A Mathematical Study to Gout Symptoms

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Abstract

Gout is a form of inflammatory arthritis characterized by sharp pain and severe swelling. Gout is known as the disease of kings since it its strongly associated with a diet rich in fructose and beer. Gout has a substantial effect on physical function, productivity, quality of life, and health care costs. It often causes severe pain and physical disability. Furthermore, Gout has no cure and it can lead to death. Gout is common in most countries in North America, Western Europe and Asia. More than eight million people in the U.S., almost 4% of the population, are estimated to suffer from gout. Gout is caused by the chronic elevation of uric acid levels in the blood. Recent studies suggest that a high uric acid concentration is the result of a dynamical process that highlights the interactions between leptin production, insulin resistance, low muscle mass and a diet rich in fructose. Once individuals develop hyperuricemia or reach a high uric acid concentration greater than 7 mg/dL for men and 6 mg/dL for women, they become susceptible to developing gout. We propose a novel dynamic system to analyze and determine the connections between a diet involving different levels of fructose (in both adult men and women in the U.S.) and the concentration of uric acid in the blood. Our model simulations suggest that adult males under a diet containing levels of fructose stimulating a 0.5 uric acid growth rate, could surpass the high uric acid concentration threshold after around 10000 days, while women pass the threshold in about 5000 days with a diet stimulating a 0.4 growth rate.

1 Introduction

Gout is the most common form of inflammatory arthritis and is caused by the chronic elevation of serum uric acid levels above the saturation level for monosodium urate crystal formation [1]. The deposition of monosodium urate crystals, which occurs predominantly in peripheral joints and long-term deposition of monosodium urate crystals, can result in joint damage. Gout has a substantial effect on physical function, productivity, quality of life, and health care costs. It

often causes severe pain and physical disability. Gout is also associated with metabolic syndrome, cardiovascular diseases and renal diseases [2–4]. Furthermore, Gout has no cure and it can lead to death [5,6].

The proportion of individuals within a population with gout is highly variable across various regions of the world. However, gout is common in most countries in North America , Western Europe and Asia [1,7]. More than eight million people in the U.S., almost 4% of the population, are estimated to suffer from gout [8]. Although no formal survey has been undertaken in Canada, gout is generally thought to affect 3% of adults [9]. Greece has the highest reported prevalence of gout in Europe, at 4.75% of the adult population [10]. Using data from the Aotearoa New Zealand Health Tracker, in which the case definition of gout was consistent across ethnic groups, Pacific islanders and Maori had a threefold greater risk of gout than those of European descent after adjustment for age and sex, the crude prevalence estimates in adults being 7.63%, 6.06% and 3.24% in 2009 in these three groups respectively [11].

Gout is associated with increased blood levels of uric acid, called hyperuricemia. Uric acid is the end product of purine metabolism in humans, which is mainly known for its harmful effects such as gout and uric lithiasis, as well as its association with renal disease, metabolic syndrome, hypertension [1,12]. Although there is no universally accepted definition of hyperuricemia, it is often defined as an in-blood uric acid concentration greater than 7 mg/dL for men and greater than 6.0 mg/dL for women [13]. In women, high levels of uric acid are mainly found in postmenopausal women, African Americans, patients with renal disease and alcohol intake [14]. Physiologically, uric acid plasma concentrations increases with age; they are lower in women of childbearing age and, in post menopause women, it increase to comparable concentrations to those found in males [2].

Uric acid is the end product of purine metabolism in humans due to the loss of uricase activity by the evolution of hominids, which leads to higher uric acid levels in humans [15]. Uric acid is formed by the liver and mainly excreted by the kidneys and intestines [16]. The main mechanism of excretion of the concentrations of uric acid occurs by means of renal excretion, hence, glomerular function markers are positively associated with hyperuricemia. Several factors are associated as cause and consequences of high uric acid concentration, eg. diet, obesity [15,17,18]. while the role played by a diet on high uric acid concentration has not yet been fully clarified, a high intake of fructose-rich industrialized food and high beer intake seem to influence uricemia [19]; this association has categorized gout as the disease of kings.

Generally, nutrients are assimilated and ingested in the bloodstream after eating. Once visceral adiposity reach a threshold of lipid storage, the body begins to synthesize and secrete leptin and insulin. Leptin production and insulin resistence can increase uric acid serum concentrations since an increase in their synthesis reduces the excretion of uric acid. Observations show that uric acid

concentration increases in blood with insulin resistance since hyperinsulinemia could cause lower renal uric acid excretion [20]. In addition, several studies found that uric acid serum concentrations are also related to leptin concentration [21], thus suggesting it as a factor responsible for uric acid concentration increase in obese patients [22]. Furthermore, low muscle mass is negatively associated with the concentration of uric acid [23] and oxidative stress produced by excessive uric acid can influence muscle mass reduction. Muscle mass reduction is associated with low-intensity chronic inflammation that causes uric acid levels to increase in order to protect the organism against the moderate oxidative stress.

With continuous improvements in living standards, the metabolic syndrome in developed countries is also increasing [1]. Mathematical and computational modeling has become a widely accepted tool in biology and the medical sciences. Recently, mathematical models have been proven to be an effective research methodology for human metabolic processes whether their use is to explain processes behind empirical observations or to create new testable hypotheses. For instance, Curto *et al.* [24] analyzed three mathematical models of purine metabolism in humans, for physiological and moderately pathological perturbations in metabolites or enzymes; the results of the three models are consistent with clinical findings. Tolic *et al.* [25], analyzed a mathematical model of the insulin-glucose feedback regulation in men and the results suggest that interactions between the oscillatory insulin supply and the receptor dynamics can be of minute significance only.

On the other hand, theoretical results have been implemented to develop new hypotheses and strategies in treating metabolic conditions. For example, Li and Kuang [26] analyzed a mathematical model of glucose-insulin with a time delay that provides qualitatively robust dynamics for a hypothetical clinical application. Song and Thomas [27] developed a differential equation model describing the dynamics of stored energy in the form of fat mass, lean body mass, and ketone body mass during prolonged starvation. They were able to determine the amount of time an individual with specific initial conditions will survive starvation. Pearson *et al.* [28] derived a system of differential equations that describes the transport between and storage in different tissues of the human body and the results were confirmed by experimental data. Similarly, Song *et al.* [29] analyzed a model of insulin delivery with impulsive and time delays and demonstrated that a smaller dose with higher delivery frequency is better. Furthermore, theoretical models have also been proposed to describe different processes in the human body. For instance, Jacquier et al. [30] proposed a mathematical model of the leptin-leptin receptor system based on the assumption that leptin is a regulator of its own receptor activity; Zhao et al. [31] poposed a model describing the role of leptin in the regulation of adipose tissue mass and Rodriguez et al. [32] proposed a model of neuroinflammation in individuals with Parkinson's Disease. Similarly, the interaction between insulin, leptin, uric acid and the metabolism is complex, but the dynamics could be accurately

captured using a mathematical model and an analysis similar to the ones previously mentioned. In this paper we would like to propose a mathematical model that describes the interaction between insulin, leptin, uric acid and the metabolism and to our knowledge this process has never been modeled before.

