

$$x_2 = x_{20} + (k_{12} x_{10} - k_{23} x_{20}) t + \frac{1}{2} \left[2 x_{20} (k_{12} + k_{23}) - 2 k_{23} x_{20}\right] t^2$$

(20)

$$x_3 = x_{30} + (x_{20} k_{23}) t + \frac{k_{23}}{2} \left[(x_{10} - k_{12} + k_{23}) x_{20}\right] t^2$$

(21)

The variations of $x_1(t)$, $x_2(t)$ and $x_3(t)$ Vrs small time ‘t’ are illustrated for a select range of values of $k_{12}$, $k_{21}$, $k_{23}$ (vide Figure-6 to Figure-9) and for the initial values $x_{10} = 150$, $x_{20} = 125$ and $x_{30} = 65$ of thyroxin, iodine and bile, respectively.
Asymptotic variation of $x_1(t)$, $x_2(t)$ and $x_3(t)$ (variation for large range time $t'$)

In this case $e^{Mt}$ dominates over $e^{-Mt}$ (since $M>0$) and

\[
\cosh Mt \approx \frac{e^{Mt}}{2} \quad \text{and} \quad \sinh Mt \approx \frac{e^{-Mt}}{2}
\]

Hence the asymptotic expression for $x_1(t)$, $x_2(t)$, $x_3(t)$ are

\[
x_1 = \frac{e^{-t(K-M)}}{2M} \left[(x_{20}k_{21} + x_{10}(M + K - k_{12})\right] \quad (22)
\]

\[
x_2 = \frac{e^{-t(K-M)}}{2M} \left[(2x_{10}k_{12} + x_{20}(M - K))\right] \quad (23)
\]

\[
x_3 = \frac{e^{t(K-M)}}{2M} \left[(x_{20}k_{23} - (x_{10} + x_{20})(M + K)\right] + (x_{10} + x_{20} + x_{30}) \quad (24)
\]

CONCLUSIONS

For large range time ‘t’, each of $x_1(t)$, $x_2(t)$ and $x_3(t)$ decrease exponentially with the Characteristic time

\[
1 \quad k - \sqrt{k^2 - k_{12}k_{23}}
\]

REFERENCES


