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Estimation of Intestinal Absorption Rate Using Convolution Integral Technique with Matlab and Simulink

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Abstract

The intestinal absorption of molybdenum in healthy human volunteers was extrapolated from the data on the simultaneous oral and intravenous administration of stable isotopes ^{95}Mo and ^{96}Mo. The extrapolated data were analyzed by the combine use of convolution integral technique and MATLAB software. The new technique, which is a graphical user interface stand alone application known as BT Estimator was developed to perform the simulation of this analysis and for application to other elements of radiological importance. The results showed that molybdenum was rapidly absorbed into circulation. This information is significant in the application of the new ICRP model of human alimentary tract.

Keywords: absorption rate, fractional absorption rate, convolution integral, intravenous, oral.

1.0 Introduction

In the evaluation of the internal dose after ingestion of radioactive materials, the knowledge of the rate at which these materials are absorbed through the human gut wall into the systematic circulation is crucial [1]. In view of the incorporation of several elements of radiological importance in the ingestion pathway, and the similarities often found in their metabolic process in the body system, an application that will automate the process of simulating the numerical values of both the fractional absorption rate F(t) and absorption rate B(t) from oral and injected plasma clearance determined experimentally. This paper therefore present the data analysis from experimental design in the work on the rate of intestinal absorption of molybdenum in humans [2] with the view to simulating appropriate model that could be adjusted in other element of radiological importance.

Data of tracer concentration in blood plasma samples from volunteers for both the intravenous and oral load of different isotopic tracers using proton activation analysis conducted for a period of two (2) months [2] was analyzed using the convolution integral technique for which no prior assumption concerning the kinetic governing the passage, or on the structure of the model are required. Coupled with this analysis is a self developed standalone application in Matlab and Simulink for curve fitting the tracers data obtained, for solving numerically the absorption and fractional absorption rate, and plotting the B(t) function for any particular time (within the duration of experiment) of a graphical user interface.

2.0 Material and Method

Overview

The main objective of this work is to perform analysis on extrapolated data that are obtained from the work of Gussani et al [2]. In the experiment, ***(0.35mg total Mo enriched in ^{95}Mo)*** and ***(0.53mg total Mo enriched in ^{96}Mo)*** where administered intravenously and orally simutanouesly to healthy volunters and thereafter results of the plasma clearance (using Proton Activation Analysis) in both mode of

administration was obtained at intervals for six (6) hours. The extrapolated data obtained from the experiment was plotted (plasma clearance against time) and fitted

using Matlab to obtain analytical expressions that best describe the experimental data points. Thereafter, the two

analytical expressions was convoluted to obtained the B(t) function for Molybdenum in the intestine. Effort was also made to show the variance of this parameter to the concentration administered and the form of administration.

Finally, a stand alone application to request the time after administration from the user via a graphical user interface, and to estimate the rate of absorption for that time was developed using Mathlab. The Matlab program is also designed to generate the plasma clearance for that time and to recreate the exact path trace by the Molybenenum for that time in a graphic window.

Extrapolation of Data

Data needed for the analysis was extrapolated from the work done on the Rate of intestinal absorption of Molybdenum in human [2]. The data from the concentration in blood plasma of oral tracer ^{96}Mo and injected tracer ^{95}Mo for 7 volunteers (3 males, 4 female, ages ranging from 28 to 59) following intravenous injection of 0.35mg molybdenum and oral administration of 0.53mg molybdenum in 100ml of water was scanned and cropped to fit to page. Thereafter, grid lines were manually inserted from the workspace of CorelDraw 12 on the scanned material with precise interval starting from the origin and moving through the x and y-axis as shown in figure 1. With the gridlines all inserted, data for the plasma clearance with time for each forms of administration were read from the printed hardcopy and the values of the concentration of ^{95}Mo in blood plasma at time t_{int} (ng/g), (C_{int}), time after administration for injected tracer (mins), (T_{int}), the concentration of ^{96}Mo in blood plasma at time tint (ng/g), (C_{oral}) and time after administration for oral tracer (mins), (T_{oral}) are presented in table 1.

Curve Fitting the Data

The process of curve fitting involves the determination of mathematical expression that best describe the path traced by a curve. In this case, suitable expressions that can best be fitted to both modes of administrations are the primary objective of curve fitting. The fitting process was done using MATLAB curve fitting tool.

