Mathematically Modeling the Role of Triglyceride Production on Leptin Resistance

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Abstract

Diet-induced obesity is becoming more common all over the world, which is increasing the prevalence of obesity-induced chronic diseases such as diabetes, coronary heart disease, cancer, and sleep-apnea. Many experimental results show that obesity is often associated with an elevated concentration of plasma leptin and triglycerides. Triglycerides inhibit the passage of leptin across the blood brain barrier (BBB) to signal the hypothalamus to supress appetite. However, it is still not clear how triglyceride concentration affects leptin transport across the BBB and energy balance. In this paper, we propose a novel ordinary differential equations model describing the role of leptin in the regulation of adipose tissue mass. Analytical and numerical results are analyzed using biologically relevant parameter values. Additionally, we perform sensitivity analysis of the equilibria and study the sensitivity of triglyceride production on leptin resistance. Equilibria analysis and simulation results show that triglyceride production plays an important role in determining the fat mass in an individual. As weight increases, the occurrence of leptin resistance increases. Obesity enhances the likelihood of creating a vicious circle, where more fat mass leads to greater leptin resistance. Thus, control of the triglyceride production may be effective in reducing the occurrence of leptin resistance. Our results may provide new insight into the impact

of triglycerides on the regulation of leptin and adipose tissue mass, supporting a focus on triglyceride reduction as a potential weight management strategy.

1 Introduction

In 2014, more than 1.9 billion adults were overweight, over 600 million were obese, and most of the world's population live in countries where overweight and obesity increase mortality (WHO, [39]). Diet-induced obesity is becoming more common all over the world, which has increased the prevalence of obesity-induced chronic diseases, such as, diabetes, coronary heart disease, cancer and sleep-apnea [34]. Obesity is a chronic disease, and there are many factors that contribute to obesity, including environment, genetics, and cultural factors. Furthermore, experimental results show that obesity is often associated with elevated concentrations of plasma leptin [10].

Leptin is a product of the obese gene (OB) and plays a key role in the regulation of appetite, food intake and metabolism. Leptin provides the brain with signals that regulate energy intake and energy expenditure [23]. Leptin was identified an adipocyte-derived peptide hormone that circulates in the blood in concentrations proportional to whole body adipose tissue mass [42]. The major effects of leptin are alterations of energy balance, but it also affects basal insulin secretion, insulin resistance, and fatty acid oxidation [12]. Specifically, leptin elevation signals satiety and decreases hunger which leads to diminished energy intake [17]. Leptin in the blood can be free or bound to soluble leptin receptors (sOB-R) [21]. The leptin receptor is in the cytokine receptor family and the ratio of leptin to sOB-R decreases with weight loss [20]. The free leptin is suggested to be the bioactive form, as it is found in cerebrospinal fluid where the sOB-R is not found [22]. Leptin is sequestered in the blood by sOB-R which downregulates leptin binding to membrane bound leptin receptors (OB-Rb) [40] and excess sOB-R strongly inhibits OB-R binding [41]. Additionally, the proportion of bound leptin is much lower in obese than lean subjects [31], which indicates that obese patients have resistance to free leptin.

In the case of obesity, leptin concentration increases but hunger still remains which

indicates leptin resistance [14]. The direct mechanism of leptin resistance is unknown, but it is likely related to the transfer of leptin through the BBB [30]. Leptin crosses the BBB at an insulin independent, saturable rate [4], but this rate is decreased by elevated triglycerides which occurs in both starvation and obesity [2]. Additionally, mouse experiments show that high–fat feeding induces leptin resistance [12]. Reducing free triglycerides may be a method for improving leptin sensitivity. However, calorie restriction has been shown to decrease leptin levels far below the expected levels predicted by the decrease in fat mass [29]. Thus calorie restriction induces an elevated state of hunger. The mechanisms by which leptin mediates energy balance seems to be related to energy intake but not energy expenditure. However, glucose uptake is strongly associated with body mass index (BMI) and body fat percent [15]. Additionally, since lean body mass (LBM) correlates positively with RMR [14], leptin seems ineffective in increasing metabolism. Moreover, leptin concentration has a diurnal pattern [12] but is not affected by individual meals [38].

Triglycerides inhibit the passage of leptin across the BBB to signal the hypothalamus to suppress appetite. However, it is still not clear how triglyceride concentration affects leptin transport across the BBB and energy balance. The role of triglyceride production on the leptin resistance is a complicated problem with unknown mechanisms. Thus, we would like to know how leptin resistance affects weight management and whether obesity is a self-perpetuating state. In this paper, we will focus on two problems: (1) How does triglyceride concentration affect leptin transport across BBB and energy balance; (2) what factors contribute to the occurrence of leptin resistance.

As a growing number of people suffer from obesity, understanding the mechanisms by which leptin and triglycerides influence energy balance has been a subject of intensive research [17]. Interaction between leptin, fat tissues and metabolism by using a mathematical model is an effective research method. For example, Pearson et al. [28] derived a system of coupled differential equations that describe the transport of glucose between and storage in different tissues of the human body. Tam et al. [35] developed a physiologically–based mathematical model to simulate the regulatory effects of the leptin pathway on murine energy homeostasis. Song and Thomas [32] 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. Jacquier et al. [13] proposed a mathematical model of the leptin–leptin receptor system, based on the assumption that leptin is a regulator of its own receptor activity. Pattaranit and Van den Berg [27] proposed models for glucostasis, based on the glucose-insulin feedback control loop, and considered extensions to long-term energy balance, dislipidaemia and obesity. These results using a mathematical model motivate us to explore the biological implications of the relationship of leptin, obesity, and metabolism. One may refer to [19] for more relevant references.

The rest of this paper is organized as follows. The model formulation is presented in the next Section. In Section 3, model positivity and the existence conditions of equilibria of the model are established. A no triglyceride production scenario is considered as a baseline model, and a quasi-steady state approximation scenario is considered to analyze the dynamical behaviors of a reduced system, in which we obtain the local stability condition of the equilibria. In Section 4, we first estimate the biologically relevant parameters of our model and carry out numerical simulation of the model to support our theoretical results. Then, we compare the change of dynamical behaviors with respect to some important parameters, i.e., triglyceride production. We perform sensitivity analysis of two important existence and stability conditions in Section 5. In Section 6, we discuss the results of this research, and provide insight into the impact of triglycerides on the regulation of leptin and adipose tissue mass, supporting a focus on triglyceride reduction as a potential weight management strategy. In the final section, we list some potential short-comings and future directions.

2 Model Formulation

In this section, we present a mathematical model to study the role of leptin in the dynamics of energy balance. The model is based on the biological process proposed by Friedman and Halaas [11]. Generally, nutrients are ingested and absorbed in the blood-

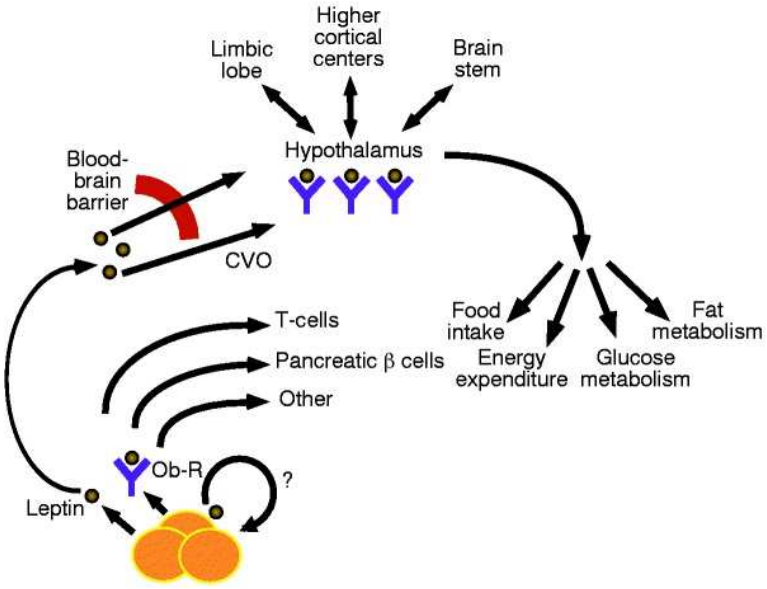

Figure 1: The leptin action pathway (source: Friedman and Halaas [11]).

stream after eating. Once adipocytes reach a threshold of lipid storage, these cells can synthesize and secrete leptin which travels through the circulatory system. It across the blood brain barrier to bind to receptors in the hypothalamus. Leptin activates two kinds of neuron signals in the hypothalams: pro–opiomelanocortin (POMC) and the agouti–related–protein (AgRP) neurons. POMC pathway responds to leptin through neuropeptides (such as the precursor of a-melanocyte-stimulating hormone), which can reduce the appetite of an individual [40]. Banks et al. [2] suggested that triglyceride–mediated leptin resistance may have evolved as an anti-anorectic mechanism during starvation. Decreasing triglycerides may potentiate the anorectic effect of leptin by enhancing leptin transport across the BBB. Thus, triglyceride-mediated leptin resistance plays an important role in leptin transport (One may see Figs. 1 and 2 for more details).

