Model of α-linolenic acid metabolism

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OVERVIEW

the UNIVERSITY of GREENWICH

Introduction
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Introduction

- *A mathematical model of α-linolenic acid metabolism is derived from the experimental data of plasma concentration [1] at different times for 18:3n-3, 20:5n-3 , 22:5n-3 and 22:6n-3 in 95 healthy volunteers who have been ingested with 1g of isotope tracer of α-linolenic acid.*
- *Mathematical methods based on inverse problems for the identification of unknown kinetics parameters in the system of ODEs using time series measurements.*
- *The goal of this model is to obtained kinetics parameters which can be used to quantify the biosynthesis of long chain n-3 PUFA beginning with α-linolenic acid.*

Compartmental model of α-linolenic acid metabolism

- *A physiological compartmental model of α-linolenic acid metabolism is employed with well-known consideration of metabolic pathway for α-linolenic.*

Assumptions

- *The liver is the main site for the biosynthesis of fatty acid.*
- *As a liver biopsy was not possible in these subjects therefore in this study rate constants determined from the model represents kinetics of fatty acid from their plasma pool concentrations.*
- *The model presumes that each rate constant reflects several steps of the metabolism that occur within the liver [1]*
- *It is assumed that this kinetic function is similar to the appearance of all the fatty acids measured in the plasma.*

Compartmental model for the metabolism of α-linolenic acid

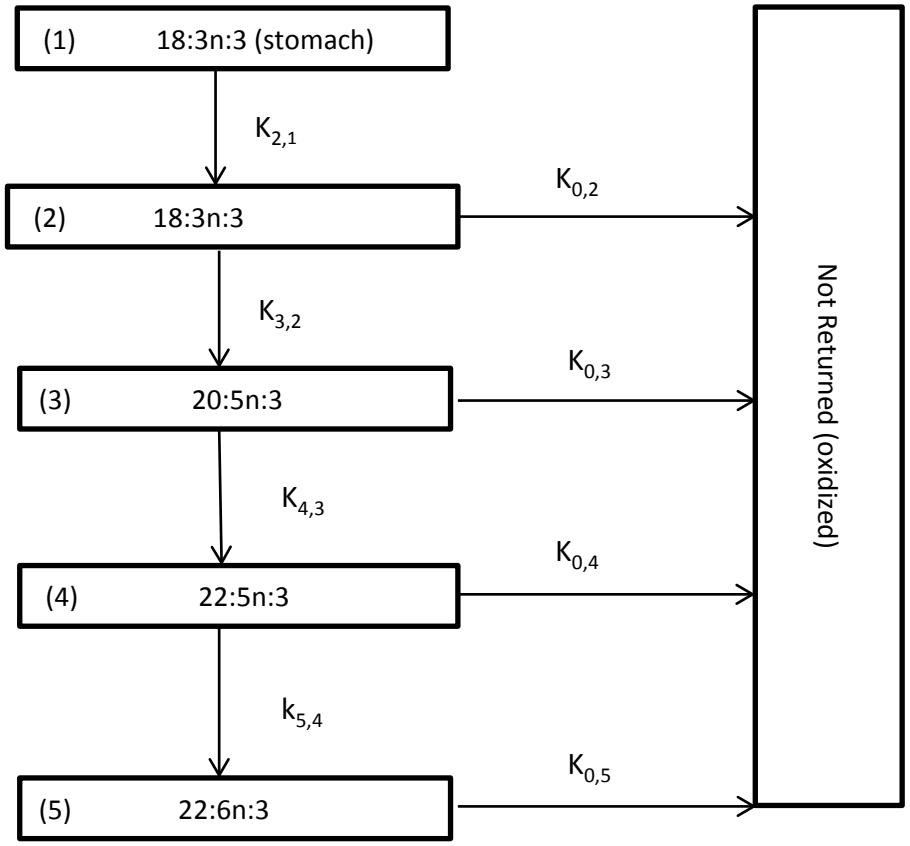


Fig 1: Compartmental model for the metabolism of α-linolenic acid.

