Artigo de Discussão

Some insights into an integrative mathematical model: a prototype-model for bodyweight and energy homeostasis

Algumas discussões em um modelo matemático integrativo: um modelo protótipo para homeostase do peso corporal e energia

Algunos debates sobre un modelo matemático integrador: un modelo prototipo para la homeostasis del peso corporal y energía

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Abstract: The ambition of this document is to set in evidence the prerequisite for integrative (mathematical) models, mechanism-based models, for appetite/bodyweight control. For achieving this goal, it is provided a scrutinized literature review and it is organized them in such a way to make the point. The quantitative methods exploited by the authors are called differential equations solved numerically; they are discussed briefly since it is not our goal herein to handle details. On the current state of the art, there is no mathematical model to the best of the author's knowledge targeting at integrating several hormones at once in mathematical descriptions: even for single hormones, the literature is either occasional or do not exist at all; it is depicted some results for simple models already built. As it can be seen, the functions and roles seem fuzzy, most hormones seem to be piloting the same undertaking. The key challenge from a mathematical modeling perspective is how to separate properly the mechanisms of each hormone. The kind of pursuit presented herein could initiate an imperative cascade of mathematical modeling applied to metabolism of bodyweight control and energy homeostasis.

Descriptors: Insulin; Glucose; Homeostasis; Mathematical Models; Systems Biology.

Resumo: O escopo deste trabalho é colocar em evidência a necessidade de modelos matemáticos integrativos, modelos baseados em mecanismos, para investigar controle de apetite e peso corporal. De forma a atingir essa meta, uma revisão seletiva da literatura é apresentada e o material é organizado de modo a defender a visão. Os métodos quantitativos empregados são chamados equações diferenciais resolvidas numericamente; estas não são discutidas

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em detalhes devido ao fato de fugir do desígnio do trabalho. No estado correte da arte, aparentemente não existem modelos que buscam descrever matematicamente hormônios de uma forma única e integrada, mesmo para hormônios únicos, a literatura ou é insuficiente ou não existe em muitos casos. Resultados preliminares são apresentados para algumas tentativas incipientes. Como pode ser visto, a funcionalidade e importância de cada hormônio pode ser abstrusa, em muitas casos poder-se-ia chegar à conclusão de que vários hormônios empenham a mesma função. O desafio-chave do ponto de vista matemático é como entender a posição de cada hormônio no processo como um todo. Trabalhos como o defendido aqui podem gerar uma onda de modelos matemáticos aplicados ao controle de peso e homeostase energético.

Descritores: Insulina; Glucose; Homeostase; Modelos Matemáticos; Biologia de Sistemas.

Resumen: El objetivo de este trabajo es poner de relieve la necesidad de modelos matemáticos de integración, basado en modelos mecanismos para controlar el apetito y el peso corporal. Con el fin de lograr este objetivo, una revision selectivo de la literatura se presenta y el material se organiza para defender la visión. Los métodos cuantitativos utilizados son llamados ecuaciones diferenciales resuelven numéricamente; éstos no se discuten en detalle debido al hecho de escapar del alcance del trabajo. En el estado actual de la técnica correte, al parecer, non hay modelos que tratan de describir matemáticamente las hormonas de manera única e integrada, incluso para las hormonas individuales, la literatura es escasa o inexistente. Los resultados preliminares se presentan en algunos intentos incipientes. Como puede verse, la funcionalidad y la importancia de cada hormona pueden ser confusos, en muchos casos se puede llegar a la conclusión de que varias hormonas cometen la misma función. El desafío clave de un punto de vista matemático es cómo entender la posición de cada hormona en el proceso como un todo. Proyectos como abogado por aquí puede generar una ola de modelos matemáticos aplicados para el control de peso y la homeostasis energética.

Descriptores. Insulina; Glucosa; Homeostasis; Modelos Matemáticos; Biología de Sistemas.

1. Introduction

The determination to unify for integrating in the biological sciences is

ubiquitous in several areas these days, an eminent photograph of this key attempt is *Systems Biology*, in theories comparable to multiscale modeling; e.g. from gene to metabolism, from metabolism to cell behavior, from cell behavior to tissue, and similar modeling paradigms. By taking advantage of the possibilities brought alongside systems biology and alike, one can bump into audacious philosophies and paradigms; e.g. the virtual human[1], or virtual pancreas[2].

