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RESEARCH ARTICLE

A COMPARISON OF DIFFERENT SOLUTION APPROACHES FOR A MATHEMATICAL MODEL OF HEMODIALYSIS.

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Abstract

Mathematical models were developed to gain a better understanding of many biological processes. The basic aim of present study was to establish a new technique in order to solve problems in the field of mathematical modeling. A mathematical model for hemodialysis with some modification was reviewed in this study. Different mathematical techniques, Laplace Transforms, Eigenvalue, and integrating factor for linear differential equations of the model were used, in all cases unique solution were obtained for dialytic interval.

Introduction:-

Kidney is the major organ to clean blood by removing excess fluid, minerals and wastes. Moreover, it produces a hormone that keeps the bones strong. When the kidney fails harmful wastes build up in the body, due to which blood pressure may rise and the body may retain excess fluid which has to be removed. Hemodialysis is the most common method used to treat advanced and permanent kidney failure. In hemodialysis blood is allowed to flow through a special filter that removes wastes and extra fluids. The clean blood is then returned back to the body.

Mathematical modeling for dialysis has not long history, first bi-compartmental model of a typical profiled heomodialysis session for setting suitable sodium profiles was proposed in 2000 (Stephen *et al*., 2000) . In the same year another model known as one- and two-compartment model for hemodialysis with aim to analyze the course of treatment and to predict the effect of dialysis procedures was also published (Ziolko*et al*., 2000). But the results on modeling of uric acid concentrations have not been published till 2007. Present study is based on the Mathematical model for solute kinetics in hemodialysis patients proposed by Cronin-Fine in 2007 including the modeling of uric acid concentration.

Material And Methods:-

The motivation for this research was to modify the model equations presented by previous researchers in the field of mathematical modeling for hemodialysis and present different solution approaches for Mathematical model of hemodialysis.

The mathematical model for hemodialysis used in this study is a three compartment model, Organ Mass OM, Muscle Mass and Adipose Tissue Compartment MMAT, and Extracellular Compartment E (Cronin Fine *et al.*, 2007). Block diagram of the model was presented in Fig-1.

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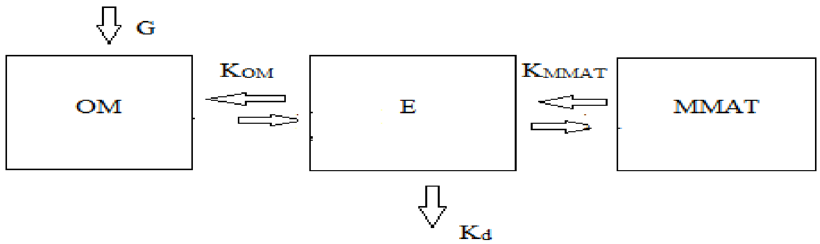
Set of three 1st order differential equations of the model were Equations 1-3. Equation no 4 and 5 were for dialytic interval whereas equation no 6 and 7 were for inter-dialytic interval. Solution of the model was presented by three different approaches Laplace transform, Eigenvalue and integrating factor of linear differential equations.

$$V_{OM}\frac{dC_{OM}}{dt}=G-K_{OM}(C_{OM}-C_E) \quad (1)$$

$$V_{MMAT}\frac{dC_{MMAT}}{dt}= \quad K_{MMAT}(C_E - C_{MMAT}) \quad (2)$$

$$V_E\frac{dC_E}{dx}= K_{OM}(C_{OM}- C_E) - K_{MMAT}(C_E - C_{MMAT}) - K_dC_E \quad (3)$$



COMPARTMENT MODEL

Refining the Governing Equations:-

To make the solution more manageable, Organ Mass (OM) was assumed to be at a steady-state, $d(C_{OM})/dt=0$.

So $K_{OM}(C_{OM} - C_E) = G$,

which was used in Equation (3), yielding equation (4) and eliminating equation (1). The resultant equations were for dialytic interval with manageable solutions (Eq. 4 and Eq.5).

$$V_{MMAT}\frac{dC_{MMAT}}{dt} = K_{MMAT}(C_E-C_{MMAT}) \quad (4)$$

$$V_E\frac{dC_E}{dx} = G-K_{MMAT}(C_E-C_{MMAT})-K_dC_E \quad (5)$$

The dialysis clearance term (K_dC_E) in equation (5) was eliminated to modified the equations for interdialytic interval, yeilding equation (6). It was still impossible to find an explicit solution for the pair of equations (4 and 5) because these equations could be combined as one equation with two variables, which was by definination unsolvable. Therefore an additional equation (7a) was developed, which described the solute mass-balance for the interdialytic interval. This additional Equation resulted in a pair of equations (6 and 7a) for the inter-dialytic interval with manageable solutions as given below.

$$V_E\frac{dC_E}{dx} =G-K_{MMAT}(C_E-C_{MMAT}) \quad (6)$$

$$G = V_E\left(C_E - C_{E_0}\right) + V_{MMAT}\left(C_{MMAT} - C_{MMAT_0}\right) \quad (7a)$$

This equation was found to be inadequate and need modification. Equation (7a) was corrected to a new version of equation (7b) and given below:

$$G = K_d\left(C_E - C_{E_0}\right) + K_{MMAT}\left(C_{MMAT} - C_{MMAT_0}\right). \quad (7\text{ b})$$