The curve fitting process was done by plotting the raw data from table (1) in excel workbook format. The data for oral tracer and injected tracer were saved as oraldata.xls and injecteddata.xls respectively. Thereafter, the saved files were imported into the Matlab workspace using the import command statement (**import filename.xls)**. The curve fitting toolbox GUI was initialised using the command statement **(cftool).** The raw extrapolated data were plotted and smoothened. The moving average smoothen with span 5 was applied to the oral tracer dataset while the locally weighted scatter plot smooth with span 0.25 was applied to the injected tracer dataset. Thereafter, dataset were fitted using the GUI fitting as shown in figure 2.

Exponentials Curve fitting for the injected tracer

Bi-exponential function was used for the fitting of the injected tracer plasma clearance; the injected smoothed curve is of the form

$$F = ae^{(bx)} + ce^{(dx)} \qquad (2.1)$$

And the resulting equation that best fit the injected tracer curve is given as;

$$F(t) = 7.306e^{(-0.01466t)} + 16.47e^{(-0.0014215t)} \qquad (2.2)$$

Goodness of fit: SSE: 6.295, R-square: 0.9852, Adjusted R-square: 0.9728, RMSE: 1.024

Polynomials Curve fitting for the Oral tracer

Polynomial models are given by

$$G = p1x^n + p2x^{n-1} + p3x^{n-2} \ldots + p(n+1) \qquad (2.3)$$

The result of fitting the oral tracer plasma clearance curve into a polynomial fit yields;

$$G(t) = 2.757x10^{-11}t^5 - 4.093x10^{-8}t^4 + 2.3x10^{-5}t^3 - 0.005971t^2 + 0.6516t - 6.207 \qquad (2.4)$$

Goodness of fit: SSE: 1.0425, R-Square: 0.9967, Adjusted R-square: 0.9955, RMSE: 0.3610

The injected and oral curve fitting using equations (2.2) and (2.4), respectively, are as shown in figure 3.

Applying the Convolution Integral Technique

The convolution integral technique was used for the analysis of the expression that describes the behavior of the tracers in both modes of administrations.

The concentration per unit intake of the oral tracer at time t, expressed as G(t), is linked to the plasma clearance per

unit intake of the injected tracer F(t) by the convolution integral

$$G(t) = B(t) * F(t) = \int_0^t B(\tau).F(t-\tau).\delta\tau \qquad (2.5a)$$

$$G(t) = B(t) * F(t) = \sum B(\tau).F(t-\tau).\Delta t \qquad (2.5b)$$

Where B (τ) = rate of entry of the oral tracer into the blood plasma at time t. And τ is the variable of integration.

The Laplace transform of equation (2.5*a*) gives

$$L\big(G(t)\big) = L[B(t) * F(t)] = L\int_0^t [B(\tau).F(t-\tau).\delta\tau] = L[B(t)].L[F(t)] = B(s).F(s) \qquad (2.6)$$

Thus

$$L[B(t)] = \frac{L[G(t)]}{L[F(t)]} \qquad (2.7)$$

The inverse Laplace transform of equation (2.7) gives the expression for B(t). The analytical expression for G(t) even when available, could be very complicated in the estimation of B(t). Hence, a numerical solution of the equation (2.5b) was preferred for approximate solution of B(t).

To do this, finite time intervals Δt were considered, given by

$$G(k.\Delta t) = \sum_{(i=0)}^{k} \big(B(i.\Delta t).F\big((k-i).\Delta t\big).\Delta t\big) \qquad (2.8)$$

Where k = 0,1,2 ……

Considering the time interval of Δt = 1min, it was very possible to obtain the value of B(0) from equation (2.8) by making k=0 to get

$$G(0) = B(0).F(0) \Rightarrow B(0) = \frac{(G(0))}{(F(0)}$$

For k = 1,

$$G(1) = B(0)F(1) + B(1)F(0) \Rightarrow B(1) = \frac{(G(1) - B(0)f(1))}{F(0)}$$

For k = 2,

$$G(2) = B(0)F(2) + B(1)F(1) + B(2)F(0)$$

$$\Rightarrow B(2) = \frac{(G(2) - B(0)F(2) - B(1)F(1))}{F(0)}$$

By iteration, it was possible to build up the whole vector B (i). i.e. to obtain a numerical expression for B(t).