The rest of this paper is organized as follows. The model formulation is presented in the Section 2. In Section 3, we present the mathematical analysis for the developed model and for several specific cases. In Section 4, we run simulations and present some results directly linking fat mass, diet and uric acid concentration. Finally in Section 5, we list several short-comings for our models and future directions to improve this study.

2 Methodology

In this paper, we would like to study what is the relationship between Uric acid(U), Fat mass(F), Muscle mass(M), Leptin(L) and Insulin resistance(I) using mathematical models.In particulr, we will be using a system of differential equations to describe the process of the interaction between food and body composition on the total uric acid concentration.

2.1 Model Description

The model is primarily based on the biological process proposed by Erick Prado de Oliveira and Roberto Carlos Burini [23].

Assuming that the main factors affecting uric acid concentration are the following variables: fat mass (F), muscle mass (M), leptin (L) and insulin resistance (I) (see Figure 1 and Table 1).

Table 1: Definition of state variables

Variables	meanings	Unit
F	fat mass in body	kg
M	muscle mass in body	kg
L	concentration of leptin in body	ug/dL
I	concentration of insulin in body	ug/dL
U	concentration of uric acid in body	mg/dL

After reducing the system presented the mechanism, we obtain the system presented in Figure 1, which will be used through out this study. The system focuses on the interaction between the interaction of food intake and body composition. We say that food intake promotes fat, muscle and uric acid growth. At the same time, high quantities of fat promote the secretion of Leptin and

Insulin. Leptin reduces appetite and thus has a direct impact on the growth rates of fat, muscle and uric acid. Excess insulin promotes resistance and both leptin and insulin resistance reduce excretion of uric acid from the body. Low muscle mass also reduce excretion of uric acid and hence increase uric acid concentration in the body. Lastly, high levels of uric acid promotes muscle death. From these specific interactions we are able to derive and propose the following system of differential equations.
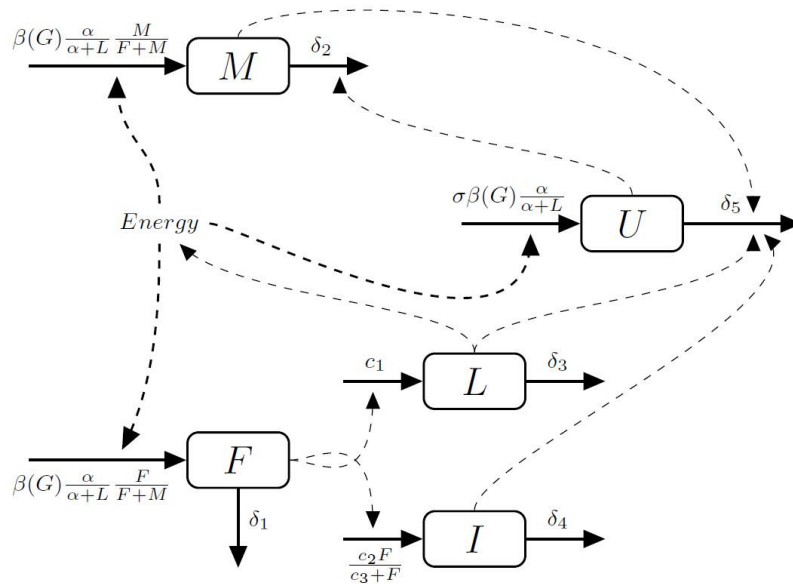

Figure 1: Schematic diagram of the mathematical model.

$$\frac{dF}{dt} = \beta(G)\left(\frac{\alpha}{\alpha+L}\right)\left(\frac{F}{F+M}\right) - \delta_1 F,$$

$$\frac{dM}{dt} = \beta(G)\left(\frac{\alpha}{\alpha+L}\right)\left(\frac{M}{F+M}\right) - \delta_2 M - \varepsilon_1 U M,$$

$$\frac{dL}{dt} = c_1 F - \delta_3 L, \tag{1}$$

$$\frac{dI}{dt} = \frac{c_2 F}{c_3 + F} - \delta_4 I,$$

$$\frac{dU}{dt} = \sigma\beta(G)\frac{\alpha}{\alpha+L} - \mu(L, I, M)U.$$

with initial conditions

$$F(0) > 0, M(0) > 0, L(0) > 0, I(0) > 0, U(0) > 0.$$

and where $\beta(G)$ denotes energy intake rate as a function of body weight G; Function $\mu(L, I, M)$ denotes the excretion rate of uric acid which decreases when L, I increase, and increases when M increases.

All definition parameters can be find in Table 2.

Table 2: Definition of the parameters

Parameters	Biological meanings	Unit
α	half saturation constant of the leptin energy intake reduction	ug/dL
c_1	production rate of leptin from fat mass	μg/kg dL day
c_2	fat mass is transported across insulin	μg/dL day
c_3	half saturation constant of insulin secretion	kg
δ_1	decay rate of fat mass	1/day
δ_2	decay rate of muscle mass	1/day
δ_3	decay rate of leptin	1/day
δ_4	decay rate of insulin	1/day
ε_1	rate of muscle mass reduction due to uric acid	dL/μg day
σ	production rate of uric acid from energy intake	mg/(dL kg day)

3 Model analysis

Due to the complexity of the general model, the analysis is complicated and thus in this section, we will discuss several special cases of the general Model (1).

3.1 Case 1

We assume $G = F + M + B$, where B denotes bone mass and is constant. We assume that the functions $\beta(G) = \beta * (F + M + B) = \beta(F + M + B)$, and $\mu(L, I, M) = \frac{\delta_5}{\eta + \gamma_1 L + \gamma_2 I} + \varepsilon_2 M$, where parameters $\beta, \eta, \gamma_1, \gamma_2, \delta_5, \varepsilon_2$ are constant and listed in Table 3. Then we can obtain the following

model:

$$\frac{dF}{dt} = \beta(F + M + B)\left(\frac{\alpha}{\alpha + L}\right)\left(\frac{F}{F + M}\right) - \delta_1 F,$$

$$\frac{dM}{dt} = \beta(F + M + B)\left(\frac{\alpha}{\alpha + L}\right)\left(\frac{M}{F + M}\right) - \delta_2 M - \varepsilon_1 UM,$$

$$\frac{dL}{dt} = c_1 F - \delta_3 L, \tag{2}$$

$$\frac{dI}{dt} = \frac{c_2 F}{c_3 + F} - \delta_4 I,$$

$$\frac{dU}{dt} = \sigma\beta(F + M + B)\left(\frac{\alpha}{\alpha + L}\right) - \frac{\delta_5 U}{\eta + \gamma_1 L + \gamma_2 I} - \varepsilon_2 MU.$$

Table 3: Definition of the parameters

Parameters	Biological meanings	Unit
β	energy intake rate to body	1/day
δ_5	decay rate of uric acid	1/day
ε_2	constant rate of uric acid influence muscle mass	dL/(μg day)
η	constant rate	μg/dL
γ_1	constant rate of leptin influence uric acid	dL/ug
γ_2	constant rate of insulin influence uric acid	dL/ug

For model (2), the equilibria and stability analysis are still complicated. Hence, we will be running simulations and present the results in section 4.

