A short-term dynamical model for ghrelin

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Abstract:
Ghrelin, a peptide hormone, occupies a crucial role in food intake control. Differently from other hormones contributing to energy homeostasis, usually exerting their regulating action by signaling satiety (e.g. leptin), ghrelin is known to stimulate appetite and, in general, to upsurge the propensity of animals to seek out food and start eating. Medical and experimental literature has shown that approximately 70-80% of ghrelin production occurs in the stomach, whilst the great part of ghrelin control, leading to ghrelin suppression soon after a meal administration, is exerted by signals originated in the small intestine. This note proposes a mathematical model for ghrelin dynamics, focusing the attention on its short-term 24 hours dynamics. The proposed model conforms to the established physiology by introducing a minimal multi-compartmental structure of the gastrointestinal tract. Model parameters are set in order to fit plasma ghrelin concentration data taken from the literature, related to an experiment in humans: simulation-based ghrelin predictions provide promising results if compared to real data. Besides to offer a proper description of the short-term ghrelin dynamics, the model can be thought of as a module of a bigger multi-compartmental structure, aiming to account for the "web of hormones" (including, e.g., leptin and insulin) related to food intake and energy homeostasis.

Keywords: Mathematical Physiology; Ghrelin; Energy Homeostasis

1. INTRODUCTION

Body weight control occurs according to physiological mechanisms properly balancing energy expenditure with food intake. Prolonged energy imbalance in favor of adipose tissue accumulation usually favors obesity, a body weight dysregulation precursor of many chronic diseases (e.g. diabetes), Flier (2004); Kahn et al. (2006). Relevant literature has highlighted the role of numerous endocrine food intake regulators, such as cholecystokinin, peptide YY, glucagon-like peptide-1 (GLP-1), leptin, insulin and ghrelin, Cummings & Overduin (2007); Duca & Covasa (2012). Among these, ghrelin is the only known orexigenic (that means: appetite stimulating) hormone, known to intensify the physiological inclination of species to hunt for food and start eating, Schwartz et al. (2000): experiments consisting in exogenous ghrelin administration support the idea that ghrelin is a physiological meal initiator, since it acts centrally to stimulate food intake, Tschöp et al. (2000); Nakazato et al. (2001); Asakawa et al. (2001).

It is known that food intake controls in feedback ghrelin production. Experiments in rats and humans clearly show that plasma ghrelin levels rise before meals and quickly decrease after food consumption, Tschöp et al. (2000); Cummings et al. (2001); Tschöp et al. (2001); Shiia et al. (2002). Although most ghrelin is produced by the stomach, a post-gastric chemosensory feedback is supposed to be required in ghrelin control, since neither gastric distension nor the presence of nutrients in the stomach lumen are required for postprandial ghrelin suppression, Tschöp et al. (2000); Shiia et al. (2002); Williams et al. (2003). More in details, Overduin et al. (2005) showed by experiments that, in mice, nutrient-related ghrelin downregulation does not necessitate the incidence of nutrients in the two-first segments of the gastrointestinal tract (i.e., stomach and duodenum), identifying the foremost physiological contribution by intestinal indicators positioned descending the ligament of Treitz, physically located between duodenum and jejunum. These experimental results were achieved in rats, and have been confirmed by experiments on humans in Parker et al. (2005), showing that intra-gastric and intra-duodenal glucose infusions suppress plasma ghrelin concentration quite equally, with the apparent delay in ghrelin suppression found out in intra-gastric glucose administration (with respect to intra-duodenal) in agreement with the time for nutrients to leave the stomach towards

the small intestine. Instead, by varying the caloric content, keeping unaffected macronutrient distribution of meals, the intensity and time period of postprandial ghrelin suppression are dependent on the dose and the number of ingested calories: big meals inhibit ghrelin more systematically than small meals, Blom et al. (2005); Callahan et al. (2004).

Medical sciences and experimental literature have demonstrated that the majority of ghrelin release comes from the stomach (about 80%), with a secondary source in the small intestine (mostly from duodenum), Kojima et al. (1999); Date et al. (2000): experiments on rats reported in Ariyasu et al. (2001) showed that surgical elimination of the entire stomach (i.e., gastrectomy) decreases plasma ghrelin concentration by 60-80%; this result has been confirmed in humans undergoing gastric resection with a 70% reduction in circulating ghrelin, Jeon et al. (2004).