This study's focus was to determine whether modeling could provide an explanation for the level of toxin concentration in extracellular compartment during dialysis and in between dialysis treatment. So in this section the different solution procedures for dialytic and inter-dialtic intervals were presented in detail to comprehend the mathematical model of hemodialysis which is as under:

Explicit Solution (Dialytic interval)

Consider equations (4) and (5)

$$\frac{dC_{MMAT}}{dt} = \frac{K_{MMAT}}{V_{MMAT}}C_E - \frac{K_{MMAT}}{V_{MMAT}}C_{MMAT}$$

$$\frac{dC_E}{dx} = \frac{G}{V_E} - \frac{K_{MMAT}}{V_E}C_E + \frac{K_{MMAT}}{V_E}C_{MMAT} - \frac{K_d}{V_E}C_E$$

$$\left(D + \frac{K_d + K_{MMAT}}{V_E}\right)C_E - \frac{K_{MMAT}}{V_E}C_{MMAT} = \frac{G}{V_E} \quad (8)$$

$\left(D + \frac{K_{MMAT}}{V_{MMAT}}\right) C_{MMAT} - \frac{K_{MMAT}}{V_{MMAT}} C_E = 0$ (9)

Multiplying (8) by $\frac{K_{MMAT}}{V_{MMAT}}$and (9) by $(D + \frac{K_d + K_{MMAT}}{V_E})$

$(D + \frac{K_d + K_{MMAT}}{V_E})\ (\frac{K_{MMAT}}{V_{MMAT}})C_E - \frac{{K_{MMAT}}^2}{V_{MMAT}V_E} C_{MMAT} = \frac{G}{V_E}\frac{K_{MMAT}}{V_{MMAT}}$

$(D + \frac{K_d + K_{MMAT}}{V_E})\left(D + \frac{K_{MMAT}}{V_{MMAT}}\right) C_{MMAT} - (D + \frac{K_d + K_{MMAT}}{V_E})\frac{K_{MMAT}}{V_{MMAT}} C_E = 0$

$(D + \frac{K_d + K_{MMAT}}{V_E})\left(D + \frac{K_{MMAT}}{V_{MMAT}}\right) C_{MMAT} - \frac{{K_{MMAT}}^2}{V_{MMAT}V_E} C_{MMAT} = \frac{G}{V_E}\frac{K_{MMAT}}{V_{MMAT}}$

By solving the above equation we got

$$\left[D^2 + \left\{\frac{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}}{V_E V_{MMAT}}\right\} D + \frac{K_{MMAT}}{V_{MMAT}V_E} K_d\right] C_{MMAT} = \frac{G}{V_E}\frac{K_{MMAT}}{V_{MMAT}}$$

The characteristic equation

$$D^2 + \left\{\frac{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}}{V_E V_{MMAT}}\right\} D + \frac{K_{MMAT}}{V_{MMAT}V_E} K_d = 0$$

By using quadratic formula we got

$$D = -\frac{1}{2\,V_E V_{MMAT}}$$

$$C_{MMAT} = r_1 e^{-\frac{1}{2\,V_E V_{MMAT}}\left[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} - \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]} + r_2 e^{-\frac{1}{2\,V_E V_{MMAT}}\left[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} - \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]}$$

For particular solution

$$C_{MMAT_P} = \frac{1}{D^2 + \left\{\frac{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}}{V_E V_{MMAT}}\right\} D + \frac{K_{MMAT}}{V_{MMAT}V_E} K_d}\frac{G}{V_E}\frac{K_{MMAT}}{V_{MMAT}} e^{0\,C_{MMAT}}$$

$$C_{MMAT_P} = \frac{V_E V_{MMAT}}{D^2 V_E V_{MMAT} + \left((V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\right)\boldsymbol{D} + K_d K_{MMAT}}\frac{G}{V_E}\frac{K_{MMAT}}{V_{MMAT}} e^{0\,C_{MMAT}}$$

$$C_{MMAT_P} = \frac{G}{K_d}$$

$$C_{MMAT} = r_1 e^{-\frac{1}{2\,V_E V_{MMAT}}\left[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} - \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]} + r_2 e^{-\frac{1}{2\,V_E V_{MMAT}}\left[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} - \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]} + \frac{G}{K_d} \quad \text{(A)} .$$

Now multiply (8) by $\left(D + \frac{K_{MMAT}}{V_{MMAT}}\right)$and (9) by $\frac{K_{MMAT}}{V_{MMAT}}$ and adding we got

$\left[D^2 + \left\{\frac{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}}{V_E V_{MMAT}}\right\} D + \frac{K_{MMAT}}{V_{MMAT}V_E} K_d\right] C_E = \frac{G}{V_E}\frac{K_{MMAT}}{V_{MMAT}}$

Characteristic equation was

$$D^2 + \left\{\frac{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}}{V_E V_{MMAT}}\right\} D + \frac{K_{MMAT}}{V_{MMAT}V_E} K_d = 0$$

$$D = -\frac{1}{2\,V_E V_{MMAT}} C_E = k_1 e^{-\frac{1}{2\,V_E V_{MMAT}}\left[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} - \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]} + k_2 e^{-\frac{1}{2\,V_E V_{MMAT}}\left[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} - \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]}$$

