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Stability Analysis of the Mathematical Modelling of Folate Cycle and DNA Methylation

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Abstract

In the mammalian genome, DNA methylation could be used to deduce health conditions associated with ageing and many other pathological conditions. In addition, folate is nutritionally vital for improving human health and growth. Folate is also essential in the activity of mammalian epigenetics, through its transfer of methyl groups for the DNA methylation reaction. Furthermore, folate, as part of the $B12$ vitamins, not only plays a key role in our diet, but is involved in the mechanism of DNA synthesis, maintenance of DNA methylation, and metabolism of the amino acids required for growth and cell division, especially during pregnancy and infancy. Investigations have shown that vitamin deficiency $B12$ has effects in all age groups, although to a higher degree among older people, infants, and pregnant women. Over the years, many mathematical models have been constructed, but none explicitly captured the complexity of the interdependent biochemical and molecular mechanisms of folate metabolism and DNA methylation. In this paper, we develop and assembled an all-inclusive model that connects folate metabolism and DNA methylation, and we investigated the stability of the system. We were also able to show that the system is stable, which is a basis for further analysis like bifurcation analysis and its applications.

Keywords: Folate, DNA Methylation, Methionine, DNA Methyltransferase, S-Adenosyl Methionine.
MSC2010: 06F20.

1 Introduction

The term 'folate' also known as vitamin $B9$ is used to designate a group of water-soluble compounds that have the same vitamin function and constitute natural folate, the pharmacological compounds folic and folacin [1,2]. The human body obtains folate from numerous dietary sources such as dark green vegetables, grains, and legumes because it cannot produce it on its own. Folate was first called and known as folic acid in 1941. It was extracted from spinach (folium, means leaf in Latin) and exhibited to be a growth factor for streptococcus lactis R [3,4]. Folate is nutritionally vital

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for the enhancement of human health and growth. The importance of folate for human health cannot be overemphasised. However, the basic function of folate is to transport one carbon unit needed for various biochemical reactions in an organism during metabolism [5], but the appropriate consumption of folate is essential for the stability of the activity of folate coenzymes in the system through the transfer of the one carbon unit needed for routine metabolism and modulation [6]. Studies have shown that folate as part of the B vitamins not only plays a key role in our diet but is much more involved in the synthesis of DNA, RNA, methionine, pyrimidines and purines, the maintenance of DNA methylation and the metabolization of amino acids necessary for growth and cell division, especially during pregnancy and infancy [7].

Furthermore, numerous cellular processes are dependent on a sufficient supply of folate $B-$Vitamin and are impeded from optimal functioning in times of insufficient folate intake [8]. Folate is also involved in the process of regeneration of methionine from homocysteine [8]. Scott and Gregory reported in their study that in the mammalian system, about 0.8% of the entire body folate pool is estimated to be lost by excretion every day [9]. In the development of squamous cell carcinoma (SCC) cancer, Piyathilake et al demonstrated in their study how folate is involved as the limiting vitamin for DNA methylation [10]. Medically, vitamin deficiency B has been shown to lead to serious pathological consequences, including anaemia and neural tube defects (NTD) in babies [11, 12]. Furthermore, Berry et al. observed that a pregnant woman can minimise the possibility that her baby has a neural tube defect if she is placed on folic acid during the first 28 days of conception [11, 12]. In addition, a low level of dietary folate has been associated with the development of many cancers (breast, cervical, colon, prostate, and esophageal squamous cell carcinoma) [10]. In addition, polymorphisms in folate-related gene coding are associated with early miscarriage among pregnant women.
Cardiovascular disease, cognitive impairment, and Alzheimer's disease in elderly people have been reported to be associated with a deficiency of B vitamins, and a study has not yet shown whether B vitamins can be used to reduce these impairments [13, 14]. However, understanding these findings has raised some objections. However, despite the great importance of folate for human health, there has been concern about the effect of excessive folic acid on the human body and its health implications. Naderi et al in a study observed that excessive folic acid consumption can lead to solving the problem of B vitamin deficiency, but at the expense of folate susceptibility to cancers of different forms [15].
Cardiovascular disease, cognitive impairment, and Alzheimer's disease in elderly people have been reported to be associated with a deficiency in B vitamins, and a study has not yet shown whether B vitamins can be used to reduce these impairments [13, 14]. However, understanding these findings has raised some objections. However, despite the great importance of folate for human health, there has been concern about the effect of excessive folic acid on the human body and its health implications. Naderi et al in a study observed that excessive folic acid consumption can lead to solving the problem of B vitamin deficiency, but at the expense of folate susceptibility to cancers of different forms [15].

1.1 Folate metabolism

Folate metabolism, also known as one-carbon metabolism, is a combination of different biological operations that affect several variables such as transporters, substrates, coenzymes, enzymes, and metabolites [16]. Folate metabolism is essential and plays an major role in the mechanism of nucleic acid synthesis and the balance of the precursor pools of deoxynucleotide triphosphate (dNTP) necessary for DNA synthesis, the formation and maintenance of DNA methylation forms necessary for tissue-specific gene expression and the creation of chromatin [17]. Folate is the precursor in the formation of tetrahydrofolate (THF). Tetrahydrofolate is folate in its metabolically active form [14], a carbon donor and acts as a cofactor of many enzymes, maintains optimal metabolism and regulation in a system, and plays other vital roles in the one-carbon metabolism. Folate, vitamin $B6$, vitamin $B12$, and methionine correlate in function [17]. Folate acts as coenzymes and functions

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primarily as acceptors or donors of one-carbon unit that are necessary for various interdependent reactions of the folate-mediated one-carbon metabolism cycle.

The role of folate in the movement of the one-carbon unit in the metabolism system is vital. The unit of one-carbon is available at different proportions of oxidation. All of the oxidised one-carbon compounds span from methane, the much-reduced level, to carbon dioxide, the highest oxidised level. During metabolism, in addition to carbon dioxide, a carbon unit is created in the cell and passes through the pathway in interdependent reactions as a folate product [18]. In mammals, the metabolic pathways in which interdependent reactions occur have various vital functions, including regulation of gene expression through the transfer of methyl group to DNA [19] and glutathione synthesis, which is an essential body antioxidant [20], and also involve the detoxification and deletion of reactive oxygen species from the human system [21].

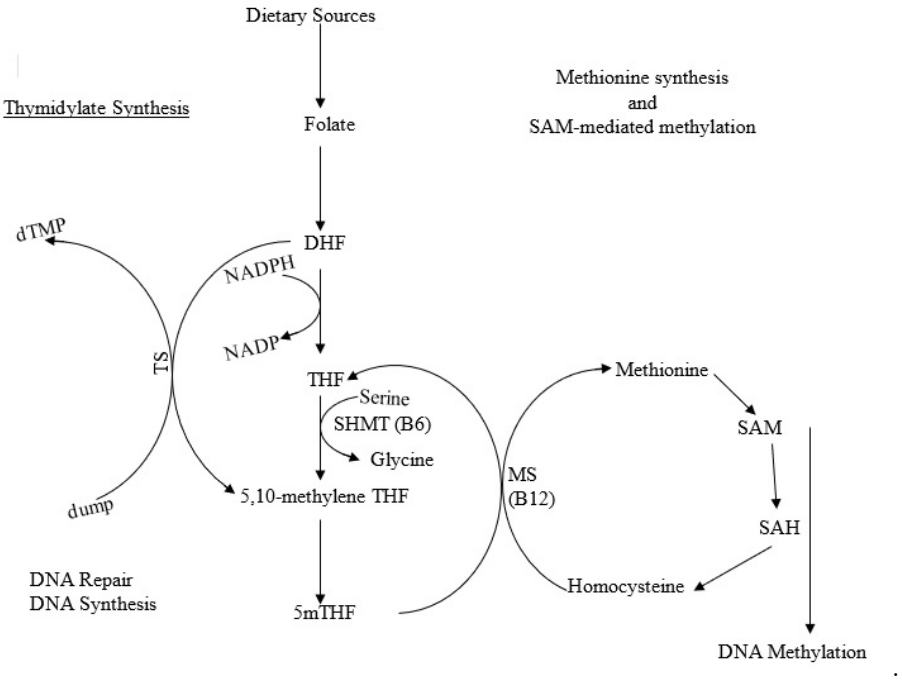

Figure 1: Depict of the interactive reactions in folate metabolism [17]. The schematic diagram illustrates the process in which folate interacts with DNA synthesis and DNA methylation via enzymatic interdependent reactions. The arrows depict the enzymatic reactions and direction flow.The abbreviations used are: DNA methyltransferase, (DNMT1, DNMT3a, and DNMT3b); Deoxyuridine monophosphate, (dUMP); Dihydrofolate, (DHF); Dihydrofolate reductase, (DHFR); Methionine synthase, (MS); Methylenetetrahydrofolate reductase, (MTHFR); Nicotinamide adenine dinucleotide phosphate, (NADP); Nicotinamide adenine dinucleotide phosphate hydrogen, (NADPH); Serine hydroxy methyltransferase, (SHMT); S-adenosylmethionine, (SAM); S-adenosylhomocysteine, (SAH); Tetrahydrofolate, (THF); Thymidylate synthase, (TS).