More details in ghrelin and in the experiments investigating how it regulates (and is regulated by) food intake can be found in the reviews Cummings (2006); Al Massadi et al. (2014); Müller et al. (2015) and references therein.

Ghrelin is identified as being involved in both short-term control (i.e. daily appetite control) and long-term control (metabolism of fats), Tschöp et al. (2000); Manickam & Lakshmi (2015). This note proposes a mathematical model for ghrelin, related to the daily short-term appetite control. Differently from Lakshmi & Velvizhi (2015); Manickam & Lakshmi (2015), where the modeling focus was on statistical or black-box models, here we propose a mathematical model that stems from basic and established physiological facts, highlighted in the last 15 years. The present model belongs to the wider class of dynamical models aiming at reproducing metabolism regulation (possibly involving, among the others, players like fat and fat-free mass, glucose, insulin, leptin and other food intake regulators). Though covering a specific and somehow reduced part of the problem, the present model focuses on a hormone usually ignored from the "*big picture*", except from Jacquier et al. (2014), where ghrelin dynamics is detailed within a long-term scenario involving the body weight dynamics on a horizon of weeks. In Jacquier et al. (2014) ghrelin is controlled by the energy intake, quantified by means of the available food and a "*hunger*" signal. On the other hand, here we explicitly account for the nutrients in the Gastro-Intestinal (GI) tract as responsible for the fast postprandial ghrelin suppression. The GI is coarsely modeled by a 2-compartmental system. The former tract, GI_1 ideally represented by stomach and duodenum, receives nutrients (e.g. by meals) but does not play an active role in ghrelin control; the latter tract, GI_2 ideally represented by jejunum and the first part of ileum, is responsible for signals regulating ghrelin suppression. A known feedback from nutrients in the small intestine (i.e. GI_2) triggering the release of hormones regulating the gastric emptying (i.e. GI_1) is as well considered, Brener et al. (1983); Lieverse et al. (1995); Matzinger et al. (1998). See Pires (2017) for a larger and more comprehensive literature review on energy homeostasis, appetite control and food intake.

The paper is organized as follows. Next Section is devoted to introduce the equations of the ghrelin dynamical model, with a short description of the qualitative behavior of the model solutions. Section 3 details how model parameters have been set to fit plasma ghrelin concentration samples taken from the humans' experiments reported in Cummings et al. (2001). Promising results motivate further investigation, possibly accounting for a model extension to other players involved in metabolism regulation.

2. SHORT-TERM MODEL FOR GHRELIN

The present model explicitly accounts for the gastrointestinal tract as the place where signals controlling ghrelin suppression are originated. A formal partition of the gastrointestinal part in the following 2 compartments is proposed. One embodying stomach and duodenum, both discounted to play an active role in postprandial ghrelin suppression; the other embodying jejunum and the rest of the small intestine involved in postprandial ghrelin suppression. This partition is coherent with the experimental literature that showed that ghrelin regulation is mediated by intestinal signals situated downward the ligament of Treitz, the physical junction between duodenum and jejunum (see, e.g. Williams et al. (2003); Overduin et al. (2005); Cummings (2006) and references therein). Accordingly, we denote GI_1 and GI_2 the nutrients in the two compartments, measured in litres. GI_1 empties in favor of GI_2 with no nutrients elimination, and GI_2 empties in favor of the large intestine (not modeled):

$$\begin{aligned} \frac{dGI_1}{dt} &= F(t) - f_1\big(GI_2(t)\big)GI_1(t), \\ \frac{dGI_2}{dt} &= f_1\big(GI_2(t)\big)GI_1(t) - k_{2x}GI_2(t). \end{aligned} \tag{1}$$

$F(t)$, [L/h], refers to the input of the system, modeling the food ingestion rate in the stomach, and k_{2x}, [L^{-1}], stands for the GI_2 linear clearance rate. The model accounts also for the feedback of nutrients in the small intestine triggering the production of appetite-related hormones (e.g. cholecystokinin (CCK) and glucose like peptide 1 (GLP-1)) that slow the gastric emptying, Brener et al. (1983); Lieverse et al. (1995); Matzinger et al. (1998). This feedback is modeled by the following saturating function representing the emptying rate of GI_1:

$$f_1(GI_2) = \frac{k_{12}}{1+\sigma GI_2}, \tag{2}$$

with k_{12}, [h^{-1}], denoting the maximal emptying rate, occurring far away from meals when GI_2 is supposed to be empty and σ, [L^{-1}], quantifying the feedback action of GI_2 on GI_1 emptying rate.