For particular solution

$$C_{E_P} = \frac{1}{D^2 + \left\{\frac{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}}{V_E V_{MMAT}}\right\} D + \frac{K_{MMAT}}{V_{MMAT}V_E} K_d}\frac{G}{V_E}\frac{K_{MMAT}}{V_{MMAT}} e^{0\,C_E}$$

$$C_{E_P} = \frac{V_E V_{MMAT}}{D^2 V_E V_{MMAT} + \left((V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\right) \boldsymbol{D} + K_d K_{MMAT}} \frac{G}{V_E} \frac{K_{MMAT}}{V_{MMAT}} e^{0\,C_E}$$

$$C_{E_P} = \frac{G}{K_d}$$

The general solution was:

$$C_E = k_1 e^{-\frac{1}{2V_E V_{MMAT}}\left[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} - \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]} +$$
$$k_2 e^{-\frac{1}{2V_E V_{MMAT}}\left[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} - \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]} + \frac{G}{K_d}$$

(B)

Thus the solutions of the systems were given by (A) and (B) for some choice of constants r_1, r_2, k_1, k_2.

$$\begin{vmatrix} D + \frac{K_d + K_{MMAT}}{V_E} & -\frac{K_{MMAT}}{V_E} \\ -\frac{K_{MMAT}}{V_{MMAT}} & \left(D + \frac{K_{MMAT}}{V_{MMAT}}\right) \end{vmatrix}.$$

After substituting (A) and (B) in (9), results obtained were

$$k_1 = \frac{r_1}{2} - \frac{r_1}{2V_E}\left[\frac{K_d V_{MMAT}}{K_{MMAT}} + V_{MMAT} - \frac{1}{K_{MMAT}}\sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]$$

And

$$k_2 = \frac{r_2}{2} - \frac{r_2}{2V_E}\left[\frac{K_d V_{MMAT}}{K_{MMAT}} + V_{MMAT} + \frac{1}{K_{MMAT}}\sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]$$

Putting the value of k_1 and k_2 in (B) we got final solution for dialytic interval which was exactly the same as in (Cronin Fine *et al.*, 2007)

$$C_E = r_1 \varphi_1 e^{\omega_1 t} + r_2 \varphi_2 e^{\omega_2 t} + \frac{G}{K_d} \qquad (10)$$

Where

$$\omega_1 = -\frac{1}{2V_E V_{MMAT}}\left[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} - \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]$$

$$\omega_2 = -\frac{1}{2V_E V_{MMAT}}\left[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} + \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]$$

$$\varphi_1 = \frac{1}{2} - \frac{1}{2V_E}\left[\frac{K_d V_{MMAT}}{K_{MMAT}} + V_{MMAT} - \frac{1}{K_{MMAT}}\sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]$$

$$\varphi_2 = \frac{1}{2} - \frac{1}{2V_E}\left[\frac{K_d V_{MMAT}}{K_{MMAT}} + V_{MMAT} + \frac{1}{K_{MMAT}}\sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right].$$

Equation (10) is the explicit solution for dialytic interval where r_1 and r_2 were constants of integration. Obtained solution indicates how concentration of toxins in extracellular compartment C_E variedover time. The constant of integrations were obtained by assuming C_E at t=0 was equal to C_{MMAT} due to steady state kinetics.

Explicit Solution (Inter-dialytic interval)

Eq(6) *become*

$$\frac{dC_E}{dx} = \frac{G}{V_E} - \frac{K_{MMAT}}{V_E} C_E + \frac{K_{MMAT}}{V_E} C_{MMAT} \qquad (11)$$

Eq (7b) became

$$C_{MMAT} = \frac{G - K_d\left(C_E - C_{E_O}\right) + K_{MMAT} C_{MMAT_O}}{K_{MMAT}} \qquad (12)$$

$$\frac{dC_E}{dx} + C_E\left(\frac{K_{MMAT}}{V_E} + \frac{K_d}{V_E}\right) = \frac{2G}{V_E} + \frac{K_d}{V_E} C_{E_0} - \left(\frac{K_{MMAT} C_{MMAT_O}}{V_E}\right)$$

Here integrating factor was $e^{\left(\frac{K_{MMAT}}{V_E} + \frac{K_d}{V_E}\right)t}$, then by multiplying above equation by integrating factor as follows:

$$\frac{d}{dt}\left(e^{\left(\frac{K_{MMAT}}{V_E} + \frac{K_d}{V_E}\right)t} C_E\right) = e^{\left(\frac{K_{MMAT}}{V_E} + \frac{K_d}{V_E}\right)t}\left[\frac{2G}{V_E} + \frac{K_d}{V_E} C_{E_0} - \left(\frac{K_{MMAT} C_{MMAT_O}}{V_E}\right)\right]$$

Integrating further solution obtained were given below

$$C_E = \frac{2G + K_d C_{E_0} - K_{MMAT}C_{MMAT_O}}{V_E} + ce^{-\left(\frac{K_{MMAT}}{V_E} + \frac{K_d}{V_E}\right)t}. \qquad (13)$$

Equation (13) represented the explicit solution in case of the inter-dialytic interval, where c was constant. The constant was obtained by assuming C_E at t = o and was denoted by C_{E0}.

