Supplementary Material – Model Details

for

A mathematical model gives insights into nutritional and genetic aspects of folate-mediated one-carbon metabolism

Michael C. Reed,[1*], H. Frederik Nijhout,[2], Marian Neuhouser[3],Jesse Gregory[4], Barry Shane[5], S. Jill James[6], Alanna Boynton[3,7], Cornelia M. Ulrich[7]

[1] Department of Mathematics, Duke University, Durham, NC 27708
[2] Department of Biology, Duke University, Durham, NC 27708
[3] Fred Hutchinson Cancer Research Center, Seattle, WA 98109-1024.
[4] Food Science & Human Nutrition Department, University of Florida, Gainsville, FL 32611
[5] Department of Nutritional Sciences & Toxicology, University of California, Berkeley, CA 94720
[6] Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR 72202
[7] Department of Epidemiology and the Interdiscisplinary Graduate Program in Nutritional Sciences, University of Washington, WA 98195

The model consists of 10 differential equations that express the rate of change of each of the substrates in the rectangular boxes in Figure 1.

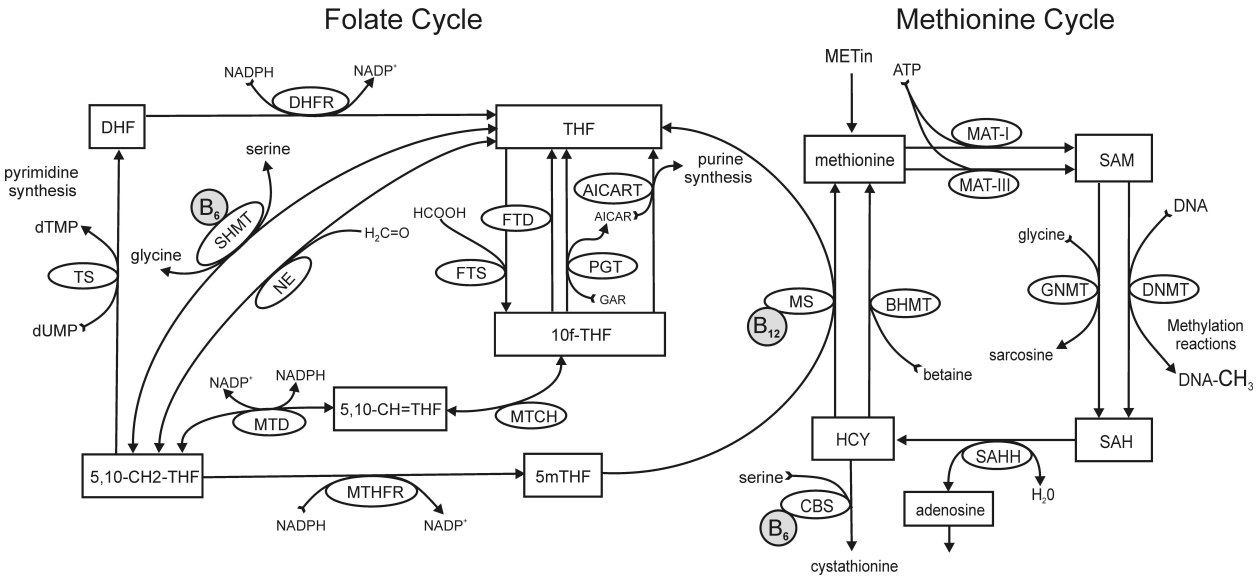

Figure 1: **Folate and Methionine Metabolism.** The enzymes are: AICART, aminoimidazolecarboxamide ribonucleotide transferase; BHMT, betaine-homocysteine methyltransferase; CBS, cystathionine β-synthase; DHFR, dihydrofolate reductase; DNMT, DNA-methyltransferase; FTD, 10-formyltetrahydrofolate dehydrogenase; FTS, 10-formyltetrahydrofolate synthase; GNMT, glycine N-methyltransferase; MAT, methionine adenosyl transferase; MS, methionine synthase; MTD, 5,10-methylenetetrahydrofolate dehydrogenase; MTCH, 5,10-methenyltetrahydrofolate cyclohydrolase; MTHFR, 5,10-methylenetetrahydrofolate reductase; PGT, Phosphoribosyl glycinamidetransformalase; SAHH, S-adenosylhomocysteine hydrolase; SHMT, serinehydroxymethyltransferase; TS: thymidylate synthase.