Ghrelin plasma concentration, [pg/mL] is the third state variable (denoted by H), obeying to a linear clearance rate k_{hx}, [h^{-1}], with the production rate partially suppressed by GI_2. The regulating action of GI_2 is modeled by the following saturating function:

$$f_2(GI_2) = \frac{\beta}{1+\gamma GI_2}, \tag{3}$$

with β, [pg/mL/h], denoting the maximal ghrelin production rate, far away from meals when GI_2 is supposed to be empty and γ, [L^{-1}], quantifying the inhibitory action of nutrients in GI_2 on the ghrelin production rate. In summary:

$$\frac{dH}{dt} = f_2\big(GI_2(t)\big) - k_{hx}H(t). \tag{4}$$

A block-diagram scheme is reported in Fig. 1, where the block involving CCK and GLP-1 is not explicitly rendered by the model.

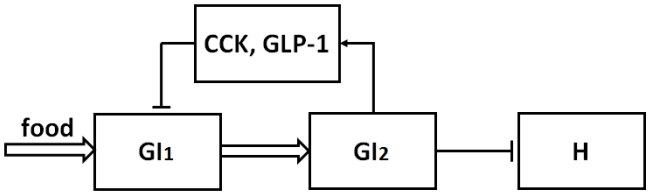

Fig. 1. Ghrelin model block diagram scheme. Double arrows refer to nutrient transfer; other lines refer to control actions.

Simulations are carried out with $F(t)$ having the formal structure of a piecewise constant function, with the non-trivial parts related to the food ingestion periods. According to a standard daily food assumption, $F(t)$ accounts for 3 meals (breakfast, lunch and dinner), with the meals sharing the same ingestion rate r, [L/h], that refers to different ingestion periods, namely τ_b, τ_l, τ_d, [h]. In summary, $F(t)$ has the following form:

$$F(t) = \begin{cases} r, & \text{if} \quad t \in [t_b, t_b + \tau_b] \\ r, & \text{if} \quad t \in [t_l, t_l + \tau_l] \\ r, & \text{if} \quad t \in [t_d, t_d + \tau_d] \\ 0, & \text{elsewhere} \end{cases} \tag{5}$$

where t_b, t_l, t_d are the initial times for breakfast, lunch and dinner. A possible shape for input $F(t)$ is reported in Fig. 2.

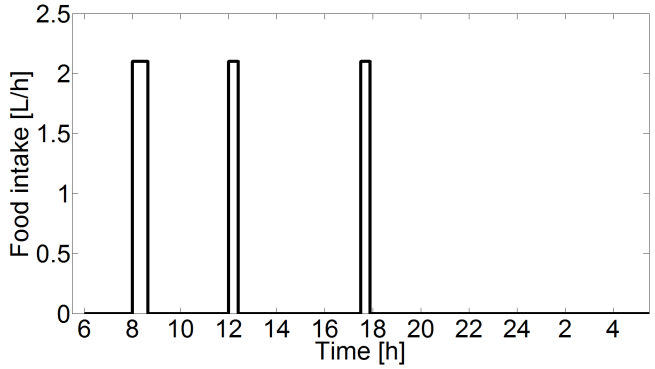

Fig. 2. Food intake function F, according to a breakfast, lunch and dinner occurring at 8:00, 12:00 and 17:30. The three meals last less than an hour each.

2.1 Qualitative behavior analysis

Main features of the qualitative behavior of the solutions are here reported, showing the mathematical coherence of the model.

Lemma 1. Model (1)-(4) admits nonnegative solutions for any nonnegative initial conditions and input $F(t) \geq 0$.

Proof. Consider the GI_1 dynamics and let $GI_1(0) \geq 0$. According to the continuity of the solution, $GI_1(t)$ would become negative if there existed a $\bar{t} > 0$ such that $GI_1(\bar{t}) = 0$ and $\frac{dGI_1}{dt}\big|_{t=\bar{t}} < 0$. But this is a contradiction because:

$$\left.\frac{dGI_1}{dt}\right|_{t=\bar{t}} = F(\bar{t}) - f_1\big(GI_2(\bar{t})\big)GI_1(\bar{t}) = F(\bar{t}) \geq 0. \tag{6}$$