Physiologically speaking, glucose control, which implies in energy homeostasis and bodyweight changes, is a quite dense and intricate bio-process. Accordingly, it is a process with players in different hierarchal phases and stages. As one illustration of such an allegation, one could pick out "eating" (food intake) that is controlled by ghrelin and fat mass controlled by leptin. On this paper, the researchers dissert on an idealized insight called unceremoniously the "big glucose model." In view of that, the perception was born from the perceived lack of models that mathematically take a glimpse of glucose control in an integrative line of attack, typically it is done using predominantly insulin[3]; a seminar study is presented by Jacquier and co-works[4], it was also detected independently by Tam and co-works[5].

1.1 Objective(s) /motivations

The objective of this work is to set in evidence the prerequisite for integrative mathematical models, mechanism-based models, for appetite/bodyweight control. This ambition was born from the surveillance that no existent model so far to the best of our knowledge had integrated efficaciously more than one hormone, even for one hormone the models are infrequent or centered in one hormone, i.e. insulin; see[4] for a nice case. Notwithstanding we provide a literature survey and some mathematical discussions, it is out of our scope to either discuss mathematical details or make a complete literature review. As sub-objectives, we can point out: a) discuss some problems in the medical literature when reporting hormone workings, that is, try to point out where needs further investigations; b) pave the way for an upcoming (ongoing) model; c) captivate the reader regarding mathematical models in hormonal control. The motivation for pursuing this goal(s) is that metabolic medical conditions related to eating is quite common in our modern society, and solutions rarely can be tested a priori, e.g. diets or medical products.

1.2 Organization of the manuscript

In the upcoming section, section 2, it is discussed some literatures. In the following section, section 3, it is discussed briefly the methods. Since this work is not an "experimental" work, this section is added for the sake of completeness. The authors plan to come back in other papers with more details since it is an ongoing project. The next section, section 4, it is provided some results and discussions, it was overlapped in a single section due to the nature of the current work, which is not presenting a set of experiments and make the interpretation, rather it is to present an idea, the aim on this section is to give the reader a flavor of the current endeavors. Finally, section 5, presents the conclusions and final remarks. Some references, scrutinized, are given for the reader to have an idea of the pillars of the current work.

2. Literature review

2.1 The "big glucose model": *an integrative interpretation of glucose-bodyweight control*

The overlapping of hormonal receptiveness to nutrient (load) availability is primary for metabolic control[0]; likely the best examples of medical conditions that appear as a result of this system failing to work properly or completely is diabetes and leptin resistance[7]. Accordingly, metabolism is the imperative bio-process in which living systems balance the energy available and the energy demanded on such a way that the organism will not find itself in circumstances of lacking energy after a profusion of foodstuff[8-9]; medical conditions comparable to anorexia nervosa and morbid obesity are in general positively correlated with malfunctioning of the metabolic machinery. Independently of scientific advances, our body works, and it is a miracle of control system in practice. Accordingly, glucose is constantly converted to glycogen, "the battery of living systems," and it is constantly brought back to the bloodstream in times of necessity. As puts it[9], "This [energy deposit mechanism] ensures an adequate plasma concentration of energy substrates to sustain tissue metabolism at all times."

Notwithstanding the astonishing advancements made over the past few decades in unscrambling many of the molecular pathways involved in energy (homeostasis) regulation, a rather cloudy understanding of "*how all the pieces fit together to function as an integrated system"*[5] is what can be

found for the most part in the scientific community; this last sentence summarizes well the motors (rationales) of the current ongoing endeavor. As a representative case, recently a new hormone long ago guessed was finally identified, called *neuromedin U*[0], firstly screened off in fruit fly, called *limostatin*. Basically this hormone aforesaid works when we are fasting, it avoids glucose to be stored in situations in which it supposes to be available; practically, it seems to inhibit the master-hormone insulin.

A careful literature analysis provides us a substantial aggregate of hormones and molecules involved in the complex process of food intake, feeding, and managing energy. Consequently, food is equal energy, energy is equal work. Undeniably, it is done work by the human body from simple tasks, e.g. sleeping, to more complex and elaborated tasks, e.g. playing our favorite sport game.

2.2 A brief look at a dense and intricate process

A painstaking literature analysis endow us with a large number of hormones and molecules related somehow to the complex process of eating and managing energy; "the regulation of food intake in humans is an extraordinarily complicated process that researchers have only begun to understand"[7]. See upcoming sections, in special figure 1.