In addition, folate also contributes a lot to the activity of methionine regeneration. During interdependent reactions in the circle pathways (Figure 1), 5-methyltetrahydrofolate (5mTHF) can be re-circulated into tetrahydrofolate (THF) where it is used in the methionine synthase (MS) enzymatic process to re-methylate homocysteine (Hcy) to methionine and reproduce tetrahydrofolate the metabolically dynamic form of folate. Methionine synthase (MS) is an enzyme in humans that needs vitamin $B12$ to function, and its job is to produce methionine from homocysteine

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(Hcy). Methionine, being an important amino acid, is vital for the obtaining of homocysteine in the metabolism process [22]. Furthermore, on the righthand side of Figure 1, which is the activated methyl cycle, methionine adenosyltransferase (MAT-I and MAT-III) initiates the first step by catalysing methionine to produce SAM. SAM in turn is converted to s-adenosylhomocysteine (SAH) via transmethylation reactions. The SAH is then transformed to Hcy, allowing the normal flow of the methyl cycle [23]. Furthermore, SAH is one of the products of reactions of methyl group transfer, in which SAM is a necessity, and it functions as a selective inhibitor for the substrate [24]. The SAM and Hcy metabolites affect the enzymes that accelerate their synthesis and determine the activation and inhibition of various enzymes in the system [25].

1.2 DNA Methylation

DNA methylation is one of the most studied epigenetic modifications and its importance for mammalian genome development cannot be overstated [26]. The methylation of the DNA substructure has been established to be a vital epigenetic work to modulate gene expression in the activity of the genome of an organism [9]. In the mammalian genome, DNA methylation occurs predominantly in CpG dinucleotides, precisely when a methyl group (CH_3) of s-adenosyl methionine (SAM) is transferred to the fifth carbon ($C5$) of the cytosine base, and the process is regulated by DNA methyltransferase (see Figure 1.2). The pattern and range of DNA methylation are intrinsically dynamic, due to the characteristics of the methylation process. Intriguingly, several compelling studies have intimated that changes in DNA methylation could be vital to regulating ageing in humans [28]

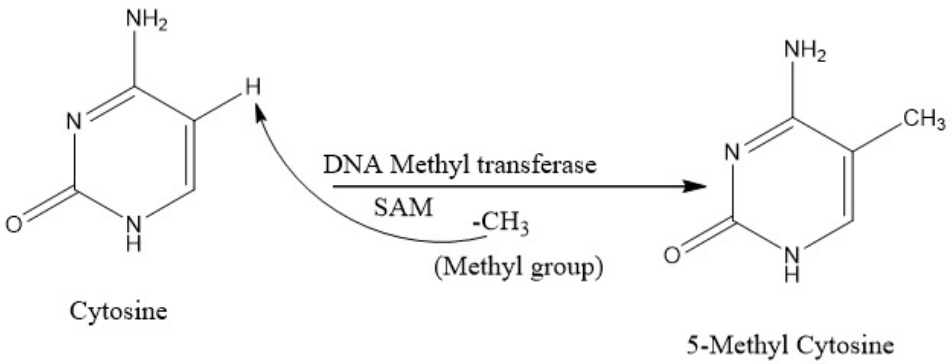

Figure 2: Depict of how a methyl group (CH_3) is transferred to the $C5$ position of the cytosine base. The DNA methyltransferase ($DNMT3a/3b$) catalyzes the methyl group transfer from SAM to the cytosine bases.

Mathematical models have been crucial in investigating the complexity of folate metabolism and DNA methylation. During the past year, several early efforts have been made to mathematically capture explicitly the complexity of the interdependent biochemical and molecular mechanisms of the connectivity of both folate metabolism and DNA methylation and its full dynamics, but none has captured it, none that we are aware of. In this paper, we are able to construct the DNA methylation model, link it to the two existing systems, the folate cycle and the methionine cycle, and investigate the stability of the system.

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1.3 Aims and Objectives

Our aim is to assemble a mathematical model that simulates the numerous interlinked biochemical reactions in three connected biochemical cycles which comprise the folate cycle, methionine cycle, and DNA methylation cycle and use the model to further our understanding of human ageing.

The objectives are as follows.

1. To create a DNA methylation model and connect it to the existing folate-methionine cycle through $DNMT$ (DNA methyltransferase).
2. Investigate the stability of the system.

2 Mathematical Backgrounds and Methods

In this section, we state without proofs some basic mathematical definitions and theorems used for the mathematical investigations and construction of some of the existing and proposed models. A flow chart is also presented depicting the techniques used to build the proposed model.

2.1 Strategy for model construction

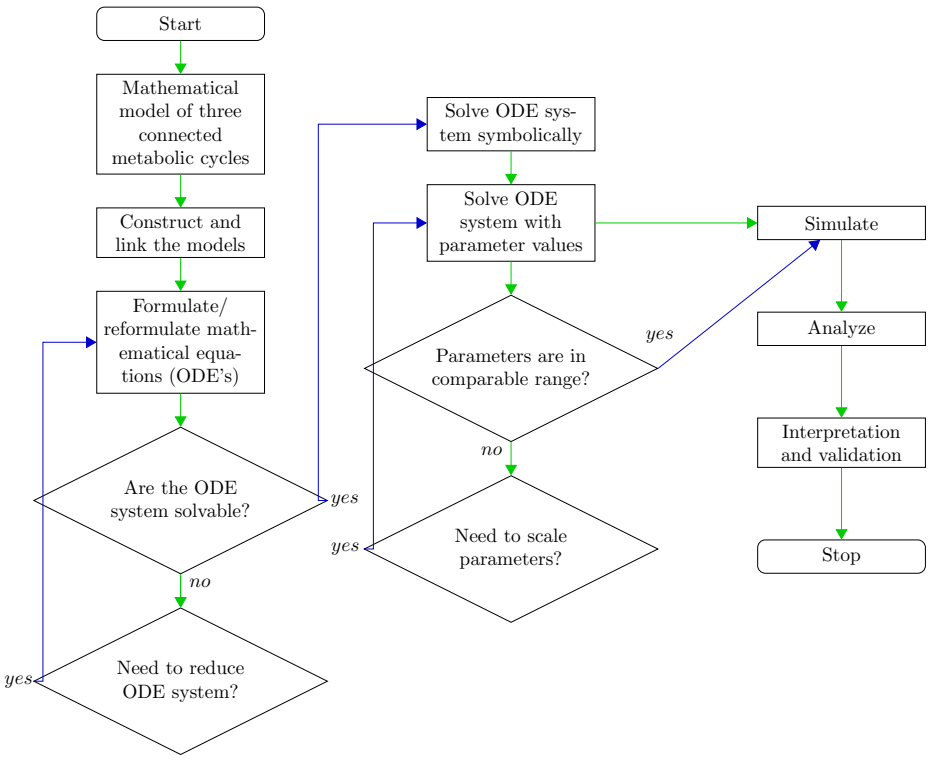

Figure 3: Schematic of the three biochemical cycle model: A flowchart developed to visualize the steps involved in the model's construction. Outlines: Forward (green) and backward (blue) steps were highlighted.