Therefore we conclude that GI_1 never becomes negative. Similarly, it can be proven that if $GI_2(0) \geq 0$, also GI_2 is kept positive. Indeed, $GI_2(t)$ would become negative if there existed a $\bar{t} > 0$ such that $GI_2(\bar{t}) = 0$ and $\frac{dGI_2}{dt}\big|_{t=\bar{t}} < 0$. But this is a contradiction because:

$$\begin{aligned} \left.\frac{dGI_2}{dt}\right|_{t=\bar{t}} &= f_1\big(GI_2(\bar{t})\big)GI_1(\bar{t}) - k_{2x}GI_2(\bar{t}) \\ &= f_1(0)GI_1(\bar{t}) \geq 0 \end{aligned} \tag{7}$$

since $GI_1(t)$ is shown to never become negative, according to the previous step. To prove the nonnegativity of the third state variable follows the same lines of the previous steps. □

Regards to stability analysis, consider $F(t) \equiv \bar{F}$ as a constant input for $t \geq 0$. This could be the case of a trivial null input $\bar{F} = 0$ or, in general, it may refer to a positive constant input, possibly related to a clinical experiment providing a constant nutrient infusion. In any case, the model exhibits a unique equilibrium point:

$$GI_{1,eq} = \frac{\bar{F}}{f_1(GI_{2,eq})}, \quad GI_{2,eq} = \frac{\bar{F}}{k_{2x}}, \quad H_{eq} = \frac{f_2(GI_{2,eq})}{k_{hx}} \tag{8}$$

that clearly reduces to the trivial triple

$$GI_{1,eq} = 0, \quad GI_{2,eq} = 0, \quad H_{eq} = \frac{\beta}{k_{hx}} \tag{9}$$

for $\bar{F} = 0$.

Lemma 2. The equilibrium point (8) is asymptotically stable whatever $\bar{F} \geq 0$ is chosen.

Proof. The asymptotic stability is proven by showing that the Jacobian J computed in (8) has eigenvalues with negative real part. According to the model equations (1)-(4) we have:

$$J_{eq} = \begin{bmatrix} -f_1(GI_{2,eq}) & -f_1'(GI_{2,eq})GI_{1,eq} & 0 \\ f_1(GI_{2,eq}) & -k_{2x} + f_1'(GI_{2,eq})GI_{1,eq} & 0 \\ 0 & f_2'(GI_{2,eq}) & -k_{hx} \end{bmatrix} \tag{10}$$

In case of $\bar{F} = 0$ the Jacobian simplifies in

$$J_{eq} = \begin{bmatrix} -k_{12} & 0 & 0 \\ k_{12} & -k_{2x} & 0 \\ 0 & -\beta\gamma & -k_{hx} \end{bmatrix} \tag{11}$$

readily providing three negative real eigenvalues. In case of $\bar{F} > 0$, the triangular shape of J_{eq} in (10) allows to readily compute the eigenvalue associated to ghrelin dynamics (asymptotically stable, equal to $-k_{hx}$). The other 2 eigenvalues are the roots of the following second order polynomial:

$$\begin{aligned} d(\lambda) = \lambda^2 + (k_{2x} + f_1(GI_{2,eq}) - f_1'(GI_{2,eq})GI_{1,eq})\lambda \\ + k_{2x}f_1(GI_{2,eq}), \end{aligned} \tag{12}$$

providing negative real roots taking into account that $f_1'(GI_{2,eq}) < 0$ whatever the model parameters. □

Parameter	Measurement unit	Value
k_{12}	h^{-1}	2.30
k_{2x}	h^{-1}	0.71
σ	L^{-1}	0.20
k_{hx}	h^{-1}	2.354
β_d	mg/mL/h	1591
β_n	mg/mL/h	1238
γ	L^{-1}	1.29
t_{night}	h	27

Table 1. Model parameters fitting experimental data.

3. MODEL PARAMETERS IDENTIFICATION

The validity of the proposed model is evaluated by showing that it is able to replicate a set of sampled data coming from experiments on human, Cummings et al. (2001), where plasma ghrelin concentration was measured on a 24h daily experiment on a total of 10 healthy subjects, who were administered 3 standard meals (breakfast at 8:00, lunch at 12:00 and dinner at 17:30) approximating an average American diet. Experimental data are taken from Fig. 1 of Cummings et al. (2001) and are reported in Fig. 3 (bold circles). The corresponding upper and lower bounds are taken as well from Cummings et al. (2001). A somehow unexpected fact is that ghrelin decreases far from the last dinner (the decrease starts later than midnight). Such a fact, providing a similar effect to a further light meal during the night, is motivated in Cummings et al. (2001) by ghrelin correlation with late night high levels of leptin. This fact is represented in our model by the further assumption that the maximal ghrelin production rate β switches from a diurnal higher value β_d to a smaller nocturnal value β_n representing a different slower metabolism during the night. In summary:

$$\beta = \begin{cases} \beta_d, & t \in [6h, t_{\text{night}}) \\ \beta_n, & \text{elsewhere} \end{cases} \tag{13}$$

with t_{night} denoting the time instant when the switch occurs.