3.2   Case 2

For case 2, we suppose function $\beta(G)$ and $\mu(\mu(L, I, M))$ are the same as in case 1. In addition we now assume that food allocation is proportional to the body weight G. We can now simplify simplify model (2) to:

$$\frac{dF}{dt} = \beta\frac{\alpha}{\alpha + L}F - \delta_1 F,$$

$$\frac{dM}{dt} = \beta\frac{\alpha}{\alpha + L}M - \delta_2 M - \varepsilon_1 UM,$$

$$\frac{dL}{dt} = c_1 F - \delta_3 L, \tag{3}$$

$$\frac{dI}{dt} = \frac{c_2 F}{c_3 + F} - \delta_4 I,$$

$$\frac{dU}{dt} = \sigma\beta(F + M)\left(\frac{\alpha}{\alpha + L}\right) - \frac{\delta_5}{\eta + \gamma_1 L + \gamma_2 I}U - \varepsilon_2 UM.$$

Model (3) has four equilibria with explicit form:

$$E_3^1 = (0, 0, 0, 0, 0),$$

$$E_3^2 = \left(0, \frac{(\delta_2 - \beta)\delta_5}{\eta(\beta\varepsilon_2 - \beta\varepsilon_1\sigma - \varepsilon_2\delta_2)}, 0, 0, \frac{\beta - \delta_2}{\varepsilon_1}\right),$$

$$E_3^3 = \left(\frac{\alpha\delta_3(\beta - \delta_1)}{c_1\delta_1}, 0, \alpha(\frac{\beta}{\delta_1} - 1), \frac{\alpha c_2\delta_3(\beta - \delta_1)}{\delta_4(\alpha\delta_3(\beta - \delta_1) + c_1c_3\delta_1)}, U_*\right),$$

$$E_3^4 = \left(\frac{\alpha\delta_3(\beta - \delta_1)}{c_1\delta_1}, M_3^*, \alpha(\frac{\beta}{\delta_1} - 1), \frac{\alpha c_2\delta_3(\beta - \delta_1)}{\delta_4(\alpha\delta_3(\beta - \delta_1) + c_1c_3\delta_1)}, \frac{\delta_1 - \delta_2}{\varepsilon_1}\right)$$

where

$$U^* = \frac{\alpha\delta_3\sigma(\beta - \delta_1)\left(\alpha^2\delta_3\delta_4\gamma_1(\beta - \delta_1)^2 + \alpha\delta_1(\beta - \delta_1)(c_1c_3\delta_4\gamma_1 + c_2\delta_3\gamma_2 + \delta_3\delta_4\eta) + c_1c_3\delta_1^2\delta_4\eta\right)}{c_1\delta_1\delta_4\delta_5(\alpha\delta_3(\beta - \delta_1) + c_1c_3\delta_1)},$$

$$M_3^* = \frac{\alpha^2\delta_3^2\varepsilon_1\sigma(\beta - \delta_1)^2(\alpha\delta_4\gamma_1(\beta - \delta_1) + \delta_1(c_2\gamma_2 + \delta_4\eta)) + \Lambda}{c_1(\delta_1(\varepsilon_2 - \varepsilon_1\sigma) - \delta_2\varepsilon_2)(\alpha^2\delta_3\delta_4\gamma_1(\beta - \delta_1)^2 + \alpha\delta_1(\beta - \delta_1)(c_1c_3\delta_4\gamma_1 + c_2\delta_3\gamma_2 + \delta_3\delta_4\eta) + c_1c_3\delta_1^2\delta_4\eta)};$$

$$\Lambda = \alpha c_1\delta_1\delta_3\delta_4(\beta - \delta_1)(c_3\varepsilon_1\sigma(\alpha\gamma_1(\beta - \delta_1) + \delta_1\eta) + \delta_5(\delta_2 - \delta_1)) + c_1^2c_3\delta_1^2\delta_4\delta_5(\delta_2 - \delta_1).$$

For Model (3) we can easily see that all solutions are positively invariant.

Next, we study the existence and stability conditions for the equilibria of the system,

Theorem 3.1 (i) Model (3) always has equilibrium $E_3^1 = (0, 0, 0, 0, 0)$, when $\beta < \delta_1$ and $\beta < \delta_2$, then equilibrium E_3^1 is globally asymptotically stable; Otherwise, it is unstable;

(ii) If $\delta_2 < \beta < \delta_1$ and $\beta\varepsilon_1\sigma > \varepsilon_2(\beta - \delta_2)$, then equilibrium E_3^2 exist, and if $\Phi < 0$, then it is a locally stable,

where

$$\Phi = \sqrt{\alpha^2 c_3^2\delta_5\epsilon_1^2\eta^2\left(\beta^2\epsilon_1^2\sigma^2(4\eta(\delta_2 - \beta) + \delta_5) + 8\beta\epsilon_1\epsilon_2\eta\sigma(\beta - \delta_2)^2 + 4\epsilon_2^2\eta(\delta_2 - \beta)^3\right)} - \alpha\beta c_3\delta_5\epsilon_1^2\eta\sigma;$$

(iii) If $\delta_1 < \beta < \delta_2$, then equilibrium E_3^3 exist;

(iv) If $\beta > \delta_1 > \delta_2$ and $M_3^* > 0$, then equilibrium E_3^4 exist.

Proof. (i) For Model (3), we can easy find that equilibrium $E_3^1 = (0, 0, 0, 0, 0)$ always exist.

The linearization matrix of Model (3) is

$$J_1 = \begin{pmatrix} \beta\frac{\alpha}{\alpha+L} - \delta_1 & 0 & -\frac{\alpha\beta F}{(\alpha+L)^2} & 0 & 0 \\ 0 & \frac{\alpha\beta}{\alpha+L} - \delta_2 - \varepsilon_1 U & -\frac{\alpha\beta M}{(\alpha+L)^2} & 0 & \varepsilon_1 M \\ c_1 & 0 & -\delta_3 & 0 & 0 \\ \frac{c_2c_3}{(c_3+F)^2} & 0 & 0 & \delta_4 & 0 \\ \frac{\alpha\beta\sigma}{\alpha+L} & \frac{\alpha\beta\sigma}{\alpha+L} - \varepsilon_2 U & -\frac{\alpha\beta\sigma(F+M)}{(\alpha+L)^2} + \frac{\gamma_1\delta_5 U}{(\eta+\gamma_1 L+\gamma_2 I)^2} & \frac{\gamma_2\delta_5 U}{(\eta+\gamma_1 L+\gamma_2 I)^2} & -\frac{\delta_5}{\eta+\gamma_1 L+\gamma_2 I} - \varepsilon_2 M \end{pmatrix}.$$