- *The structure of the model consists of five compartments.*
- *The rectangle represents each metabolite of the fatty acid in the metabolism process.*
- *Compartment 1 represents administration of the isotope (1g) via the gastro-intestinal tract.*
- *Compartments 2 to 5 represent n-3 fatty acid in the plasma following on successive steps in desaturation and elongation of the label fatty acid.*
- *The fractional transfer rate K_{ij} is the fraction of the substrate that is transferred from substrate compartment j to product compartment i.*
- *The arrows indicating K_{0j} is the fraction of the substrate that is irreversibly lost by each compartment j.*

The system of differential equations

$$\frac{dc_5}{dt} = k_{5,4}c_4 - k_{0,5}c_5 \quad (1)$$

$$\frac{dc_4}{dt} = k_{4,3}c_3 - k_{0,4}c_4 - k_{5,4}c_4 \quad (2)$$

$$\frac{dc_3}{dt} = k_{3,2}c_2 - k_{0,3}c_3 - k_{4,3}c_3 \quad (3)$$

$$\frac{dc_2}{dt} = k_{2,1}c_1 - k_{0,2}c_2 - k_{3,2}c_2 \quad (4)$$

$$\frac{dc_1}{dt} = -k_{21}c_1 \quad (5)$$

The parameters $k_{5,4}$, $k_{4,3}$, $k_{3,2}$, $k_{2,1}$, $k_{0,5}$, $k_{0,4}$, $k_{0,3}$ and $k_{0,2}$ of the differential equations are to be estimated by means of linear least squares method using measured data.

Concentration assumption in the stomach

Assuming the concentration of 18:3n-6 in stomach follows a decreasing quadratic function wrt time:

$$at^2 + bt + c$$

Here the parameters a and b can be included in the inverse problem formulation and c is known from the initial condition of the concentration in the stomach.

Results & experimental data

Estimated parameters

Kinetics Parameters	*Estimated values*
k21	0.000425
k02	0.1449
k32	0.00030
k03	0.0015
k04	0.0476
k43	0.01317
k05	0.0124
k54	0.0101

Time series experimental data

Time	c2	c3	c4	c5
0	0.0026	0.0000	0.0001	0
8	0.6690	0.0067	0.0008	0.0001
24	0.0952	0.0082	0.0026	0.0003
48	0.0524	0.0073	0.0019	0.0010
72	0.0034	0.0054	0.0005	0.0007
96	0.0212	0.0014	0.0004	0.0007
168	0.0036	0.0007	0.0003	0.0019

Subject 18 was used in the above experiment to determine the respective values of the kinetics parameters. The parameters obtained are close to those obtained in the reference paper [1] in which their results were calculated by means of the software WIMSAM.

Fatty acids composition of serum cholesteryl esters (%) from healthy subjects supplemented with hempseed and flaxseed oils for 4 weeks: Data obtained from School of Science

Fatty acids	Hempseed oil		Flaxseed oil	
	0 week	4 week	0 week	4 week
n-6				
18:2n-6- LA	50.90	56.65	49.89	52.90
18:3n-6- GLA	0.57	1.19	0.65	0.43
20:3n-6 -DGLA	0.53	0.75	0.53	0.42
20:4n-6-AA	4.01	4.10	4.38	3.52
n-3				
18:3n-3-ALA	0.98	1.30	0.96	4.13
20:5n-3-EPA	1.22	1.10	1.46	1.72
22:6n-3-DHA	0.37	0.33	0.44	0.34

Fatty acids composition of serum triglycerides (%) from healthy subjects supplemented with hempseed and flaxseed oils for 4 weeks: Data obtained from School of Science

Fatty acids	Hempseed oil		Flaxseed oil	
	0 week	4 week	0 week	4 week
n-6				
18:2n-6	17.99	25.54	17.03	19.46
18:3n-6	0.43	1.01	0.47	0.36
20:3n-6	0.38	0.55	0.34	0.38
20:4n-6	2.20	2.33	2.12	1.85
n-3				
18:3n-3	2.05	3.76	1.71	9.66
20:5n-3	2.64	1.59	1.45	2.00
22:6n-3	1.97	1.41	1.68	1.45

We need at least three columns of data for Hempseed oil and three columns of data for Flaxseed oil – not enough data at different time points in calculating the derivatives.

