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In silico modelling of mass transfer & absorption in the human gut

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ABSTRACT

An *in silico* model has been developed to investigate the digestion and absorption of starch and glucose in the small intestine. The main question we are aiming to address is the relative effect of gastric empting time and luminal viscosity on the rate of glucose absorption. The results indicate that all factors have a significant effect on the amount of glucose absorbed. For low luminal viscosities (e.g. lower than 0.1 Pas) the rate of absorption is controlled by the gastric emptying time. For viscosities higher than 0.1 Pas a 10 fold increase in viscosity can result in a 4 fold decrease of glucose absorbed. Our model, with the simplifications used to develop it, indicate that for high viscosity luminal phases, gastric emptying rate is not the controlling mechanism for nutrient availability. Developing a mechanistic model could help elucidate the rate limiting steps that control the digestion process.

1. Introduction

Understanding digestive processes is important in addressing diet related diseases, such as obesity, which are becoming a major problem all around the world. A World Health Organisation report in 2014 stated that 39% of adults were overweight and 13% were obese; also stating that the obesity rate was most prevalent in the Americas and least in the south-east Asian regions (WHO, 2014). Specifically in the UK around a quarter of adults were classified as obese as of 2014 (HSCIC, 2014); it has been estimated that obesity will cost the UK society £50billion per annum by 2050 (McPherson et al., 2007). In order to address some of the food related diseases and design healthier foods it is important to understand the behaviour of foods during digestion using *in silico* as well as *in vivo* and *in vitro* studies.

Modelling has been extensively used in a variety of systems e.g., pharmaceuticals (Peng and Cheung, 2009; Stoll et al., 2000), biological systems such as the insulin-glucose system (Makroglou et al., 2006; Pedersen and Cobelli, 2014). Simulation of biological processes allows for investigation into phenomena that are difficult to examine or study *in vivo* and *in vitro*. In this work we will be modelling digestion in the gut as a series of ideal reactors, a concept introduced in the late 1980's (Penry and Jumars, 1986, 1987), with wide applications in the area of pharmacokinetics (Ni et al., 1980; Peng and Cheung, 2009; Stoll et al., 2000).

Mathematical models have been developed to investigate the digestion of foods using different approaches: A compartmental approach with a CSTR small intestine was used by Dalla Man et al. (2006) assuming that changes in gastric emptying rate have the largest effect on absorption (Dalla Man et al., 2006), this work showed good agreement with absorption from oral glucose tolerance tests. Bastianelli et al. (1996) simulated the movement and absorption of different nutrients simultaneously with a multiple compartmental approach (Bastianelli et al., 1996), which was able to predict nutrient absorption patterns and transit times. A model developed by Taghipoor et al. (2012) used a system of ODEs to simulate the movement and absorption from a food bolus within the intestine highlighting the effect dietary fibre has on slowing the bolus break down (Taghipoor et al., 2012, 2014).

Despite the fact that mathematical models provide insight into digestion; they typically use parameters that are obtained empirically, which limits their predictive capability.

1.1. Starch digestion

Starch is the largest source of carbohydrate in the human diet (Singh et al., 2010). In the small intestine, α-amylase will convert starch to oligosaccharides, and brush boarder enzymes (e.g., glucoamylase) will hydrolyse the oligosaccharides to glucose, which can then be absorbed. The conversion of oligosaccharide to glucose and absorption of glucose by sodium-dependent glucose cotransporter 1 (SGLT-1) proteins through the epithelium will be rapid and

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will not be rate limiting (Bastianelli et al., 1996; Lentle and Janssen, 2011; Stumpel et al., 2001).

The kinetics of starch hydrolysis by α-amylase has been studied by a number of authors with the amylase substrate isolated from a variety of sources. Both bacterial and human α-amylase have been found to follow Michaelis–Menten kinetics (Ikram-Ul-Haq et al., 2010; komolprasert and Ofoli, 1991; Satomura et al., 1984; Yankov et al., 1986), although it has also been reported that this is only followed for low substrate concentrations and at high concentrations a modified 1st order kinetics can be used (komolprasert and Ofoli, 1991). Inhibition of α-amylase by high D-glucose concentrations has been reported on some occasions (Steverson et al., 1984; Yankov et al., 1986), which has been reported to have a large effect at concentration greater than 300 g/L (Yankov et al., 1986), though this is a high concentration that is unlikely to be encountered *in vivo*.

1.2. Gastric emptying

Gastric emptying rate is often considered to be the rate limiting step in the absorption of nutrients (Hellstrom et al., 2006; Mourot et al., 1988). The delivery of gastric content to the duodenum is controlled by the pyloric sphincter (Hellstrom et al., 2006), whilst the stomach acts as a reservoir for consumed food, and mechanically and chemically breaks down the content (Kong and Singh, 2008).

Table 1 shows a selection of studies of the gastric emptying rate for different liquid solutions. Gastric emptying is quantified with a half-time (time for half the content to empty the stomach by volume) and calorific empting rate. These studies were selected as they have a comprehensive description of the physical properties of the fluids and the calorific content.