Hence, the Jacobian matrix around E_3^1 is

$$J(E_3^1) = \begin{pmatrix} \beta - \delta_1 & 0 & 0 & 0 & 0 \\ 0 & \beta - \delta_2 & 0 & 0 & 0 \\ c_1 & 0 & -\delta_3 & 0 & 0 \\ \frac{c_2}{c_3} & 0 & 0 & -\delta_4 & 0 \\ \beta\sigma & \beta\sigma & 0 & 0 & -\frac{\delta_5}{\eta} \end{pmatrix}$$

The characteristic polynomial of the matrix $J(E_3^1)$ is:

$$(\lambda - (\beta - \delta_1))(\lambda - (\beta - \delta_2))(\lambda + \delta_3)(\lambda + \delta_4)(\lambda + \frac{\delta_5}{\eta}) = 0 \qquad (*)$$

The eigenvalues of the characteristic polynomial (*) is

$$\lambda_1 = \beta - \delta_1, \quad \lambda_2 = \beta - \delta_2, \quad \lambda_3 = -\delta_3, \quad \lambda_4 = -\delta_4, \quad \lambda_5 = -\frac{\delta_5}{\eta}.$$

Thus, we can obtain that $E_3^1 = (0,0,0,0,0)$ is locally asymptotically stable if $\beta < \delta_1$ and $\beta < \delta_2$, otherwise it is unstable.

From the first equation of system (3), we have

$$\frac{dF}{dt} = \beta \frac{\alpha}{\alpha + L} F - \delta_1 F \leq (\beta - \delta_1)F. \qquad (**)$$

Integrating both sides of $(**)$ and taking limit yields

$$\lim_{t\to\infty} F(t) \leq \lim_{t\to\infty} F(0)e^{(\beta-\delta_1)t}.$$

If $\beta < \delta_1$ then $\lim_{t\to\infty} F(t) = 0$.

From the second equation of system (3), we have

$$\frac{dM}{dt} = \beta \frac{\alpha}{\alpha + L} M - \delta_2 M - \varepsilon_1 U M \leq (\beta - \delta_2)M.$$

Similarly, we have $\lim_{t\to\infty} M(t) = 0$, if $\beta < \delta_2$.

For the third equation of system (3), multiplying by the factor $e^{\delta_3 t}$, we have

$$\frac{d(Le^{\delta_3 t})}{dt} = e^{\delta_3 t}\frac{dL}{dt} + \delta_3 Le^{\delta_3 t} = c_1 Fe^{\delta_3 t}. \qquad (***)$$

We can find that solution of the the differential equation $(***)$ is

$$L(t) = L(0)e^{-\delta_3 t} + e^{-\delta_3 t} \int_0^t c_1 Fe^{\delta_3 t}ds.$$

Then we have $\lim_{t\to\infty} L(t) = 0$ if $\lim_{t\to\infty} F(t) = 0$. Similarly, we also have $\lim_{t\to\infty} I(t) = 0$ if $\lim_{t\to\infty} F(t) = 0$.
For the final equation of system (3), we get $\lim_{t\to\infty} U(t) = 0$ when $\lim_{t\to\infty} F(t) = 0$, $\lim_{t\to\infty} M(t) = 0$,

$\lim\limits_{t \to \infty} L(t) = 0$ and $\lim\limits_{t \to \infty} I(t) = 0$. In conclusion, we can deduce that equilibrium E_3^1 is globally asymptotically stable when $\beta < \delta_1$ and $\beta < \delta_2$.

The result show that if individuals are not able to get a minimal energy intake, then they will die.

(ii) For Model (3), when $\beta < \delta_1$, we can obtain

$$\frac{dF}{dt} = \beta\frac{\alpha}{\alpha + L}F - \delta_1 F \leq (\beta - \delta_1)F$$

then $F(t) \to 0$ when $t \to \infty$.

From the third and fourth equations of model (3), we can easy find that $L(t) \to 0$ and $I(t) \to 0$ when $F(t) \to 0$. Hence, when $\beta > \delta_2$ and $\beta\varepsilon_1\sigma > \varepsilon_2(\beta - \delta_2)$, then $M = \frac{(\delta_2 - \beta)\delta_5}{\eta(\beta\varepsilon_2 - \beta\varepsilon_1\sigma - \varepsilon_2\delta_2)} > 0$ and $U = \frac{\beta - \delta_2}{\varepsilon_1} > 0$, hence equilibrium E_3^2 exist.

The linearization matrix of Model (3) around E_3^2 is

$$J(E_3^2) = \begin{pmatrix} \beta - \delta_1 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta(\beta - \delta_2)\delta_5}{\alpha\eta(\beta(\epsilon_2 - \epsilon_1\sigma) - \delta_2\epsilon_2)} & 0 & \frac{(\beta - \delta_2)\delta_5\epsilon_1}{\eta(\beta(\epsilon_2 - \epsilon_1\sigma) - \delta_2\epsilon_2)} \\ c_1 & 0 & -\delta_3 & 0 & 0 \\ \frac{c_2}{c_3} & 0 & 0 & -\delta_4 & 0 \\ \beta\sigma & \frac{-\beta\epsilon_2 + \delta_2\epsilon_2 + \beta\epsilon_1\sigma}{\epsilon_1} & \frac{(\beta - \delta_2)\delta_5\left(\frac{\gamma_1}{\epsilon_1} + \frac{\beta\eta\sigma}{\alpha\beta\epsilon_2 - \alpha\delta_2\epsilon_2 - \alpha\beta\epsilon_1\sigma}\right)}{\eta^2} & \frac{(\beta - \delta_2)\delta_5\gamma_2}{\epsilon_1\eta^2} & \frac{\beta\delta_5\epsilon_1\sigma}{\beta\epsilon_2\eta - \delta_2\epsilon_2\eta - \beta\epsilon_1\sigma\eta} \end{pmatrix}$$

The eigenvalues of the matrix $J(E_3^2)$ are:

$$\lambda_1 = \beta - \delta_1, \qquad \lambda_2 = -\delta_3, \qquad \lambda_3 = -\delta_4,$$

$$\lambda_4 = \frac{\sqrt{\alpha^2 c_3^2 \delta_5 \epsilon_1^2 \eta^2 \left(\beta^2 \epsilon_1^2 \sigma^2 (4\eta(\delta_2 - \beta) + \delta_5) + 8\beta\epsilon_1\epsilon_2\eta\sigma(\beta - \delta_2)^2 + 4\epsilon_2^2\eta(\delta_2 - \beta)^3\right)} - \alpha\beta c_3\delta_5\epsilon_1^2\eta\sigma}{2\alpha c_3\epsilon_1\eta^2(\beta\epsilon_1\sigma - \beta\epsilon_2 + \delta_2\epsilon_2)}$$

$$\lambda_5 = -\frac{\sqrt{\alpha^2 c_3^2 \delta_5 \epsilon_1^2 \eta^2 \left(\beta^2 \epsilon_1^2 \sigma^2 (4\eta(\delta_2 - \beta) + \delta_5) + 8\beta\epsilon_1\epsilon_2\eta\sigma(\beta - \delta_2)^2 + 4\epsilon_2^2\eta(\delta_2 - \beta)^3\right)} + \alpha\beta c_3\delta_5\epsilon_1^2\eta\sigma}{2\alpha c_3\epsilon_1\eta^2(\beta\epsilon_1\sigma - \beta\epsilon_2 + \delta_2\epsilon_2)}$$

From the value of λ_4, λ_5, we have the denominator greater than 0 if $\beta\varepsilon_1\sigma > \varepsilon_2(\beta - \delta_2)$. Hence, we can see that λ_4, λ_5 have negative real parts when $\Phi < 0$.