2.3 Food Intake *vs.* Metabolism: *bodyweight control as a soup of entangled hormones*

In the subsequent drawing, figure 1, it was systematized several hormones and molecules (in general peptides) that play an important role in glucose control; it is the by-product of a literature review done by the authors. The coming text disserts on each of them, and others, in a brief approach, more information was added to the attached file; which also is not an exhaustive discussion of them. The most imperative to apprehend is that glucose is the main energy source of the body and it must be refuelled from time to time. However, this time to time aforesaid is not always predictable, and how biological system must manage the energy already present until the next meal is the reason for this "web of hormones."

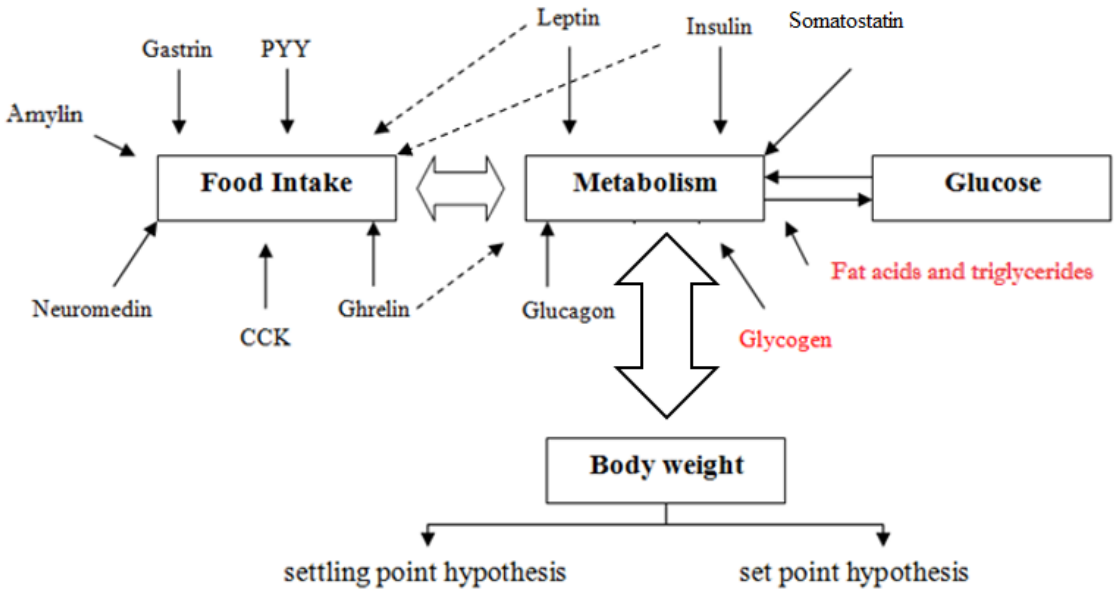

Figure 1. Schematic viewpoint of the hormones involved in the appetite control and metabolism. In red are important players, but are not hormones. The dashed arrows intend to show hormones that play more than one control function on the diagram, the challenge is to build a complete diagram on this style, even in layers, that is, one hormone may control others; e.g. some researches point out that leptin can control insulin somehow[14]. This diagram is mathematical modeling biased. The "fat" arrow between body weight and metabolism intends to say that the metabolism is a short-term dynamic process, from seconds to hours. whereas the body weight usually changes in a long-term scale, from days to months. Source: own elaboration[12].

2.4 A few import hormones and players

2.4.1 Insulin

Insulin, essentially, lowers blood glucose levels as it increases glucose uptake in peripheral tissues[7] and liver; additionally, it inhibits glycogen breaking down, glycogenolysis. Furthermore, insulin levels in the blood reflect both circulating energy (i.e., glucose) and stored energy (i.e., adipose tissue, visceral fat tissue) [0,7]. The scheme below attempts to depict this picture, figure 2.