Besides the usual request to minimize the mean squared error between real and simulated ghrelin samples, the parameter identification procedure aimed as well at reproducing meaningful time-course evolutions for the gastro-intestinal compartments. Being related to the food volume in the earlier gastro-intestinal tract (related to stomach and duodenum, both discounted to play an active role in postprandial ghrelin suppression) we required the emptying of GI_1 in the intermeal interval, see Fig. 4.

Model parameters to be estimated are the clearance rates k_{12}, k_{2x}, k_{hx}, the food ingestion rate r, the maximal diurnal and nocturnal ghrelin production rates β_d, β_n, the inhibitory coefficients for ghrelin production rate, γ, and for GI_1 emptying, σ, and the switching time for nocturnal ghrelin production rate, t_{night}, reported in Table 1. Further parameters are related to the input (the food intake) and are the food ingestion rate r as well as the lengths of the meals τ_b, τ_l and τ_d, Table 2.

Ghrelin fitting is reported in Fig. 3, and corresponding GI_1 and GI_2 food volumes are reported in Figs. 4 and 5.

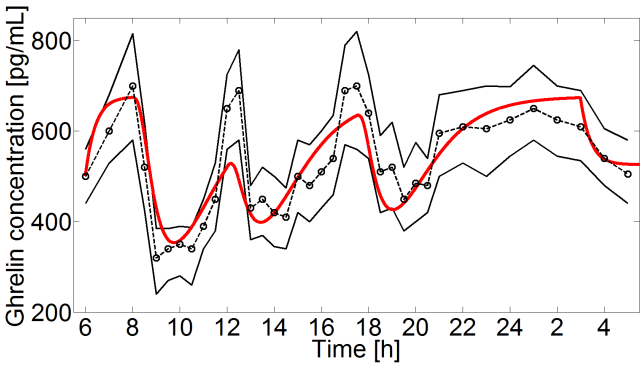

Fig. 3. Ghrelin time course from simulated model (continuous red line), compared to the experimental data (circles).

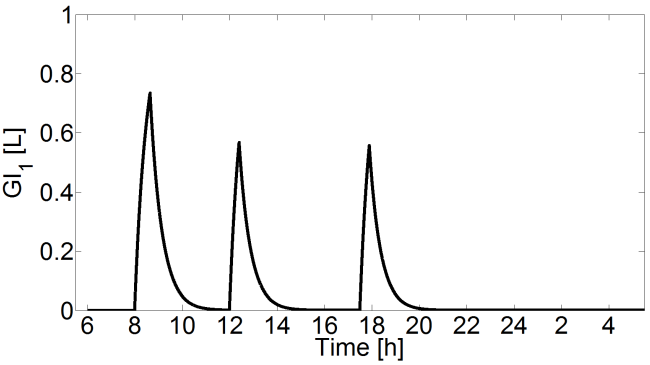

Fig. 4. Time course of food volume in stomach/duodenum.

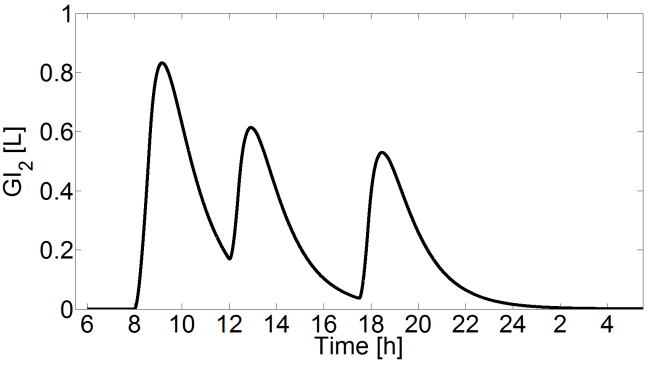

Fig. 5. Time course of food volume in the jejunum/ileum.

Parameter	Measurement unit	Value
r	L/h	2.1
τ_b	h	0.65
τ_l	h	0.41
τ_d	h	0.40

Table 2. Food intake parameters.