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2.2 Some basic definitions and theorems

Consider the initial value problem

$$y^{'}(t) = f(t, y(t)), \qquad y(t_0) = y^0 \tag{2.1}$$

where

$$f : \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}^n, y \in \mathbb{R},\ y = \begin{pmatrix} y_1^{'}(t) \\ \vdots \\ y_n^{'}(t) \end{pmatrix},\ f(t, y(t)) = \begin{pmatrix} f_1(t, y(t)) \\ \vdots \\ f_n(t, y(t)) \end{pmatrix}, \text{ and } y^0 = \begin{pmatrix} y_1^0 \\ \vdots \\ y_n^0 \end{pmatrix}$$

The existence and uniqueness of the solution of the initial value problem (2.1) depend on the following theorems

Theorem 2.1. *(Existence of solution) [28–32]*
Assume that $f(t, y(t))$ is continuous in a rectangle $R = \{(t, y_1, \ldots, y_n) : |t - t_0| \leq \alpha, |y_i - y_i^0| \leq \beta, i = 1, \ldots, n\}$. Then the initial value problem (2.1) has one or more solutions in the interval $|t - t_0| \leq h$, where h is greater than zero.

Theorem 2.2. *(Uniqueness of solution) [28–32]*
Assume that $f(t, y(t))$ and $\dfrac{\partial f(t, y(t))}{\partial y_i}, i = 1, \ldots, n$ are continuous in a rectangle $R = \{(t, y_1, \ldots, y_n) : |t - t_0| \leq \alpha, |y_i - y_i^0| \leq \beta, i = 1, \ldots, n\}$. Then the initial value problem (2.1) has a maximum of one solution in the interval $|t - t_0| \leq h$, where h is greater than zero.

The initial value problem (2.1) has a unique solution $y(t)$ defined in the interval $|t - t_0| \leq h$, where h is a positive number if theorems (2.1) and (2.2) are merged. The next corollary is considered to obtain the value of h.

Lemma 2.3. *(Interval of existence and uniqueness) [28–32]*
Since $f(t, y)$ is continuous in a closed and bounded domain, it is necessarily bounded in R, that is, $\exists\ \Phi_i > 0, i = 1, \ldots, n$, such that $\Phi_i = \max\limits_{(t, y_1, \ldots, y_n) \in R} |f_1(t, y)|$, for every $(t, y_1, \ldots, y_n) \in R$. Then IVP (2.1) has a unique solution in the interval $|t - t_0| \leq h$, where $h = min\left\{\alpha, \frac{\beta_1}{\Phi_1}, \cdots, \frac{\beta_n}{\Phi_n}\right\}$.

2.3 Stability of Ordinary Differential Equations

In this subsection, we highlight some procedures and techniques used in analysing the stability of ODE systems. We also present some basic definitions before the stability analysis.

Definition 2.4. *(Equilibrium point) [31]*
Consider the autonomous ordinary differential equation

$$y^{'} = f(y(t)) \tag{2.2}$$

Then a solution $y_0(t)$ is called an equilibrium point (or critical point) of equation (2.2) when $f(y_0(t)) = 0$.

Definition 2.5. *(Equilibrium point) [2]*
Consider the non-autonomous ordinary differential equation

$$y^{'} = f(t, y(t)) \tag{2.3}$$

Then a solution $y_0(t)$ is called an equilibrium point (or critical point) of equation (2.3) when $f(t, y_0(t)) = 0$.

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Definition 2.6. *(Stability of linear systems) [31]*
Let $y = \phi(t)$ be a solution of the differential equation

$$y^{'} = f(y) \tag{2.4}$$

Then the solution $y = \phi(t)$ of the equation (2.4) is said to be stable if any other solution $\theta(t)$ of the differential equation (2.4) that starts close to $\phi(t)$ at $t = 0$, stays close to $\phi(t)$ for any $t \geq 0$. Otherwise, the solution $y = \phi(t)$ of equation (2.4) is unstable. That is, if there exists at least one solution $y = \theta(t)$ of (2.4) that started close to $\phi(t)$ at $(t = 0)$ but stops to stay close to $\phi(t)$ for all $t \geq 0$. Then the solution $y = \phi(t)$ of the equation (2.4) is said to be unstable. To be more specific, the solution $\phi(t)$ is stable if for every $\epsilon > 0$, there exists $\delta = \delta(\epsilon)$ such that

$$|\theta_i(t) - \phi_i(t)| < \epsilon \quad \text{if} \quad |\theta_i(0) - \phi_i(0)| < \delta(\epsilon) \quad i = 1, \ldots, n$$

for every solution $\theta(t)$ of (2.4).

The above definition 2.4 is also applicable for the corresponding non-autonomous system of the form

$$y^{'} = f(t, y(t))$$

Definition 2.7. *(Asymptotically stable) [31]*
A solution $y = \phi(t)$ of the differential equation (2.4) is called asymptotically stable if it is stable and if any solution of $\Theta(t)$ of (2.4) that starts very close to $\phi(t)$ actually converges to $\phi(t)$ as $t \to \infty$. Specifically, the equilibrium solution $y(t) = y^0$ of (2.4) is asymptotically stable if any solution $\Theta(t)$ of (2.4) that starts close to y^0 in $(t = 0)$ not only stays close to y^0 for all t, but converges to y^0 as $t \to \infty$.

Consider the linear differential equation

$$y^{'} = Ay \tag{2.5}$$

where A is an $n \times n$ matrix ($A \in \mathbb{R}_{n\times n}$) and $y \in \mathbb{R}^n$
$y = 0 \in \mathbb{R}^n$ is an equilibrium point of (2.5).

Theorem 2.8. *(Stability of a linear ODE system) [31]*

(i) Every solution $y = \phi(t)$ of equation (2.5) and $y = 0 \in \mathbb{R}^n$ is stable if all the eigenvalues of matrix A have negative real parts.

(ii) Every solution $y = \phi(t)$ of equation (2.5) and $y = 0 \in \mathbb{R}^n$ is unstable if at least one of the eigenvalues of matrix A has a positive real part.

(iii) Assume that A has some eigenvalues $\lambda_1 = i\sigma_1, \ldots, \lambda_K = i\sigma_k$. $\sigma_j \in \mathbb{R}$ $j = 1, \ldots, k$, with multiplicity $m_1, \ldots, m_k$ respectively. Thus, it follows that the characteristic polynomial of matrix A can be expressed as

$$p(\lambda) = (\lambda - i\sigma_1)^{m_1} \ldots (\lambda - i\sigma_k)^{m_k} q(\lambda).$$

where $q(\lambda)$ is a polynomial with roots that have real negative parts. Then, if A has m_j linearly independent eigenvectors corresponding to $\lambda_j = i\lambda_j$, then every solution of $y = \phi(t)$ of (2.5) is stable. Otherwise, any solution of $\phi(t)$ is unstable.

3 Model Formulation

In this section, we assemble and link the co-dynamics of the three metabolic cycles, namely the folate cycle and the methionine cycle, and a proposed model of the DNA methylation cycle, see

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Figure 4. The folate cycle is adapted from Nijhout et al [12]. Nijhout and colleagues constructed a mathematical model for the folate cycle on the basis of typical biochemical kinetic equations, with the assumption that all reactions are bimolecular. The model was able to determine the methyl trap hypothesis, methotrexate, and predicts the consequences of $B12$ vitamin deficiencies. The methionine cycle is adapted from Reed et al [25]. We also formulate the ordinary differential equations governing the model from the co-dynamics of the three cycles. The model has a total of eleven compartments which form the ODE's.