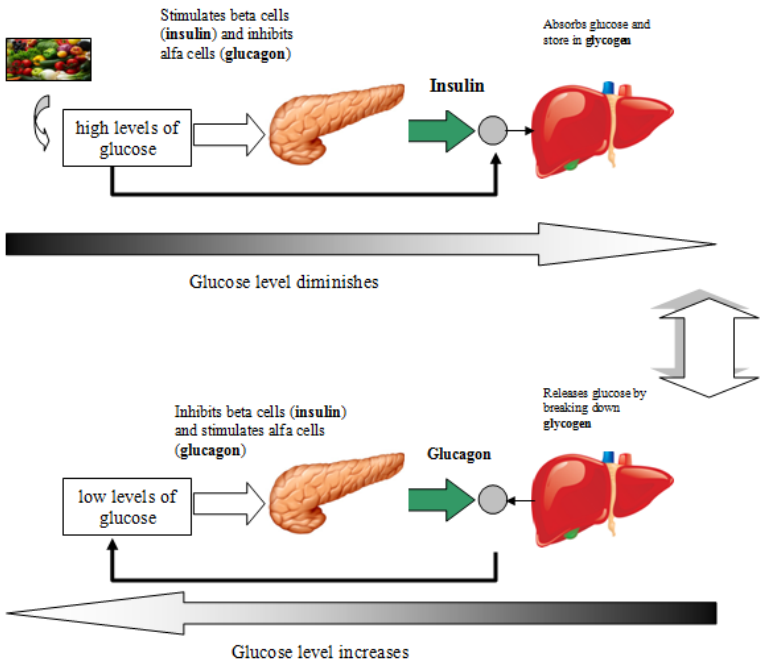

Figure 2. The insulin-glucagon back-and-forth. On this picture one has the relationship between insulin, glucagon, glycogen, and glucose. Source: own elaboration.

In the coming scheme, figure 3, it is highlighted other hormones that work in parallel with insulin. Further, it is not in general recognized the role of insulin as appetite controller, alongside leptin and ghrelin.

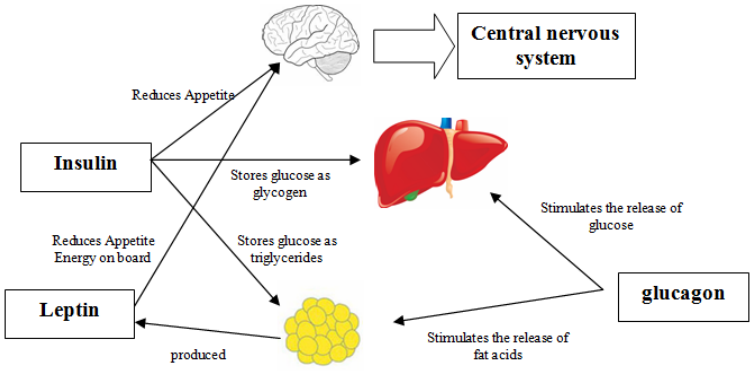

Figure 3. Several players in the energy store-expenditure interplay. This scheme aims to depict a small network around glucose control, which implies in food intake and body weight changes. Source: own elaboration.

Several mathematical models were developed all over the years[3] on the hope to clarify the insulin importance in glucose control; however they have been based just on a small number of players, e.g. insulin-glucagon, insulin-

glucose, and so on; in spite of the success to explain several experimental data.

2.4.2 Glucagon

Glucagon is a hormone secreted by the alpha cells of the pancreas that decreases food intake[7,13]. Likewise, glucagon is the "hormone of starvation," in contrast to leptin known as the "the hormone of satiety," and levels of glucagon do increase when someone fasts. Further, glucagon mainly stimulates glucose production either by breaking down glycogen or by "producing" more glucose (*gluconeogenesis*) in the liver/fat tissue, particularly during the fasting condition or when the body has an increased need for glucose[7]. Glucagon seems to work directly on the liver to inhibit food intake[7,13]; recently some unknown pathways between liver and brain began to be understood[18]. As seen from figures 2 and 3, it is the antagonist molecule of insulin. Accordingly, insulin asks the cells to store glucose either in the liver cells as glycogen or in fat cells as triglycerides, whereas glucagon orders them to be released. The hormones that control appetite can be classified into satiety/satiation related and fat-correlated[7,13]: glucagon is not fat-correlated, i.e. it is not positively/negatively correlated with bodyweight, which means different from insulin it is just a satiety hormone.

2.4.3 Leptin

Leptin is a signal of adiposity[10,11], it is positively correlated with fat-mass, body mass index; it triggers food intake when it is low and inhibit food intake when it is high*. Moreover, it has been proposed as a co-worker with insulin to control and monitor body adiposity and metabolism[10]. Consequently, several researches has been carried out to understand it properly, more than just an adiposity-metabolism controller[11,14-6]. It is not clear yet, but leptin seems to work with ghrelin on the food intake control. Leptin and ghrelin can be placed into two big groups[13]: in this case leptin and similar hormones would work to increase/decrease the functionality of ghrelin and similar hormones directed connected to meal-patterns control, i.e. short term signals and long-term signals. In view of that, it is a long-term hormone signal, whereas ghrelin and insulin are short-term hormonal signals.

* This sentence can be problematic if seen mathematically. It gives the idea of 'threshold,' which is just a mathematical trick. There is no true evidence that biological systems work like threshold models.

