Taste and the regulation of food intake: insights and comments

Sabor e regulação da ingestão de alimentos: ensaios e comentários

Sabor y regulación de la ingestión de alimentos: ensayos y comentarios

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Abstract

A modest archetypal of satiation is that it boils down primarily to two categories of signals transmitted from the gastrointestinal tract to the brain: stomach and intestine sensing and metabolism. Novel investigations endow us with the view that an extension of this traditional model is conceivable and called for, wherein intestinal satiation is the byproduct not only from signals related to the caloric content of ingested nutrients, but also from noncaloric properties of 'tastant molecules' in foodstuff. On this paper we discuss a recently published paper regarding the impact of tastants (e.g., noncaloric substance widely used as taste enhancers) on hunger and food intake. We gather the in vivo results (nasoduodenal infusions of tastants) with a recently developed mathematical model for ghrelin by the author and co-workers and we successfully replicate in silico part of the findings. The key results from the abovementioned paper and replicated herein is that tastant can inhibit hunger; with different levels of impact, umami being the strongest one, and the union of them being even stronger.

Key words. Ghrelin; Eating; taste; mathematical biology; Computer Simulation; Flavor Intensifier.

Resumo

Um modelo básico da satisfação se resume a simplesmente dois termos, dois grupos de sinais sendo transmitidos do trato gastrointestinal ao cérebro: 1) estômago e 2) sinais e metabolismo vindos do intestino. Investigações recentes têm propiciado um modelo estendido desta visão clássica, e necessário para modelos mais realísticos. Nesta forma de pensar, satisfação intestinal é a soma não somente de sinais relacionados a valores calóricos do alimento, mas também de substância não-calóricas presente em refeições. Neste artigo, discute-se um artigo publicado recentemente por terceiros relacionado ao impacto de "saborizante" (*tastants*), substância sem valores calóricos usadas largamente na indústria como forma de reforçar sabores em alimentos, na sensação

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de fome e consumo de alimentos. Une-se os dados/resultados *in vivo* (infusões de sabores direto no duodeno) com um modelo em desenvolvimento pelo autor e colaboradores, assim conseguindo-se replicar parte dos resultados do artigo analisado. O resultado-chave do artigo mencionado é o fato fisiológico que sabores conseguem independentemente diminuir fome e consumo de alimentos; com diferente nível de impacto, sendo umami o mais forte, e soma dos sabores ainda mais forte.

Descritores. Grelina; Ingestão de Alimentos; Paladar; Simulação por Computador; Realçador de Sabor.

Resumen

Un modelo básico de satisfacción se reduce a sólo dos contribución, dos grupos de señales que se transmiten desde el tracto gastrointestinal al cerebro: 1) estómago y 2) señales y metabolismo intestinal. Recientes investigaciones han dado lugar a una modelo ampliada de la vista clásica, necesaria para modelos más realistas. En este punto de vista, satisfacción intestinal es la suma de no sólo señales relacionadas con valores calóricos de los alimentos, pero también de sustancias no calórico presente en las comidas. En este artículo se describe un artículo publicado recientemente por terceros relacionados con el impacto de "saborizante" (*tastants*), sustancias sin valores calóricos utilizados ampliamente en la industria como una manera de mejorar los sabores en los alimentos, en la sensación de hambre y el consumo de alimentos. Se une los datos/resultados *in vivo* (infusión de saborizante directamente en el duodeno) con un modelo en desarrollo por el autor y colaboradores, por lo tanto capaz de replicar parte de los resultados de el artículo citado. El resultado fundamental de este artículo supracitado es el factor fisiológico que los sabores pueden reducir de forma independiente el hambre y la ingesta de alimentos; con un nivel de impacto diferente, umami siendo el más fuerte, y la suma de los sabores siendo incluso más fuerte.