As a result, equilibrium E_3^2 exist and is locally stable when $\beta < \delta_1$, $\beta > \delta_2$, $\beta\varepsilon_1\sigma > \varepsilon_2(\beta - \delta_2)$, and $\Phi < 0$.

(iii) For the Model (3), when $\beta < \delta_2$, we can obtain

$$\frac{dM}{dt} = \beta\frac{\alpha}{\alpha + L}M - \delta_2 M - \varepsilon_1 UM < (\beta - \delta_2)M$$

then $M(t) \to 0$ when $t \to \infty$. The result show that the muscle mass will die out if $\beta < \delta_2$.

When $\beta > \delta_1$, we can find that $\frac{\alpha\delta_3(\beta - \delta_1)}{c_1\delta_1} > 0$, $\alpha(\frac{\beta}{\delta_1} - 1) > 0$, $\frac{\alpha c_2\delta_3(\beta - \delta_1)}{\delta_4(\alpha\delta_3(\beta - \delta_1) + c_1 c_3\delta_1)} > 0$, $U_* > 0$. Hence, E_3^3 exists.

(iv)We know that $\frac{\alpha\delta_3(\beta-\delta_1)}{c_1\delta_1} > 0$, $\alpha(\frac{\beta}{\delta_1} - 1) > 0$, $\frac{\alpha c_2\delta_3(\beta-\delta_1)}{\delta_4(\alpha\delta_3(\beta-\delta_1)+c_1c_3\delta_1)} > 0$, when $\beta > \delta_1$ and $\frac{\delta_1-\delta_2}{\varepsilon_1} > 0$ when $\delta_1 > \delta_2$. Hence, Model (3) has a positive equilibrium E_4^4 when $\beta > \delta_1 > \delta_2$ and $M_3^* > 0$. □

Theorem 3.1 shows that the condition for global asymptotically stability of equilibrium E_3^1, namely, when energy intake rate $\beta < \delta_1$ and $\beta < \delta_2$, then Fat, Muscle, Insulin, Leptin and Uric acid all die or get depleted.

3.3 Case 3

From Model (3), we suppose $\gamma_2 = 0$, namely we don't consider the influence of insulin on the excretion of uric acid, thus we consider the following model:

$$\begin{aligned}
\frac{dF}{dt} &= \beta\frac{\alpha}{\alpha+L}F - \delta_1 F, \\
\frac{dM}{dt} &= \beta\frac{\alpha}{\alpha+L}M - \delta_2 M - \varepsilon_1 UM, \\
\frac{dL}{dt} &= c_1 F - \delta_3 L, \\
\frac{dU}{dt} &= \sigma\beta(F+M)\left(\frac{\alpha}{\alpha+L}\right) - \frac{\delta_5}{\eta+\gamma_1 L}U - \varepsilon_2 UM.
\end{aligned} \tag{4}$$

For Model (4), we find the following equilibrium points:

$E_4^1 = (0,0,0,0)$,

$E_4^2 = \left(0, \dfrac{\delta_5(\beta-\delta_2)}{\eta(\beta\sigma\varepsilon_1 - \beta\varepsilon_2 + \delta_2\varepsilon_2)}, 0, \dfrac{\beta-\delta_2}{\varepsilon_1}\right)$,

$E_4^3 = \left(\dfrac{\alpha\delta_3(\beta-\delta_1)}{c_1\delta_1}, 0, \dfrac{\alpha(\beta-\delta_1)}{\delta_1}, \dfrac{\alpha\delta_3\sigma(\beta-\delta_1)(\alpha\gamma_1(\beta-\delta_1)+\delta_1\eta)}{c_1\delta_1\delta_5}\right)$,

$E_4^4 = \left(\dfrac{\alpha\delta_3(\beta-\delta_1)}{c_1\delta_1}, \dfrac{\alpha\delta_3\sigma\varepsilon_1(\beta-\delta_1)(\alpha\gamma_1(\beta-\delta_1)+\delta_1\eta)+c_1\delta_1\delta_5(\delta_2-\delta_1)}{c_1(\alpha\gamma_1(\beta-\delta_1)+\delta_1\eta)(\delta_1(\varepsilon_2-\sigma\varepsilon_1)-\delta_2\varepsilon_2)}, \dfrac{\alpha(\beta-\delta_1)}{\delta_1}, \dfrac{\delta_1-\delta_2}{\varepsilon_1}\right)$.

Again we primarily study the existence and stability condition of the equilibria.

Let

$$\begin{aligned}
A_1 &= \frac{\delta_1(\delta_1-\beta)\delta_3}{c_1\beta}, \\
A_2 &= \frac{\delta_1^2(c_1\delta_1(\delta_1-\delta_2)\delta_5 - \alpha(\beta-\delta_1)\delta_3\varepsilon_1(\alpha\gamma_1(\beta-\delta_1)+\delta_1\eta)\sigma)}{c_1\alpha\beta(\alpha\gamma_1(\beta-\delta_1)+\delta_1\eta)(\delta_1(\varepsilon_2-\varepsilon_1\sigma)-\delta_2\varepsilon_2)}, \\
A_3 &= -\frac{\varepsilon_1(c_1\delta_1(\delta_2-\delta_1)\delta_5 + \alpha(\beta-\delta_1)\delta_3\varepsilon_1(\alpha\gamma_1(\beta-\delta_1)+\delta_1\eta)\sigma)}{c_1(\alpha\gamma_1(\beta-\delta_1)+\delta_1\eta)(\delta_1(\varepsilon_2-\varepsilon_1\sigma)-\delta_2\varepsilon_2)}, \\
B &= \frac{-\delta_1\varepsilon_2 + \delta_2\varepsilon_2 + \delta_1\varepsilon_1\sigma}{\varepsilon_1},
\end{aligned}$$

$$C = (\delta_1 - \delta_2) \left(\frac{\gamma_1 \delta_5}{\varepsilon_1 \left(\alpha \gamma_1 \left(\frac{\beta}{\delta_1} - 1 \right) + \eta \right)^2} + \frac{\delta_1 \left(c_1 \delta_1^2 \delta_5 - \alpha(\beta - \delta_1)\delta_3 \varepsilon_2 (\alpha \gamma_1 (\beta - \delta_1) + \delta_1 \eta) \right) \sigma}{c_1 \alpha \beta (\alpha \gamma_1 (\beta - \delta_1) + \delta_1 \eta)(\delta_1 (\varepsilon_2 - \varepsilon_1 \sigma) - \delta_2 \varepsilon_2)} \right),$$

$$D = \frac{\varepsilon_1 \left(c_1 \delta_1^2 \delta_5 - \alpha(\beta - \delta_1)\delta_3 \varepsilon_2 (\alpha \gamma_1 (\beta - \delta_1) + \delta_1 \eta) \right) \sigma}{c_1 (\alpha \gamma_1 (\beta - \delta_1) + \delta_1 \eta)(\delta_1 (\varepsilon_2 - \varepsilon_1 \sigma) - \delta_2 \varepsilon_2)}.$$

and

$$a_1 = \delta_3 - D,$$

$$a_2 = -(A_1 C + A_3 B + \delta_3 D),$$

$$a_3 = A_1 C D - A_3 B \delta_3,$$

$$a_1 = A_1 A_3 B C.$$

Theorem 3.2 Consider system (4):