2.4.4 Glycogen

Glycogen is one of the molecules by which energy is stored in humans, the second is in fat cells as triglycerides[9]. Accordingly, it is stored in the liver and released in times of *hypoglycemia* (low levels of glucose in the bloodstream, in contrast to hyperglycemia), it is triggered by glucagon.

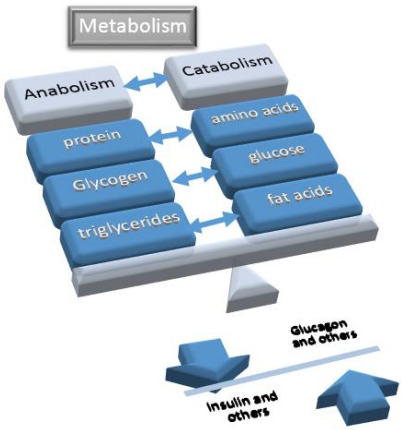

Figure 4. The metabolism can be steered towards anabolism (i.e. "synthesis of energy") or catabolism ("burning of energy") by the combination of several hormones, glycogen is generally controlled by glucagon and insulin. Source: based on[9].

2.4.5 Triglycerides

Triglycerides (fat and oil) consist of three fatty acid molecules joined to a molecule of glycerol[7]. Hydrolysis of triglycerides, controlled by glucagon, within adipose tissue releases free fatty acids into the blood and it is compensated by insulin which increases fat storage as triglycerides. Additionally, free fatty acids can be used as an immediate source of energy by many organs, but the brain; they can also be converted by the liver into derivatives called ketone bodies. Triglycerides can be hydrolyzed into glycerol and fatty acids. Fatty acids are of individual significance because they can be transformed into copious molecules of acetyl CoA that can enter Krebs cycles and generate a large amount of ATP[9].

2.4.6 Ghrelin

Ghrelin is an imperative hunger/satiety signal secreted by the stomach[7,9] with effects in several places in the body, e.g. hypothalamus; it was discovered in 1999, about four years after its sister

leptin. Ghrelin secretion rises between meals*, when the stomach is empty, and stimulates hunger, our propensity to start out a meal; furthermore, it has been suggested a gastric emptying role. As the stomach fills during a meal, the secretion of ghrelin rapidly falls and hunger is thereby reduced**; it has been suggested a postgastric feedback influence by nutrient load, e.g. glucose control. However, one recent study demonstrated raised levels of ghrelin in dieters who lost weight. If this raised ghrelin level enhances appetite, it may partially explain why it is so difficult for most dieters to maintain their weight loss. It is produced by several points within the body such as pancreas (ε-cells), stomach, and heart.

3. Methods

All the data delivered herein are *in silico*, i.e. computer simulations; whenever compulsory, we shall indicate third-part – i.e., *in vivo* and *in vitro* – results with references. The mathematics on this manuscript boils down to *Ordinary Differential Equations* (ODE) organized in a system. The system was solved numerically, using the automatic routines from Matlab®/Simulink™. The system was building using the block diagrams of Simulink; it was set to be used adaptive steps and all the simulations were carried out in a home-like computer: Processor - Intel(R) Core(TM) i7-4500. CPU @ 1.80GHz 2.40 GHz. RAM: 8 GB. Operation System Windows 64 bit. None of the simulations lasted more than seconds. A variable-step method (*Dormand-Prince*) was applied for solving numerically the ordinary differential equations available within Matlab, called by Simulink, where Simulink was controlled and run from a m-File properly designed for that. See[17] for discussion on this kind of strategy for solving systems of ODEs.

4. Discussions/Results

When a theoretical physicist comes to a lab for testing his ultimate model, likely his/her model will be confronted with classical models, his/her math double-checked, his/her references controlled. In view of that, if everything is okay, they are given green light for testing their models. On the other hand, if the same thought experiment is carried out with a theoretical biologist, the output probably will be different. It happens

* There have been some controversies on the literature regarding its secreting laws; exactly how it works, the stimuli that triggers its release or suppression.

** Be careful with this sentence, the falling down of ghrelin in bloodstream as result of eating is something complex, it is an ongoing research by the author mathematically speaking.

because we have no way to ensure that a mathematical model will work, it is called the unreasonable effectiveness of mathematics. Thus, the past goes in favor of physicists and alike, not for theoretical biology. There are two ways to solve the aforesaid setback: 1) theoretical biologists struggler to copy the physicists' efforts, therefore enjoying the same "privileges;" 2) new theories are developed specially for biology and medicine, "complicate" (well-elaborated) models are developed and tested, as the results go in favor, the field of studies starts to gain "respect." The former pathway is most likely to be a dead end, whereas the latter is possibly the way. And this can be achieved just by models such as the one discussed herein.