The mathematical model merges two previously published models on the folate cycle [24] and the methionine cycle [23]. These cycles are connected not only by the MS reactions but also by the inhibition of MTHFR bt SAM and GNMT by 5mTHF. In [23], $[5mTHF]$ was calculted indirectly since the folate cycle was not present. Now it is calculated explicitly by solving the differential equations for the folate cycle. Because of these differences, it is not surprising that the balance of some substrates in the initial combined model differed somewhat from those reported in the literature and generated by the previous independent cycle models. We therefore modified somewhat a few parameters (within published ranges) to obtain appropriate concentrations. These changes were: the V_{max} of MTHFR was reduced from 6000 to 5000 μM/hr; the V_{max} of the CBS reaction was reduced from 100,000 to 90,000 μM/hr; the V_{max} of the GNMT reaction was increased from 160 to 288 μM/hr; the inhibition constants for SAH on GNMT and DNMT were lowered from 18 to 10.8 μM and from 1.4 to 0.84 μM, respectively; the V_{max} values of the TS and DHFR reactions were increased 100

fold (from 50 to 5000 μM/hr) to simulate the conditions of rapid growth. In the *in silico* experiments described in the text, the model parameters and equations were those given below, except for the parameter whose effect was being tested in a particular experiment.

For simplicity of notation, we will use the following abbreviations:

$$
\begin{aligned}
5mTHF &= \text{5-methyltetrahydrofolate} \\
THF &= \text{tetrahydrofolate} \\
DHF &= \text{dihydrofolate} \\
CH2F &= \text{5-10-methylenetetrahydrofolate} \\
CHF &= \text{5-10-methenyltetrahydrofolate} \\
10fTHF &= \text{10-formyltetrahydrofolate} \\
MET &= \text{methionine} \\
SAM &= \text{S-adenosylmethionine} \\
SAH &= \text{S-adenosylhomocysteine} \\
HCY &= \text{homocysteine} \\
metin &= \text{the rate of input of methionine to the system in } \mu\text{M/hr}
\end{aligned}
$$

The following other substrates are assumed to have constant concentrations (μM):

$[GAR] = 10$	glycinamide ribonucleotide
$[AICAR] = 2.1$	aminoimidazolecarboxamide ribonucleotide
$[NADPH] = 50$	nicotinamide adenine dinucleotide phosphate
$[GLY] = 1850$	glycine
$[SER] = 468$	serine
$[BET] = 50$	betaine
$[HCOOH] = 500$	formate
$[H_2C = O] = 500$	formaldehyde
$[DUMP] = 20$	deoxyuridine monophophate

For each of the biochemical reactions indicated by a reaction arrow in Figure 1, we denote the velocity of the reaction (in μM/hr) by a capital V whose subscript is the acronym for the enzyme that catalyzes the reaction. Thus, for example, the velocity of the methione synthase reaction is denoted by V_{MS}. Each of these velocities depends on the current values of one or more of the metabolite concentrations and possibly also on one or more of the other inputs that are assumed constant. The 10 differential equations express the time rate of change (in μM/hr) of each of the 10 substrates in terms of the velocities. One can see explicitly what each of the velocities depends on.