In general

$$B(t) = \frac{(G(t) - \sum_{i=0}^{(t-1)} B(i)F(t-i))}{F(0)}$$

$$B(t) = \frac{(G(t) - M)}{F(0)}$$

Where $M = \sum_{(i=0)}^{(t-1)} B(i)\,F(t-i)$ (2.9)

Equation (2.9) is estimated recursively (i.e. iterated) and the value of M is inserted into equation (2.8) to obtain the value B (t) at t = time within the duration of the experiment.

This iteration process forms a valuable algorithm for code development.

In general, for any value of B (i), the procedure above is iterated continually. Hence the needs for a computer program to perform the operation of iteration. This is one of the major functions of the present software.

Estimation of Fractional Absorption Rate F (t)

If B(t) is the function describing the rate of intestinal absorption of the tracer, the fraction absorbed up to time t (duration of the investigation) known as the fractional absorption rate is given by

$$f_T = \int_0^T B(t)dt \qquad (2.10)$$

or alternatively by $f_T = \sum_{(i=0)}^{n} B(i.\Delta t).\Delta t$ Where n = T/Δt

Consider T = 10 minutes, (note that Δt = 1min), n = 10/1 = 10

$$f_T = \sum_{1}^{10} B(i) = B(1) + B(2) + B(3) + \ldots\ldots + B(10) \qquad (2.11)$$

Equation (2.11) shows that fractional absorption rate is the summation of individual rate of absorption over the whole duration of experiment.

Software Design and Deployment

Overview of BT_ Estimator

The application is design in a graphical user interface (GUI) and is a stand-alone application where all operation is carried-out on the GUI as shown in figure 4. The user loads the excel files where the data for the radionuclide is saved. The file to be loaded can be browse to via the current directory list box on the BT Estimator GUI. Thereafter, the Estimator is used to perform the following tasks;

- **Plot the imported data**: Perform the plotting operation by clicking the plot data pushbutton. The plot is displayed on the curve visualiser axes.
- **Curve Fit Data** : The process of smoothing, plotting the smoothen curve, and fitting the curves to best fit mathematical expressions is done using the Curve Fit pushbutton.
- **Estimate rate of intestinal absorption B (t) function**: This process is executed using Estimate Bt pushbutton. The user inputs the time (within the duration of the experiment) into the time-text edit box labeled 'input time', then click the Estimate Bt pushbutton and observed the result from the 'output result' just below the pushbutton.
- **Estimate fractional absorption rate F (t) value**: This process is similar to the process carried out for the B (t) estimation. Only that in this case, the Estimate Ft pushbutton is clicked.
- **Plot B_t Function**: The plot Bt Function pushbutton is used to plot the Bt values from time zero to time t entered by the user. The resulting graph is displayed on the curve visualiser axes.
- **Reset the GUI**: The reset pushbutton when clicked re-initialized the BT Estimator GUI in other to make it ready for use for next operation.
- **Use some Menu bar components**: The menu bar was embedded to include just file menu and some necessary components such as print, close, save and open. As there names imply, the open is used to open any file right from the BT Estimator interface.
- **Update Variable**: the update variable pushbutton function both for initializing the whole BT Estimator GUI including the pushbuttons for all other operations and to update the select variable list box with the variables that has being imported.

3.0 Result and Discussion

Table 2 shows the F(t) values obtained for volunteer #7 after administration of 0.53mg ^{96}Mo dissolved in 100ml of water via simulation using the software, Figure 5 shows the absorption rate, B(t) function and figure 6 shows the fractional absorption rate F(t).

The fractional absorption rate into the systemic circulation was rapid having its peaks at 155 minutes with a value of 1.3090. The greater part of the absorption took place in the first 120mins with F (t) values rising shapely from 0.0168 at 12mins to 1.3090 at 160mins. With such a rapid process, the timing of sample withdrawal may indeed play a significant role in the characterization of the both F (t) and B (t) function, in particular during the rising phase.

As observed in fig (5), the rate of absorption B (t) function shows rapid absorption for the first 20 minutes with a gradually decline. However, most of the absorption also took place in the first 120 minutes. Hence, a precise detailed definition of the initial part of the B (t) curve would therefore require frequent measurements at very short times after injection, but this is limited by ethical considerations related to conduct of volunteer studies and practical consideration.