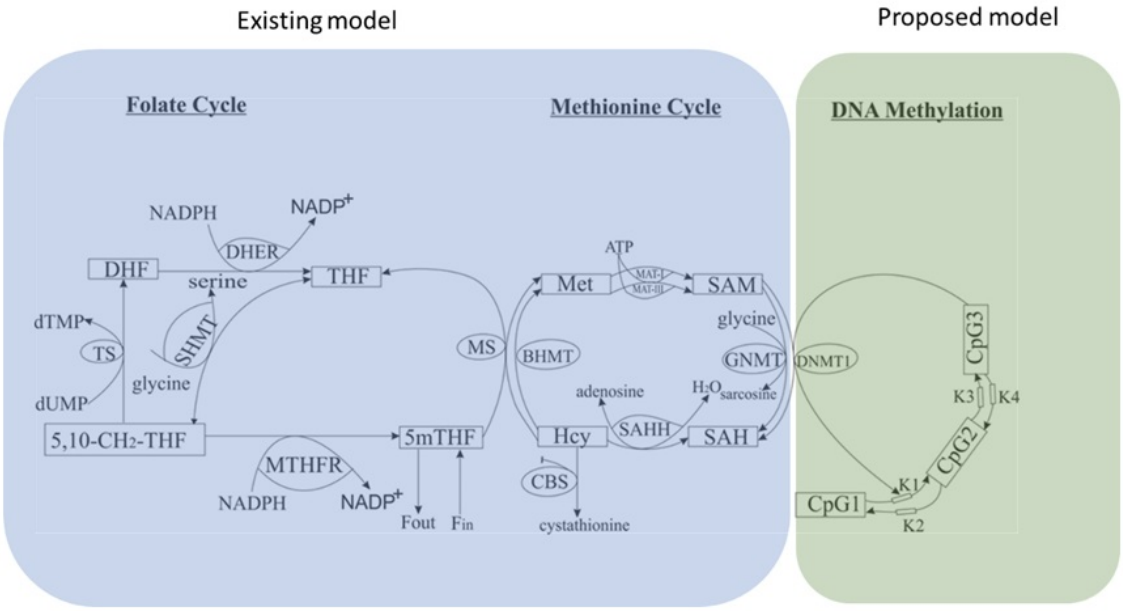

Figure 4: Simplified schematic of two existing models of folate cycle and methionine cycle, and a proposed model of DNA methylation cycle. The folate cycle is adapted from [12] and the methionine cycle is adapted from [25] and the DNA methylation model is the proposed constructed model. The substrates are shown in rectangular boxes, and the enzymes are enclosed in ovals. The arrows are the transitional flow of enzymatic activity. The full names of all the abbreviations are in Tables 1, 2 and 3.

Table 1: Model variables and their corresponding biochemical terms

Variables	Abbreviation	Biochemical terms
x_1	[5,10-CH_2-THF]	5,10-methylenetetrahydrofolate
x_2	[5mTHF]	5-methyltetrahydrofolate
x_3	[DHF]	Dihydrofolate
x_4	[THF]	Tetrahydrofolate
x_5	Hcy	Homocysteine
x_6	Met	Methionine
x_7	SAM	S-adenosyl methionine
x_8	SAH	S-adenosyl homocysteine
x_9	CpG_1	Unmethylated CpG dyads
x_{10}	CpG_2	Hemimethylated CpG dyads
x_{11}	CpG_3	Methylated CpG dyads

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Table 2: Model parameters and their corresponding Biochemical terms

Parameters	Abbreviations	Biochemical terms
$\alpha 1$	SHMT	Serine hydroxymethyltranferase
$\alpha 2$	Ser	Serine
$\alpha 3$	TS	Thymidylate synthase
$\alpha 4$	dUMP	Deoxyuridine monophosphate
$\alpha 5$	MTHFR	methylenetetrahydrofolate reductase
$\alpha 6$	NADPH	Nicotinamide adenine dinucleotide
$\alpha 7$	DHFR	Dihydrofolate Reductase
$\alpha 8$	gly	Glycine
$\alpha 9$	MS	Methionine synthase
$\alpha 10$	SAHH	S-adenosylhomocysteine hydrolase
$\alpha 11$	BHMT	Betaine homocysteine s-methyltransferase
$\alpha 12$	CBS	Cystathionine
$\alpha 13$	MAT I	Methionine adenosyl transferase I
$\alpha 14$	MAT III	Methionine adenosyl transferase III
$\alpha 15$	ATP	Adenosine triphosphate
$\alpha 16$	GNMT	Glycine N-methyltransferase
$\alpha 17$	DNMT1	DNA methyltransferas1
x_6	Met	Methionine
f_1	f_{in}	folate in
f_2	f_{out}	folate out

Table 3: List of the transition rates of Methylation cycle

Parameters	Meaning
K_1	Methylation rate of unmethylated CpG dyads
K_2	Demethylation rate of hemimethylated CpG dyads
K_3	Methylation rate of hemimethylated CpG dyads
K_4	Demethylation rate of methylated CpG dyads

Translating the dynamics of the model in Figure 4 into a set of ordinary differential equations (ODEs) gives the following:

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$$\frac{d[5,10-CH_2-THF]}{dt} = SHMT[THF]Ser - TS[5,10-CH_2-THF]dUMP- MTHFR[5,10-CH_2-THF]NADPH \quad (3.1)$$

$$\frac{d[5mTHF]}{dt} = MTHFR[5,10-CH_2-THF]NADPH - MS[5mTHF]Hcy + F_1 - F_2 \quad (3.2)$$

$$\frac{d[DHF]}{dt} = TS[5,10-CH_2-THF]dUMP - DHFR[DHF]NADPH \quad (3.3)$$

$$\frac{d[THF]}{dt} = MS[5mTHF]Hcy + DHFR[DHF]NADPH - SHMT[THF]Ser \quad (3.4)$$

$$\frac{d(Hcy)}{dt} = SAHH(Hcy) - BHMT(Hcy) - MS[5mTHF](Hcy) - CBS(Hcy) \quad (3.5)$$

$$\frac{d(Met)}{dt} = MS(Hcy)[5mTHF] - BHMT(Hcy) - MATI(ATP)(Met) - MATIII(ATP)(Met) \quad (3.6)$$

$$\frac{d(SAM)}{dt} = MATI(Met)(ATP) + MATIII(Met)(ATP) - GNMT(SAM)gly - DNMT(CpG_3)(SAM) \quad (3.7)$$

$$\frac{d(SAH)}{dt} = GNMT(SAM)gly + DNMT(SAM)(CpG_3) - SAHH(Hcy) \quad (3.8)$$

$$\frac{d(CpG_1)}{dt} = DNMT(SAM)CpG_3 + K_2(CpG_2) - K_1(CpG_1) \quad (3.9)$$

$$\frac{d(CpG_2)}{dt} = K_1CpG_1 + K_4(CpG_4) - K_2(CpG_2) - (K_2+K_3)CpG_2 \quad (3.10)$$

$$\frac{d(CpG_3)}{dt} = K_3(CpG_2) - K_4(CpG_3) - DNMT(SAM)CpG_3 \quad (3.11)$$

Replacing biochemical terms with mathematical symbols

To conveniently analyse the 11×11 ODE system (3.1) to (3.11), we replaced all biochemical terms with mathematical symbols, through which we can clearly see the variables and parameters.

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$$\frac{dx_1}{dt} = \alpha_1\alpha_2x_4 - \alpha_3\alpha_4x_1 - \alpha_5\alpha_6x_1 \tag{3.12}$$
$$\frac{dx_2}{dt} = \alpha_5\alpha_6x_1 - \alpha_9x_2x_5 + f_1 - f_2 \tag{3.13}$$
$$\frac{dx_3}{dt} = \alpha_3\alpha_4x_1 - \alpha_6\alpha_7x_3 \tag{3.14}$$
$$\frac{dx_4}{dt} = \alpha_9x_2x_5 + \alpha_6\alpha_7x_3 - \alpha_1\alpha_2x_4 \tag{3.15}$$
$$\frac{dx_5}{dt} = \alpha_{10}x_5 - \alpha_{11}x_5 - \alpha_9x_2x_5 - \alpha_{12}x_5 \tag{3.16}$$
$$\frac{dx_6}{dt} = \alpha_9x_2x_5 - \alpha_{11}x_5 - \alpha_{13}\alpha_{15}x_6 - \alpha_{14}\alpha_{15}x_6 \tag{3.17}$$
$$\frac{dx_7}{dt} = \alpha_{13}\alpha_{15}x_6 + \alpha_{14}\alpha_{15}x_6 - \alpha_8\alpha_{16}x_7 - \alpha_{17}x_7x_{11} \tag{3.18}$$
$$\frac{dx_8}{dt} = \alpha_8\alpha_{16}x_7 + \alpha_{17}x_7x_{11} - \alpha_{10}x_5 \tag{3.19}$$
$$\frac{dx_9}{dt} = \alpha_{17}x_7x_{11} + k_2x_{10} - k_1x_9 \tag{3.20}$$
$$\frac{dx_{10}}{dt} = k_1x_9 + k_4x_{11} - (k_2 + k_3)x_{10} \tag{3.21}$$
$$\frac{dx_{11}}{dt} = k_3x_{10} - k_4x_{11} - \alpha_{17}x_7x_{11} \tag{3.22}$$