Solution by Laplace Transform (Dialytic Interval)

Consider

$$\frac{dC_{MMAT}}{dt} = \frac{K_{MMAT}}{V_{MMAT}}C_E - \frac{K_{MMAT}}{V_{MMAT}}C_{MMAT}$$

$$\frac{dC_E}{dx} = \frac{G}{V_E} - \frac{K_{MMAT}}{V_E}C_E + \frac{K_{MMAT}}{V_E}C_{MMAT} - \frac{K_d}{V_E}C_E$$

Taking Laplace Transform on both sides of the above equation

$$\mathcal{L}\left[\frac{dC_{MMAT}}{dt}\right] = \mathcal{L}\left[\frac{K_{MMAT}}{V_{MMAT}}C_E - \frac{K_{MMAT}}{V_{MMAT}}C_{MMAT}\right]$$

$$s\mathcal{L}[C_{MMAT}] - C_{MMAT}(0) = \frac{K_{MMAT}}{V_{MMAT}}\mathcal{L}[C_E] - \frac{K_{MMAT}}{V_{MMAT}}\mathcal{L}[C_{MMAT}]$$

$$\mathcal{L}[C_{MMAT}]\left(s + \frac{K_{MMAT}}{V_{MMAT}}\right) = \frac{K_{MMAT}}{V_{MMAT}}\mathcal{L}[C_E] + C_{MMAT}(0) \qquad (14)$$

$$\mathcal{L}\left[\frac{dC_E}{dx}\right] = \mathcal{L}\left[\frac{G}{V_E} - \frac{K_{MMAT}}{V_E}C_E + \frac{K_{MMAT}}{V_E}C_{MMAT} - \frac{K_d}{V_E}C_E\right]$$

$$s\mathcal{L}[C_E] - C_E(0) = \frac{G}{V_E}\frac{1}{S} - \frac{K_{MMAT}}{V_E}\mathcal{L}[C_E] + \frac{K_{MMAT}}{V_E}\mathcal{L}[C_{MMAT}] - \frac{K_d}{V_E}\mathcal{L}[C_E]$$

$$\mathcal{L}[C_E]\left(s + \frac{K_{MMAT}}{V_E} + \frac{K_d}{V_E}\right) = \frac{K_{MMAT}}{V_E}\mathcal{L}[C_{MMAT}] + \frac{G}{V_E}\frac{1}{S} + C_E(0) \qquad (15)$$

Multiplying (14) by $\left(s + \frac{K_{MMAT}}{V_E} + \frac{K_d}{V_E}\right)$ and (15) by $\frac{K_{MMAT}}{V_{MMAT}}$, then adding resultant was

$$\mathcal{L}[C_{MMAT}]\{(s-\omega_1)(s-\omega_2)\} = \left(s + \frac{K_{MMAT}}{V_E} + \frac{K_d}{V_E}\right)C_{MMAT}(0) + \frac{K_{MMAT}}{V_{MMAT}}\frac{G}{V_E}\frac{1}{S} + \frac{K_{MMAT}}{V_{MMAT}}C_E(0)$$

Where

$$\omega_1 = -\frac{1}{2V_E V_{MMAT}}\Big[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} - \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\Big]$$

$$\omega_2 = -\frac{1}{2V_E V_{MMAT}}\Big[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} + \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\Big]$$

$$\mathcal{L}[C_{MMAT}] = \left(s + \frac{K_{MMAT}}{V_E} + \frac{K_d}{V_E}\right)C_{MMAT}(0)\frac{1}{(s-\omega_1)(s-\omega_2)} + \frac{K_{MMAT}}{V_{MMAT}}\frac{G}{V_E}\frac{1}{S}\frac{1}{(s-\omega_1)(s-\omega_2)} + \frac{K_{MMAT}}{V_{MMAT}}C_E(0)\frac{1}{(s-\omega_1)(s-\omega_2)}$$

$$\mathcal{L}[C_{MMAT}] = \frac{G}{K_d} + \left[\frac{(\omega_1)^2 V_E V_{MMAT} C_{MMAT}(0) + \left(K_{MMAT}V_{MMAT}\left(C_E(0) + C_{MMAT}(0)\right) + K_d V_{MMAT}\right)\omega_1 + GK_{MMAT}}{V_{MMAT}V_E\omega_1(\omega_1 - \omega_2)}\right]\frac{1}{(s-\omega_1)} + \left[\frac{(\omega_2)^2 V_E V_{MMAT} C_{MMAT}(0) + \left(K_{MMAT}V_{MMAT}\left(C_E(0) + C_{MMAT}(0)\right) + K_d V_{MMAT}\right)\omega_2 + GK_{MMAT}}{V_{MMAT}V_E\omega_2(\omega_2 - \omega_1)}\right]\frac{1}{(s-\omega_2)}$$

$$\mathcal{L}[C_{MMAT}] = r_1\frac{1}{(s-\omega_1)} + r_2\frac{1}{(s-\omega_2)} + \frac{G}{K_d}\frac{1}{S}$$