Also in figure 6, the F (t) estimate was distributed around the central value of 1.09 with a standard deviation of 0.33. This estimate can be consider a good approximation of the F (t) value as T (duration of experiment) tends to infinity.

As a way of comparison, [3] found that intestinal absorption of Mo supplied as aqueous solution is almost complete (>90%, for Mo < 5mg), plasma clearance is fast, with mean sojourn time in the transfer compartment put at about 100 minutes. Similar findings by [2] also affirm that molybdenum is rapidly absorbed significantly at the first 80
minutes, with F(t) values centrally distributed around 0.98 with 0.11 deviations. More so, in the work of [4] molybdenum was most efficiently absorbed with value of about 88-93%. [5] showed that molybdenum in blood was put at 1.2892.

Table 1: Extrapolated data for the injected and oral tracer plasma clearance

Cint	**Tint**	**Coral**	**Toral**
22.5	15	1	10
16.5	23	3.4	20
15.5	32	4.5	29
15.2	48	14	46
14.3	61	18	60
14.2	78	23.8	78
12	90	20.5	92
10.5	120	17.2	121
7.8	185	14.1	184
7.8	245	10	245
5.2	364	6	362
2.6	480	4.5	480
TABLE 1			

Table 2: The simulated fractional absorption values estimated by BT Estimator.

T	F (t)	T	F (t)	T	F (t)	T	F (t)	T	F (t)	T
0	-0.2611	50	0.7222	100	1.1945	150	1.3086	200	1.2785	250
1	-0.2373	51	0.7365	101	1.1995	151	1.3088	201	1.2776	251
2	-0.2136	52	0.7507	102	1.2044	152	1.3089	202	1.2766	252
3	-0.1899	53	0.7646	103	1.2091	153	1.3090	203	1.2756	253
4	-0.1665	54	0.7783	104	1.2137	154	1.3091	204	1.2746	254
5	-0.1431	55	0.7918	105	1.2182	155	1.3090	205	1.2737	255
6	-0.1198	56	0.8050	106	1.2225	156	1.3090	206	1.2727	256
7	-0.0967	57	0.8181	107	1.2267	157	1.3089	207	1.2717	257
8	-0.0737	58	0.8309	108	1.2308	158	1.3088	208	1.2708	258
9	-0.0509	59	0.8435	109	1.2347	159	1.3086	209	1.2698	259
10	-0.0282	60	0.8559	110	1.2385	160	1.3083	210	1.2689	260
11	-0.0056	61	0.8681	111	1.2422	161	1.3081	211	1.2679	261
12	0.0168	62	0.8801	112	1.2458	162	1.3078	212	1.2670	262
13	0.0390	63	0.8919	113	1.2492	163	1.3074	213	1.2661	263