Reduction from a 11×11 to a 4×4 System

The 11− dimensional system (3.12) to (3.22) is reduced to a 4− dimensional system due to its high level of non-linearity by applying the quasi-steady-state approximation (QSSA). We assume that some of the variables change much faster than the other variables and get to a steady state. The dynamics of the last three equations (3.20) − (3.22) are preserved, as they constitute the proposed model and also the dynamics of equation (3.18) that linked the folate model and the DNA methylation model.

$$\begin{aligned}
\frac{dx_7}{dt} &= \alpha_{13}\alpha_{15}x_6 + \alpha_{14}\alpha_{15}x_6 - \alpha_8\alpha_{16}x_7 - \alpha_{17}x_7x_{11} \\
\frac{dx_9}{dt} &= \alpha_{17}x_7x_{11} + k_2x_{10} - k_1x_9 \\
\frac{dx_{10}}{dt} &= k_1x_9 + k_4x_{11} - (k_2 + k_3)x_{10} \\
\frac{dx_{11}}{dt} &= k_3x_{10} - k_4x_{11} - \alpha_{17}x_7x_{11}
\end{aligned} \tag{3.23}$$

The reduced set of ODEs system can also be written as:

$$\begin{aligned}
\frac{dx_7}{dt} &= \Lambda - \alpha_8\alpha_{16}x_7 - \alpha_{17}x_7x_{11} \\
\frac{dx_9}{dt} &= \alpha_{17}x_7x_{11} + k_2x_{10} - k_1x_9 \\
\frac{dx_{10}}{dt} &= k_1x_9 + k_4x_{11} - (k_2 + k_3)x_{10} \\
\frac{dx_{11}}{dt} &= k_3x_{10} - k_4x_{11} - \alpha_{17}x_7x_{11}
\end{aligned} \tag{3.24}$$

where $\Lambda = \alpha_{13}\alpha_{15}x_6 + \alpha_{14}\alpha_{15}x_6$
Within our modelling framework, we are interested in the evolution of the total conserved pool of

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all substrates and metabolites explicitly defined as

$$C = x_7(t) + x_9(t) + x_{10}(t) + x_{11}(t), \quad C > 0. \tag{3.25}$$

3.1 Existence and Uniqueness

Differentiating the system (3.24) along with an initial value $\mathbf{x^0}$ form an IVP.
Consider the initial value problem

$$x^{'}(t) = f(t, x(t)), \qquad x(0) = x^0 \tag{3.26}$$

where

$$x(t) = \begin{pmatrix} x_7(t) \\ x_9(t) \\ x_{10}(t) \\ x_{11}(t) \end{pmatrix}, \; x^0 = \begin{pmatrix} x_7^0 \\ x_9^0 \\ x_{10}^0 \\ x_{11}^0 \end{pmatrix} \text{ and } f(t, x(t)) = \begin{pmatrix} f_7(x(t)) \\ f_9(x(t)) \\ f_{10}(x(t)) \\ f_{11}(x(t)) \end{pmatrix} = \begin{pmatrix} \Lambda - \alpha_8\alpha_{16}x_7 - \alpha_{17}x_7x_{11} \\ \alpha_{17}x_7x_{11} + k_2x_{10} - k_1x_9 \\ k_1x_9 + k_4x_{11} - (k_2 + k_3)x_{10} \\ k_3x_{10} - k_4x_{11} - \alpha_{17}x_7x_{11} \end{pmatrix}$$

It is straightforward that f is continuous in $R = \{(t, X_7, X_9, X_{10}, X_{11}) : t \leq T, |x_7 - x_7^0| \leq C, |x_9 - x_9^0| \leq C, |x_{10} - x_{10}^0| \leq C, |x_{11} - x_{11}^0| \leq C\}$.
Furthermore, the partial derivatives $\dfrac{\partial f(t,x(t))}{\partial x_7}$, $\dfrac{\partial f(t,x(t))}{\partial x_9}$, $\dfrac{\partial f(t,x(t))}{\partial x_{10}}$, and $\dfrac{\partial f(t,x(t))}{\partial x_{11}}$ are continuous in R, since

$$\frac{\partial f(x(t))}{\partial x_7} = \begin{pmatrix} \dfrac{\partial f_7(x(t))}{\partial x_7} \\ \dfrac{\partial f_9(x(t))}{\partial x_7} \\ \dfrac{\partial f_{10}(x(t))}{\partial x_7} \\ \dfrac{\partial f_{11}(x(t))}{\partial x_7} \end{pmatrix} = \begin{pmatrix} -\alpha_8\alpha_{16} - \alpha_{17}x_{11} \\ \alpha_{17}x_{11} \\ 0 \\ -\alpha_{17}x_{11} \end{pmatrix}$$

$$\frac{\partial f(x(t))}{\partial x_9} = \begin{pmatrix} \dfrac{\partial f_7(x(t))}{\partial x_9} \\ \dfrac{\partial f_9(x(t))}{\partial x_9} \\ \dfrac{\partial f_{10}(x(t))}{\partial x_9} \\ \dfrac{\partial f_{11}(x(t))}{\partial x_9} \end{pmatrix} = \begin{pmatrix} 0 \\ -k_1 \\ k_1 \\ 0 \end{pmatrix}$$

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$$\frac{\partial f(x(t))}{\partial x_{10}} = \begin{pmatrix} \frac{\partial f_7(x(t))}{\partial x_{10}} \\ \frac{\partial f_9(x(t))}{\partial x_{10}} \\ \frac{\partial f_{10}(x(t))}{\partial x_{10}} \\ \frac{\partial f_{11}(x(t))}{\partial x_{10}} \end{pmatrix} = \begin{pmatrix} 0 \\ k_2 \\ -(k_2+k_3) \\ k_3 \end{pmatrix}$$

$$\frac{\partial f(x(t))}{\partial x_{11}} = \begin{pmatrix} \frac{\partial f_7(x(t))}{\partial x_{11}} \\ \frac{\partial f_9(x(t))}{\partial x_{11}} \\ \frac{\partial f_{10}(x(t))}{\partial x_{11}} \\ \frac{\partial f_{11}(x(t))}{\partial x_{11}} \end{pmatrix} = \begin{pmatrix} -\alpha_{17}x_7 \\ \alpha_{17}x_7 \\ k_4 \\ -k_4 - \alpha_{17}x_7 \end{pmatrix}$$

Hence, from Theorem 2.1 and 2.2 the IVP has a unique solution in the interval $|t-t_0| < h \implies t < h$, noting that $t_0 = 0$ and $t \geq 0$, for some $h > 0$. Furthermore, from Lemma 2.3 we have

$$h = min\left\{T, \frac{C}{M_7}, \frac{C}{M_9}, \frac{C}{M_{10}}, \frac{C}{M_{11}}\right\}$$

where $M_7 = \underset{(x_7,x_9,x_{10},x_{11})\in R}{max}|f_7(x(t))|$, $M_9 = \underset{(x_7,x_9,x_{10},x_{11})\in R}{max}|f_9(x(t))|$, $M_{10} = \underset{(x_{10},x_9,x_{10},x_{11})\in R}{max}|f_{10}(x(t))|$, and $M_{11} = \underset{(x_7,x_9,x_{10},x_{11})\in R}{max}|f_{11}(x(t))|$.

Thus, a unique solution of the IVP is quaranteed.

4 Stability of the equilibrium state of the system

Solving for the reduced 4− dimensional system (3.24) equilibrium points symbolically was complicated due to the system's non linear nature, so available parameter values are substituted to solve for the equilibrium points and eigenvalues via Mathematica.