Based on the flow chart as given in Fig. 2, our state variables are:

F: the fat mass in body (kg),

L_p: the concentration of leptin in blood (μg/dL),

L_b: the concentration of leptin in brain (μg/dL),

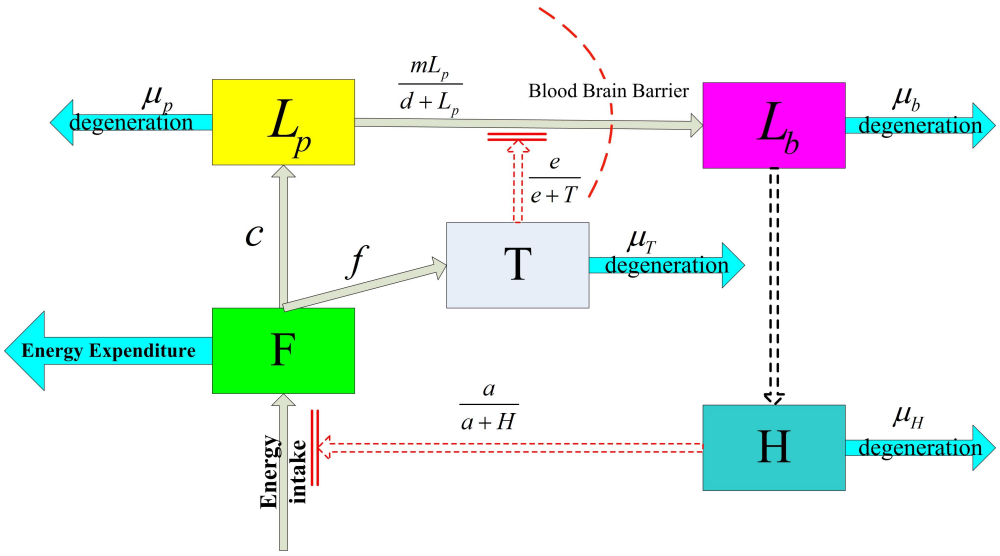

Figure 2: Flow chart of leptin action pathway.

T: the concentration of plasma triglyceride (mg/dL),

H: the concentration of hypothalamus related hormones (HRH) (IU/dL). (International units per deciliter).

Next, we first list some assumptions:

(1) Experimental results show that dietary intake is associated with body mass [18, 37]. Thus, we assume that the average food ingested is proportional to the fat mass at a constant rate b.

(2) Leptin can decrease an individual's food intake [17]. We assume that as leptin concentration increases, hypothalamus activity increases and energy intake decreases according to $\frac{a}{a+H(t)}$, where a is the half saturation constant of hypothalamus related hormone that decreases energy intake to one half.

(3) Adipose tissue can produce triglyceride [21], and we adjust leptin transport across the blood brain barrier by triglycerides with the function $\frac{e}{e+T(t)}$, where e is the half saturation constant of plasma triglyceride inhibition.

(4) Leptin is transported across the BBB by a saturable transporter [4]. Thus, we use a nonlinear saturable function $\frac{mL_p(t)}{d+L_p(t)}$ to describe this phenomenon with a maximum

transport rate, m, and the half saturate constant of leptin transport across BBB, d.

According to the mechanisms above, we can derive the following model:

$$\begin{cases} \frac{dF}{dt} = \left(\frac{ab}{a+H} - \delta\right) F, \\ \frac{dL_p}{dt} = cF - \frac{mL_p}{d+L_p}\frac{e}{e+T} - \mu_p L_p, \\ \frac{dL_b}{dt} = \frac{mL_p}{d+L_p}\frac{e}{e+T} - \mu_b L_b, \\ \frac{dT}{dt} = fF - \mu_T T, \\ \frac{dH}{dt} = nL_b - \mu_H H, \end{cases} \tag{1}$$

with initial conditions

$$F(0) = F_0 > 0,\ L_p(0) = L_{p0} > 0,\ L_b(0) = L_{b0} > 0,\ T(0) = T_0 > 0,\ H(0) = H_0 > 0. \tag{2}$$

All of parameters are positive constants and the corresponding biological meanings are listed in Table 1.

Table 1. The biological meanings of the parameters in model (1)

Parameters	Biological meanings	unit
a	half saturation of the HRH energy intake reduction	IU/dL
b	desired energy intake proportional to fat mass	1/day
δ	energy expenditure proportional to fat mass	1/day
c	secretion rate of leptin by fat mass	μg/dL day
m	maximum transport of leptin across BBB	μg/dL day
d	half saturation constant of leptin transport across BBB	μg/dL
e	half saturation constant of plasma triglyceride inhibition	mg/dL
f	production rate of triglyceride from fat mass	mg/kg dL day
n	production rate of HRH	IU/μg day
μ_p	decay rate of plasma leptin	1/day
μ_b	decay rate of leptin in brain	1/day
μ_H	decay rate of hypothalamus related hormones	1/day
μ_T	decay rate of plasma triglyceride	1/day

3 Mathematical analysis

In this section, we first consider some basic properties of model (1). Then, we shall discuss the stability of equilibria in two specific scenarios.

3.1 Basic properties of model (1)

Since $F(t) = 0, L_p(t) = 0, L_b(t) = 0, T(t) = 0, H(t) = 0$ is an equilibrium of model (1) and the trajectories of model (1) can not intersect with each other, all solutions of model (1) must remain positive.

Model (1) always has the fat-free equilibrium $E^0 = (0, 0, 0, 0, 0)$, which represents an extreme situation where an individual cannot obtain enough energy intake and they die.

The coexistence equilibria of model (1) may be negative, but the positive solutions are considered to be physiologically meaningful. Let $E^* = (F^*, L_p^*, L_b^*, T^*, H^*)$ be the positive equilibrium of model (1). Define

$$\Pi = \frac{f^2(L_b^*)^2\mu_b^2\left(\frac{d\mu_p}{L_b^*\mu_b} - 1\right)^2 + c^2e^2\mu_T^2\left(\frac{m}{L_b^*\mu_b} - 1\right)^2 + 4fL_b^*\mu_b ce\mu_T}{2ce\mu_T\left(\frac{m}{L_b^*\mu_b} + 1\right) fL_b^*\mu_b\left(\frac{d\mu_p}{L_b^*\mu_b} + 1\right)}. \tag{3}$$

We have the following results on the existence of equilibria of model (1).

Theorem 3.1.

1. *Model (1) always has the fat-free mass equilibrium* $E_0 = (0, 0, 0, 0, 0)$.