Where

$$r_1 = \frac{(\omega_1)^2 V_E V_{MMAT} C_{MMAT}(0) + \left(K_{MMAT}V_{MMAT}\left(C_E(0) + C_{MMAT}(0)\right) + K_d V_{MMAT}\right)\omega_1 + GK_{MMAT}}{V_{MMAT}V_E\omega_1(\omega_1 - \omega_2)}$$

$$r_2 = \frac{(\omega_2)^2 V_E V_{MMAT} C_{MMAT}(0) + \left(K_{MMAT}V_{MMAT}\left(C_E(0) + C_{MMAT}(0)\right) + K_d V_{MMAT}\right)\omega_2 + GK_{MMAT}}{V_{MMAT}V_E\omega_2(\omega_2 - \omega_1)}$$

Using inverse Laplace Transform
$C_E = r_1 e^{\omega_1 t} + r_2 e^{\omega_2 t} + \frac{G}{K_d}$.
Now multiplying (14) by $\frac{K_{MMAT}}{V_E}$ and (15) by $\left(s + \frac{K_{MMAT}}{V_{MMAT}}\right)$, and adding resultant was

$$\mathcal{L}[C_E]\{(s - \omega_1)(s - \omega_2)\} = \left(\frac{K_{MMAT}}{V_E}\right) C_{MMAT}(0) + \left(s + \frac{K_{MMAT}}{V_{MMAT}}\right)\frac{G}{V_E}\frac{1}{S}$$

$$+ \left(s + \frac{K_{MMAT}}{V_{MMAT}}\right) C_E(0) .$$

$$\mathcal{L}[C_E] = \left(\frac{K_{MMAT}}{V_E}\right) C_{MMAT}(0)\frac{1}{(s-\omega_1)(s-\omega_2)} + \left(s + \frac{K_{MMAT}}{V_{MMAT}}\right)\frac{G}{V_E}\frac{1}{S}\frac{1}{(s-\omega_1)(s-\omega_2)}$$

$$+ \frac{1}{(s-\omega_1)(s-\omega_2)}\left(s + \frac{K_{MMAT}}{V_{MMAT}}\right) C_E(0) .$$

After simplifying the obtained results were

$$\mathcal{L}[C_E] = \frac{G}{K_d} + \left[\frac{(\omega_1)^2 V_E V_{MMAT} C_E(0) + \left(K_{MMAT}V_E\left(C_E(0) + C_{MMAT}(0)\right) + GV_{MMAT}\right)\omega_1 + GK_{MMAT}}{V_{MMAT}V_E\omega_1(\omega_1 - \omega_2)}\right]\frac{1}{(s - \omega_1)}$$
$$+ \left[\frac{(\omega_2)^2 V_E V_{MMAT} C_E(0) + \left(V_E K_{MMAT}\left(C_E(0) + C_{MMAT}(0)\right) + GV_{MMAT}\right)\omega_2 + GK_{MMAT}}{V_{MMAT}V_E\omega_2(\omega_2 - \omega_1)}\right]\frac{1}{(s - \omega_2)}$$

$$\mathcal{L}[C_E] = k_1\frac{1}{(s-\omega_1)} + k_2\frac{1}{(s-\omega_2)} + \frac{G}{K_d}\frac{1}{S}$$

Where

$$k_1 = \frac{(\omega_1)^2 V_E V_{MMAT} C_E(0) + \left(K_{MMAT}V_E\left(C_E(0) + C_{MMAT}(0)\right) + GV_{MMAT}\right)\omega_1 + GK_{MMAT}}{V_{MMAT}V_E\omega_1(\omega_1 - \omega_2)}$$
$$k_2 = \frac{(\omega_2)^2 V_E V_{MMAT} C_E(0) + \left(K_{MMAT}V_E\left(C_E(0) + C_{MMAT}(0)\right) + GV_{MMAT}\right)\omega_2 + GK_{MMAT}}{V_{MMAT}V_E\omega_2(\omega_2 - \omega_1)}$$

Inverse Laplace Transform yield was

$$C_E = k_1 e^{\omega_1 t} + k_2 e^{\omega_2 t} + \frac{G}{K_d} . \qquad (D)$$

Thus the solution of the system must be of the forms given by (C) and (D) for some choice of constants r_1, r_2, k_1, k_2.
The determinant of operational coefficients of the system was

$$\begin{vmatrix} D + \frac{K_d + K_{MMAT}}{V_E} & -\frac{K_{MMAT}}{V_E} \\ -\frac{K_{MMAT}}{V_{MMAT}} & \left(D + \frac{K_{MMAT}}{V_{MMAT}}\right) \end{vmatrix}$$

Putting (C) and (D) in (15) after simplification obtained results were

$$k_1 = \frac{r_1}{2} - \frac{r_1}{2V_E}\left[\frac{K_d V_{MMAT}}{K_{MMAT}} + V_{MMAT} - \frac{1}{K_{MMAT}}\sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]$$

And

$$k_2 = \frac{r_2}{2} - \frac{r_2}{2V_E}\left[\frac{K_d V_{MMAT}}{K_{MMAT}} + V_{MMAsT} + \frac{1}{K_{MMAT}}\sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]$$

Puting value of k_1 and k_2 in (D) solution obtained was

$$C_E = r_1\varphi_1 e^{\omega_1 t} + r_2\varphi_2 e^{\omega_2 t} + \frac{G}{K_d} \qquad (16)$$