14	0.0611	64	0.9034	114	1.2525	164	1.3070	214	1.2651	264
15	0.0830	65	0.9148	115	1.2557	165	1.3066	215	1.2642	265
16	0.1047	66	0.9260	116	1.2588	166	1.3062	216	1.2633	266
17	0.1263	67	0.9369	117	1.2618	167	1.3057	217	1.2624	267
18	0.1476	68	0.9477	118	1.2647	168	1.3052	218	1.2615	268
19	0.1688	69	0.9582	119	1.2674	169	1.3046	219	1.2606	269
20	0.1898	70	0.9686	120	1.2701	170	1.3041	220	1.2598	270
21	0.2106	71	0.9787	121	1.2726	171	1.3035	221	1.2589	271
22	0.2312	72	0.9887	122	1.2750	172	1.3028	222	1.2580	272
23	0.2516	73	0.9984	123	1.2774	173	1.3022	223	1.2572	273
24	0.2718	74	1.0080	124	1.2796	174	1.3015	224	1.2564	274
25	0.2918	75	1.0174	125	1.2818	175	1.3008	225	1.2556	275
26	0.3116	76	1.0265	126	1.2838	176	1.3001	226	1.2548	276
27	0.3312	77	1.0355	127	1.2858	177	1.2993	227	1.2540	277
28	0.3506	78	1.0444	128	1.2876	178	1.2986	228	1.2532	278
29	0.3698	79	1.0530	129	1.2894	179	1.2978	229	1.2524	279
30	0.3887	80	1.0614	130	1.2911	180	1.2970	230	1.2516	280
31	0.4075	81	1.0697	131	1.2927	181	1.2961	231	1.2509	281
32	0.4260	82	1.0777	132	1.2942	182	1.2953	232	1.2502	282
33	0.4443	83	1.0856	133	1.2956	183	1.2945	233	1.2495	283
34	0.4625	84	1.0934	134	1.2969	184	1.2936	234	1.2488	284
35	0.4803	85	1.1009	135	1.2982	185	1.2927	235	1.2481	285
36	0.4980	86	1.1083	136	1.2994	186	1.2918	236	1.2474	286
37	0.5155	87	1.1155	137	1.3005	187	1.2909	237	1.2467	287
38	0.5327	88	1.1225	138	1.3015	188	1.2900	238	1.2461	288
39	0.5497	89	1.1294	139	1.3025	189	1.2891	239	1.2455	289
40	0.5665	90	1.1361	140	1.3033	190	1.2882	240	1.2448	290
41	0.5831	91	1.1427	141	1.3041	191	1.2872	241	1.2442	291
42	0.5994	92	1.1490	142	1.3049	192	1.2863	242	1.2436	292
43	0.6155	93	1.1553	143	1.3056	193	1.2853	243	1.2431	293
44	0.6314	94	1.1613	144	1.3062	194	1.2844	244	1.2425	294
45	0.6471	95	1.1672	145	1.3067	195	1.2834	245	1.2420	295
46	0.6626	96	1.1730	146	1.3072	196	1.2824	246	1.2414	296
47	0.6778	97	1.1786	147	1.3076	197	1.2815	247	1.2409	297
48	0.6928	98	1.1840	148	1.3080	198	1.2805	248	1.2404	298
49	0.7076	99	1.1893	149	1.3083	199	1.2795	249	1.2400	299

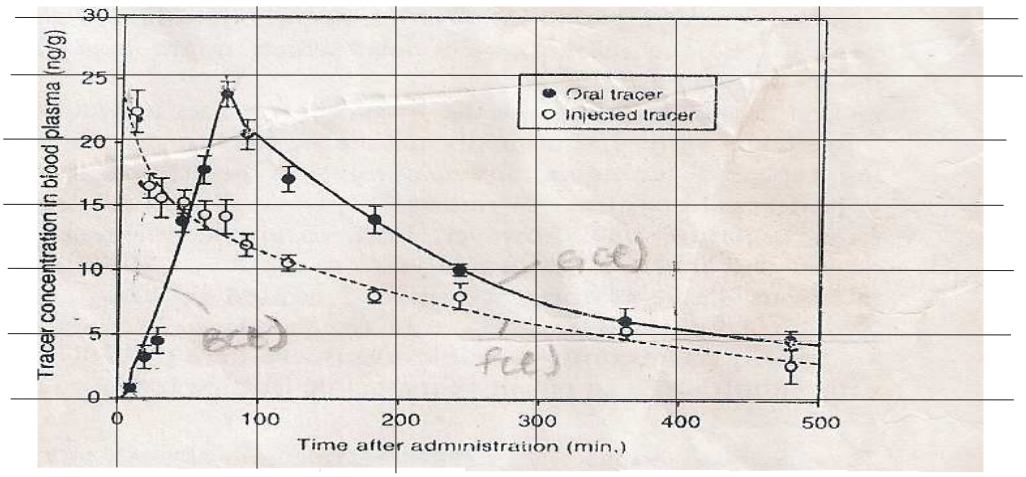

Fig 1: The Scanned document with gridlines inserted [2]