$$
\begin{aligned}
\frac{d[5mTHF]}{dt} &= V_{MTHFR}([CH2F],[NADPH],[SAM],[SAH]) - V_{MS}([5mTHF],[HCY]) \\
\frac{d[THF]}{dt} &= V_{FTD}([10fTHF]) + V_{MS}([5mTHF],[HCY]) + V_{PGT}([10fTHF],[GARP]) \\
&\quad + V_{ART}([10fTHF],[AICARP]) - V_{FTS}([THF],[HCOOH],[10fTHF]) \\
&\quad - V_{SHMT}([SER],[THF],[GLY],[CH2F]) - V_{NE}([THF],[H_2C=O],[CH2F]) \\
&\quad + V_{DHFR}([DHF],[NADPH]) \\
\frac{d[DHF]}{dt} &= V_{TS}([DUMP],[CH2F]) - V_{DHFR}([DHFR],[NADPH]) \\
\frac{d[CH2F]}{dt} &= V_{SHMT}([SER],[THF],[GLY],[CH2F]) + V_{NE}([THF],[H_2C=O],[CH2F]) \\
&\quad - V_{TS}([DUMP],[CH2F]) - V_{MTHFR}([CH2F],[NADPH],[SAM],[SAH]) \\
&\quad - V_{MHD}([CH2F],[CHF]) \\
\frac{d[CHF]}{dt} &= V_{MHD}([CH2F],[CHF]) - V_{MCH}([CHF],[10fTHF]) \\
\frac{d[10fTHF]}{dt} &= V_{MCH}([CH2],[10fTHF]) + V_{FTS}([THF],[HCOOH],[10fTHF]) \\
&\quad - V_{PGT}([10fTHF],[GARP]) - V_{ART}([10fTHF],[AICARP]) - V_{FTD}([10fTHF]) \\
\frac{d[MET]}{dt} &= V_{BHMT}([HCY],[BET],[SAM],[SAH]) + V_{MS}([5mTHF],[HCY]) + metin(t) \\
&\quad - V_{MATI}([MET],[SAM]) - V_{MATIII}([MET],[SAM]) \\
\frac{d[SAM]}{dt} &= V_{MATI}([MET],[SAM]) + V_{MATIII}([MET],[SAM]) \\
&\quad - V_{GNMT}([SAM],[SAH],[5mTHF]) - V_{DNMT}([SAM],[SAH]) \\
\frac{d[SAH]}{dt} &= V_{GNMT}([SAM],[SAH],[5mTHF]) + V_{DNMT}([SAM],[SAH]) \\
&\quad - V_{SAAH}([SAH],[HCY]) \\
\frac{d[HCY]}{dt} &= V_{SAAH}([SAH],[HCY]) - V_{CBS}([HCY],[SAM],[SAH]) \\
&\quad - V_{BHMT}([HCY],[BET],[SAM],[SAH]) - V_{MS}([5mTHF],[HCY]);
\end{aligned}
$$

For many of the velocities, we assume that their dependence on substrates has Michaelis-Menten form. V_{FTD} is uni-directional with one substrate and has the form:

$$V = \frac{V_{max}[S]}{K_m + [S]}.$$

V_{SAAH}, V_{MCH}, and V_{MHD} are reversible Michaelis-Menten with one substrate in each term. $V_{ART}, V_{TS}, V_{DHFR}, V_{PGT}$, and V_{MS} are modeled by random order Michaelis-Menten with two substrates:

$$V = \frac{V_{max}[S_1][S_2]}{(K_{m,1} + [S_1])(K_{m,2} + [S_2])}.$$

V_{SHMT} is assumed to be reversible random order Michaelis-Menten kinetics kinetics with two substrates in each term. For all these velocities the form is clear and the K_m and V_{max} values appear in Table 3, below, along with references.

We now discuss remaining velocities individually.

BHMT. The kinetics of $BHMT$ are Michaelis-Menten with the parameters $K_{m,1} = 12$, $K_{m,2} = 100$, and $V_{max} = 1125$ [8],[32]. The form of the inhibition of $BHMT$ by SAM was derived by non-linear regression on the data of [9] and scaled so that it equals 1 when the methionine input rate is 100 μM/hr.

$$V_{BHMT} = e^{-.0021([SAM]+[SAH])} e^{+.0021(77.2)} \frac{V_{max}[HCY][BET]}{(K_{m,1} + [HCY])(K_{m,2} + [BET])}$$

CBS. The kinetics of CBS are standard Michaelis-Menten with $K_m = 1000$ taken from [11] and $V_{max} = 90,000$. The form of the activation of CBS by SAM was derived by non-linear regression on the data in [16] and [19] and scaled so that it equals 1 when the methionine input rate is 100 μM/hr.