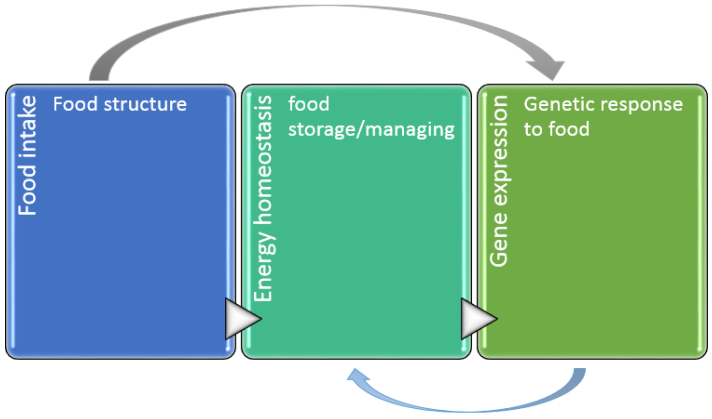
Descriptores. Ghrelina; Ingestión de Alimentos; Gusto; Simulación por Computador; Reforzante del Sabor.

1. Introduction

As diet-associated healthiness issues remain increasing worldwide, there has been a recognition within the research community of the essential for more comprehensive awareness of the behavior of foods as they are processed within the human digestive system[6], which certainly includes hormonal control, i.e. how foodstuff affects hormonal production and how this production/state regulate food intake/processing. Inquiries to comprehend the contributing factor of food

intake has its heritages in the field of 'regulatory physiology,' which originated from the investigations of the scientists Claude Bernard and Walter Cannon[3]. However, from a hormonal point of view, not too much was done until the last decades; namely due to technological advances, e.g. knockout mouse. Leptin, published officially in 1999, paved the way for most of this revolution[5]; food intake started to be seen as hormonal issue, rather than just a volition subject. Below it is depicted the many facets nowadays in 'food science' (i.e., scientific investigations into how food is either processed by the human body or how its intake is controlled). The second key hormone was ghrelin.

Figure 1. Schematic view of several types of scientific investigations into 'food science'



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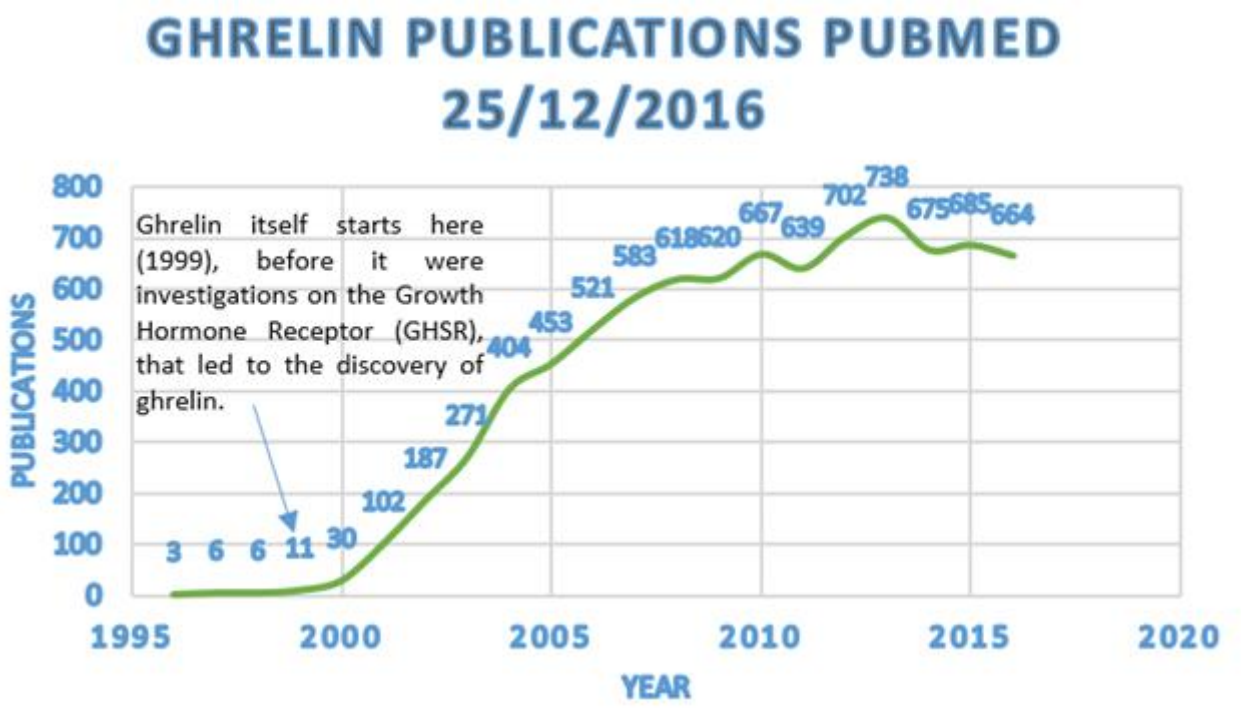
Basically some studies are concerned about gene expression and food intake, e.g. nutritional systems biology[8]. On the other hand, it is important how food intake affects energy homeostasis, e..g. studies in obesity. And so for. Source: own elaboration.

After 30 years working with peptides, Masayasu Kojima and co-workers were able to identify a small protein able to bind and activate efficiently an orphan receptor: this protein was ghrelin and the orphan receptor was the growth hormone secretagogue receptor (GHSR), at the present time basically called the ghrelin receptor[10]. Ghrelin was encountered truly unexpectedly in the stomach of rats[11] and it is a relatively small (poly) peptide: 28 amino acids, compared to 51 and 167, for insulin and leptin, respectively. Furthermore, it is a powerful appetite stimulant, an orexigenic hormone, in fact the only one of its kind: it is a peripheral signal, and it is produced mainly by the stomach, in small portions in other parts such as intestines, brain, and pancreas. Scientific

interest in ghrelin has grown exponentially since its discovery in 1999, see figure 1.

Figure 2. Ghrelin publications since 1996, ghrelin was offically published by Masayasu Kojima and co-workers[11] in 1999. Source: sampled from PubMed (http://www.ncbi.nlm.nih.gov/pubmed) on 25/12/2016.



'Tastant', the key concept herein, is a water-soluble chemical that triggers a 'taste sensation' by activating taste receptor cells (TRCs) and producing activity in taste-related pathways in the nervous system; their imperative effects in food intake/appetite is still an ongoing research topic[1,2]. In humans, there are four universally acknowledged taste sensitivity: salty, sour, bitter and sweet. Some recent endeavors point out to umami, described as "savory", meat-like taste, as a fifth taste component[9]. The imperative result in recent times reported and exploited herein is that taste receptors are also expressed in the small intestine[2].

A modest archetypal of satiation (i.e. fullness, the time between meals) is that it boils down primarily to two categories of signals transmitted from the gastrointestinal tract to the brain: stomach (i.e. mechanoreceptors) and intestine sensing and mebolism (i.e. chemoreceptors and energy homeostasis). Both of the aforementioned signals are activated by feeding patterns (ingested food). Notwithstanding, this models have been defied (extended), on the hope to make it more realistic; e.g., with the concept of

hedonic pathways computing with homeostasis pathways.

Novel investigations endow us with the view that an extension of this aforementioned-traditional model is conceivable and called for, wherein intestinal satiation is the byproduct not only from signals related to the caloric content (e.g. carbohydrates, fats and proteins) of ingested nutrients, but also from noncaloric properties (sensed mainly by the taste-receptors at the tougue and intestine) of 'tastant molecules' in foodstuff. Endeavours made public lately conjecture up that enteroendocrine cells (intestinal cells) also express taste receptors on their luminal membranes[(1)].

Long-acting adiposity hormones (e.g., leptin and insulin) that adjust body mass eventually interfere with eating behavior at the level of individual meals (i.e., short-term phenomena, in general controlled by short-acting hormones, e.g. ghrelin). Mathematically, it poses a problem, how to integrate different timescale dynamics, one in days, leptin and insulin, and the others in hours, ghrelin and insulin, notwithstanding, both controlling fat mass and meal patterns. It would also be of ultimate concern to understand whether tastants can cooperate directly with glucose homeostasis in addition to satiation/satiety[(1)]. It would place tastants in spotlight, since it would likely explain results that cannot be explained right now, for instance why obese individuals possess low levels of ghrelin (i.e. the orexigenic signal), but they still eat like otherwise. The role of noncaloric tastants, whether it can activate the circuit activated by caloric substances to improve glucose homeostasis, remains to be determined.