2. *If* $b < \delta$ *or* $\frac{e\mu_T m}{L_b^*\mu_b} < fF^* + e\mu_T$, *then model (1) has no positive equilibrium;*

3. *If* $b > \delta$, $\frac{e\mu_T m}{L_b^*\mu_b} > fF^* + e\mu_T$, $A_3 > 0$ *and* $A_2 < 0$, *then the positive equilibria are given by*

$$A_1F^{*2} + A_2F^* + A_3 = 0,$$

where

$$\begin{aligned} A_1 &= cf, \\ A_2 &= fL_b^*\mu_b\left(\frac{d\mu_p}{L_b^*\mu_b} - 1\right) - ce\mu_T\left(\frac{m}{L_b^*\mu_b} - 1\right), \\ A_3 &= e\mu_T L_b^*\mu_b\left(\frac{d\mu_p}{L_b^*\mu_b} + \frac{m}{L_b^*\mu_b} - 1\right). \end{aligned} \tag{4}$$

A saddle node bifurcation occurs at $\Pi = 1$, *i.e.,*

(i) if $\Pi = 1$, *then model (1) has a unique positive equilibrium* $E^* = (F^*, L_p^*, L_b^*, H^*, T^*)$, *where*

$$F^* = \frac{-A_2}{2A_1}; \tag{5}$$

(iii) if $\Pi > 1$, *then model (1) has two distinct endemic equilibria* $E_1^* = (F_1^*, L_{p1}^*, L_{b1}^*, H_1^*, T_1^*)$ *and* $E_2^* = (F_2^*, L_{p2}^*, L_{b2}^*, H_2^*, T_2^*)$, *where*

$$F_{1,2}^* = \frac{-A_2 \pm \sqrt{A_2^2 - 4A_1A_3}}{2A_1}. \tag{6}$$

Proof. The equilibria has an explicit form for two variables:

$$H^* = \frac{a(b-\delta)}{\delta} \quad L_b^* = \frac{\mu_H H^*}{n} = \frac{a\mu_H(b-\delta)}{n\delta} \tag{7}$$

If $b > \delta$, then $H^* > 0, L_b^* > 0$. And the other equilibria depend on F^*:

$$T^* = \frac{fF^*}{\mu_T}, \quad L_p^* = \frac{d(fF^* + e\,\mu_T)}{e\mu_T \frac{m}{L_b^*\mu_b} - (fF^* + e\mu_T)}, \tag{8}$$

If $\frac{e\mu_T m}{L_b^*\mu_b} > fF^* + e\mu_T$, then $L_p^* > 0$. Substituting (6) and (7) into $\frac{dL_p(t)}{dt} = 0$ of model (1), then the equilibria F^* is a root of the following equation,

$$L_b^*\mu_b(A_1F^{*2} + A_2F^* + A_3) = 0. \tag{9}$$

The existence of the equilibria depend on the positivity of

$$F^* = \frac{-A_2 \pm \sqrt{A_2^2 - 4A_1A_3}}{2A_1},$$

which gives 4 possibilities.

(1) $A_1 > 0$ always holds;

(2) $A_3 < 0$ gives 1 positive and 1 negative equilibria regardless of the sign of A_2;

(3) $A_3 > 0$ and $A_2 > 0$ gives 0 positive equilibrium;

(4) $A_3 > 0$ and $A_2 < 0$ give rise to 3 cases:

(i) if $A_2^2 - 4A_1A_3 > 0$, there are 2 positive equilibria; (ii) if $A_2^2 - 4A_1A_3 = 0$ there is 1 positive equilibria; (iii) if $A_2^2 - 4A_1A_3 < 0$ there are no positive equilibrium. Thus,

if $A_3 > 0$ and $A_2 < 0$, we may have a saddle node bifurcation. Following we check aforementioned condition:

Case (1):

If $A_3 < 0$, then

$$\frac{d\mu_p}{L_b^*\mu_b} + \frac{m}{L_b^*\mu_b} - 1 < 0,$$

which independently implies that

$$\frac{d\mu_p}{L_b^*\mu_b} - 1 < 0, \ \frac{m}{L_b^*\mu_b} - 1 < 0.$$

However, since

$$L_p^* = \frac{d(fF^* + e\mu_T)}{e\mu_T \frac{m}{L_b^*\mu_b} - (fF^* + e\mu_T)} = \frac{d}{\frac{e\mu_T}{fF^*+e\mu_T}\frac{m}{L_b^*\mu_b} - 1},$$

and

$$0 < \frac{e\mu_T}{fF^* + e\mu_T} < 1,$$

we have

$$\frac{e\mu_T}{fF^* + e\mu_T}\frac{m}{L_b^*\mu_b} - 1 < \frac{m}{L_b^*\mu_b} - 1 < 0,$$

which implies that $L_p^* < 0$. Thus $A_3 < 0$ is an invalid condition for the equilibria.

Case (2):

If $A_3 > 0$ and $A_2 < 0$, then $\frac{e\mu_p}{L_b^*\mu_b} + \frac{m}{L_b^*\mu_b} - 1 > 0$.

$$\begin{aligned} A_2^2 - A_1A_3 &= \left[fL_b^*\mu_b\left(\tfrac{d\mu_p}{L_b^*\mu_b} - 1\right) - ce\mu_T\left(\tfrac{m}{L_b^*\mu_b} - 1\right)\right]^2 - 4cfe\mu_T L_b^*\mu_b\left(\tfrac{d\mu_p}{L_b^*\mu_b} + \tfrac{m}{L_b^*\mu_b} - 1\right) \\ &= f^2(L_b^*)^2\mu_b^2\left(\tfrac{d\mu_p}{L_b^*\mu_b} - 1\right)^2 + c^2e^2\mu_T^2\left(\tfrac{m}{L_b^*\mu_b} - 1\right)^2 + 4fL_b^*\mu_b ce\mu_T \\ &\quad -2ce\mu_T\left(\tfrac{m}{L_b^*\mu_b} + 1\right)fL_b^*\mu_b\left(\tfrac{d\mu_p}{L_b^*\mu_b} + 1\right), \end{aligned} \tag{10}$$

Notice that $\Pi > 1$ implies $A_2^2 - 4A_1A_3 > 0$, $\Pi = 1$ implies $A_2^2 - 4A_1A_3 = 0$, and $\Pi < 1$ implies $A_2^2 - 4A_1A_3 < 0$. Thus, the proof of Theorem 3.1 is completed . □

Remark 3.1. Theorem 3.1 shows that a saddle node bifurcation occurs when $\Pi = 1$ (see Fig. 3). This implies that as the effect of triglyceride production f increases, more fat mass accumulates and produces more triglycerides. The effect of triglyceride on an individual's weight may result in different situations:

1. more fat mass → more triglyceride → high probability of leptin resistance → eat more → increase body mass → obesity;

2. less fat mass → less triglyceride → low probability of leptin resistance → eat less → maintain body mass → normal.

Thus, Π plays an important role in determining the occurrence of leptin resistance.

Theorem 3.2. If $b < \delta$, then the fat-free equilibrium of model (1) E_0 is global asymptotically stable; if $b > \delta$, then E_0 is unstable.

Proof. The linearization matrix of model (1) around the fat-free equilibrium E_0 is

$$J = \begin{pmatrix} b-\delta & 0 & 0 & 0 & 0 \\ c & -\frac{m}{d}-\mu_p & 0 & 0 & 0 \\ 0 & \frac{m}{d} & -\mu_b & 0 & 0 \\ f & 0 & 0 & -\mu_T & 0 \\ 0 & 0 & n & 0 & -\mu_H \end{pmatrix}, \tag{11}$$

The characteristic polynomial of the linearization matrix (11) is:

$$[\lambda-(b-\delta)]\big(\lambda+\frac{m}{d}+\mu_p\big)(\lambda+\mu_b)(\lambda+\mu_T)(\lambda+\mu_H)=0. \tag{12}$$

The eigenvalues of the characteristic polynomial (12) is:

$$\lambda_1=(b-\delta),\ \lambda_2=-\frac{m}{a}-\mu_p<0,\ \lambda_3=-\mu_b<0,\ \lambda_4=-\mu_T<0,\ \lambda_5=-\mu_H<0.$$

Thus, we can conclude that E_0 is locally stable if $b < \delta$, whereas unstable if $b > \delta$.