(i) Model (4) always has equilibrium $E_4^1 = (0,0,0,0)$, when $\beta < \delta_1$ and $\beta < \delta_2$, then equilibrium E_4^1 is globally asymptotically stable; Otherwise, it is unstable;

(ii) If $\delta_2 < \beta < \delta_1$, and $\beta \varepsilon_1 \delta > \varepsilon_2 (\beta - \delta_2)$, then equilibrium E_4^2 exist, and if $\Psi < 0$, then it is a locally stable equilibrium,

where

$$\Psi = \sqrt{\alpha^2 \delta_5 \eta^2 \epsilon_1^2 \left(\beta^2 \sigma^2 \varepsilon_1^2 (4\eta(\delta_2 - \beta) + \delta_5) + 8\beta \eta \sigma \varepsilon_1 \varepsilon_2 (\beta - \delta_2)^2 + 4\eta \varepsilon_2^2 (\delta_2 - \beta)^3 \right)} - \alpha \beta \delta_5 \eta \sigma \varepsilon_1^2;$$

(iii) If $\delta_1 < \beta < \delta_2$, then equilibrium E_4^3 exists; and if $\Omega < 0$ and $\Pi < 0$, then it is a locally stable equilibrium,

where

$$\Omega = \frac{1}{2} \left(\frac{c_1 \delta_1 \delta_3 \delta_5 (4\delta_1(\delta_1 - \beta) + \beta \delta_3)(\alpha \gamma_1 (\beta - \delta_1) + \delta_1 \eta)}{\sqrt{\beta c_1^2 \delta_1^2 \delta_3 \delta_5^2 (4\delta_1(\delta_1 - \beta) + \beta \delta_3)(\alpha \gamma_1 (\beta - \delta_1) + \delta_1 \eta)^2}} - \delta_3 \right)$$

$$\Pi = -\frac{\alpha \delta_3 \sigma \varepsilon_1 (\beta - \delta_1)(\alpha \gamma_1 (\beta - \delta_1) + \delta_1 \eta)}{c_1 \delta_1 \delta_5} + \delta_1 - \delta_2$$

(iv) If $\beta > \delta_1 > \delta_2$ and $H > 0$, then the positive equilibrium E_4^4 exists, if $\Delta_1 > 0, \Delta_2 > 0, \Delta_3 > 0, \Delta_4 > 0$ then it is a locally stable equilibrium,

where

$$H = \frac{\alpha \delta_3 \sigma \varepsilon_1 (\beta - \delta_1)(\alpha \gamma_1 (\beta - \delta_1) + \delta_1 \eta) + c_1 \delta_1 \delta_5 (\delta_2 - \delta_1)}{c_1 (\alpha \gamma_1 (\beta - \delta_1) + \delta_1 \eta)(\delta_1 (\varepsilon_2 - \sigma \varepsilon_1) - \delta_2 \varepsilon_2)}$$

and

$$\Delta_1 = a_1, \quad \Delta_2 = a_1 a_2 - a_3, \quad \Delta_3 = a_1 a_2 a_3 - a_1^2 a_4 - a_3^2, \quad \Delta_4 = a_4 \Delta_3.$$

Proof. For Model (4), we can calculate the Jacobian matrix:

$$J_2 = \begin{pmatrix} \beta\frac{\alpha}{L+\alpha} - \delta_1 & 0 & -\frac{\alpha\beta F}{(L+\alpha)^2} & 0 \\ 0 & \frac{\alpha\beta}{\alpha+L} - \delta_2 - \varepsilon_1 U & -\frac{\alpha\beta M}{(L+\alpha)^2} & M\varepsilon_1 \\ c_1 & 0 & -\delta_3 & 0 \\ \frac{\alpha\beta\sigma}{L+\alpha} & \frac{\alpha\beta\sigma}{L+\alpha} - \varepsilon_2 U & -\frac{\alpha\beta\sigma(F+M)}{(L+\alpha)^2} + \frac{\gamma_1\delta_5 U}{(\eta+\gamma_1 L)^2} & -\frac{\delta_5}{\eta+\gamma_1 L} - \varepsilon_2 M \end{pmatrix}.$$

(i),(ii) the proof is similar to the one for Theorem 4.1.

(iii) For Model (4), if $\delta_1 < \beta < \delta_2$, then equilibrium E_4^3 exists. From J_2, we have that the Jacobian matrix around E_4^3 is

$$J(E_4^3) = \begin{pmatrix} 0 & 0 & \frac{\delta_1(\delta_1-\beta)\delta_3}{c_1\beta} & 0 \\ 0 & \delta_1 - \delta_2 - \frac{\alpha(\beta-\delta_1)\delta_3\epsilon_1(\alpha\gamma_1(\beta-\delta_1)+\delta_1\eta)\sigma}{c_1\delta_1\delta_5} & 0 & 0 \\ c_1 & 0 & -\delta_3 & 0 \\ \delta_1\sigma & \frac{\left(c_1\delta_1^2\delta_5 - \alpha(\beta-\delta_1)\delta_3\epsilon_2(\alpha\gamma_1(\beta-\delta_1)+\delta_1\eta)\right)\sigma}{c_1\delta_1\delta_5} & \frac{(\beta-\delta_1)\delta_1^2\delta_3(\alpha\gamma_1-\eta)\sigma}{c_1\beta(\alpha\gamma_1(\beta-\delta_1)+\delta_1\eta)} & -\frac{\delta_5}{\alpha\gamma_1\left(\frac{\beta}{\delta_1}-1\right)+\eta} \end{pmatrix}.$$