On this paper, we discourse on the freshly published work "*Taste and the regulation of food intake: it's not just about flavor*"[(1)], which is an introduction/invitation to the more detailed investigation[(2)]. The aim is to pin down the important points about the abovementioned paper, bearing in mind the author of the just referred work made considerable contributions to the area of ghrelin dynamics from an experimental stanpoint; the hormone known to control appetitie and added up herein from a computational pespective to the findings of[(2).] The author of the current manuscript is working on the dynamics from a biomathematical standpoint; some simulations are presented herein. Opportunally, we are going to raise some highlights (i.e. questions and issues), however the references are omitted, keeping in mind it is not the target of this essay to be a complete review.

A good question posed by[(1)] is: *Could minimally caloric dietary supplements containing umami tastants help promote weight loss?)* Umami (monosodium L-glutamate and 5'-ribonucleotides, used in the food industry as flavor enhancers) is one of the

five basic tastes human can sense, a meat-like taste; the others are bitter, salty, sour and sweet. If it is possible, it would be possible to "lie" to the brain, making diets easier; as suggests[1], delivered in capsules. For instance, in experimental results, it was demonstrated that dieters experience a higher ghrelin level, which means that they suppose to feel more hunger than the average people. It explains partially why dieting is so difficult to maintain. So, if tastants can really influence hormones such as ghrelin, directly or indirectly, it is of ultimate interesting to have it pinned down. Thus, tastants nicely sharpen up our glimpse of the understated manner whereby the gastrointestinal tract beautifully controls food intake and energy homeostasis.

On the remaining part of the paper, we shall discuss the mathematical description created for this scientific debate. Basically the model, without known experimental results, proposes that ghrelin may be working alongside tastants, but in an independent pathway; as pins down[2], there is no definitive results regarding the role of tastants in the control of satiety/satiation peptides. On the upcoming section, it is presented the mathematical model used to generate figure 9. In the following section to that, we discuss the computer results, in silico experiments. Finally, we present some conclusions and final remarks, followed by the references cited herein.

2. Methods

2.1 Ghrelin Model

The ghrelin dynamics centered in the gastrointestinal tract is given below[13,14].

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

This system (model) fundamentally says that: as foodstuff enters the stomach and reaches the duodenum, ghrelin production is suppressed. Other factors was found to influence ghrelin, e.g. leptin, insulin and nutrient loads, but neglected herein for the sake of simplicity. See upcoming tables for explanations, see discussion section for further details.

Table I. Parameters for the model (1)[*].

Parameter	Meaning	Value
β	Ghrelin production rate, (pg/ml)min^{-1}.	2
α	Relative importance of each compartments. Dimensionless. It takes values from 0 to 1. In mathematics it is generally called convex combination.	0.5
Cl	Ghrelin Clearance Rate, min^{-1}.	0.02
δ	Dimension/scaling factor, min^{-1}.	1
N	Number of meal, dimensionless.	1
k_{SD}	Transference rate from stomach to duodenum, min^{-1}.	0.01
k_{DX}	Transference rate from duodenum to "compartment X (out of the system)," min^{-1}.	1
γ_i; 1,2.	Compartment factor, it expresses how strong the compartment is regarding ghrelin production suppression, weighting factor. g^{-1}.	100

Table II. State variables for the model (1).

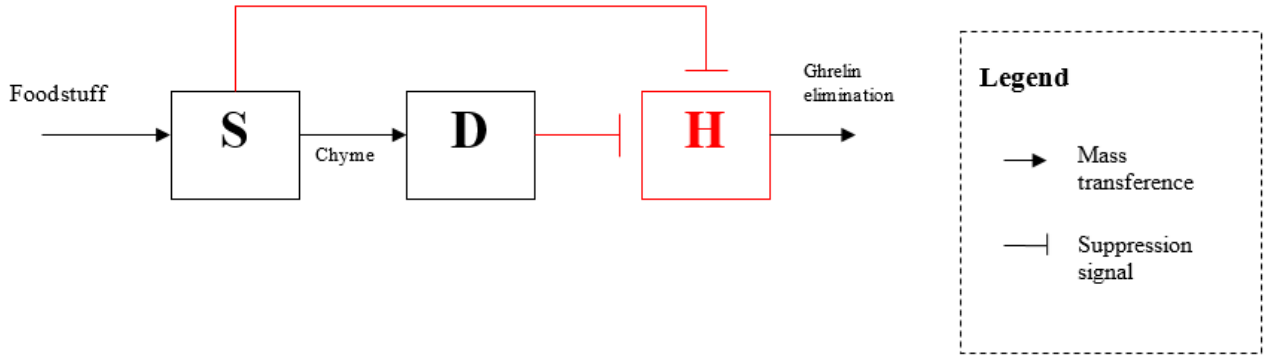
Parameter	Meaning	Value
S	Food in stomach, g.	N/A
D	Food in duodenum, g.	N/A
H	Ghrelin dynamics, it captures the time-profile of ghrelin, pg/ml.	N/A