From the first equation of model (1), we can get

$$\frac{dF(t)}{dt}=\left(\frac{ab}{a+H(t)}-\delta\right)F(t)\le(b-\delta)F(t). \tag{13}$$

Integrating both sides of (13) and taking limit yields

$$\lim_{t\to\infty}F(t)\le\lim_{t\to\infty}F_0e^{(b-\delta)t}.$$

If $b < \delta$ then $\lim_{t\to\infty} F(t) = 0$. From the second equation of model (1), we can get

$$\frac{dL_p(t)}{dt}=cF(t)-\frac{mL_p(t)}{d+L_p(t)}\frac{e}{e+T(t)}-\mu_pL_p(t)\le cF(t)-\mu_pL_p(t). \tag{14}$$

Multiplying by the factor $e^{\mu_p t}$ and integrating both sides of (14), we have

$$L_p(t) \leq L_{p0}e^{-\mu_p t} + e^{-\mu_p t}\int_0^t cF(s)e^{\mu_p s}ds. \tag{15}$$

Taking the limit on both sides of (15) results in

$$\lim_{t\to\infty} L_p(t) \leq \lim_{t\to\infty} L_{p0}e^{-\mu_p t} + \lim_{t\to\infty} e^{-\mu_p t}\int_0^t cF(s)e^{\mu_p s}ds.$$

If $\lim_{t\to\infty} F(t) = 0$ then $\lim_{t\to\infty} L_p(t) = 0$. From the third equation of model (1) we know that

$$\frac{dL_b(t)}{dt} \leq \frac{mL_p(t)}{d + L_p(t)} - \mu_b L_b(t). \tag{16}$$

Taking the limit on both sides of (16), and it follows from $\lim_{t\to\infty} L_p(t) = 0$ that $\lim_{t\to\infty} L_b(t) = 0$. Similarly, we can prove that $\lim_{t\to\infty} T(t) = 0$ and $\lim_{t\to\infty} H(t) = 0$. We therefore can conclude that E_0 is globally asymptotically stable if $b < \delta$. $\square$

3.2 Two specific scenarios

Now, we consider a special case of the model (1) viewed as a baseline model used to compare the effect of triglyceride production on fat mass and plasma leptin.

Scenario (i): No triglyceride production

If $f = 0$, then $\frac{dT(t)}{dt} = -\mu_T T(t)$, and we have $\lim_{t\to\infty} T(t) = \lim_{t\to\infty} T_0 e^{-\mu_T t} = 0$. We can simplify model (1) to:

$$\begin{cases} \frac{dF(t)}{dt} = \left(\frac{ab}{a+H(t)} - \delta\right) F(t), \\ \frac{dL_p(t)}{dt} = cF(t) - \frac{mL_p(t)}{d+L_p(t)} - \mu_p L_p(t), \\ \frac{dL_b(t)}{dt} = \frac{mL_p(t)}{d+L_p(t)} - \mu_b L_b, \\ \frac{dH(t)}{dt} = nL_b(t) - \mu_H H(t). \end{cases} \tag{17}$$

The model has two equilibria with explicit form:

$$EE_0 = (0, 0, 0, 0),\ EE^* = (F^*, L_P^*, L_b^*, H^*),$$

where $F^* = \frac{\mu_b L_b^*(m-\mu_b L_b^*)+d\mu_p\mu_b L_b^*}{c(m-\mu_b L_b^*)}, L_p^* = \frac{d\mu_b L_b^*}{m-\mu_b L_b^*}, L_b^* = \frac{a\mu_H(b-\delta)}{n\delta}$, and $H^* = \frac{a(b-\delta)}{\delta}$. Then we have

Theorem 3.3. For model (17),

(i) if $b < \delta$, then model (17) has a fat–free equilibrium EE_0, and it is stable;

(ii) if $b > \delta$, and $\frac{mn\delta}{a\mu_b\mu_H(b-\delta)} > 1$, then model (17) has one positive equilibrium EE^*, and it is semi-stable.

Proof. (i) It similar to the proof of Theorem 3.2, so we omit it.

(ii) We can calculate that The linearization matrix of model (1) around the positive equilibrium EE^* is

$$J = \begin{pmatrix} 0 & 0 & 0 & 0 \\ c & -\frac{md}{(d+L_p^*)^2} - \mu_p & 0 & 0 \\ 0 & \frac{md}{(d+L_p^*)^2} & -\mu_b & 0 \\ 0 & 0 & n & -\mu_H \end{pmatrix}. \tag{18}$$

The eigenvalues of characteristic polynomial of the linearization matrix of model (17) around the positive equilibrium EE^* are given by:

$$\lambda_1 = 0,\ \lambda_2 = -\frac{md}{(d+L_p^*)^2} - \mu_p < 0,\ \lambda_3 = -\mu_b < 0,\ \lambda_4 = -\mu_H < 0.$$

One of the eigenvalues of the characteristic polynomial of matrix (18) is $\lambda = 0$, thus we can only know that the positive equilibrium EE^* is semi–stable, and its stability needs to be determined by center manifold theory.

Scenario (ii): Quasi-steady state approximation

Since it is difficult to analyze the stability of model (1), we consider the long-term behavior by analyzing a quasi-steady state approximation, which can provide biological insight about the effect of triglyceride production on leptin resistance.

We assume the quasi-steady states for leptin in brain and triglyceride. This is a reasonable assumption, since the time scales of these processes are much shorter than the other factors, e.g., fat mass, hypothalamus related hormones, plasma leptin. Letting L_b, and H go to quasi-steady state, i.e., $T(t) \to \frac{fF(t)}{\mu_T}$ and $L_b(t) \to \frac{mL_p(t)}{\mu_b(d+L_p(t))}\frac{e}{e+\frac{fF(t)}{\mu_T}}$. Then,

we obtain the following system:

$$\begin{cases} \frac{dF(t)}{dt} = (\frac{ab}{a+H(t)} - \delta)F(t), \\ \frac{dL_p(t)}{dt} = cF(t) - \frac{mL_p(t)}{d+L_p(t)}\frac{s}{s+F(t)} - \mu_p L_p(t), \\ \frac{dH(t)}{dt} = \frac{rmL_p(t)}{d+L_p(t)}\frac{s}{s+F(t)} - \mu_H H(t), \end{cases} \tag{19}$$

where $s = \frac{e\mu_T}{f}, r = \frac{1}{n\mu_b}$.

Model (19) has a fat–free equilibrium point $E_0 = (0, 0, 0)$ and the following equilibria:

$$H^* = \frac{a(b-\delta)}{\delta},\ L_{pi}^* = \frac{d(fF_i^* + e\,\mu_T)}{\frac{e\mu_T mn}{\mu_H H^* \mu_b} - (fF_i^* + e\mu_T)},\quad i = 1, 2,$$

and F^* is a root of equation given by:

$$\frac{\mu_H \mu_b H^*}{n}(A_1 F^{*2} + A_2 F^* + A_3) = 0, \tag{20}$$

where A_1, A_2, A_3 are given in (4), which H^* is replaced by L_b^*. Thus, according to Theorem 2.1, we know that if $b > \delta, \frac{mn\delta}{\mu_H \mu_b a(b-\delta)} > \frac{fF_i^*}{e\mu_T} + 1, i = 1, 2,\ A_2 < 0, A_3 > 0$ and $\Pi > 0$, then model (19) has two positive equilibria $E_1^* = (F_1^*, L_{p1}^*, H^*)$ and $E_2^* = (F_2^*, L_{p2}^*, H^*)$, where $F_1^* > F_2^*$.

Let

$$\Phi = \Phi_1 \Phi_2,\quad \text{where}\quad \Phi_1 = \frac{\mu_p L_{p1}^*}{s + F_1^*} - \frac{cd}{d + L_{p1}^*},\quad \text{and}\quad \Phi_2 = \frac{\mu_p L_{p2}^*}{s + F_2^*} - \frac{cd}{d + L_{p2}^*}.$$

Following we study the stability of the equilibria, E_0, E_1^* and E_2^*.

Theorem 3.4. For the system of equations as shown in (19),

1. If $b < \delta$, then it has only the fat-free equilibrium $E_0 = (0, 0, 0)$, and it is stable;
2. If $b > \delta, \frac{mn\delta}{\mu_H \mu_b a(b-\delta)} > \frac{fF_i^*}{e\mu_T} + 1, i = 1, 2$, and $A_2 < 0, A_3 > 0$ and $\Pi > 1$, then it has two positive equilibria E_1^* and E_2^*, and if $\Phi < 0$, then it has a locally stable equilibrium and an unstable equilibrium.