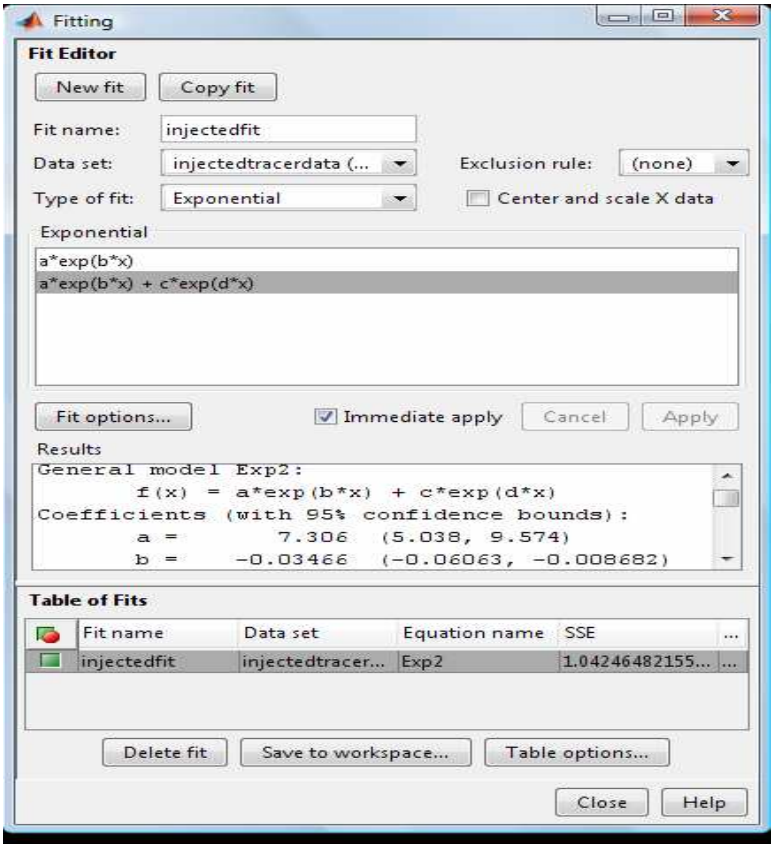

Fig 2: Fitting GUI for the Injected Tracer Fitting

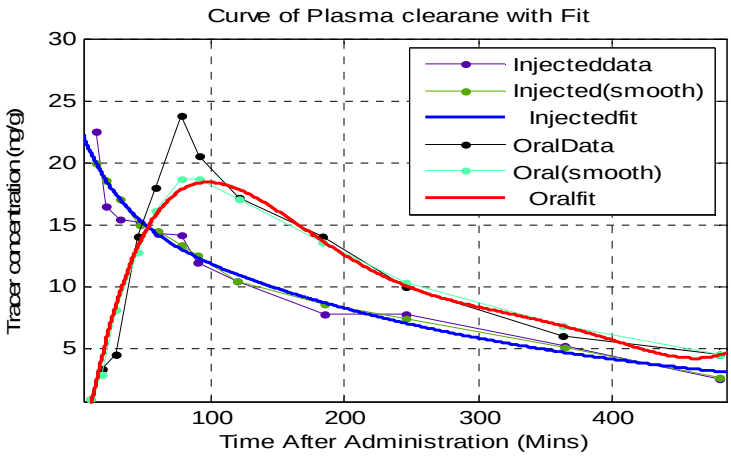

Fig 3: Fitted Graph of both Tracers

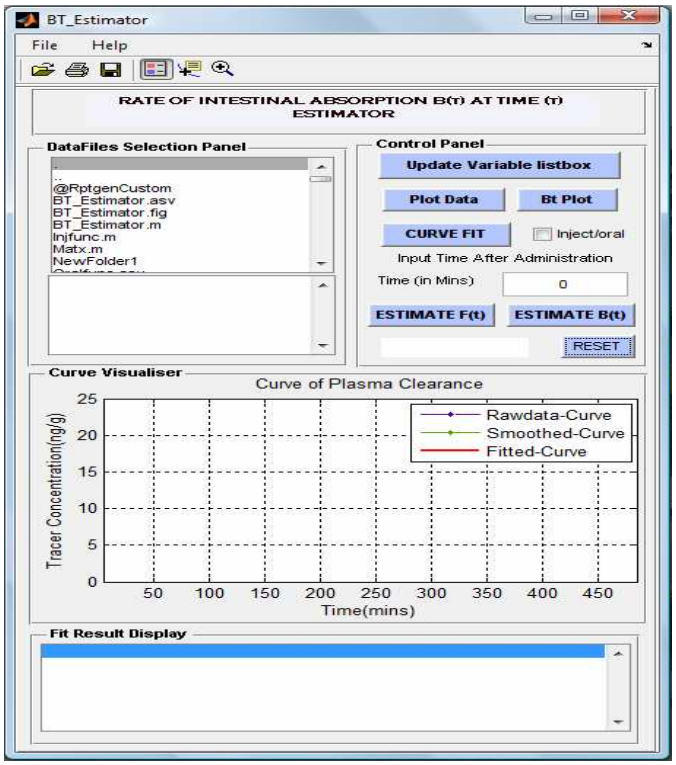

Fig 4: BT Estimator graphical user interface (GUI)