As we have seen from the previous sections, the control of glucose is pretty complicate physiologically. Classically, any problem with glucose control, hyperglycemia, is treated with insulin; insulin itself is not simple, it has several time-scale, mainly short and long one. Some experiments have been pointing out that maybe facing the problem just from the insulin standpoint is comparable to trying to "hammer" any sharp edge you see. Some experiments have been showing for instance that leptin can control insulin, insulin can control ghrelin and vice versa. This portrays a network-like dynamics, not modeled so far, except for insolated experiments. If one does their homework well, these kind of relationship could be predicted even before one makes the experiments, what has been done in physics for centuries for their own systems: the theory guides the experiments, not the experiments guide the theory.

On this section we will discuss three cases: two already published by independent groups[4,5] and the other being a model developed by the authors[12]. However, the cases are quite simple compared to all the discussions so far: as often happens in mathematical modelling, details are neglected. The challenge aimed is to improve these models in future works. From the three cases, one model can be built, which is an ongoing research[*].

4.1 Energy balance and defense of a stable body weight: a leptin based model[**]

[*] See 'Logan, J. David and Wolesensky, Willian R. Mathematical methods in biology. Pure and Applied Mathematics: a Wiley-interscience Series of Texts, Monographs, and Tracts. John Wiley& Sons, Inc. 2009' for a nice account of mathematical models in biological and medical sciences.

[**] See[17] for further discussions or https://www.researchgate.net/publication/23714748_A_Mathematical_Model_of_Murine_Metabolic_Regulation_by_Leptin_Energy_Balance_and_Defense_of_a_Stable_Body_Weight/reviews/118501.

Below it is presented a mathematical model for leptin dynamics[5,17]. This model is applied for studying what is called the settling point hypothesis: a theory that tries to explain the body weight changes based on diet patterns rather than genetic susceptibility. We are not going to discuss the details of this model, see[5,17] for more details.

$$\frac{d(\text{Lep}_{\text{plasma}} \times \text{BloodVolume})}{dt} = \text{FM} \times \text{R}_{\text{sys}} - \text{GFR} \times \text{RenClearance} \times \text{Lep}_{\text{plasma}}$$

$$\frac{dE(t)}{dt} = \rho_{food} k_4 \left(1 - \frac{Lep_{brain}}{k_5 + Lep_{brain}}\right) - k_6 BM \left(1 + k_7 \frac{Lep_{brain}}{k_8 + Lep_{brain}}\right)$$

$$Lep_{brain} = k_1 \frac{Lep_{plasma}}{k_2 + Lep_{plasma}} + k_3 Lep_{plasma}$$

$$FM = \frac{E(t)}{\rho_{fat}}$$

$$BM = FM + FFM$$

Figure 5. A mathematical model for leptin dynamics. Source: based on[5].

The model is composed of two ordinary differential equations and three algebraic equations. The first ordinary equations, the first equation, describes the production of leptin and elimination in blood plasma: all the relations are first order, they are proportional to a constant and a state variable. For the leptin production, it is proportional to fat mass, whereas for leptin elimination from plasma, it is proportional to clearance rate and glomerular filtration rate of the kidneys. The second ordinary differential equation is for energy expenditure, it says that food intake is "inversely" proportional to leptin in the brain, and energy expenditure is proportional to body mass and leptin in the brain. The functions used to create saturation effects are called Michaelis Menten equation, developed in the context of biochemistry. The third equation, an algebraic equation, describes the transference of leptin from blood plasma to the brain: it is not clear from the paper[5] why it was used an algebraic equation instead of a differential equation, after discussions with co-workers, it seems that a differential equation would be better in

order to model "delays" rates. The fourth equation is used to model the relation between energy and fat mass: it is considered fat mass density, energy content to make the conversion. The last equation is for body mass: the sum of fat and free-fat mass. This model cannot be applied when muscle mass increases, once the free-fat mass is considered constant; in[4] it is discussed a possibility to consider free-fat mass, see upcoming system (1-10). It is employed the body mass to "validate" the model against samples from mice; the parameters are taken from the literature. For the case, the authors of the aforementioned model were able to get a good representation[*].