Proof. The linearization matrix of model (19) around E_1^* is

$$J = \begin{pmatrix} 0 & 0 & -\frac{abF_1^*}{(a+H^*)^2} \\ c + \frac{ms}{(s+F_1^*)^2}\frac{L_{p1}^*}{d+L_{p1}^*} & -\frac{md}{(d+L_{p1}^*)^2}\frac{s}{s+F_1^*} - \mu_p & 0 \\ -\frac{rms}{(s+F_1^*)^2}\frac{L_{p1}^*}{d+L_{p1}^*} & \frac{rmd}{(d+L_{p1}^*)^2}\frac{s}{s+F_1^*} & -\mu_H \end{pmatrix}. \tag{21}$$

The characteristic polynomial of the linearization matrix (21) is:

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{22}$$

where

$$\begin{aligned}
a_1 &= \frac{md}{(d+L_{p1}^*)^2}\frac{s}{s+F_1^*} + \mu_H + \mu_p > 0,\\
a_2 &= \frac{ms}{(s+F_1^*)^2}\frac{L_{p1}^*}{d+L_{p1}^*}r\frac{abF_1^*}{(a+H^*)^2} + \mu_p\mu_H + \mu_H\frac{md}{(d+L_{p1}^*)^2}\frac{s}{s+F_1^*} > 0,\\
a_3 &= \frac{ms}{(s+F_1^*)(d+L_{p1}^*)}\left(\frac{\mu_p L_{p1}^*}{s+F_1^*} - \frac{cd}{d+L_{p1}^*}\right),
\end{aligned}$$

Using the Routh-Hurwitz criteria yields that

$$\begin{aligned}
H_1 &= a_1 > 0,\\
H_2 &= a_1a_2 - a_3\\
&= \left(\mu_H + \tfrac{md}{(d+L_p^*)^2}\tfrac{s}{s+F^*}\right)\left(r\tfrac{ms}{(s+F^*)^2}\tfrac{L_p^*}{d+L_p^*}\tfrac{abF^*}{(a+H^*)^2} + \mu_p\mu_H + \mu_H\tfrac{md}{(d+L_p^*)^2}\tfrac{s}{s+F^*}\right)\\
&\quad +\mu_p^2\mu_H\tfrac{md}{(d+L_p^*)^2}\tfrac{s}{s+F^*} + cr\tfrac{abF^*}{(a+H^*)^2}\tfrac{md}{(d+L_p^*)^2}\tfrac{s}{s+F^*} > 0,
\end{aligned}$$

and it follows from $a_3 > 0$ that $H_3 > 0$. Thus, we can derive that: If $\frac{\mu_p L_{p1}^*}{s+F_1^*} > \frac{cd}{d+L_{p1}^*}$, then the positive equilibrium $E_1^* = (F_1^*, L_{p1}^*, H^*)$ is locally stable. Similarly, if $\frac{\mu_p L_{p2}^*}{s+F_2^*} > \frac{cd}{d+L_{p2}^*}$, then the positive equilibrium $E_2^* = (F_2^*, L_{p2}^*, H^*)$ is locally stable. $\Phi = \Phi_1\Phi_2 < 0$ implies $\frac{\mu_p L_{p1}^*}{s+F_1^*} > \frac{cd}{d+L_{p1}^*}$ or $\frac{\mu_p L_{p2}^*}{s+F_2^*} > \frac{cd}{d+L_{p2}^*}$, thus the proof is completed.

□

Remark 3.2. Theorem 3.4 implies that the condition for stability of either positive fat mass equilibria F_i^* depend on $\Phi < 0$. From a biological viewpoint, the stability of a positive fat mass equilibrium is determined by Φ, which can be defined as the fat mass stability condition.

4 Parameters estimation and simulation

In this section, we first explain the various parameters and their biologically relevant values displayed in Tables 2 and 3. Then, we use these parameters to numerically check

the obtained theoretical results. Next, we simulate some extreme situations to discuss the role of triglyceride and energy intake on the models dynamical behaviors, which can provide meaningful biological insight.

4.1 Parameters estimation

- The half maximum transfer rate constant of leptin across BBB is d. Since a 50% reduction of BBB net influx of leptin was found at 339ng per mouse [4], we assume a similar concentration for humans, and calculate the concentration in human blood based on the volume of mouse blood, which is approximately 95ml/kg, and the mice used in the study were CD-1 which have a body weight of approximately 35g, thus we have

$$d = \frac{339\text{ng}}{\text{mouse}} \frac{\text{mouse}}{35\text{g}} \frac{1000\text{g}}{\text{kg}} \frac{\text{kg}}{95\text{mL}} \frac{100\text{mL}}{\text{dL}} \frac{\mu\text{g}}{1000\text{ng}} = 10.1955\mu\text{g/dL}.$$

- The maximum transfer rate of leptin across the BBB is m. The rate of transfer of radiolabeled leptin was measured to be $(5.87)10^{-4}$mL/g-min, which was negatively affected by labeled leptin [4]. Thus there is a maximum saturable rate of transfer. The perfusion is μL of blood per gram of brain tissue, measured by radiolabeled leptin. The amount of transfered peptide is determined by a ratio of counts per minute (cpm) of brain tissue compared to blood cpm. Then the brain/blood ratio is a fraction of counts per gram of brain per counts per μL of blood [3]. Assuming that the ratio of counts per minute is the same as that of total molecule and the brain mass for an adult human is about 1.4 kg [9], we can calculate that

$$m = (5.87)10^{-4} \frac{\text{mL}}{\text{g min}} (1400\text{g}) \frac{1}{5\text{L blood}} \frac{\text{L}}{1000\text{mL}} \frac{24 \cdot 60\text{min}}{\text{day}} = 0.2367/\text{day}.$$

- The half maximum BBB transfer rate inhibition by triglyceride is e. The relation between triglyceride concentration and leptin transport during whole milk administration fit a regression $Y = 22.6 - 0.044X$, where Y is brain/serum ratio in μL/g and X is triglyceride concentration in mg/dL [2]. So we assume that e is the value

of X that yields $Y = 11.3$. Utilizing

$$11.3 = 22.6 - 0.044X$$

results in $X = e = 256.82$, which is just slightly above the clinical threshold for elevated triglycerides (200mg/dL).

- The production rate of leptin by fat mass is c. The rate of whole body leptin production averaged 3.2 ng/100 $\text{g}^{-1}\text{min}^{-1}$ as a function of fat mass [16]. Thus for our purposes we rescale to μg/dL assuming an average person has 5L of blood:

$$\frac{3.2\text{ng}}{100\text{g}}\frac{\mu\text{g}}{1000\text{ng}}\frac{1}{5\text{L}}\frac{\text{L}}{10\text{dL}}\frac{1000\text{g}}{\text{kg}}\frac{24\cdot 60\text{min}}{\text{day}} = 0.9216\frac{\mu\text{g}}{\text{dL kg day}}.$$

- The fat "burning" rate is δ. Under conditions of no food intake ($b = 0$), Consolazio [7] showed that an average of 9.5% of body weight is reduced in 10 days. Additionally, fluid loss was about 650g per day over the 10 days, which we ignored in the fat mass reduction. The body fat percent was not listed, but assumed to be about 27.45%. With a starting average weight of about 77 kg, we can calculate

$$G(10) = (0.2745)(77)e^{-\delta 10} = (0.2745)\left((1-.095)(77) + (0.65)(10)\right),$$

then we can get $\delta = 0.05215$ day^{-1} .

- The production rate of triglyceride T by fat mass is f. It is variable on diet and its rate changes based on fructose consumption [33].

- The production of hypothalamus related hormones stimulated by letpin in brain is n. Since H is a pseudo biological term that represents a variety of downstream signalling pathways, there is no measure from literature.

- In males, mean percentage body fat is about 22.9 % . In females, mean percentage body fat is about 32.0 % [6]. Thus, we can take a mean value of mean percentage body fat of males and females, 27.45 %. Taking a 77kg normal individual as an example, we can get the initial value of fat mass is $77\text{kg} \times 27.45\% = 21.1365$ kg.