Legend: N/A, not applicable, it is calculated in the simulations.

In the next scheme, it is depicted model (1) making use of box diagrams.

[*] Parameters arbitrarily chosen for discussion reasons. The same for the remaining tables.

Figure 3. Box diagram for the system (1). Foodstuff enters the stomach, then it is transferred to the duodenum. The presence of food in the two compartments aforementioned inhibits the production of ghrelin.



2.2 Tastant Model

Each tastant dynamics is modeled as:

$$\frac{dT_i}{dt} = u_{T_i} - Cl_{T_i} * T_i \quad (2)$$

The first term for equation (2) models the tastant input in the small intestine, alongside foodstuff in our case, it is a constant representing percentage multiplied by the stomach output, i.e.,

$$u_{T_i} = \eta_{T_i} * k_{SD} S$$

Different from[2], herein it is modelled the case in which the tastant is administered mixed up in the foodstuff; nasoduodenal catheter is applied directly to the duodenum in the case of[2]. Figure 4 shows the equation for hunger dynamics with explanation for each term.

Figure 4. Mathematical description for appetite/hunger control based on tastant signals, see upcoming take for parameters and state variables. Source: own elaboration.

This term models how hunger changes with ghrelin concentrations. It says that ghrelin can trigger hunger up to a certain limit after which hunger no longer grows. If we assume that hunger is the interaction between ghrelin and receptors for instance in the brain, it can be used to model "ghrelin resistance."

$$\frac{dh}{dt} = \beta_h \frac{H^n}{k_h^n + H^n} - \left(\prod_{i=1}^{5} \varphi_i + \sum_{i=1}^{5} T_i + cl_{hunger} \right) * h$$

This term models the factors that can decrease/inhibit hunger. The first term is for the observation that the tastants work "better" together; sort of "emergent properties:" the sum of the part is smaller than the all. The second term is the individual contributions of the tastants and finally the last term is a basal hunger falling-off.

Where:

$$\varphi_i = \frac{T_i^s}{k_i^s + T_i^s} \quad (3)$$

See upcoming scheme, figure 5.

Figure 5. Schematic view of the tastant-ghrelin dynamic model. Source: own elaboration.

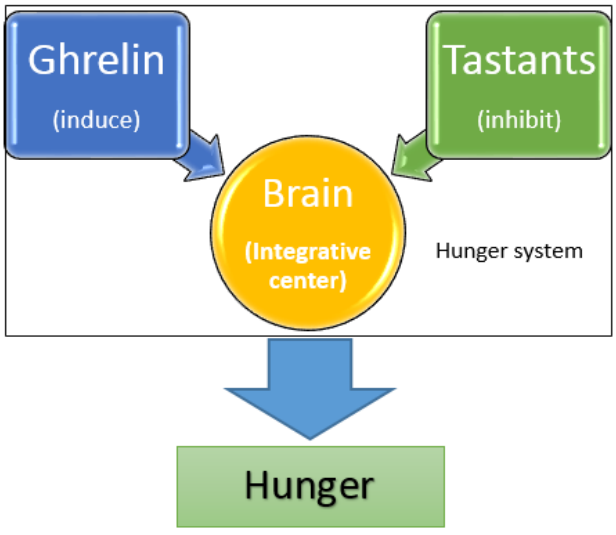


Table III. Parameters for the model (2-3) and figure 3.