$$V_{CBS} = \left(\frac{V_{max}[HCY]}{K_m + [HCY]}\right)\left(\frac{(1.2)([SAM] + [SAH])^2}{(30)^2 + ([SAM] + [SAH])^2}\right)$$

DNMT. The DNA methylation reaction is given as a uni-reactant scheme with SAM as substrate. That is, the substrates for methylation are assumed constant. Their variation can be modeled by varying the V_{max}. The kinetic constants, $V_{max} = 180$, $K_m = 1.4$, and $K_i = .84$ are from [12].

$$V_{DNMT} = \frac{V_{max}[SAM]}{K_m(1 + \frac{[SAH]}{K_i}) + [SAM]}$$

GNMT. The first factor of the $GNMT$ reaction is standard Michaelis-Menten with $V_{max} = 288$, and $K_m = 63$ estimated from [25], Figure 8. The second term is product inhibition by SAH from [28] with $K_i = 10.8$. The third term, the long-range inhibition of $GNMT$ by $5mTHF$, was derived by non-linear regression on the data of [39], Figure 3, and scaled so that it equals 1 when the methionine input rate is 100 μM/hr.

$$V_{GNMT} = \left(\frac{V_{max}[SAM]}{K_m + [SAM]}\right)\left(\frac{1}{1 + \frac{[SAH]}{K_i}}\right)\left(\frac{4.38}{0.35 + [5mthf]}\right)$$

MAT-I. The MAT-I kinetics are from [35], Table 1, and we take $V_{max} = 260$ and $K_m = 41$. The inhibition by SAM was derived by non-linear regression on the data from [35], Figure 5.

$$V_{MAT\text{–}I} = \left(\frac{V_{max}[MET]}{K_m + [MET]}\right)(0.23 + (0.8)e^{-(0.0026)[SAM]})$$

MAT-III. The methionine dependence of the $MAT-III$ kinetics is from [26], Figure 5, fitted to a Hill equation with $V_{max} = 220$, $K_m = 300$. The activation by SAM is from [35], Figure 5, fitted to a Hill equation with $K_a = 360$.

$$V_{MAT\text{–}III} = \left(\frac{V_{max}[MET]^{1.21}}{K_m + [MET]^{1.21}}\right)\left(1 + \frac{(7.2)[SAM]^2}{(K_a)^2 + [SAM]^2}\right)$$

MTHFR. The first factor in the formula for the MTHFR reaction velocity

$$V_{MTHFR} = \frac{V_{max}[CH2F][NADPH]}{(K_{m,1} + [CH2F])(K_{m,2} + [NADPH])} \cdot \frac{(6.1)(10)}{10 + [SAM] - [SAH]}$$

is standard Michaelis-Menten with $K_{m,1} = 50$, $K_{m,2} = 16$, and $V_{max} = 5000$ taken from [21][13][7].

The inhibition of $MTHFR$ by SAM, the second factor, was derived by non-linear regression on the data of [17][37] and has the form $10/(10 + [SAM])$. In addition, SAH competes with SAM for binding to the regulatory domain of $MTHFR$. It neither activates nor inhibits the enzyme [37] but prevents inhibition by SAM; thus, we take our inhibitory factor to be:

$$I = \frac{10}{10 + [SAM] - [SAH]},$$

The factor 6.1 scales the inhibition so that it has value 1 when metin = 100 μM/hr.

NE. The kinetics of the non-enzymatic reversible reaction between THF and CH2F are taken to be mass action.

$$V_{NE} \;=\; k1[THF][H_2C=O] - k2[CH2F],$$

The rate constants k1 = 0.3 and k2 = 23.2 are taken from [14][22].

Table 3. Model kinetic parameter values (time in hrs., concentrations in μM).

