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Effect of chyme viscosity and nutrient feedback mechanism on gastric emptying

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HIGHLIGHTS

- Gastric emptying rate linked to intestinal bioaccessability by feedback mechanism.
- Gastric secretion model links the secretion rate to the gastric viscosity.
- Model fits emptying of low and high viscosity liquid meals.

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ABSTRACT

A comprehensive mathematical model of the digestive processes in humans could allow for better design of functional foods which may play a role in stemming the prevalence of food related diseases around the world. This work presents a mathematical model for a nutrient based feedback mechanism controlling gastric emptying, which has been identified *in vivo* by numerous researchers. The model also takes into account the viscosity of nutrient meals upon gastric secretions and emptying. The results show that modelling the nutrient feedback mechanism as an on/off system, with an initial emptying rate dependent upon the secretion rate (which is a function of the gastric chyme viscosity) provides a good fit to the trends of emptying rate for liquid meals of low and high nutrient content with varying viscosity.

1. Introduction

Numerical modelling of the digestive system has been carried out from both a pharmacokinetic (Di Muria et al., 2010; Peng and Cheung, 2009; Stoll et al., 2000; Yu et al., 1996), and a food science perspective (Bastianelli et al., 1996; Dalla Man et al., 2006; Logan et al., 2002; Moxon et al., 2016; Penry and Jumars, 1986, 1987; Taghipoor et al., 2012, 2014). The general approach is to break the digestive system into compartments which can be described as ideal reactors. The stomach is typically described as a Continuous Stirred Tank Reactor (CSTR), whereas the small intestine has been described as a single CSTR, multiple CSTRs in series, or as a Plug Flow Reactor (PFR). Most of these models take only the dosage of the nutrient or drug into account when modelling the absorption, ignoring the physical properties of the meal, such as viscosity, and the interactions with the digestive system or other meal components. Here we will present a simple model to describe the influence of viscosity upon gastric processes (e.g., Marciani et al., 2001, etc.) and the effect of the nutrient based feedback mechanism upon gastric emptying (e.g., Brener et al., 1983, etc.). The aim is to develop a model which takes into account physical and chemical properties of the meal and can provide a greater understanding of food digestion. This could help in the development of functional foods to combat diet related diseases, such as obesity and type-2 diabetes, which are becoming increasingly more prevalent in modern society (Popkin, 2006; Jew et al., 2009).

The presence of a nutrient based feedback mechanism, also referred to as ’duodenal brake’, has been observed by numerous researchers (Brener et al., 1983; Calbet and MacLean, 1997; McHugh and Moran, 1979; Shahidullah et al., 1975), by measuring gastric emptying rate with intraduodenal nutrient secretions. This mechanism allows for the pyloric sphincter to control the emptying of gastric content into the duodenum depending upon the amount of nutrient already present in the proximal small intestine, ensuring a constant rate of calories per minute entering the small intestine, and the nutrient type (Calbet and MacLean, 1997). The sensing of nutrients in the intestine is carried out by taste

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receptors, similar to those found in the mouth and nasal cavity, e.g., the T1R family of receptors allows for the sensing of sugars (Depoortere, 2014; Young, 2011). The stimulation of these sensors induces the secretion of the hormone Cholecystokinin (CCK), which acts to decrease the gastric emptying rate and increase satiety (Depoortere, 2014), and/or slow gastric emptying via stimulation of the vagal nervous system (Young, 2011).

Whilst nutrient content will have an effect upon the gastric emptying rate other meal properties will also have an influence. The volume of a meal has been shown to speed up gastric emptying (Hunt and Stubbs, 1975). The viscosity of the chyme can also have an effect upon the gastric emptying rate, with some experimental results showing higher viscosities increase the gastric emptying rate of nutrient meals (Shimoyama et al., 2007; Vist and Maughan, 1995), while others show the opposite (Yu et al., 2014; Marciani et al., 2001). For non-nutrient meals, it has been shown that the gastric volume shows little variation with the viscosity of the meals input (over a 1000 times increase in zero shear viscosity), but that the level of secretions will be much greater with higher viscosities - resulting in large drops in the viscosity of the chyme (Marciani et al., 2000).

This work will build upon a model previously developed in Moxon et al. (2016). The aim is to demonstrate the viscosity of a liquid meal affects the mass transfer of nutrients within the intestine, and will influence the gastric emptying rate via a feedback mechanism. Further to this a model for the secretion of gastric juices is proposed, assuming the rate of secretion is influenced by the gastric chymes viscosity, and that the emptying rate previously assumed constant (γ) (Moxon et al., 2016), is affected by the meal and gastric properties. The work will attempt to fit model outputs to experimental data and gain numerical values for the constants used in the model from the experiments.