Parameter	Meaning	Value
β_h	Ghrelin effect on hunger, dimensionless.	0.1
n	Steepness of the Hill function. An integer number.	1
k_h	Threshold constant.	200
cl_{hunger}	How quickly/slowly hunger is automatically declined.	0.001
s	Steepness of the Hill function. An integer number.	1
k_i	Threshold constant for each tastant.	0.01
Cl_{Ti}	Clearance rate for the tastant, herein assumed from the duodenum, either by absoption or by elimination from the gut.	0.0001
η_{T_i}	Proportion of tastant 'i'; in order to eliminate one parameter, we do not require the sum of the proportions to be '1' due to mass conservation; further, the mass of tastant is expected to be pretty small compared to the foodstuff, which means that mass balance can be neglected.	0.1% (0.001)

Table IV. State variables for model (2-3) and figure 3.

Parameter	Meaning	Value
T_i	Tastant 'i'. In spite of the fact they are 5 tastants, we just use 3, umami, bitter and sweet, as does(2).	N/A
h	Hunger calculated by the model, used as the mean value for the reported hunger.	N/A

Legend: N/A, not applicable, it is calculated in the simulations.

2.3 Reported Hunger Model

The reported hunger is given by:

$$h_{reported} \sim N(h, \sigma) \quad (4)$$

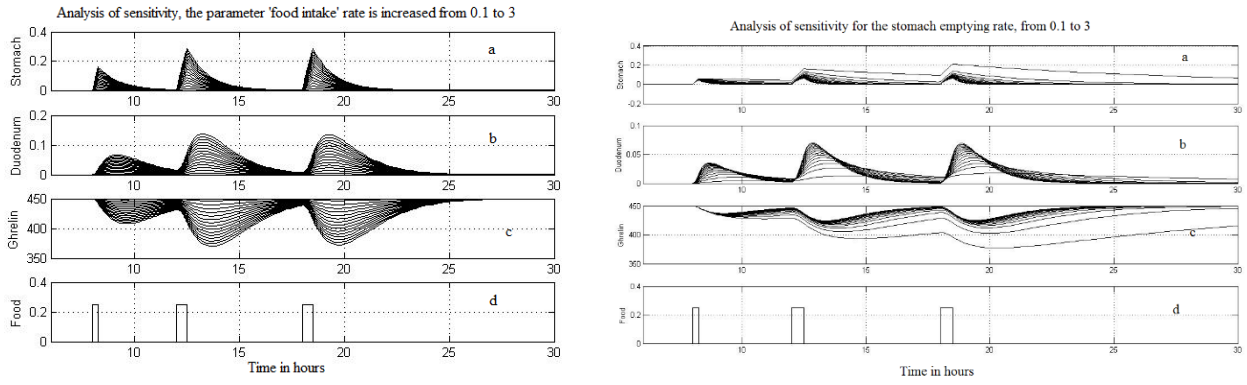
This equation says that one will report hunger probabilistically, with uncertainly due to subjectivity given by σ, but always around the true value: with high probability assigned to the "true" value, in our case the one given by the mathematical model (1-3), and low probability for distant values. By 'distant' values it is meant for instance when one is hunger and they say otherwise. Any other function could have been used, such as the Cauchy distribution, known to accept distant values with higher probability.

2.4 Simulation settings

All the simulation was done using Matlab©/Simulink™ R2013b: the models were built in Simulink using its graphical option, which uses Matlab routines to run. The parameters used were reported in table I-IV. It was applied an adaptive numerical integrator, all controlled by standard routines from Simulink. All the code can be provided under request, under the Creative Commons License*.

3. Results

Figure 6. Computer-generated simulations for the system (1). In a), it is changed the rate of foodstuff, how fast one eats, each curve is for a different parameter value, the parameter is omitted herein; in b) it is simulated the stomach emptying rate, each curve is a different value.



a) b)

* https://creativecommons.org/licenses/by/4.0/. Retrieved on 31/07/2016.

Figure 7. Analysis of sensitivity for sigma, the standard deviation of the Gaussian function. Source: own elaboration.