In Table 1 the measurement methods can be separated in 3 groups: breath sampling, aspiration, and imaging (e.g. MRI/Scintigraphy/Sonography). The most common method for measuring gastric emptying rates in a medical setting is Scintigraphy, where meals are labelled with ^{99m}Tc, and distributions of these radioisomers are taken using gamma cameras (Punkkinen et al., 2006). Punkkinen et al. (2006) compared this to the ^{13}C breath test, where a meal is labelled with ^{13}C and breath samples are taken and the ratio of ^{13}C–^{12}C can be used to calculate the volume remaining in the stomach. The group found that the ^{13}C breath test gives significantly longer emptying half-time than Scintigraphy and that there was no correlation between the half-lives of the two methods (Punkkinen et al., 2006). This could explain why the results by Shimoyama et al. (2007) have longer emptying rates when compared to the rest of the table (also shown in Fig. 1).

Scintigraphy has also shown 70% slower emptying rates than double sampling aspiration, where a dye is added to a meal and samples are taken directly from the stomach via catheter and emptying inferred (Beckers et al., 1992), although this is not evident from the data presented in Table 1. Good agreement in measured emptying rates with MRI (Feinle et al., 1999; Schwizer et al., 1992) and ultrasonography (Hveem et al., 1996) are also shown in literature.

Fig. 1 shows a plot of half-time of emptying against the calorific content of the meal for different measurement methods. As one can see the resulting emptying times depend on the method of measurement. As previously explained the ^{13}C method results in a significantly higher estimation of gastric emptying time; this results in a large uncertainty on parameters used in models as a large variety of sources have to be considered typically each employing a different method.

As can be seen in Fig. 1, an increase in calorific content results in an increase of gastric emptying time, but the scarcity of the data points do not allow us to conclude upon the nature of the relationship. This could be explained from observations widely reported in literature of a feedback mechanism from the small intestine (controlled by nutrient sensors) that is thought to be the main controlling mechanism of gastric emptying rate (Brener et al., 1983; Calbet and MacLean, 1997; McHugh, 1983; Shimoyama et al., 2007).

Whilst in Table 1 there is a clear trend with emptying rate and the calorific content, the link between the emptying rate and viscosity or volume of meal consumed is not clear. Prior to the initiation of this feedback mechanism, there is an initial rapid emptying rate, which is independent of the nutrient content of the meal. Some researchers suggest that this rate will be controlled by the volume of fluid in the stomach (Brener et al., 1983; Moran et al., 1999), while others point to the effect of viscosity (Marciani et al., 2001; Shimoyama et al., 2007), with more viscous meals causing greater distension of the antral region relative to the proximal; and also resulting in a great volume of gastric secretions (Marciani et al., 2001). However, contradictory results on the effect of viscosity on gastric emptying have been reported, as seen in Table 1. The effect of gastric secretions could play a key role in determining gastric viscosity (see for example (Marciani et al., 2000)).

The last two results in Table 1 indicate the difference in emptying between two meals of the same constitution, one in solid/liquid form and one as a soup. There is a difference between how solids and how liquids will empty from the stomach, with solids requiring a reduction in particle size, to around 1–2 mm, before they can empty (Hellstrom et al., 2006). The current work will focus on the ingestion of liquid meals and the gastric processes will not be considered, other than the emptying to the small intestine.

1.3. Modelling of absorption in the small intestine

Within the intestinal lumen the chyme (mixture of consumed food and secretions from the digestive system) will be propelled aborally and via peristaltic contractions, which may also provide mixing of the nutrients (Janssen et al., 2007). Segmentation contractions will mix the chyme with no movement axially along the intestine (Ganong, 2005). The flow of nutrients along the digestive tract has been studied by numerous authors using computation fluid dynamics (CFD). Studies have been carried out to look at the mixing effects in the stomach (Ferrua and Singh, 2010, 2011; Kuzo et al., 2010), the flow at the gastroduodenal junction (Dillard et al., 2007), and the flow in the intestine (Love et al., 2013; Nadeem et al., 2012; Riahi and Roy, 2011; Tripathi, 2011; Tripathi et al., 2011). These studies indicate that flow dynamics will affect the movement of nutrients to the luminal wall; this mass transfer can be an important parameter in nutrient bioaccessibility (whether the nutrients are in a form which can be absorbed).

In silico (computer simulated) studies of absorption in the small intestine have been carried out for drug and foods using different methodologies. In pharmacokinetics, two main types of models have been used: non-compartmental and compartmental. Non-compartmental models are generally developed by fitting a mathematical expression to *in vivo* data, hence the fitted parameters will be accurate only for the system analysed and will not offer any predictive capability. In compartmental models, the system is divided in to compartments each representing a different physiological process; each with different mathematical expressions. A well formulated model should offer a certain amount of predictive capability (Peng and Cheung, 2009).

In literature the small intestine has been modelled as a single compartment (Dalla Man et al., 2006; Di Muria et al., 2010), as multiple compartments (Bastianelli et al., 1996; Yu et al., 1996) or as

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