4.2 A Predictive Model of the Dynamics of Body Weight and Food Intake: leptin, ghrelin and glucose

[*] See for an alternative formulation of the problem using optimal control theory Pires, JG. Some discussions into biomathematics: mathematical biology, biomathematics, and theoretical biology and alike. http://www.academia.edu/15185683/Algumas_discuss%C3%B5es_em_Biomatem%C3%A1tica_biologia_matem%C3%A1tica_bioengenharia_biologia_te%C3%B3rica_e_Cia. Retrieved on 23/07/2016.

$$\frac{dS}{dt} = \frac{\Delta_E}{\rho_W x + \rho_S} \quad (1) \qquad \frac{dW}{dt} = \frac{\Delta_E x}{\rho_W x + \rho_S} \quad (2) \qquad \frac{da}{dt} = f(t) - c(a,h). \quad (3)$$

$$\frac{dl}{dt} = \gamma_2 S - \gamma_1 l \quad (4) \qquad \frac{du}{dt} = \mu_1 c(a,h) - \mu_2 u \quad (5) \qquad \frac{de}{dt} = \frac{v_2}{1 + v_1 c(a,h)} - v_3 e \quad (6)$$

$$\frac{dh}{dt} = \frac{\alpha_1 e}{1 + \alpha_2 l} - \beta(\alpha_3 + u)h \quad (7) \qquad \Delta_E = EI - EE = c(a,h) - R(\rho_W W + \rho_S S + \xi) \quad (8)$$

$$x \equiv dW/dS = \zeta + \psi . \exp(\kappa . S) \quad (9)$$

$$\frac{dR}{dt} = \epsilon \left(\frac{1}{\tau} \int_{t-\tau}^{t} c(a(v),h(v))dv - \frac{1}{\tau'} \int_{t-\tau'}^{t} c(a(v),h(v))dv \right) \quad (10)$$

Figure 6. A mathematical model for leptin dynamics. Source: based on[4].

The explanation for the equations, from left to right, from up to down, is following. The first equation is for body fat: it says that fat is produced as a response to energy intake, which is given by the equation 8. Furthermore, fat will inhibit its production exponentially, equation 9. The second equation is for free-fat mass: it says the same for fat, except that we have an activation, the higher x, the more free-fat mass is produced, with a limit given by equation 8, which is the energy balance, matter cannot be created unless there exist enough energy for that. Equation 3 is for food available for consumption: it is the mass balance between input and consumption. The next equation is for leptin: it is just the balance between production and elimination. The next equation is glucose: glucose is entered by food consumption and eliminated by a linear rate; see that this a simplified model[3]. The next equation is for ghrelin, see upcoming section for more: it is inhibited as food is eaten and eliminated from bloodstream. The next one is for hunger, an abstract concept made "touchable:" Ghrelin and leptin influences hunger. By applying the reasoning of[13], we are saying that ghrelin increases appetite linearly, with leptin influencing the sensitivity of the brain/valgus nervous to leptin. The next equation, which influences equations 1 and 2, is an energy balance: energy comes by food intake and it is eliminated by a basal rate, transformation to matter, and metabolism (thermogenesis). The next equation is a way for saying the response to fat mass increase is slow for small values but significant for high values: it makes the Michaelis-Menten/Hill equation goes to zero or

maximum value faster than normal, a way to achieve the system saturation faster. The last equation is a way to simulate thermogenesis: it disappears when no food restriction is applied. For further details, see the original publication[4].

4.3 Ghrelin Mathematical Modeling centered on the Gastrointestinal Tract

Consider the upcoming system.

$$\frac{dH(t)}{dt} = \beta \frac{1}{1+\gamma_1 \alpha S(t) + \gamma_2 (1-\alpha) D(t)} - Cl \cdot H(t)$$
$$\frac{dS(t)}{dt} = \delta \sum_{i=1}^{N} m_i - k_{SD} S(t)$$
$$\frac{dD(t)}{dt} = k_{SD} S(t) - k_{DX} D(t),$$

Figure 7. A mathematical model for ghrelin dynamics. Source: based on own work[12].

The aforementioned system was created to model ghrelin mechanisms coming from the gastrointestinal tract[12,19]. The first equation is for ghrelin dynamics: it says that ghrelin production is inhibited from a constant-basal rate by stimuli coming from stomach and duodenum. The alpha parameter was introduced to make a model "controversy-proof": some says the stomach is key, others point out the key role of the duodenum, by changing alpha from 0 to 1, it is possible to change the role of each compartment compared to each other. The last part is just the elimination rate. This equation can be generalized:

$$A = \beta \frac{1}{1+\sum_{i=1}^{C} \gamma_i \alpha_i x_i}$$

Where: $\sum_{i=1}^{C} \alpha_i = 1$; x_i, are factors, e.g. glucose, that controls ghrelin. This term replaces the first term in the first equations of figure 7.