- The triglyceride level is a blood test to measure the amount of triglycerides in blood. The normal value ranges of triglyceride may vary slightly among different laboratories, but a typical average is about 150 mg/dL [24].

- The remaining parameter values were chosen to qualitatively, match observations from literature.

Table 2. The value of the parameters in model (1)

Parameters	Value	source	unit
a	1.9	assumed	IU/mL
b	0.073	assumed	1/hour
δ	0.05215	[7]	1/hour
c	0.9216	[16]	μg/dL hour kg
m	0.2367	[4, 3, 9]	μg/dL hour
d	10.1955	[4]	μg/dL
e	256.82	[2]	mg/dL
f	0.4	[33]	mg/dL kg day
n	0.025	assumed	IU/ dL day
μ_p	2	assumed	1/day
μ_b	0.2	assumed	1/day
μ_H	0.01	assumed	1/day
μ_T	0.0571	assumed	1/day

Table 3. The intial value of model (1)

Parameters	Value	source	unit
F_0	21.1365	[6]	kg
L_{p0}	1.2	[26]	μg/dL
L_{b0}	0.12	calculated	μg/dL
T_0	150	[24]	mg/dL
H_0	0.1	assumed	IU/dL

4.2 Bifurcation simulation

Theorem 3.1 demonstrates that food intake greater than expenditure ($b > \delta$) is not sufficient to guarentee a positive equilibria. There exists a condition, $\Pi \geq 1$, that is necessary for any nontrivial equilibria to appear. The nontrivial equilibria that occur for $\Pi > 1$ comes in a pair, the low-fat equilibra and the high-fat equilibria. Thus this condition gives rise to a saddle node bifurcation. To analyze the stability of these equilibria, we must rely on numerical simulations as the eigenvalues are analytically intractable. Using the parameter values in Table 2, we compare the equilibrium value of fat mass (F^*) as the triglyceride production rate (f) varies.

The bifurcation diagram (Fig. 3) shows that the reduced fat equilibrium is locally attractive, while the high-fat mass equilibria is unstable. This indicates that for a given rate of triglyceride production, the initial fat-mass will determine if trajectories approach the reduced-fat equilibria or increase to infinity. Additionally, as triglyceride production approaches 0, the basin of attraction becomes much larger which means it is easier to maintain weight under this condition. On the other hand, for larger values of triglyceride production, there is a much smaller basin of atraction for initial quantities of fat mass. The location of the bifurcation point with respect to f is variable as the condition, Π, depends on many parameters.

To get a sense of how the bifurcation diagram changes as we vary a biologically controllable parameter, we choose various values of desired energy intake (b). Varying b is akin to an individual making a rational choice to change dietary practices, a factor not intrinsically present in our model. We choose a low value ($b = 0.009$), medium value ($b = 0.0094$), and large value ($b = 0.0099$) to demonstrate the effect dietary habits have on the stability of the system. The bifurcation point with respect to f moves closer to 0 as food intake (b) increases (Fig 4.). Conversely, this implies that intentional calorie restriction can provide an individual with high triglyceride production the ability to maintain weight at the reduced-fat equilibria.

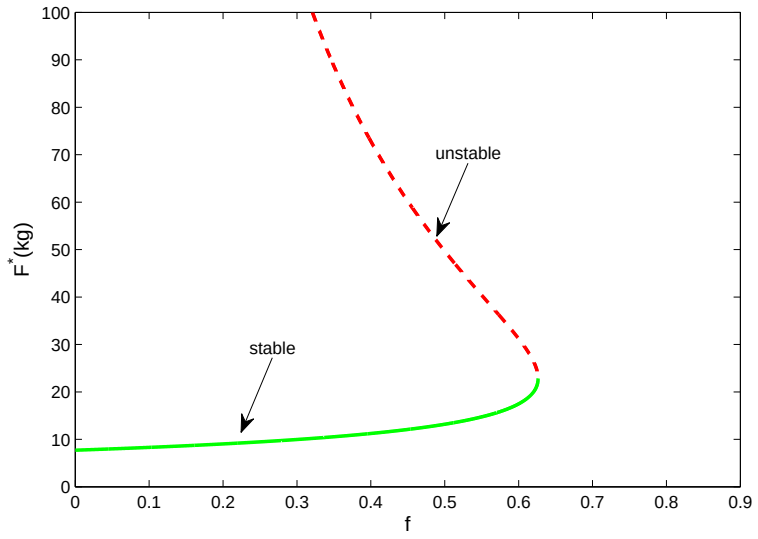

Figure 3: Saddle node bifurcation diagram of model (1) as f varies.

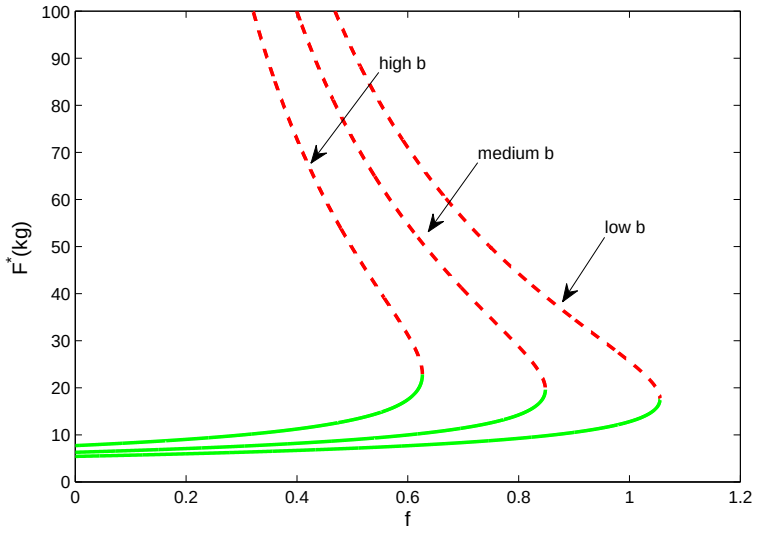

Figure 4: The saddle node bifurcation diagram of model (1) with respect to bifurcation parameter f for $b = 0.009$ (low), $b = 0.0094$ (medium), and $b = 0.0099$ (high).

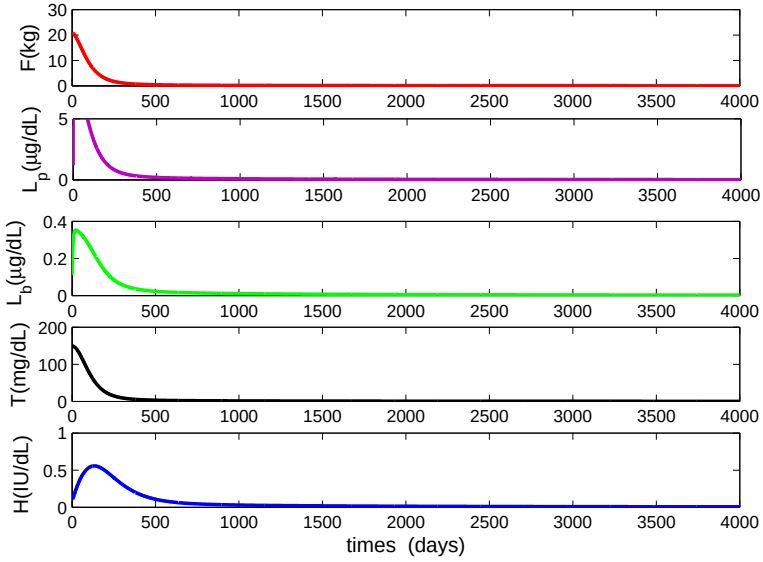

Figure 5: The trajectories of model (1) when $b < \delta$ the fat-free equilibrium is stable.

4.3 Numerical simulation

In this subsection, we shall check the obtained theoretical results in Section 3. First, we choose $b = 0.007 < \delta$, which is a situation of fasting or strict food intake reduction. It follows from Theorem 3.2 that the fat-free equilibrium E_0 is stable (see Fig. 5). This is a extreme situation that, if continued indefinitely, will result in death. This result is obvious from empirical observation of reality. Secondly, we use the parameter values listed in Tables 2 and 3 to carry out simulations of model (1) in order to check the condition given in Theorem 3.4 as follows:

$$b - \delta = 0.022 > 0, A_2 = -29.05 < 0, A_3 = 301.57 > 0, \Pi = 1.32 > 0,$$

$$\frac{mn\delta}{\mu_H \mu_b a(b-\delta)} - \frac{fF_i^*}{e\mu_T} - 1 = \{2.42, 0.94\} > 0, \text{and } \Phi = -0.13 < 0.$$

According to Theorem 3.4, we know that one of the positive equilibria, E_1^* or E_2^* is locally stable and the other is unstable. This is also supported by the bifurcation diagram, Fig. 3. In this case, the low fat mass equilibrium E_2^* is locally stable (see Fig. 6). This result

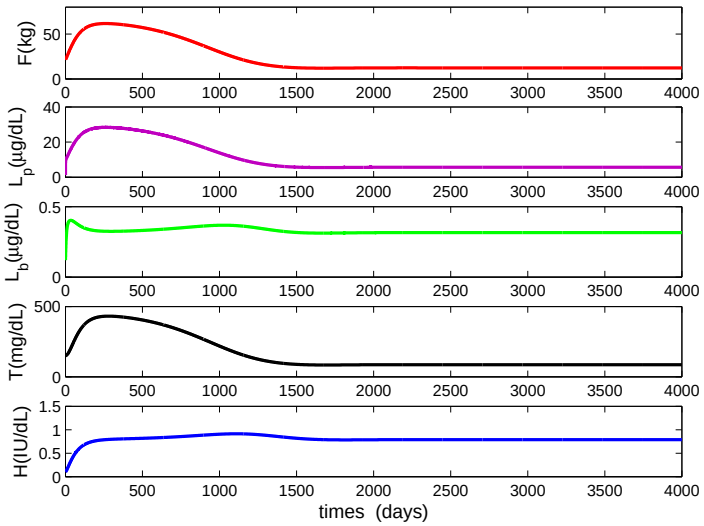

Figure 6: The trajectories of model (1) when the conditions in Theorem 3.4 are satisfied, then the reduced fat equilibrium is locally stable.

means that balancing food intake and energy expenditure by the hypothalamus plays an important role in maintaining the body mass at a reasonable level.

Now, we consider an extreme situation. Letting $b = 0.18$, we can see from Fig. 7 that the fat mass grows to infinity due to overfeeding (b is large), and the triglyceride and plasma leptin also grow to infinity. However, the leptin in brain quickly goes to zero, meaning the hypothalamus does not receive any signal to reduce appetite, suggested by the simulation since the concentration of hormones goes to zero. This process reflects the important role that the triglycerides play in determining the leptin transport across the BBB.

5 Uncertainty quantification

The body works to regulate energy balance and maintain weight. When people lose fat mass quickly, the body starts to reduce leptin production significantly more so than

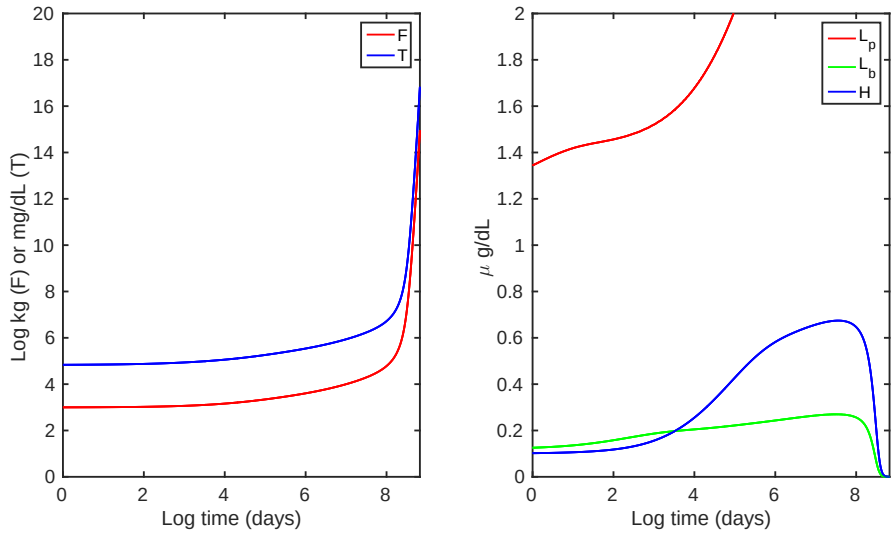

Figure 7: The trajectories of model (1) with the x-axes in log scales, when b and f are large: the fat mass grows to infinity.

would be predicted by the loss of adipose tissue. Our model does not account for this phenomena since we focus on studying weight gain instead of weight loss. Framed this way, the most important biological threshold is that between maintaining a sustainable weight and accumulating fat into morbid obesity. There likely isn't a single biological switch that toggles between normal weight and obesity, but our model predicts such a switch in the form of a saddle node bifurcation. This implies two key features: (1) varying a biological condition such as triglyceride production could play a key role in leptin resistance, and (2) even with a "healthy" level of triglyceride production, too much fat–mass can induce leptin resistance.

Uncertainty quantification is applied to determine which parameters are the most influential on the outcome of model (1), and it is used to analyze equilibrium points, time or important conditions [1]. In the previous section, two important conditions are introduced: Π and Φ, which have significant biological implications. Thus, we perform the sensitivity with respect to the positive equilibrium condition Π and stability condition

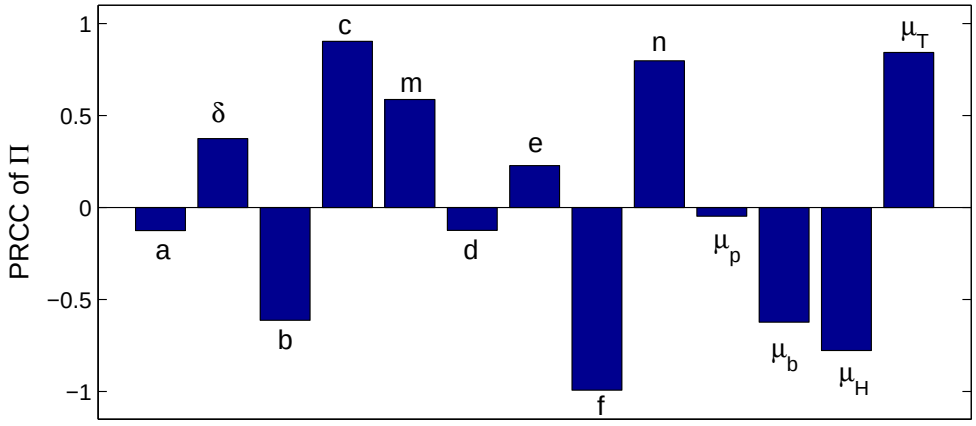

Figure 8: The uncertainty quantification of Π.

Φ (see Figs. 8 and 9).

In Fig. 8, it is clear that the production rate of triglyceride (f), the desired energy intake (b), and the decay rates of plasma leptin and HRH (μ_b, μ_H) are negatively correlated with Π. The secretion rate of leptin (c), the decay rate of plasma triglyceride (μ_T), the energy expenditure (δ), the maximum transport of leptin across the BBB (m), and the production rate of HRH (n) are positively correlated with Π. Thus, this provides for us the information that:

- the triglyceride dynamics (f, μ_T) affect the dynamics of fat mass most significantly;
- the energy intake (b) and energy expenditure (δ) have a close, but less significant, relationship with the fat mass evolution;
- the leptin (c, m, μ_b) plays an important role in controlling the fat mass.
- and the hypothalamus related hormones dynamics (n, μ_H) affect the energy balance significantly.