The eigenvalues of the matrix $J(E_4^3)$ are

$$\lambda_1 = -\frac{\delta_1\delta_5}{\alpha\gamma_1(\beta - \delta_1) + \delta_1\eta},$$

$$\lambda_2 = \frac{1}{2}\left(-\frac{c_1\delta_1\delta_3\delta_5(4\delta_1(\delta_1 - \beta) + \beta\delta_3)(\alpha\gamma_1(\beta - \delta_1) + \delta_1\eta)}{\sqrt{\beta c_1^2\delta_1^2\delta_3\delta_5^2(4\delta_1(\delta_1 - \beta) + \beta\delta_3)(\alpha\gamma_1(\beta - \delta_1) + \delta_1\eta)^2}} - \delta_3\right),$$

$$\lambda_3 = \frac{1}{2}\left(\frac{c_1\delta_1\delta_3\delta_5(4\delta_1(\delta_1 - \beta) + \beta\delta_3)(\alpha\gamma_1(\beta - \delta_1) + \delta_1\eta)}{\sqrt{\beta c_1^2\delta_1^2\delta_3\delta_5^2(4\delta_1(\delta_1 - \beta) + \beta\delta_3)(\alpha\gamma_1(\beta - \delta_1) + \delta_1\eta)^2}} - \delta_3\right),$$

$$\lambda_4 = -\frac{\alpha\delta_3\sigma\varepsilon_1(\beta - \delta_1)(\alpha\gamma_1(\beta - \delta_1) + \delta_1\eta)}{c_1\delta_1\delta_5} + \delta_1 - \delta_2.$$

It is easy to show that $\lambda_1 < 0$ and $\lambda_2 < 0$ when $\beta > \delta_1$. Hence, equilibrium E_4^3 exists and is locally stable when $\delta_1 < \beta < \delta_2$, $\Omega < 0$ and $\Pi < 0$.

(iv) When $\beta > \delta_1 > \delta_2$ and $H > 0$, then equilibrium E_4^4 exists and all component of E_4^4 are positive. From J_2, we have that the Jacobian matrix around E_4^4 is

$$J(E_4^4) = \begin{pmatrix} 0 & 0 & A_1 & 0 \\ 0 & 0 & A_2 & A_3 \\ c_1 & 0 & -\delta_3 & 0 \\ \delta_1\sigma & B & C & D \end{pmatrix}$$

The characteristic polynomial of the matrix $J(E_4^4)$ is

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0$$

Using the Routh-Hurwitz criteria yield that the equilibrium E_4^4 is locally stable if $\Delta_1 = a_1 > 0$, $\Delta_2 = a_1a_2 - a_3 > 0$, $\Delta_3 = a_1a_2a_3 - a_1^2a_4 - a_3^2 > 0$ and $\Delta_4 = a_4\Delta_3 > 0$. Thus the proof is completed. $\qquad\square$

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Theorem 3.2 shows that the condition for stability of equilibrium E_4^4 depends on a implicit condition about parameters.

4   Simulation and Results

Based on simulations of our model and the special cases presented above combined with the knowledge that fructose is strongly associated with uric acid production, we now proceed to analyze the relationships between uric acid and energy intake. In particular, we want to explore the specific uric acid growth rates (σ) and their associated fructose proportions of the overall energy intake. Using the following parameters and initial conditions (see Table 4) $\alpha = 0.2$; $\beta = 0.6$; $\gamma_1 = 0.01$; $C_1 = 0.6$; $\gamma_2 = 0.01$; $C_2 = 1$; $C_3 = 0.01$; $\delta_1 = 0.001$; $\delta_2 = 0.001$; $\delta_3 = 0.1$; $\delta_4 = 0.01$; $\delta_5 = 0.0001$; $\eta = 20$; $\epsilon_1 = 0.00001$; $\epsilon_2 = 0.0001$; $F_0 = 88.8kg*0.165; 76.4*0.27kg$; $M_0 = 88.8*0.795; 76.4*0.6975$; $L_0 = 16$; $I_0 = 80$; $U_0 = 6.3; 4.9$; we were able to reach high levels of uric acid before losing all muscle mass.

Table 4: Average body composition by gender

	Men			Women		
Age	Fat	Muscle	Bone	Fat	Muscle	Bone
20-39	14%	82%	4%	27%	69.75%	3.25%
40-59	16.5%	79.5%	4%	29%	67.75%	3.25%
60-79	19%	77%	4%	30.5%	66.25%	3.25%
Average weight (kg)	88.8 [CDC]			76.4 [CDC]		

In Figure 2, we see the dynamics of the five variables and that 3 of them seem to reach equilibrium for the selected parameters. Nonetheless, the relationship between muscle mass and uric acid seems to be one of competition. The complexity is such that their interaction seems to eventually drive one to zero. Furthermore, we also found out that their relationship depended completely on the uric acid growth rate σ.

Using the parameters corresponding to males between 40-59 we were able to determine that the amount of time it will take to surpass the $7\mu g/dL$ threshold when $\sigma = 0.5$ is about 10000 days. Figure 3 shows the amount of time (in days) it will take to develop a high uric acid condition when $\sigma = 0.1, 0.3, 0.5$ (green, blue and red respectively). Similarly, Figure 4, shows the same threshold for American women (20-39 years old) when $\sigma = 0.1, 0.25, 0.4$ (green, blue and red respectively), suggesting that it would only take 5000 days and a production rate of $\sigma = 0.4$.
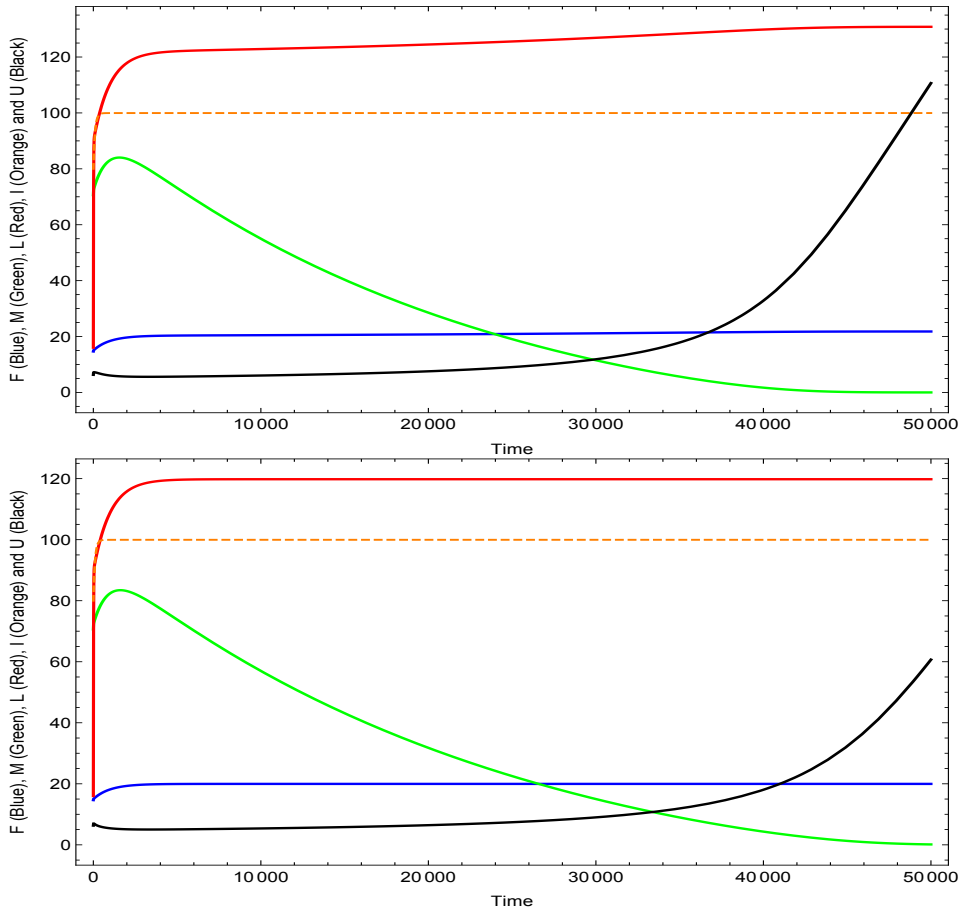
Figure 2: Simulations of the model for case 1 (above) and case 2 (below).
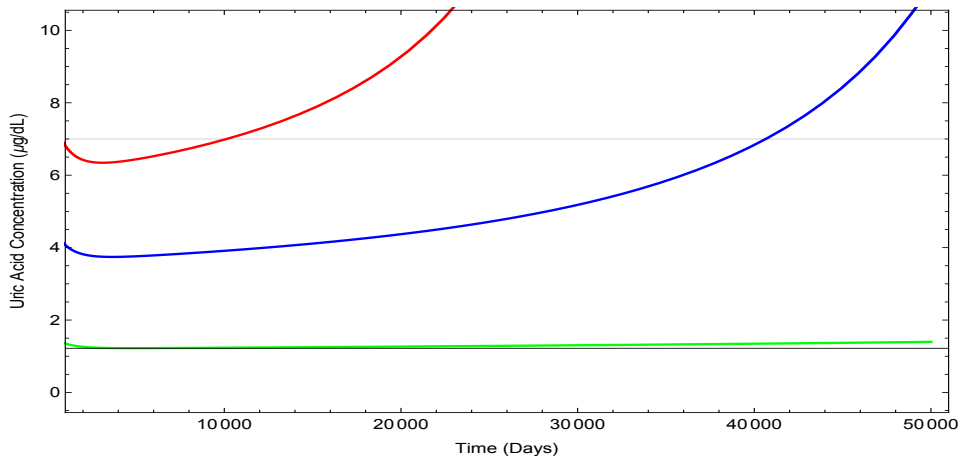