Where

$$\omega_1 = -\frac{1}{2\,V_E V_{MMAT}}\left[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} - \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]$$

$$\omega_2 = -\frac{1}{2\,V_E V_{MMAT}}\left[(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT} + \sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]$$

$$\varphi_1 = \frac{1}{2} - \frac{1}{2V_E}\left[\frac{K_d V_{MMAT}}{K_{MMAT}} + V_{MMAT} - \frac{1}{K_{MMAT}}\sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right]$$

$$\varphi_2 = \frac{1}{2} - \frac{1}{2V_E}\left[\frac{K_d V_{MMAT}}{K_{MMAT}} + V_{MMAT} + \frac{1}{K_{MMAT}}\sqrt{\{(V_E + V_{MMAT})K_{MMAT} + K_d V_{MMAT}\}^2 - 4K_d K_{MMAT} V_{MMAT} V_E}\right].$$

Solution by Laplace Transform (inter-dialytic interval)
Consider

$$\frac{dC_E}{dx} = \frac{G}{V_E} - \frac{K_{MMAT}}{V_E} C_E + \frac{K_{MMAT}}{V_E} C_{MMAT} \quad (17)$$

$$C_{MMAT} = \frac{G - V_E\left(C_E - C_{E_O}\right) + V_{MMAT} C_{MMAT_O}}{V_{MMAT}} \quad (18)$$

$$\frac{dC_E}{dx} + K_{MMAT} C_E \left(\frac{1}{V_E} + \frac{1}{V_{MMAT}}\right) = \frac{G}{V_E}\left(1 + \frac{K_{MMAT}}{V_{MMAT}}\right) + K_{MMAT}\left(\frac{C_{E_O}}{V_{MMAT}} + \frac{C_{MMAT_O}}{V_E}\right)$$

$$\mathcal{L}\left[\frac{dC_E}{dx} + K_{MMAT}\, C_E \left(\frac{1}{V_E} + \frac{1}{V_{MMAT}}\right)\right]$$

$$= \mathcal{L}\left[\frac{G}{V_E}\left(1 + \frac{K_{MMAT}}{V_{MMAT}}\right) + \mathrm{K_{MMAT}}\left(\frac{\mathrm{C_{E_O}}}{\mathrm{V_{MMAT}}} + \frac{\mathrm{C_{MMAT_O}}}{\mathrm{V_E}}\right)\right] \mathcal{L}[C_E]\left(s + K_{MMAT}\left(\frac{1}{V_E} + \frac{1}{V_{MMAT}}\right)\right)$$

$$= \left[\frac{G}{V_E}\left(1 + \frac{K_{MMAT}}{V_{MMAT}}\right) + \mathrm{K_{MMAT}}\left(\frac{\mathrm{C_{E_O}}}{\mathrm{V_{MMAT}}} + \frac{\mathrm{C_{MMAT_O}}}{\mathrm{V_E}}\right)\right]\frac{1}{\mathrm{s}}$$

$$\mathcal{L}[C_E] = \left[\frac{G}{V_E}\left(1 + \frac{K_{MMAT}}{V_{MMAT}}\right) + \mathrm{K_{MMAT}}\left(\frac{\mathrm{C_{E_O}}}{\mathrm{V_{MMAT}}} + \frac{\mathrm{C_{MMAT_O}}}{\mathrm{V_E}}\right)\right]\frac{1}{\mathrm{s}}\frac{1}{\left(s + K_{MMAT}\left(\frac{1}{V_E} + \frac{1}{V_{MMAT}}\right)\right)}$$

Simplifying the above equation, resultant obtained were as under

$$\mathcal{L}[C_E] = \left[\frac{G}{V_E}\left(1 + \frac{K_{MMAT}}{V_{MMAT}}\right) + \mathrm{K_{MMAT}}\left(\frac{\mathrm{C_{E_O}}}{\mathrm{V_{MMAT}}} + \frac{\mathrm{C_{MMAT_O}}}{\mathrm{V_E}}\right)\right]\left[\left(\frac{V_E V_{MMAT}}{K_{MMAT}\,(V_E + V_{MMAT})}\right)\left(\frac{1}{S} - \frac{1}{\left(s + K_{MMAT}\left(\frac{1}{V_E} + \frac{1}{V_{MMAT}}\right)\right)}\right)\right]$$

$$C_E = \left[\frac{G}{V_E}\left(1 + \frac{K_{MMAT}}{V_{MMAT}}\right) + \mathrm{K_{MMAT}}\left(\frac{\mathrm{C_{E_O}}}{\mathrm{V_{MMAT}}} + \frac{\mathrm{C_{MMAT_O}}}{\mathrm{V_E}}\right)\right]\left(\left(\frac{V_E V_{MMAT}}{K_{MMAT}\,(V_E + V_{MMAT})}\right)\right) -$$

$$\left[\frac{G}{V_E}\left(1 + \frac{K_{MMAT}}{V_{MMAT}}\right) + \mathrm{K_{MMAT}}\left(\frac{\mathrm{C_{E_O}}}{\mathrm{V_{MMAT}}} + \frac{\mathrm{C_{MMAT_O}}}{\mathrm{V_E}}\right)\right]\left(\left(\frac{V_E V_{MMAT}}{K_{MMAT}\,(V_E + V_{MMAT})}\right)\right) e^{-\left(\frac{1}{V_E} + \frac{1}{V_{MMAT}}\right)K_{MMAT} t}$$

$$C_E = \frac{G(V_{MMAT} + K_{MMAT}) + K_{MMAT}\left(V_E C_{E_O} + V_{MMAT} C_{MMAT_O}\right)}{K_{MMAT}(V_E + V_{MMAT})} + \frac{G(V_{MMAT} + K_{MMAT}) + K_{MMAT}\left(V_E C_{E_O} + V_{MMAT} C_{MMAT_O}\right)}{K_{MMAT}(V_E + V_{MMAT})} e^{-\left(\frac{1}{V_E} + \frac{1}{V_{MMAT}}\right)K_{MMAT} t} \quad (19)$$