This model for ghrelin is different from figure 6, previous section, in several points. First of all, this model tries to make a distinction between preprandial and postprandial signal, whereas the previous just food consumption. Secondly, some suggests that ghrelin does not work significantly with low concentration, a linear relation as before cannot grasp it. Thirdly, the previous model uses ghrelin alongside leptin in an "unmeasurable" quantity, subjective; i.e., hunger. Last but not least, the previous model spite of the fact food is

introduced, it is what is called “closed”; the mice eat as much as they can: minimum between food available or hunger. Other differences could be pointed out, but this is not the scope of the current paper.

The second equation of figure 7 is for the stomach: which is given food in discrete modes. The third equation is for the duodenum: which is governed by linear relations. Studies point out to a feedback coming from the small intestine to control the stomach/appetite, on this version of the model these details are neglected. One example of such a detail is the fact that ghrelin seems to create a feedback, controlling gastric emptying.

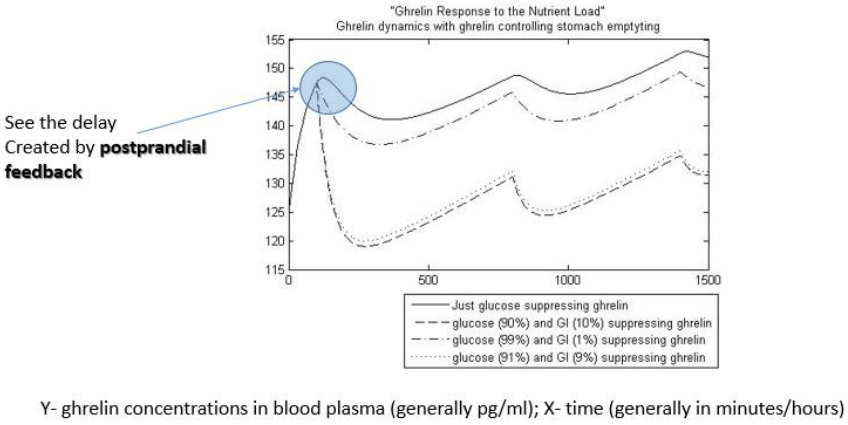

Figure 8. Some simulations for the generalized ghrelin suppression/production term. The parametrization was arbitrarily chosen just for illustration purposes. Source: based on own work[12].

4.4 Discussing the model/mathematics

The model by[5] seems to be first model on the mechanism-based approach to appetite/bodyweight control, and the model by[4] appears to be the first to go one step forward: considering better dynamics and one extra hormone and one nutrient signal (i.e., glucose). The model for ghrelin dynamics given by the author[12] seems to be the first to take into account the gastrointestinal tract and to suggest a way to add as many signal one pleases; see[18] for discussions on tastants. Several challenges come up when trying to integrate those hormones, e.g. ghrelin works in minutes, whereas leptin works in days. As Tam and co-workers presents[5], it was possible to validate their model against real data, nonetheless these model was applied to mice, not human, and studied in the scale of days; curiously, in spite of the ghrelin was already discovered at the

time of the publication, no mention was done to it. When these kind of modelling is pursued, several problem comes up. In the SysBio (Milan, 2016), it was highlighted one of this problematic: it is almost impossible to find parameters in the literature, they are scattered; not to mention the reports are not mathematical based, that is, easy to incorporate in mathematical models.

5. Conclusion and final remarks

On this short article, we have discussed the importance of an integrated model of glucose control. Glucose control poses before us a big challenge to science to understand it properly, pieces are understood day by day such as a new hormone discovered in fruit flies(0) called limostatin, in human suggested as being represented by neuromedin U. In 1996 leptin was discovered, Ghrelin in 1999, and so on. What is missing are efforts towards gathering the pieces of the puzzle and start to make sense of the big picture. Independent of our efforts and limitations, the system works, we are the proof, our brain is supplied with glucose in an almost constant rate, but we can stay even days without eating. Our muscles are given energy to work, however we never need to assign it in our thoughts. It is certainly a miracle of (bio) engineering control theory. As it can be seen, the functions and roles seem fuzzy, most hormones seem to be carrying the same undertake. The key challenge from a mathematical modeling standpoint is how to separate properly the workings of each hormone. One possibility is quite simple: like in the net force, we have several players, but just one appears, an imaginary force, which is coordinated by all the hormones. If so, the question is how to project each component on such a way to see clearly the contribution of each of them.

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