Figure 3: The relationship of uric acid concentration with the uric acid production rate as a result of energy intake in American males with ages 40-59.
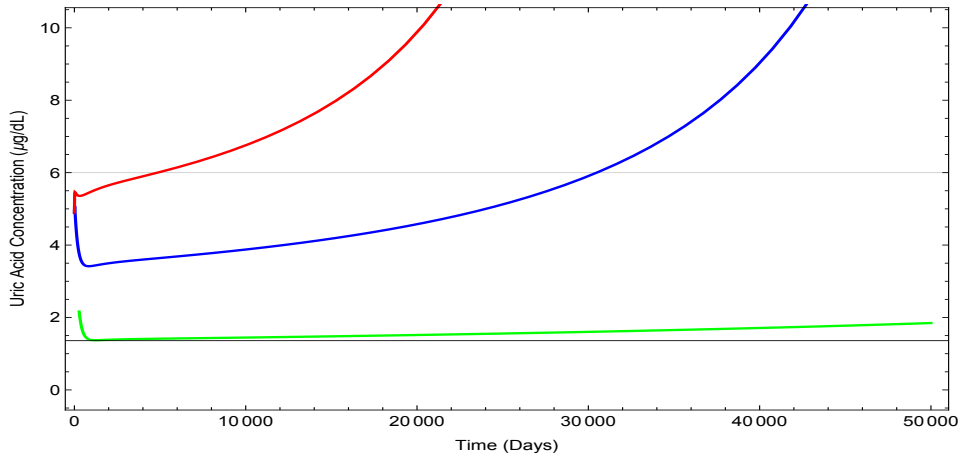
Figure 4: The relationship of uric acid concentration with the uric acid production rate as a result of energy intake in American females with ages 20-39.

From the simulations, we are able to observe a strong association between the hyperuricimia threshold and initial fat mass in combination with uric acid production rate and the amount of time required to surpass the threshold concentration for both males and females. Nonetheless, studies show that only post-menopausal women have comparable uric acid dynamics to men. This suggest that the energy intake stimulates lower levels of uric acid production when dealing with women in the first two age categories in Table 4 and thus an inhibition or an extra parameter directly impacting uric acid production.

5   Conclusion and Future work

Developed countries tend to have a higher prevalence of gout than developing countries, and seem to have increasing prevalence and incidence of the disease [1]. This suggest that the implementation of mathematical model to study gout will become more and more important. The dynamic model, we proposed in this paper describes the concentration of uric acid in the blood as a result of fat mass and energy intake (diet); since high uric acid is the primary cause of developing gout. In fact, due to the complexity of the biological mechanism of the uric acid action pathway and energy balance in an individual, we had to use a simplified form of the biological process for the concentration of uric acid. Thus, there are still many ways to improve and better calibrate this process.

In addition to fat mass, muscle mass, insulin, leptin, diet, there are many factors such as blood pressure, triglycerides and inflammation, that are known to affect the concentration of uric acid.

The models in this paper does not incorporate these factors although they could alter the stability of system. In the future, we will incorporate the effect of these factors on uric acid production and concentration.

For instance, muscle mass reduction is associated with increasing uric acid uric acid concentration levels. This is believed to be a defensive mechanism in order to protect the organism against the moderate oxidative stress associated with muscle mass decrease [?]. In this paper, we only think about the bilinear functional effect between the interaction of muscle mass and uric acid, however, it has not yet been clarified what the cause or effect is or whether there are differences in these reactions when we have individuals of both genders.

In addition, uric acid concentrations are independently related to leptin concentration [22] and insulin resistance. Elevated levels of both would lower renal UA excretion rates [20]. The models in this paper consider that effect of insulin and leptin on uric acid concentration by function $\mu(L,I) = \frac{1}{\eta+\gamma_1 L+\gamma_2 I}$; however, there are different functions that show this inhibiting influence that needs to be considered, for example, $\mu(L,I) = exp(\eta - \gamma_1 L - \gamma_2 I)$.

Furthermore, results from the study in [33] show that about 70% of daily uric acid disposal occurs via the kidneys, and in 5-25% of humans, impaired renal excretion leads to hyperuricemia. This makes the kidneys the most prominent organs involved in the control of uric acid concentration. Modeling the kidneys will help us to determine the uric acid balance more accurately. We plan to extend our model to represent the regulatory process in the renal system at the molecular level. Lastly, it is possible that pre-existing conditions that affect the kidneys could also have a direct impact on the renal uric acid excretion rates.

Finally, data collection could have a tremendous impact in the calibration of the model parameters, something that at this point is difficult to do since the dynamics of this process are not measured in gout patients. Nonetheless, further studies via mathematical models could help develop important hypotheses regarding this biological process and motivate in depth studies at the molecular level, or direct the collection of appropriate data from individuals at the different stages to the development of gout.

6   Acknowledgments

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