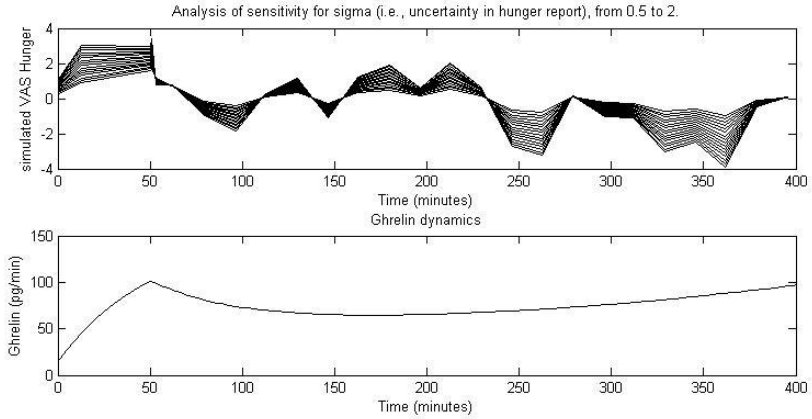


Figure 8. Analysis of sensitivity for gamma, the parameter in model (1) that changes how strongly/weakly ghrelin is suppressed by stomach/duodenum feedback. The upper graph was applied to highlight the changes, they are small since we are using a Michaelis Menten Equation, it "filters out" big variation by creating a saturation effect. Source: own elaboration.

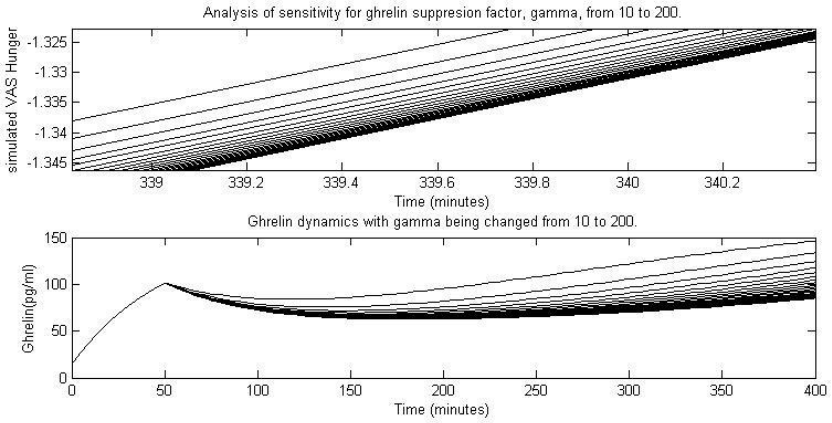
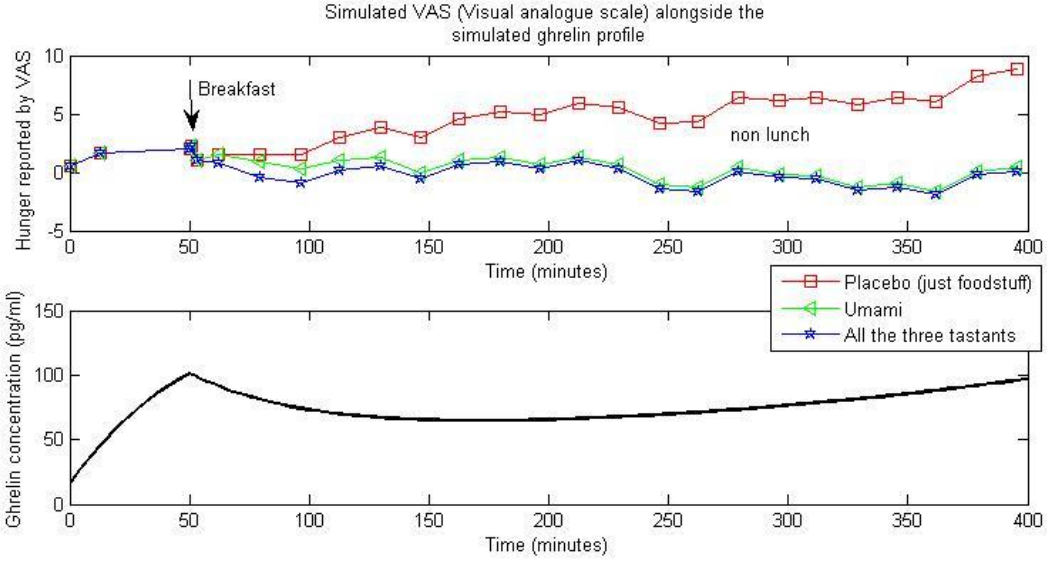


Figure 9. Computer-generated experiments for tastants and ghrelin. Source: own elaboration.