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4.1 Equilibrium points and eigenvalues of the system

Consider the system (3.24) and using the parameter values in Table 4:

$$\begin{aligned}
\frac{dx_7}{dt} &= \Lambda - \alpha_8\alpha_{16}x_7 - \alpha_{17}x_7x_{11} \\
\frac{dx_9}{dt} &= \alpha_{17}x_7x_{11} + k_2x_{10} - k_1x_9 \\
\frac{dx_{10}}{dt} &= k_1x_9 + k_4x_{11} - (k_2 + k_3)x_{10} \\
\frac{dx_{11}}{dt} &= k_3x_{10} - k_4x_{11} - \alpha_{17}x_7x_{11}
\end{aligned}$$

Table 4: Model parameter values

Parameters	Values	References
$\alpha 8$	1.85	[33, 34]
$\alpha 13$	1.32	[33]
$\alpha 14$	7.61	[33]
$\alpha 15$	10.0	[33]
$\alpha 16$	6.14	[33]
$\alpha 17$	1.47	[33]
x_6	0.45	[33, 34]
k_1	1.2	[30, 35]
k_2	1.1	[30, 35]
k_3	0.99	[30, 35]
k_4	0.8	[30, 35]

Table 4. The parameter values used for the stability and phase portrait diagrams of the model are taken from [28, 32, 33] and some of them were adjusted to illustrate the qualitative dynamics of the system.

The Equilibrium Points

Solving for the equilibrium points via Mathematica, we got:

$$\begin{pmatrix}
x_7 & x_9 & x_{10} & x_{11} \\
-0.557674 & 39.8057 & 1.13387 & -56.7464 \\
3.48777 & 1.08031 & 0.66264 & 0.110682
\end{pmatrix}$$

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The Jacobian Matrix

$$J(x_7, x_9, x_{10}, x_{11}) = \begin{pmatrix} \frac{\partial f_7}{\partial x_7} & \frac{\partial f_7}{\partial x_9} & \frac{\partial f_7}{\partial x_{10}} & \frac{\partial f_7}{\partial x_{11}} \\ \frac{\partial f_9}{\partial x_7} & \frac{\partial f_9}{\partial x_9} & \frac{\partial f_9}{\partial x_{10}} & \frac{\partial f_9}{\partial x_{11}} \\ \frac{\partial f_{10}}{\partial x_7} & \frac{\partial f_{10}}{\partial x_9} & \frac{\partial f_{10}}{\partial x_{10}} & \frac{\partial f_{10}}{\partial x_{11}} \\ \frac{\partial f_{11}}{\partial x_7} & \frac{\partial f_{11}}{\partial x_9} & \frac{\partial f_{11}}{\partial x_{10}} & \frac{\partial f_{11}}{\partial x_{11}} \end{pmatrix}$$

$$= \begin{pmatrix} -\alpha_8\alpha_{16} - \alpha_{17}x_{11} & 0 & 0 & -\alpha_{17}x_7 \\ \alpha_{17}x_{11} & -k_1 & k_2 & \alpha_{17}x_7 \\ 0 & k_1 & -(k_2 + k_3) & k_4 \\ -\alpha_{17}x_{11} & 0 & k_3 & -k_4 - \alpha_{17}x_7 \end{pmatrix}$$

The First Equilibrium Jacobian's and Eigenvalues

Using the first equilibrium points and the Jacobian matrix, we now have the first eigenvalues. The first equilibrium points, Jacobian matrix, and eigenvalues, respectively:

$$(\text{x\_7, x\_9, x\_10, x\_11}) = \begin{pmatrix} -0.557674 & 39.8057 & 1.13387 & -56.7464 \end{pmatrix}$$

$$\begin{pmatrix} 72.0582 & 0 & 0 & 0.819781 \\ -83.4172 & -1.2 & 1.1 & -0.819781 \\ 0 & 1.2 & -2.09 & 0.8 \\ 83.4172 & 0 & 0.99 & 0.0197815 \end{pmatrix}$$

$$\begin{pmatrix} \lambda_1 & \lambda_2 & \lambda_3 & \lambda_4 \\ 72.99552 & -3.11177 & -1.09546 & -1.55767 \times 10^{-16} \end{pmatrix}$$

The Second Equilibrium Jacobian's and Eigenvalues

Using the first equilibrium points and the Jacobian matrix, we now have the first eigenvalues. The first equilibrium points, Jacobian matrix, and eigenvalues, respectively:

$$(\text{x\_7, x\_9, x\_10, x\_11}) = \begin{pmatrix} 3.48777 & 1.08031 & 0.66264 & 0.110682 \end{pmatrix}$$

$$\begin{pmatrix} -11.5217 & 0 & 0 & -5.12702 \\ 0.162702 & -1.2 & 1.1 & 5.12702 \\ 0 & 1.2 & -2.09 & 0.8 \\ -0.162702 & 0 & 0.99 & -5.92702 \end{pmatrix}$$

$$\begin{pmatrix} \lambda_1 & \lambda_2 & \lambda_3 & \lambda_4 \\ -11.6659 & -5.61549 & -3.45736 & -1.91623 \times 10^{-16} \end{pmatrix}$$

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5 Main Results

5.1 The Qualitative Behaviour of the Solution

Equilibrium points help to gain more insight into the qualitative behaviour of a system. By investigating where these equilibrium points are, we can determine the optimum locations of these equilibrium points through stability analysis by classifying the full dynamics of the system, which includes determining whether the system will approach a fixed point, tend to oscillate, or grow indefinitely.

The second equilibrium point with negative real part eigenvalues shows that the system is stable:

$$\begin{pmatrix} \lambda_1 & \lambda_2 & \lambda_3 & \lambda_4 \\ -11.6659 & -5.61549 & -3.45736 & -1.91623 \times 10^{-16} \end{pmatrix}$$

Next, we plot the phase portrait of the system, using the equilibrium points available to investigate the system's behaviour.

The Phase Portrait and Trajectories of the System

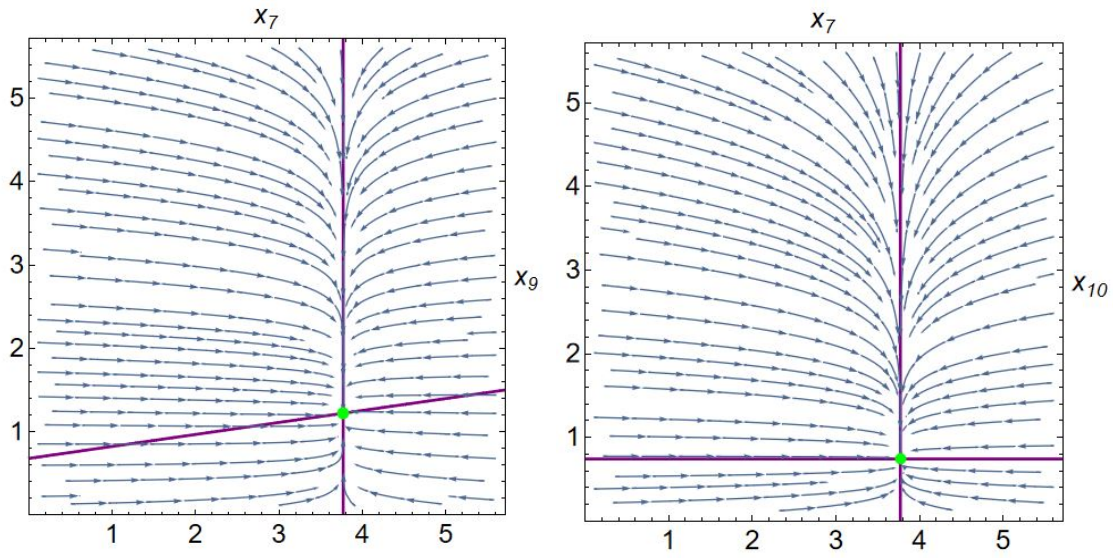

Figure 5: The phase portrait of x_7 vs x_9 and x_7 vs x_{10}. Here the trajectories converges through the nullclines towards the equilibrium point, this indicates that the system is stable at the fixed point.