The number of unknowns in one equation is more than the number of available data

Need to use adjoint method [5] or regularisation (current work).

Time-course of fatty acids concentration (μg/ml) of plasma triacylglycerol and cholesterol ester from healthy subjects

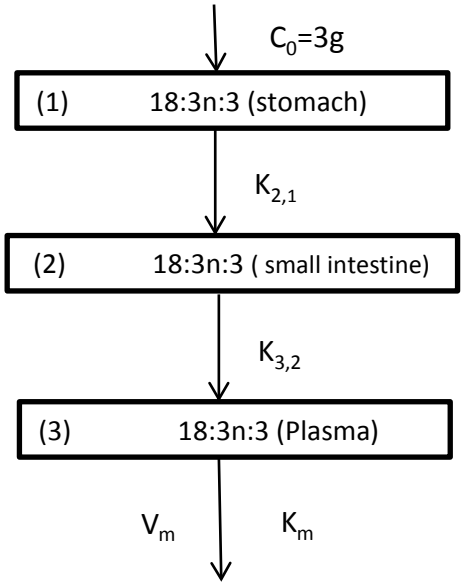
Time (h)	Triacylglycerol		Cholesterol ester	
	LA	LNA	LA	LNA
0	0	0	0	0
2	25.83	25.00	0.83	0.83
4	37.50	36.67	1.67	1.25
6	13.33	13.33	3.75	1.67
8	18.33	18.33	8.33	2.50
10	15.00	13.33	10.00	2.50
12	12.50	8.33	12.50	3.33
14	10.00	6.67	15.00	3.33
16	8.33	5.00	17.50	2.92
24	3.33	0	21.25	2.50
48	0.17	0	22.08	1.67

The model that we are considering is a very simple metabolism model of 18:3n-3 (LNA) to 20:5n-3 (EPA) and finally to 22:6n-3 (DHA). The equations are inter-related.

The data provided above, say the second column, reflecting the LNA concentration at various times for 3 g of deuterium-labelled LNA intake. A graph can be easily drawn for this LNA concentration.

However it is possible to use the data in an absorption model [3,4]. (current work)

Absorption & Elimination model



Elimination Process (Michaelis Menten Equation)

Where V_m and K_m M.M coefficient

- *The structure of the open model consists of Three compartments.*
- *The rectangle represents 18:3n:3 in the absorption scheme*

The system differential equations are:

$$\frac{dc_1}{dt} = -k_{21}c_1$$

$$\frac{dc_2}{dt} = k_{21}c_1 - k_{32}c_2$$

$$\frac{dc_3}{dt} = k_{32}c_2 - \frac{V_m c_3}{K_m + c_3}$$

References

[1] Pawlosky, R. J., et al. Physiological compartmental analysis of alpha-linolenic acid metabolism in adult humans. J. Lipid Res. 42(8):1257-1265, 2001.

[2] G. Golub Numerical Methods for solving Linear Least Squares Problems.

[3] J. E. PIETERS, M. WEDEL and G. SCHAAFSMA Parameter estimation in a three-compartment model for blood alcohol curves

[4] Bus, J. C. P., Domselaar, B. V. and Kok, J. (1975) Nonlinear least squares estimation. Report NW 17/75, Mathematical Centre, Amsterdam.

[5] S.Muller,J.Lu,P.Kugler,H.W.Engl Parameter Identification in Systems Biology: Solving Ill-posed Inverse Problems using Regularization.