In Fig. 9, we can see that the desired energy intake (b), the secretion rate of leptin (c), the decay rates of plasma leptin and HRH (μ_b, μ_H) and the production rate of triglyceride

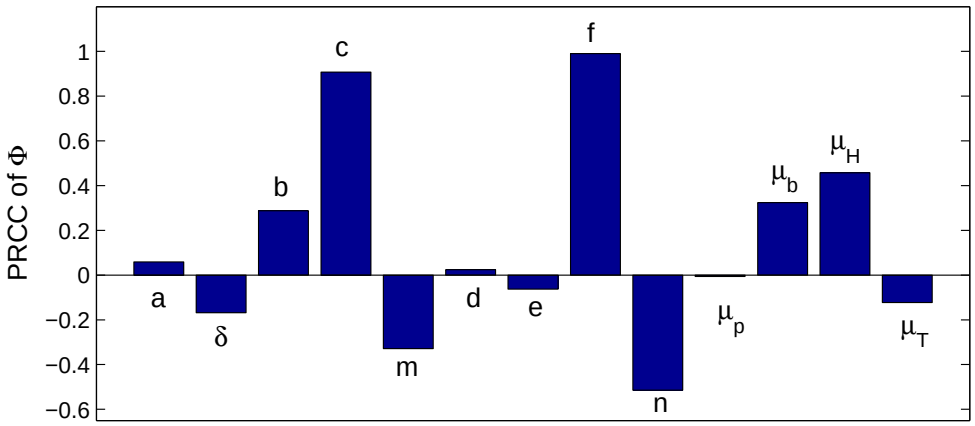

Figure 9: The uncertainty quantification of Φ.

from fat mass (f) are positively correlated with Φ. The maximum transport of leptin across the BBB (m), and the production rate of HRH (n), and the energy expenditure (δ) is negatively correlated with Φ. It is implied that if one individual wants to change his/her weight, there are many factors contributing to the change of the fat mass equilibrium (from high fat mass equilibrium to low fat mass equilibrium). For example, at the individual level, a person can:

- change dietary habits to limit the energy intake (b), especially high calorie and high fat foods;
- engage in regular physical activity to increase the energy expenditure (δ);
- leptin dynamics (c, m, μ_b) plays an important role in regulating energy intake and fat stores;
- control the triglyceride levels (f) (for example, reduce the production of triglyceride or increase the turnover rate of triglycerides);
- in order to elevate hypothalamus related hormone (n, μ_H), which helps control the energy intake by inhibiting excess feeding.

6 Discussion

By 2050, up to 60% of men and 50% of women could be classified as clinically obese. Without action, obesity-related diseases will cost billions of dollars per year [8]. A rapidly growing body of research is attempting to establish effective approaches to tackle obesity all over the world [10, 37]. Obesity, similar to other related noncommunicable diseases, is largely preventable. Triglycerides have a close relationship with obesity and cardiovascular disease, thus, understanding the role of triglyceride production on leptin resistance is not only beneficial to tackling obesity, but also to reducing the risk of cardiovascular disease.

In this research, we proposed a novel ordinary differential equation model describing the role of leptin in the regulation of adipose tissue mass. Numerical results are obtained by using the biologically relevant parameter values. The bifurcation and local stability simulation are carried out to support the theoretical results. In fact, there is a simple condition for fat free equilibria stability energy intake stored as fat must be less than fat metabolism ($b < \delta$, see Fig. 5), however in the case when $b > \delta$ we have multiple possibilities. The system exhibits 2 possible positive equilibria, the smaller of the two is the stable "healthy weight" reduced fat equilibria. The larger equilibria is unstable when it exists, and the trajectories of F, L_p, and T that start above this will grow unboundedly, while L_b and H will tend to zero (see Fig. 7). This unbounded growth corresponds to leptin resistance, where the plasma leptin levels are elevated but letpin concentration in the brain is diminished.

More importantly, the reduced fat equilibrium is attractive only locally, and the basin of attraction is strongly affected by food consumption (b) and triglyceride production (f). In fact, as b or f increase, the system undergoes a saddle node bifurcation where the two positive equilibria coalesce and disappear, leaving the system to grow unboundedly for any initial condition. The unbounded nature of this system seems problematic, but we only wish to consider a "normal range" of human eating patterns, so any extreme system behavior is interpreted as leptin resistance. The model is formulated using very simple mechanisms that approximate the behavior we see in observational studies, so we

ignore many of the complicated control mechanisms the body uses to regulate energy balance. The unbounded case represents an extreme scenario in which food consumption is completely unrestrained. In reality, other social and rational influences would usually mitigate such high food intake. However, cases of patients who are incapable of producing their own leptin due to genetic deficiencies have been recorded, and they typically become obese at an early age [25]. Leptin administration reversed this morbid obesity in most cases.

Additionally, we performed uncertainty quantification of the equilibria and studied the sensitivity of triglyceride production on leptin resistance. Equilibria analysis and simulation results showed that triglyceride production plays an important role in determining the fat mass in an individual. As weight increases, the occurrence of leptin resistance increases. Obesity enhances the likelihood of creating a vicious circle, where more fat mass leads to greater leptin resistance. Thus, control of the triglyceride production may be effective to reduce the occurrence of leptin resistance. These results may provide some meaningful biological implications. More precisely,

(1) Leptin concentration and leptin resistance are two important factors affected the pathways of controlling energy balance. Leptin plays an important role in controlling energy intake and accumulation of fat mass. Thus, reducing the occurrence of leptin resistance may be one strategy to maintain the energy balance in an individual. One interesting phenomenon is that the increase of triglyceride concentration does not trigger the leptin resistance immediately.

(2) Energy intake and energy expenditure is fundamental to control the triglyceride and leptin resistance, thus, increasing energy expenditure and decreasing energy intake are two effective strategies to lose or maintain weight. For example, changing diet habits to limit the energy intake, especially high calorie and high fat foods, or engaging in regular physical activity (60 minutes a day for children and 150 minutes spread through the week for adults [39]).

(3) Triglycerides play a key role in determining the leptin transport across the BBB. Their effect on an individual's weight may follow two different situations, vicious circle

or normal cycle. As triglyceride production increases, more fat mass accumulates and produces more triglycerides. Thus, controlling the triglyceride levels to some extent by lifestyle modifications or medications is necessary. There are many biological methods to do this, such as adding omega-3 fatty acids, limiting alcohol or taking triglyceride-lowering drugs, etc. [36].

7 Future work

In this research, we proposed a simplified models based on the leptin action pathway to explore the role of triglyceride production on the leptin resistance. In fact, due to the complex of the biological mechanism of leptin action pathway and energy balance in an individual, we use simplified form of the biological function to describe the action pathways. Thus, there are still many improvements need to do in future. For example,

(1) The key control factor in this research is the reduction in leptin transport across the BBB by triglycerides. A key assumption of our model is that triglycerides are released at a rate proportional to our fat mass. However, triglyceride production varies depending on food choice, activity, or energy intake [5]. Thus our model ignores other triglyceride regulation mechanisms that would likely alter the observed dynamics. Additionally, the method by which triglycerides affect leptin-BBB transfer is currently unknown, so the assumptions we made on the functional forms have yet to be confirmed or denied. More biological and modeling works specifically regarding BBB transport are needed to validate our assumptions.

(2) Food intake is also not constant. We assumed that, since leptin concentrations respond to body fat percent and not individual meals, the average intake should be considered. However, triglycerides can change more rapidly and this should be considered. We predict that variations in daily triglyceride concentrations might decrease the likelihood of leptin resistance. Since triglycerides are elevated during a state of starvation, this acts as protection against under eating. Both of these mechanisms should be considered in future modeling attempts.

(3) The unbounded nature of this system implies that a secondary "extreme case" control should exist so that a high fat equilibria exists in lieu of infinite growth. Perhaps a maximum, saturable function of food intake should be implemented so that the fat mass does not grow exponentially if the hypothalamus is unable to control food intake. Also, triglyceride levels are related to body fat percent, but they do not grow linearly with fat mass. Thus a maximal production rate or decreasingly increasing function of triglyceride production may be more biologically relevant.

(4) Finally, data collection and parameter estimation are difficult since the dynamics of this process are not measurable *in vivo* in human patients. Even mouse data relies on indirect measurement techniques to determine rate if leptin transfer. Thus time-series data of leptin concentrations, production rates, decay rates, or BBB transfer rates would be immensely beneficial for numerical parameter estimation. This would ensure biologically feasible parameter ranges and would allow for individualized predictions of leptin efficacy. In this ideal case, a similar model could be constructed and verified that would be useful for doctors to predict and diagnose leptin related disorders.

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