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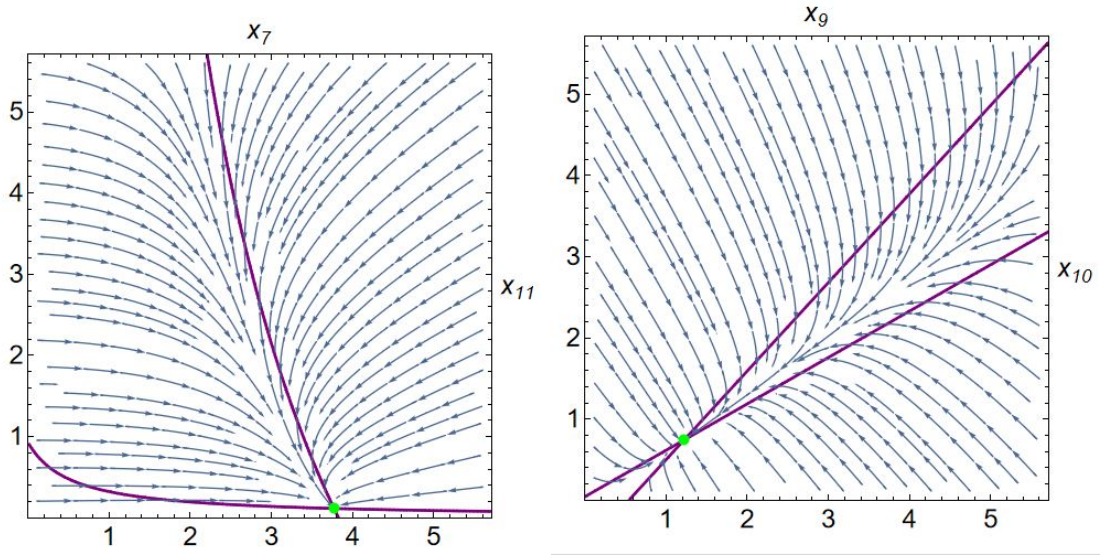

Figure 6: The phase portrait of x_7 vs x_{11}. Here the trajectories converges through the nullclines towards the equilibrium point, this indicates that the system is stable at the fixed point.

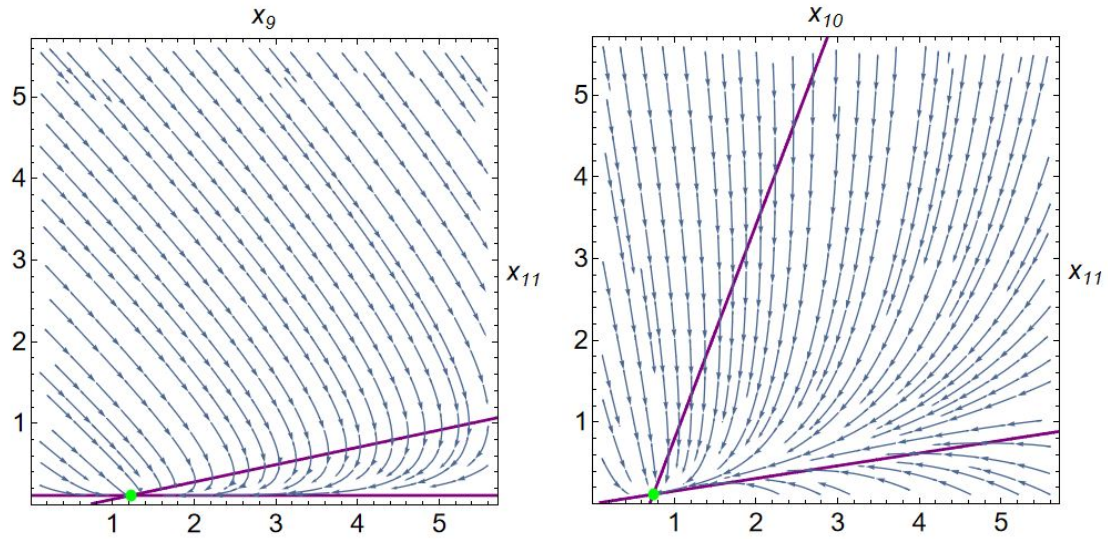

Figure 7: The phase portrait of x_7 vs x_{11}. Here the trajectories converges through the nullclines towards the equilibrium point, this indicates that the system is stable at the fixed point.

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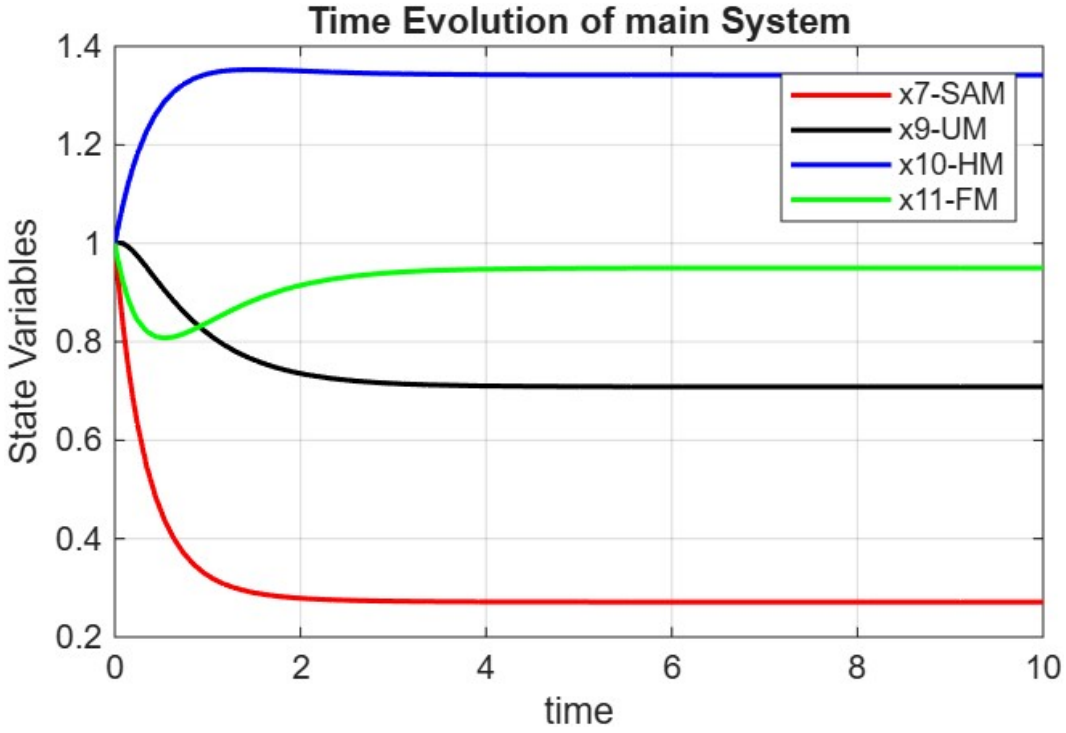

Figure 8: Depict of the time evolution of the system using initial conditions $(1, 1, 1, 1)$ to illustrate the dynamics of the system. SAM denote S-adenosyl methionine, UM denote the Unmethylated CpG dyads , HM denote the Hemimethylated CpG dyads, and FM denote the Full methylated CpG dyads.

6 Discussion and Conclusions

The focus of this paper is to build a mathematical model of three biochemical metabolic cycles and to investigate the stability of the system. We constructed the DNA methylation cycle and connected it to two existing cycles. The paper investigated the equilibrium points that helped to gain more insight into the qualitative behaviour of a system. By investigating where these equilibrium points are, we can determine the optimum locations of these equilibrium points through stability analysis by classifying the full dynamics of the system, which includes determining whether the system will approach a fixed point, tend to oscillate, or grow indefinitely. The results were illustrated by phase portraits and trajectories of the system displayed in Figures 5 to 7. In conclusion, we were able to prove the stability of the system, but noticed that stability analysis of the system alone is not enough to conduct an in-depth investigation of ageing and other human diseases. We intend to further the work by performing a bifurcation and sensitivity analysis for the system, which we believe will give us a comprehensive analysis of the implications of the system for ageing and other pathological conditions. The paper contains many references to previous works on related topics.