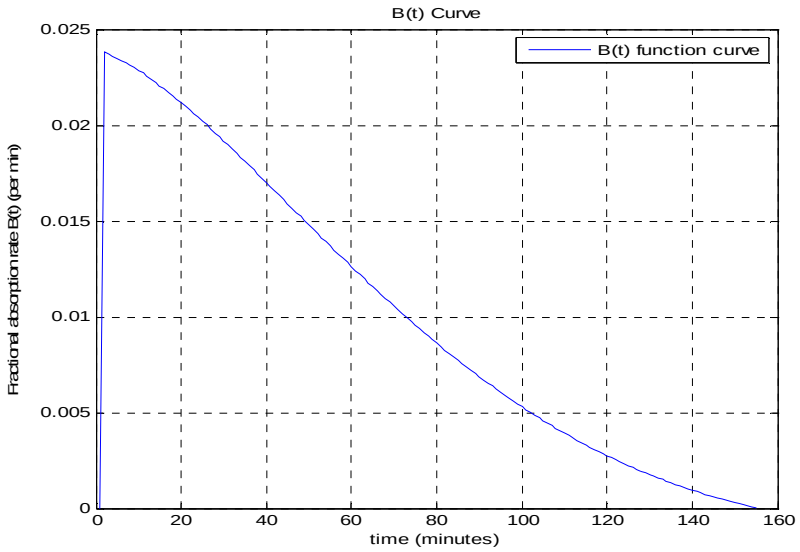

Fig 5**:** *B(t) Function curve obtained via simulation*

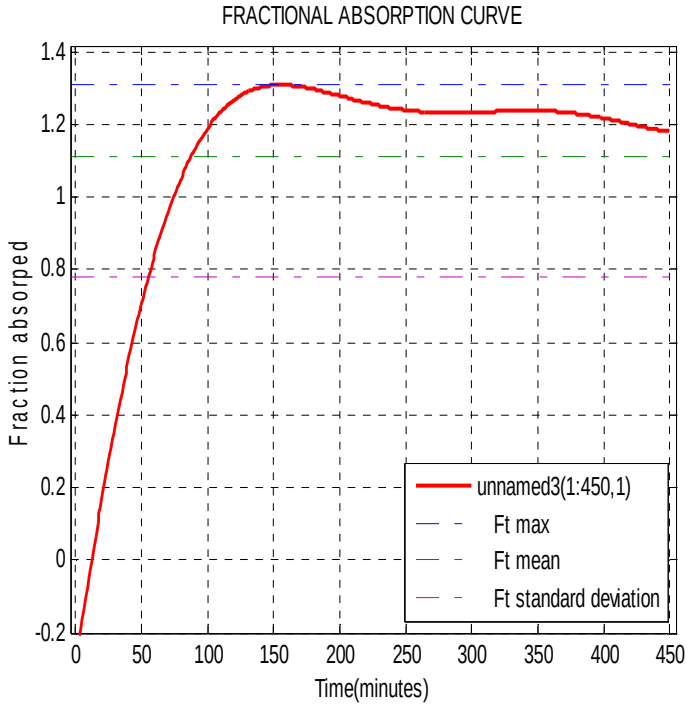

FIG 6**:** *Fractional absorption curve obtained via simulation*

4.0 Conclusion

In this work, visual and graphical system interface software was developed to automate the process of estimating B (t) function and F (t) values. The BT Estimator application enables estimation of B (t) function and F (t) values of other elements of radiological importance. It can also be use to observe the variation or effect of form of administration and concentration of administration on the B (t) function by

observing the B (t) - plot for investigations conducted for different form and concentration of tracers. The stand alone software developed was tested with the experimental data on the passage of molybdenum isotopes through the gut walls using stable isotopic tracers and the result from the analysis shows that molybdenum is rapidly and efficiently absorbed into the systemic circulation. The fractional absorption rate put approximately at 1.09 compared well with the reference value [2]. The method employed in the estimation of B (t) function and F (t) value is a conceptualized integrated approach using convolution integral technique with Matlab and Simulink software. The new approach is capable of theoretical estimation of B (t) function and F (t) value of other stable tracers once the oral and injected models are known.

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