Solution of Equations by Eigenvalues (Dialytic interval)
Equation (4 and 5) was written as:

$$\frac{dC_{MMAT}}{dt} = \frac{K_{MMAT}}{V_{MMAT}} C_E - \frac{K_{MMAT}}{V_{MMAT}} C_{MMAT}$$

$$\frac{dC_E}{dx} = \frac{G}{V_E} - \frac{K_{MMAT}}{V_E} C_E + \frac{K_{MMAT}}{V_E} C_{MMAT} - \frac{K_d}{V_E} C_E$$

For steady state $\frac{dC_{MMAT}}{dt} = 0$ & $\frac{dC_E}{dx} = 0$.

$$\frac{K_{MMAT}}{V_{MMAT}} C_E - \frac{K_{MMAT}}{V_{MMAT}} C_{MMAT} = 0$$

$$\frac{G}{V_E} - \frac{K_{MMAT}}{V_E} C_E + \frac{K_{MMAT}}{V_E} C_{MMAT} - \frac{K_d}{V_E} C_E = 0$$

Matrix form

$$\begin{bmatrix} -\left(\frac{K_{MMAT}}{V_E} + \frac{K_d}{V_E}\right) & \frac{K_{MMAT}}{V_E} \\ \frac{K_{MMAT}}{V_{MMAT}} & -\frac{K_{MMAT}}{V_{MMAT}} \end{bmatrix}\begin{bmatrix} C_E \\ C_{MMAT} \end{bmatrix} = \begin{bmatrix} -\frac{G}{V_E} \\ 0 \end{bmatrix}$$

$\det|A - \lambda I| = 0$

$$det\left\{\begin{bmatrix} -(\frac{K_{MMAT}}{V_E}+\frac{K_d}{V_E}) & \frac{K_{MMAT}}{V_E} \\ \frac{K_{MMAT}}{V_{MMAT}} & -\frac{K_{MMAT}}{V_{MMAT}} \end{bmatrix} - \lambda\begin{bmatrix}1 & 0\\ 0 & 1\end{bmatrix}\right\} = 0$$

Solving above equation obtained values of λ were

$$\lambda_1 = -\frac{1}{2\,V_E V_{MMAT}}\Big[(\mathrm{V}_E + V_{\mathrm{MMAT}})\mathrm{K}_{MMAT} + \mathrm{K}_d V_{MMAT} - \sqrt{\{(\mathrm{V}_E + V_{\mathrm{MMAT}})\mathrm{K}_{MMAT} + \mathrm{K}_d V_{MMAT}\}^{2} - 4K_d K_{MMAT} V_{MMAT} V_E}\Big]$$

$$\lambda_2 = -\frac{1}{2\,V_E V_{MMAT}}\Big[(\mathrm{V}_E + V_{\mathrm{MMAT}})\mathrm{K}_{MMAT} + \mathrm{K}_d V_{MMAT} + \sqrt{\{(\mathrm{V}_E + V_{\mathrm{MMAT}})\mathrm{K}_{MMAT} + \mathrm{K}_d V_{MMAT}\}^{2} - 4K_d K_{MMAT} V_{MMAT} V_E}\Big]$$

Eigenvectors corresponding to λ_1 were

$$\begin{bmatrix} -(\frac{K_{MMAT}}{V_E}+\frac{K_d}{V_E}) & \frac{K_{MMAT}}{V_E} \\ \frac{K_{MMAT}}{V_{MMAT}} & -\frac{K_{MMAT}}{V_{MMAT}} \end{bmatrix}\begin{bmatrix}C_E\\ C_{MMAT}\end{bmatrix} = \lambda_1\begin{bmatrix}C_E\\ C_{MMAT}\end{bmatrix}$$

By substituting the value for λ_1 In the above equation and the result obtained were C_{MMAT} in term of C_E :

$$C_{MMAT} = \left\{\frac{1}{2} - \frac{1}{2V_E}\left[\frac{K_d V_{MMAT}}{K_{MMAT}} + V_{MMAT} - \frac{1}{K_{MMAT}}\sqrt{\{(\mathrm{V}_E + V_{\mathrm{MMAT}})\mathrm{K}_{MMAT} + \mathrm{K}_d V_{MMAT}\}^{2} - 4K_d K_{MMAT} V_{MMAT} V_E}\right]\right\} C_E$$

$$\begin{bmatrix}C_E\\ C_{MMAT}\end{bmatrix} = \begin{bmatrix}C_E\\ \varphi_1 C_E\end{bmatrix} = \begin{bmatrix}1\\ \varphi_1\end{bmatrix} C_E$$

$$\varphi_1 = \frac{1}{2} - \frac{1}{2V_E}\left[\frac{K_d V_{MMAT}}{K_{MMAT}} + V_{MMAT} - \frac{1}{K_{MMAT}}\sqrt{\{(\mathrm{V}_E + V_{\mathrm{MMAT}})\mathrm{K}_{MMAT} + \mathrm{K}_d V_{MMAT}\}^{2} - 4K_d K_{MMAT} V_{MMAT} V_E}\right]$$

Eigen vector corresponding to λ_2 *was found as*

$$\begin{bmatrix} -(\frac{K_{MMAT}}{V_E}+\frac{K_d}{V_E}) & \frac{K_{MMAT}}{V_E} \\ \frac{K_{MMAT}}{V_{MMAT}} & -\frac{K_{MMAT}}{V_{MMAT}} \end{bmatrix}\begin{bmatrix}C_E\\ C_{MMAT}\end{bmatrix} = \lambda_2\begin{bmatrix}C_E\\ C_{MMAT}\end{bmatrix}$$

Substituting the value of λ_2 in the above equation and after simplification obtained results for C_E in terms of C_{MMAT} were

$$C_E = \left\{\frac{1}{2} - \frac{1}{2V_E}\left[\frac{K_d V_{MMAT}}{K_{MMAT}} + V_{MMAT} - \frac{1}{K_{MMAT}}\sqrt{\{(\mathrm{V}_E + V_{\mathrm{MMAT}})\mathrm{K}_{MMAT} + \mathrm{K}_d V_{MMAT}\}^{2} - 4\mathrm{K_d} K_{MMAT} V_{MMAT} V_E}\right]\right\} C_{MMAT}$$

$$\begin{bmatrix}C_E\\ C_{MMAT}\end{bmatrix} = \begin{bmatrix}\varphi_2 C_{MMAT}\\ C_{MMAT}\end{bmatrix} = \begin{bmatrix}\varphi_2\\ 1\end{bmatrix} C_{MMAT}$$

$$\varphi_2 = \frac{1}{2} - \frac{1}{2V_E}\left[\frac{K_d V_{MMAT}}{K_{MMAT}} + V_{MMAT} - \frac{1}{K_{MMAT}}\sqrt{\{(\mathrm{V}_E + V_{\mathrm{MMAT}})\mathrm{K}_{MMAT} + \mathrm{K}_d V_{MMAT}\}^{2} - 4\mathrm{K_d} K_{MMAT} V_{MMAT} V_E}\right]$$

The general solution was

$$\begin{bmatrix}C_E\\ C_{MMAT}\end{bmatrix} = r_1 \mathrm{e}^{t\,\lambda_1}\mathbf{v}_1 + r_2 \mathrm{e}^{t\,\lambda_2}\mathbf{v}_2. \qquad (20)$$

Here r_1, r_2 *were constants* λ_1, λ_2 *were eigenvalues and* $\mathbf{v}_1\mathbf{v}_2$ were eigenvectors, substituting the values in the above equation.

$$\begin{bmatrix}C_E\\ C_{MMAT}\end{bmatrix} = r_1\ \mathrm{e}^{t\,\omega_1}\begin{bmatrix}1\\ \varphi_1\end{bmatrix} + r_2$$

Results and Discussion:-

Solutions for dialytic and inter-dialytic interval were evaluated by three different methods and final results were represented by equations 10, 16, 19 and 20 all results were exactly the same as were presented by Cronin Fine in 2007. Comparisons of different solution approaches for mathematical model of hemodialysis were presented in Table-1.

Methods	Dialytic	Inter-dialytic
Laplace Transforms	$C_E = r_1\varphi_1 e^{\omega_1 t} + r_2\varphi_2 e^{\omega_2 t} + \frac{G}{K_d}$	$C_E = \frac{2G + K_d C_{E_0} - K_{MMAT}C_{MMAT_O}}{V_E} + ce^{-\left(\frac{K_{MMAT}}{V_E}+\frac{K_d}{V_E}\right)t}.$
Eigen Value	$C_E = r_1\varphi_1 e^{\omega_1 t} + r_2\varphi_2 e^{\omega_2 t} + \frac{G}{K_d}$	$C_E = \frac{2G + K_d C_{E_0} - K_{MMAT}C_{MMAT_O}}{V_E} + ce^{-\left(\frac{K_{MMAT}}{V_E}+\frac{K_d}{V_E}\right)t}.$
Integrating Factor	$C_E = r_1\varphi_1 e^{\omega_1 t} + r_2\varphi_2 e^{\omega_2 t} + \frac{G}{K_d}$	$C_E = \frac{2G + K_d C_{E_0} - K_{MMAT}C_{MMAT_O}}{V_E} + ce^{-\left(\frac{K_{MMAT}}{V_E}+\frac{K_d}{V_E}\right)t}.$

Table 1:- Comparison of different Solutions Approaches

Conclusion:-
The comparative study of three different solution approaches for modified model of hemodialysis were presented with an aim that in all three cases unique solutions were obtained and were exactly the same results as were published in previous study, that the extracellular solute (toxin concentration) increases more rapidly in case of inter-dialytic interval. This study can be extended further for stability analysis of the model.

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