References

[1] Mc Auley, M. T., Mooney, K. M., and Salcedo-Sora, J. E. (2018). Computational modelling folate metabolism and DNA methylation: implications for understanding health and ageing. *Briefings in Bioinformatics, 19(2), 303-317.*

[2] Smith, Z. D., and Meissner, A. (2013). DNA methylation: roles in mammalian development. Nature Reviews Genetics, 14(3), 204-220.

[3] Crider, K. S., Qi, Y. P., Yeung, L. F., Mai, C. T., Head Zauche, L., Wang, A., ... and Williams, J. L. (2022). Folic acid and the prevention of birth defects: 30 years of opportunity and controversies. *Annual Review of Nutrition, 42, 423-452.*

[4] Hoffbrand, A. V., and Weir, D. G. (2001). The history of folic acid. British Journal of Haematology*, 113(3).*

[5] Martinez, H., Benavides-Lara, A., Arynchyna-Smith, A., Ghotme, K. A., Arabi, M., and Arynchyn, A. (2023). Global strategies for the prevention of neural tube defects through the improvement of folate status in women of reproductive age. Child's Nervous System, 39(7), 1719-1736.

[6] Lee, Y., Vousden, K. H., and Hennequart, M. (2024). Cycling back to folate metabolism in cancer. *Nature Cancer, 5(5), 701-715.*

[7] Nijhout, H. F., Reed, M. C., Budu, P., and Ulrich, C. M. (2004). A mathematical model of the folate cycle: new insights into folate homeostasis. Journal of Biological Chemistry, 279(53), 55008-55016.

[8] Bhalla, P., Rengaswamy, R., Karunagaran, D., Suraishkumar, G. K., and Sahoo, S. (2022). Metabolic modeling of host–microbe interactions for therapeutics in colorectal cancer. *NPJ Systems Biology and Applications, 8(1), 1.*

[9] Sulistyoningrum, D. C., Sullivan, T. R., Skubisz, M., Palmer, D. J., Wood, S., Ueland, P. M., ... and Best, K. P. (2024). Maternal serum unmetabolized folic acid concentration following multivitamin and mineral supplementation with or without folic acid after 12 weeks gestation: A randomized controlled trial. Maternal and Child Nutrition, 20(4), e13668.

[10] Piyathilake, C. J., Johanning, G. L., Macaluso, M., Whiteside, M., Oelschlager, D. K., Heimburger, D. C., and Grizzle, W. E. (2000). Localized folate and vitamin B-12 deficiency in squamous cell lung cancer is associated with global DNA hypomethylation. *Nutrition and Cancer, 37(1), 99-107.*

[11] Kopp, Wolfgang. (2024). "Aging and "Age-related" Diseases-What is the Relation?." Aging and Disease 16, no. 3 : 1316.

[12] Ly, L., Chan, D., Landry, M., Angle, C., Martel, J., and Trasler, J. (2020). Impact of mothers' early life exposure to low or high folate on progeny outcome and DNA methylation patterns. *Environmental Epigenetics, 6(1), dvaa018.*

[13] Ebara, S. (2017). Nutritional role of folate. Congenital Anomalies, 57(5), 138-141.

[14] Ford, A. H., and Almeida, O. P. (2019). Effect of vitamin B supplementation on cognitive function in the elderly: a systematic review and meta-analysis. *Drugs and Aging, 36(5), 419-434.*

[15] Naderi, N., and House, J. D. (2018). Recent developments in folate nutrition. Advances in Food and Nutrition Research, 83, 195-213.

[16] Panetta, J. C., Paugh, S. W., and Evans, W. E. (2013). Mathematical modeling of folate metabolism. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 5(5), 603-613.*

[17] Massaro, E., and Rogers, J. (2002). Folate and human development. Scandinavian Journal of Nutrition, 46(3), 148-150.

[18] Wagner, C. (2001). Biochemical role of folate in cellular metabolism. *Clinical Research and Regulatory Affairs, 18(3), 161-180.*

[19] Ulrey, C. L., Liu, L., Andrews, L. G., and Tollefsbol, T. O. (2005). The impact of metabolism on DNA methylation. Human Molecular Genetics, 14(suppl_1), R139-R147.

[20] Wu, G., Lupton, J. R., Turner, N. D., Fang, Y. Z., and Yang, S. (2004). Glutathione metabolism and its implications for health.*The Journal of Nutrition, 134(3), 489-492.*

[21] Vargason, T., Howsmon, D. P., Melnyk, S., James, S. J., and Hahn, J. (2017). Mathematical modeling of the methionine cycle and transsulfuration pathway in individuals with autism spectrum disorder. Journal of Theoretical Biology, 416, 28-37.

[22] Stead, L. M., Jacobs, R. L., Brosnan, M. E., and Brosnan, J. T. (2004). Methylation demand and homocysteine metabolism. *Advances in Enzyme Regulation, 44(1), 321-333.*

[23] Purohit, V., Abdelmalek, M. F., Barve, S., Benevenga, N. J., Halsted, C. H., Kaplowitz, N., ... and Zakhari, S. (2007). Role of S-adenosylmethionine, folate, and betaine in the treatment of alcoholic liver disease: summary of a symposium. The American Journal of Clinical Nutrition, 86(1), 14-24.

[24] Morgan, A. E., Salcedo-Sora, J. E., and Mc Auley, M. T. (2024). A new mathematical model of folate homeostasis in E. coli highlights the potential importance of the folinic acid futile cycle in cell growth. *BioSystems, 235, 105088.*

[25] Reed, M. C., Nijhout, H. F., Sparks, R., and Ulrich, C. M. (2004). A mathematical model of the methionine cycle. Journal of Theoretical Biology, 226(1), 33-43.

[26] Dale, R., and Mosher, R. (2024). Mathematical model of RNA-directed DNA methylation predicts tuning of negative feedback required for stable maintenance. *Open Biology, 14(11).*

[27] Latham, T., Gilbert, N., and Ramsahoye, B. (2008). DNA methylation in mouse embryonic stem cells and development. Cell and Tissue Research, 331(1), 31-55.

[28] Danbaba, U. A., Aloko, M. D., and Ayinde, A. M. (2024). Mathematical modeling of mosquito borne diseases with vertical transmissions as applied to Dengue. *International Journal of Mathematical Sciences and Optimization: Theory and Applications, 10(3), 31-56.*

[29] Isah, N., Ibrahim, M. O., Isah, B. Y., and Magaji, B. A. (2024). Bifurcation Analysis of an Age Structured Malaria Model. International Journal of Mathematical Sciences and Optimization: Theory and Applications, 10(3), 106-132.

[30] Zagkos, L., Mc Auley, M., Roberts, J., and Kavallaris, N. I. (2019). Mathematical models of DNA methylation dynamics: Implications for health and ageing.*Journal of Theoretical Biology, 462, 184-193.*

[31] Braun, M., and Golubitsky, M. (1983). Differential equations and their applications (Vol. 4). New York: Springer.

[32] Nagle, R., Saff, E., and Snider, A. (2014). Fundamentals of Differential Equations.*Evaluation, 3, 4.*

*[33] Nijhout, H. F., Reed, M. C., Lam, S. L., Shane, B., Gregory III, J. F., and Ulrich, C. M. (2006). In silico experimentation with a model of hepatic mitochondrial folate metabolism.*Theoretical Biology and Medical Modelling, 3(1), 40.

[34] Nwanaji-Enwerem, J. C., Colicino, E., Gao, X., Wang, C., Vokonas, P., Boyer, E. W., ... and Schwartz, J. (2021). Associations of plasma folate and vitamin B6 with blood DNA methylation age: an analysis of one-carbon metabolites in the VA normative aging study. *The Journals of Gerontology: Series A, 76(5), 760-769.*

[35] McGovern, A. P., Powell, B. E., and Chevassut, T. J. (2012). A dynamic multi-compartmental model of DNA methylation with demonstrable predictive value in hematological malignancies. Journal of Theoretical Biology, 310, 14-20.