Parameter	Literature	Model	Reference
AICART Aminoimidazolecarboxamide ribotide transformylase			
$K_{m,10fTHF}$	5.9-50	5.9	[36][33][34][27]
$K_{m,AICAR}$	10-100	100	[36][33][27]
V_{max}	370-44400	45000	
DHFR. Dihydrofolate Reductase			
$K_{m,DHF}$	0.12-1.9	0.5	[15][36][33][3]
$K_{m,NADPH}$	0.3-5.6	4.0	[15][36][33][3]
V_{max}	350-23000	5000	[15][36][33]
FTD. 10-formyltetrahydrofolate dehydrogenase			
$K_{m,10fTHF}$	0.9	0.9	[18]
V_{max}		3300	
FTS. 10-formyltetrahydrofolate synthase			
$K_{m,THF}$	0.1 - 600	10	[36][34]
$K_{m,HCOOH}$	8 - 1000	43	[36][34]
V_{max}	100 - 486000	3000	[36][34]
MS. Methionine Synthase			
$K_{m,5mTHF}$		25	[10][1]
$K_{m,HCY}$		0.1	[2]
V_{max}		500	[2]
MTCH. 5,10-methylenetetrahydrofolate cyclo-hydrolase (positive direction is from CHF to $10fTHF$)			
$K_{m,CHF}$	4-250	250	[36][33][34]
V_{max}	880-1380000	800000	[33][34]
$K_{m,10fTHF}$	20-450	100	[36][33][34]
V_{max}	10.5-1380000	20000	[33][34]
MTD. 5,10-methylenetetrahydrofolate dehydrogenase (positive direction is from $CH2F$ to CHF)			
$K_{m,CH2F}$	2-5	2	[36][34]
V_{max}	520-594000	200000	[15][36][34]
$K_{m,CHF}$	1-10	10	[38][34]
V_{max}	594000	594000	[34]

PGT. Phosphoribosyl glycinamide transformylase

$K_{m,10fTHF}$	4.9-58	4.9	[36][33][4][5]
$K_{m,GAR}$	520	520	[36][33][4][5]
V_{max}	6600-16200	16200	[36][33][4][5]

SAHH. S-adenosylhomocysteine hydrolase
(positive direction is from SAH to HCY)

$K_{m,SAH}$		10	[23]
V_{max}		5000	[23]
$K_{m,HCY}$		1	[23]
V_{max}		5000	[23]

SHMT. Serine Hydroxymethyltransferase
(positive direction is from THF to $CH2F$)

$K_{m,SER}$	350-1300	600	[36][33][34][7][29]
$K_{m,THF}$	45-300	50	[36][33][34][30][31]
V_{max}	500-162000	40000	[15][33][34][31]
K_m^{GLY}	3000-10000	10000	[15][36][33][34][29]
$K_{m,CH2F}$	3200-10000	3200	[15][33][34][30]
V_{max}	12600-120,000,000	25000	[15][33][34]

TS. Thymidylate Synthase

$K_{m,DUMP}$	5-37	6.3	[15][36][6][20]
$K_{m,CH2F}$	10-45	14	[15][36][6][20]
V_{max}	30-4200	5000	[33][20]

The following table gives the steady-state values of all the variables and fluxes when the methionine input is 100 μM/hr and the total folate concentration is 20 μM. "frac" denotes $V_{CBS}/(V_{CBS} + V_{BHMT} + V_{MS})$, the fraction of flux arriving at HCY from SAH that is diverted to the transsulphuration pathway. Concentrations are in μM and fluxes in μM/hr.

Table 4. Steady-State Values when $metin = 100\mu$/hr and total folate is 20 μM.

$MET = 48.00$	$V_{MAT-I} = 127.1$	$CH2F = 0.90$	$V_{MTHFR} = 66.77$
$SAM = 64.42$	$V_{MAT-III} = 71.35$	$5mTHF = 4.02$	$V_{MHD} = 2444$
$SAH = 13.04$	$V_{DNMT} = 132.43$	$THF = 8.01$	$V_{MTCH} = 2444$
$HCY = 1.11$	$V_{GNMT} = 66.05$	$DHF = 0.03$	$V_{PGT} = 167.4$
$frac = 0.50$	$V_{SAHH} = 198.5$	$CHF = 1.12$	$V_{ART} = 464$
	$V_{MS} = 66.8$	$10fTHF = 5.93$	$V_{FTS} = 1340$
	$V_{BHMT} = 31.72$		$V_{FTD} = 3201$
	$V_{CBS} = 100$		$V_{SHMT} = 2151$
			$V_{NE} = 590$
			$V_{TS} = 230$
			$V_{DHFR} = 230$

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