On the abovemetioned graph, it is presented a computer-generated simulation for the tastants: umami, sweet, bitter, and combined. Placebo is the foodstuff without any kind of tastants. Different from[2], the tastants are administered orally, mixed in the foodstuff. The behavior replicated is the fact that the empirical result that tastants combined is stronger than individually administered; similar behavors in other kind of systems have already been reported in the literature, generally called emergent properties, e.g. in systems biology.

4. Discussions

van Avesaat and coworkers[2] have made known that intraduodenal infusion of the umami tastant (monosodium glutamate) and the mixture of the tastants bitter, sweet, and umami considerably hinders the propensity to start a meal and that only the grouping in addition reduces food consumption. Peculiarly, the aforementioned experiment does not affect the release of the gastrointestinal peptides cholecystokinin, GLP-1, or PYY*; no mention to ghrelin was made, unfortunately, but some considerations by[1]. So, herein we tried to replicate part of these findings, mainly: the tastants when combined are stronger in the inhibition of hunger than individually; see figure 9. As highlights[1], the results from van Avesaat and coworkers[2] endorses an enrichment of classical models in which intestinal satiation comes out not only from indicators related to the caloric content of ingested nutrients, e.g. amount and macronutrient, partially taken into account in model (1), but also from noncaloric properties of tastant molecules in food, partially model in model (1-4).

Above, results section, are more graphs for the model (1-3). In figure 6, it is done an analysis of sensitivity in the system (1): parameters are changed and simulation is done for seeing the behavior of the system. In the figure 7, one has how the subjectivity, represented by σ, can influence in the uncertainly in the reported hunger; van Avesaat and coworkers[2] applied what is called VAS (visual analogue Scale)[15]. In the figure 8, one has how the ghrelin suppression factors affect the feeling of hunger: simulations in figure 9 for comparison with[2].

As pins down[2], it should be distinguished that in the investigation of the effects of tastants in food intake and appetite control, tastants were infused without foodstuff. It is appealing to conjecture up that in the presence of a daily-like meal, effects of tastants on food intake would be larger than those observed in the in vivo experiments[2]. The model presented herein could be used to study these key question, maybe employed alongside similar experiments done by[2], but

* GLP-1 – Glucagon-like Peptide; PYY – Polypeptide YY. Those are two key satiety hormones, both having effects in food intake.

now carrying it in "normal conditions", that is, as part of the foodstuff.

Last but not least, in figure 4, in the second term for hunger dynamics, we have eliminated one parameters by setting it to '1;' we are saying that all tastants has similar impact in hunger, but as pins down[2], umami is the strongest one.

5. Conclusion and final remarks

We have discussed a mathematical model for hunger report based on experimental data from[2] and mathematics developed herein, part of the model from[13,14]. The model was able to replicate qualitatively the behaviour of hunger when food intake is accompanied with tastants, small compounds that can influence hunger and food intake without offering nutritional values. Future works are trying to replicate other behaviors found by[2], and compare the result with real experiments, the ones used herein to compare were done in different conditions, just tastants followed by food intake; so we need to assume that the pathway(s) used by caloric substances do not interefere with the one used by noncaloric ones.

In 2016, it happened in Nottingham (United Kingdom) the 10th European Conference on Mathematical & Theoretical Biology*. The meeting joined people all over the world, all of them with the same goal: studying mathematically biology and medicine; it was astonishing the number of researchers gathered in a single place with this goal in mind**. It shows that in spite of all the challenges one has to handle when apply mathematics to biology and medicine, it is still a promising topic. Human, different from mice, as an example, can be tricky to model when it comes to food intake; as so that most models out there are for mice[16,17]. Human can override the basic instincts, eating more or less in certain conditions. That makes models like the one presented herein pretty challenging, especially if a "single model" is chased.

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