It is apparent that the simulated curve reproduces with a good accuracy experimental data, since the time coarse is constrained within experimental upper and lower bounds, apart from the peak of plasma ghrelin concentration in the intermeal period between breakfast and lunch.

Further points of discussion follow. First, to achieve a good fitting, the GI_2 tract does not empties during the first intermeal period (between breakfast and lunch), it rather

empties during the second intermeal period (between lunch and dinner) and it substantially empties 6 hours after dinner. On the other hand, physiological evidence suggests that the whole small intestine never empties completely: this fact hints that not all the nutrients in the ileum contributes in ghrelin control. Instead, a reasonable interpretation could be that compartment GI_2 accounts for nutrients in jejunum and the first tract of ileum.

Second, the identification procedure showed that the feedback from GI_2 to slow the GI_1 emptying has a little (though not negligible) contribution. Indeed, looking at Fig. 5 the GI_2 compartment has the three peaks roughly between 0.6L and 0.8L, the bigger one at breakfast at about 0.8L, whereas the estimated value for parameter σ is 0.20L^{-1}. That means that k_{12} in (2) is reduced of, at most, a factor of $1+\sigma\cdot\max\{GI_2\} = 1.16$, that means about 14% reduction. A possible model extension accounting for both points of discussion could (i) separate stomach from duodenum in GI_1 (indeed, it is stomach emptying to be slowed, not duodenum), (ii) separate nutrients acting to control ghrelin (first tract of GI_2) and nutrient acting to slow stomach emptying (theoretically within the whole small intestine). In summary we would expand the present model as:

$$\begin{aligned}
\frac{dS}{dt} &= F(t) - f_1\big(\alpha_1 Il_1(t) + \alpha_2 Il_2(t)\big)S(t),\\
\frac{dD}{dt} &= f_1\big(\alpha_1 Il_1(t) + \alpha_2 Il_2(t)\big)S(t) - k_{ds}D(t),\\
\frac{dIl_1}{dt} &= k_{ds}D(t) - k_{Il12}Il_1(t),\\
\frac{dIl_2}{dt} &= k_{Il12}Il_1(t) - k_{Il2x}Il_2(t),\\
\frac{dH}{dt} &= f_2\big(Il_1(t)\big) - k_{hx}H(t).
\end{aligned} \tag{14}$$

where S, D, Il_1 and Il_2 stand for nutrients in stomach, duodenum, first and second tract of ileum, and parameters α_1 and α_2 properly weigh the ileum contribution to slow gastric emptying. Such model expansion would be of some help also to replicate experiments involving intra-gastric or intra-duodenal experiments, like the ones in Overduin et al. (2005).

4. CONCLUDING REMARKS

This note presents a short-term mathematical model of the ghrelin dynamics, describing a 24-hour period during which the standard three meals are supposed to be administered. Besides the ghrelin dynamics, the model embodies the gastrointestinal tract (by means of a 2-compartmental system), known to be responsible of the fast prandial ghrelin suppression. The gastrointestinal tract is coarsely divided in a first tract (ideally accounting for stomach + duodenum) not directly involved in ghrelin regulation, and a second tract (ideally accounting for jejunum + ileum) known to be involved in ghrelin regulation. The negative feedback of the nutrients of the small intestine on the stomach emptying is as well accounted for.

The model is based on established physiology and experimental literature, and is able to replicate *in silico* the main features of short-term ghrelin dynamics, such as sustained increase in ghrelin concentration during intermeal periods and a faster suppression soon after meal administration. The fitting of experimental data taken from the literature is promising.

Besides the model expansion detailed in (14), a finer version of the model can be devised to account for different responses to different nutrients. Experiments (e.g. Overduin et al. (2005); Parker et al. (2005)) have shown that ghrelin is downregulated less effectively by lipids compared to other macronutrients (e.g., glucose and amino acids), according to the same caloric content of the nutrient administration. This fact could be modeled by exploding the GI_2 compartment into more compartments, e.g. one for lipids, one for glucose and one for amino acids. All these modifications are compatible with the idea of the present minimal model and could be useful to replicate a wider range of experiments.

A further improvement of the model would be to account also for long-term phenomena related to ghrelin, in order to consider the present model as a *module*, possibly compatible to other existing long-term models (e.g. Jacquier et al. (2014)) detailing metabolism regulation at a larger time scale, including many other regulators involved in food intake control, like leptin, GLP-1, CCK, etc.

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