2. Model structure

The model presented builds upon previous work (Moxon et al., 2016), which assumed the stomach can be modelled as a continuous stirred reactor (i.e., fully mixed), and small intestine as a plug flow reactor and looked at how gastric emptying rate and intestinal lumen mass transfer rate can influence the absorption of nutrients. The model will link the gastric emptying rate and luminal mass transfer rate by introducing a nutrient based feedback mechanism observed from literature (Brener et al., 1983). Secretion in the stomach can be initiated via 3 different phases (Di Mario and Goni, 2014): a cephalic phase, due to anticipation of food; a gastric phase, due to the presence of food in the stomach; and an intestinal phase, via a feedback mechanism from the content of the small intestine. A secretion model will focus on how meal properties might affect the gastric phase of secretion (the phase inducing the highest volume of secretions (Di Mario and Goni, 2014)) and the influence of secretions upon the chyme viscosity, which will play a role in the gastric emptying of the meal. A schematic of the model is shown in Fig. 1.

2.1. Model development

The model presented will investigate liquid meals, with a mass of nutrient ($Stom_{N0}$ [g]) entering the stomach at $t = 0$. The stomach will be modelled as a continuous stirred tank reactor with the output emptying into the duodenum over the time period $t \in [0, t_f]$, where t_f is the final measurement time. The mass of nutrient in the stomach is represented as $Stom_N$:

$$\frac{\partial Stom_N(t)}{\partial t} = -\gamma Stom_N(t) \tag{1}$$

$$Stom_N(0) = Stom_{N0} \tag{2}$$

where γ is the gastric emptying rate in s^{-1}. It is assumed that the meal is consumed rapidly and that negligible gastric emptying or dilution of gastric content will occur before the whole meal is consumed. This assumption is more relevant for low viscosity liquid meals, which are consumed more rapidly than high viscosity meals (Marciani et al., 2001). It should also be noted that this assumption may not be appropriate if modelling the consumption of a normal (multi phase) meal, and a gastric filling function linked to time may be more appropriate in such cases.

The mass of nutrients in the small intestine will be modelled in terms of a 1-D advection-reaction equation, assuming the limiting factor in the absorption of nutrients will be the mass transfer rate within the intestinal lumen. This approach has been taken by others when looking at drug or food absorption (Stoll et al., 2000; Logan et al., 2002). It was shown by Yu et al. (1996) to give a good description of the intestinal transit time, much better than assuming a single compartment, and similar to assuming 7 CSTR compartments. The mass of nutrient in grams ($SI_N(z,t)$) will be modelled along the temporal domain and spatial domain, $z \in [0, L]$, where z is the position along the length of the intestine in metres, and L is the total length of the small intestine (=2.85 m (Stoll et al., 2000; Barrett et al., 2005)), and position $z = 0$ represents the position of the pyloric sphincter:

$$\frac{\partial SI_N(z,t)}{\partial t} = \begin{cases} \gamma Stom_N(t) - \bar{u}\,\frac{\partial SI_N(z,t)}{\partial z} - K_a SI_N(z,t) & \text{if } z = l_0 \\ -\bar{u}\,\frac{\partial SI_N(z,t)}{\partial z} - K_a SI_N(z,t) & \text{Otherwise} \end{cases} \tag{3}$$

$$SI_N(z,0) = 0 \tag{4}$$

With the following Neumann boundary conditions:

$$\left.\frac{\partial SI_N}{\partial z}\right|_{z=0} = \left.\frac{\partial SI_N}{\partial z}\right|_{z=L} = 0 \tag{5}$$

The advection term $\bar{u}$ will be the mean velocity (1.7×10^{-4} m/s (Stoll et al., 2000)). K_a is the absorption constant of the nutrients in the intestinal lumen, linked in previous work to the mass transfer coefficient in the lumen (Moxon et al., 2016), but will be estimated from experimental data and as such will take into account the effect of radial transfer and mixing upon the absorption rate.

The mass entering at time, t, to the small intestine from the stomach will be assumed to enter as a spherical bolus of radius l_0, and enter at position $z = l_0$ along the intestine.

The absorption rate of nutrients from the intestinal lumen, will be modelled as the integral of the reactive terms from Eq. (3) over the length of the intestine:

$$A(t) = \int_{z=0}^{L} K_a SI_N dz \tag{6}$$

2.2. Feedback mechanism

It will be assumed that the feedback mechanism is mediated by the bioaccessibility of the nutrient in the intestinal lumen (Depoortere, 2014), and that this controls the rate at which gastric chyme empties. Here the feedback mechanism is triggered by the rate of absorption, described by Eq. (6). From literature (Brener et al., 1983; Calbet and MacLean, 1997) it has been identified that the gastric emptying is controlled to ensure a constant rate of calories, and the model will assume the mechanism acts as an on/off switch, acting instantaneously. A maximum absorption rate, A_{max}, will be set, and if this rate is exceeded the gastric emptying rate, γ, will be set to zero: