Physiologically-based modelling of food digestion and intestinal microbiota: State of the art and future challenges. An INFOGEST review.

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Abstract

This review focuses on modelling methodologies of the gastrointestinal tract during digestion that have adopted a system view approach, and more particularly on physiologically-based compartmental models of food digestion and of the host-diet-microbiota interactions. This type of modelling appears very promising to integrate the complex stream of mechanisms that have to be considered, and to retrieve a full picture of the digestion process from mouth to colon. We may expect these approaches to become more and more accurate in the future, and serve as a useful means to gather the available knowledge, interpret postprandial *in vivo* data, and make relevant predictions. This paper intends to provide a scientific and historical background in this field of research, before discussing the future challenges and potential benefits of the establishment of such a model to study and predict food digestion and absorption in humans.

Keywords: modelling, gastrointestinal tract, digestion, transit, absorption, microbiota

1. Introduction

Investigating the effect of food composition and structure on its behavior in the human gastrointestinal (GI) tract is relevant for food developers and nutritionists in order to measure and optimize nutrient availability. Although final assessments needed to make health, nutritional and functional claims must always involve human studies, these are very expensive, time consuming and constrained by medical and ethical assessment of their acceptance. As alternatives to human and animal studies, *in vitro* experiments, which include both static and dynamic digestion models, have become very popular in recent years. The international INFOGEST network has been particularly active in this field, notably regarding the harmonization and the validation of *in vitro* digestion protocols (Brodkorb et al. 2019; Minekus et al. 2014; Mulet-Cabero et al. 2020) and on the correlation of associated results with *in vivo* data (Bohn et al. 2018; Dupont et al. 2019; Egger et al. 2016). Although *in vitro* studies have demonstrated success in evaluating the effects of food properties on digestion, they miss certain properties related to the way the body dynamically controls the digestion process. To expand our understanding of the relations between foods, or diets, with the overall function of the human GI tract and post absorptive processes, computer modelling of the digestion process appears a very promising means.

The present review focuses on mathematical models of the GI tract that have adopted a system-based approach, and more particularly on physiologically-based compartmental modelling. These methods have been applied in the veterinarian area related to animal feed sciences (Bannink et al. 2006; Bastianelli et al. 1996; Rivest et al. 2000; Strathe et al. 2008; Usry et al. 1991), and are widely used in pharmaceutics nowadays for the development of orally administered pharmaceuticals (Chetty et al. 2018; Yu 1999; Zhuang & Lu 2016). Following these works, compartmental models related to food digestion and/or postprandial metabolism have also been proposed. This review aims at providing a state of the art on these researches, before discussing future challenges associated with the modelling of food digestion and its metabolic repercussions in humans.

In section 2, this review highlights the compartmental organization of current pharmacokinetic models and their contribution to pharmaceutical development. Section 3 describes features that have been added to this compartmental approach for the modelling of food digestion and

absorption. Compared to the existing pharmacokinetic models, much more attention is needed to introduce the complexity of food materials consisting of a multiscale structure containing many components. Section 4 discusses the overall progress made in food digestion compartmental modelling, and gives an opinion on what future developments are needed.

2. Modelling the digestive tract

Computer simulation and mathematical modelling are common techniques that have proven their worth in many disciplines. Generally speaking, a mathematical model aims to describe aspects of a real-life phenomenon by using fundamental assumptions to purposefully remove unnecessary details. Consequently, a mathematical model is merely an analogy or caricature of the phenomenon and as such wrong. However, models might still accurately depict the system behaviors, and hence be very useful.

In the current discussion, we focus on dynamic (as opposed to static) models in which time-dependent changes are accounted for and which are typically characterized by systems of differential equations. Another key categorization of mathematical models is on a scale from empirical to mechanistic. Purely empirical models make no assumptions about the mechanisms controlling the system behavior, but focus solely on replicating the data. As such, they commonly fail when used for predictions outside of the range of data. Examples in pharmacokinetics include models with sum-of-inverse-Gaussian functions to describe drug absorption profiles (Csajka et al. 2005) or Bayesian p-splines to estimate pharmacokinetic parameters (Jullion et al. 2009). By contrast, a purely mechanistic model incorporates physiologically-based assumptions about the mechanisms controlling the system. For example, each compartment would have some specific physiological identification, as would the parameters associated with each compartment. Mechanistic models are predominantly applied to data to investigate whether the model mirrors the trends observed experimentally. Model parameters are estimated with caution to preserve the scientific soundness of the model. One advantage of a mechanistic over an empirical model is its ability to extrapolate beyond the data with which it was built. In pharmacokinetics, many models are semi-mechanistic, often having physiologically relevant compartments but with at least some of the parameters determined empirically.

The research on compartmental modelling has led to a number of commercial packages for pharmacological modelling of the delivery of orally administrated drugs as reviewed by others (Chetty et al. 2018; Li et al. 2018; Pentafragka et al. 2019). The difficulty in these PBPK models is that evaluation of model parameters is usually empirical rather than based on the underlying mechanisms (Aarons 2005). Nonetheless, such mathematical methodologies have been successfully developed in the pharmaceutical industry to the point where they are now often used in advance of clinical trials to help optimize the trial design for a given objective (Danhof et al. 2008; van der Graaf & Benson 2011).

Similar developments have been proposed to model food digestion and absorption in the alimentary tract with two main approaches: continuum and compartmental models. Continuum models take the tubular organization of the gastrointestinal tract as a starting point and mathematically describe the functional variation, transit, digestion and absorption by propulsive contractions as a function of the location (Labarthe et al. 2019; Moxon et al. 2016, 2017; Taghipoor et al. 2012, 2014). These models can consider simultaneously different aspects of digestion, such as the transit of the food along the intestine, enzymatic degradation of foods, and nutrients absorption. However, these models involve systems of partial differential equations structured in space, which increase in complexity for each digestive feature added, requiring efficient numeric solvers. The remainder of this review is restricted to compartmental modelling, as most generally used in pharmacokinetic modelling (Li et al. 2018; Pentafragka et al. 2019). In these models, the GI tract is represented by a series of compartments with different functionalities and digestive conditions (pH, enzyme concentrations, etc.), with typically: the mouth, stomach, small intestine, and large intestine. They sometimes include more gradual variations, as for instance the duodenum, jejunum, and ileum for the small intestine.

3. Food digestion models

3.1. What phenomena should be modelled?

Although compartmental models have found wide applications in pharmacokinetics, they are not directly suited for application in food digestion research. They usually assume specific generalized conditions, in either the fasted or fed states, but lack a suitable description of the meal properties.

Therefore, a step to advance towards application for food digestion studies is to include the effects of food composition (size, caloric density, buffering effects …) and structure (liquid or solid, inner substructures…) on the modelled mechanisms. These mechanisms are outlined in Table 1, and have recently led to a public shared reference library focusing on related *in silico* models (In silico working-group of INFOGEST 2019). Examples of how these phenomena are becoming integrated into mathematical food digestion models will be given in the next sections. Beyond these general considerations, an appropriate level of detail is needed to simulate the fate of nutrients from the foods to peripheral blood. As schematically represented in Figure 1 for starch digestion (omitting proteins and lipids to keep the figure simple), we believe that at least the lumen and the gut wall should be distinguished, and that the original substrates and end products of the enzymatic reactions should be considered. A further possible step, not considered in Table 1 and Figure 1, would consist of integrating the physiology that controls the gastrointestinal conditions of digestion (e.g. feedback mechanisms). This currently relatively unexplored aspect will be discussed in section 4.2.

3.2. Integration of the food composition in nutrients

A number of compartmental models have been developed in relation to food digestion in humans, or feed digestion in animals. Examples range from models addressing the flow and mass transfer of digesta along the gastrointestinal tract (Moxon et al. 2016; Rivest et al. 2000; Taghipoor et al. 2012; Usry et al. 1991) up to the metabolic fate of absorbed nutrients in the host (Fouillet et al. 2009; Mc Auley & Mooney 2015). However, these models do not distinguish the different food components, since they usually focus on one kind of nutrient only. In order to simulate the digestion of complex foods or meals, the first necessary step is thus to integrate their nutritional composition.

The first attempts to integrate all the main constituents of food products in a compartmental model of digestion arose from animal feed science. A very good example thereof is the modelling of digestion and absorption in pigs by Bastianelli et al. (1996), which was extended and refined by Strathe et al. (2008). In the version proposed by Strathe et al. (2008), a total of 38 coupled compartments are considered, consisting of a line-up of 4 main GI segments (stomach, proximal and distal small intestine, as well as the large intestine) subdivided into the major biochemical

compounds (including endogenous and dietary proteins, amino acids, starch and sugars, dietary lipids and fatty acids, degradable and undegradable dietary fiber). In this model, gastric emptying and intestinal transit are represented by mass action, and the rates of enzymatic degradation and absorption of nutrients are described by saturation kinetics. Model parameterization was performed based on a literature collection on the digestive physiology of pigs. Its stability was evaluated by sensitivity analysis (see section 3.5), and the quality of its predictions was assessed by comparisons with published results. Overall, the model appeared quite robust to variations of the studied parameters, and fairly predicted the digestibility of the main food components, lipid excepted, as well as the absorption profile of the studied nutrients (glucose, amino acids, and volatile fatty acids).

To the best of our knowledge, no similar model (i.e. with all nutrients) has been published yet for food or meal digestion and absorption in humans, though we are aware of at least one ongoing development (van Aken 2020) that will be exemplified in section 4.4. Human physiologically-based compartment models that include GI tract compartments have been, nonetheless, proposed to predict the metabolic fate of each of the main nutrients independently: proteins, lipids, and carbohydrates, for instance in Fouillet et al. (2009), Jelic et al. (2009), and Rozendaal et al. (2018). Although these models do not primarily focus on the mechanisms that transform food into absorbable nutrients, they are important extensions of the previously described approaches. A better representation of the functioning of the GI tract during digestion, using compartmentalization suitable to all kinds of nutrients, would thus directly serve postprandial metabolic models, by integration with other physiological compartments, such as splanchnic and peripheral organs. As an example, a total of 13 anatomical compartments, 9 of which representing non-GI tract compartments, were used by Fouillet et al. (2009) to simulate the dynamics of meal nitrogen absorption, splanchnic uptake, and metabolism, with subsequent peripheral transfer and deposition. Because the number of compartments and associated parameters increases remarkably in such models, error compensations are likely to occur and remain undetected. Beyond computational issues, this is another important reason why building and validating, a whole-body and all-nutrients physiologically-based model remains a difficult challenge.

3.3. Integration of food structure effects

The amount and the dynamics of nutrient uptake after a meal are also largely governed by food structure effects (Bornhorst et al. 2016; Dupont et al. 2018). Meals differing only by their processing conditions can even affect intestinal mucosa parameters and the microbiota composition in the colon (Beaumont et al. 2017; Oberli et al. 2018). These findings result from the influence of food structure on key mechanisms taking place in the upper parts of the GI tract: food comminution, food mixing with digestive fluids, gastric emptying kinetics, etc. For instance, it is well known that the gastric emptying kinetics of liquid meals follow an exponential behavior, whereas a lag phase is classically observed with solid meals. To properly simulate the breakdown of solid foods and their mixing with digestive fluids, computational solid mechanics and hydrodynamics modelling of oral and gastric processing may appear the best option (Ferrua & Singh 2010, 2015; Harrison et al. 2014, 2018). However, current oral and gastric computational models do not account yet for secretions and enzymatic reaction(s) and have only focused on the gastric behavior of liquids, with no or few discrete solid particles. These are moreover computationally expensive and are not easily compatible with system modelling approaches. This is why other means are classically used to try reproducing food structural effects in compartmental models.

The most commonly employed strategy is to simulate the gastric emptying kinetics with empirical equations. The oldest one, which is still among the most commonly employed, is the Elashoff equation (Elashoff et al. 1982), which assumes that the fraction of meal in the stomach follows a power exponential decay. As recently reviewed by Muttakin et al. (2019), other equations have been proposed for the evolution of gastric volume (Siegel et al. 1988), or by introducing exponential pre-factors to enable representing a delayed sigmoidal behavior (Kong & Singh 2009), as generally observed with solid foods.

Another strategy consists in assuming several gastric sub-compartments (Dalla Man et al. 2006; Le Feunteun et al. 2014; Sicard et al. 2018; van Bentum & Nelson 2011) to incorporate non-ideal mixing. For instance, two gastric sub-compartments were used by Le Feunteun et al. (2014) to simulate protein digestion of differently structured dairy protein matrices in mini-pigs: one to represent the matter that is retained within the stomach (large particles, matter too far from the pylorus, etc.), and another to represent the matter that is well mixed with the secretions and is

ready to be emptied. Such a strategy enables representing heterogeneous gastric content with a delayed emptying for solid foods, meanwhile avoiding simulating unreasonable gastric volume or secretions.

However, none of these above options is perfect. New developments thus remain to be proposed to relate more directly food structural properties with their behavior in the upper parts of the GI tract, and in particular with their kinetics of gastric emptying and of enzymatic degradation. Nonetheless, the growing interest of food scientists for the fate of food during digestion is currently leading to an increasing body of physical models on the behavior of foods in the dynamic conditions of the GI tract. Examples include models of the buffering capacity of foods in the stomach (Luo et al. 2018; Mennah-Govela; Mennah-Govela et al. 2019), the swelling of protein gels (van der Sman et al. 2020), the softening of carbohydrate foods (Drechsler & Bornhorst 2018), the mechanical breakdown of solid foods (Drechsler & Ferrua 2016), or the mass transfer and absorption in the intestine (Moxon et al. 2016; Taghipoor et al. 2012, 2014). A reaction-diffusion model of the gastric digestion of meat proteins, which takes into account enzyme and proton diffusion into bolus particles with consideration of buffering effects, has even been proposed recently by Sicard et al. (2018). Given that mechanistic digestion models which aim at integrating the physical properties of foods remain in their early stages, and that this research area has become very active, it is expected that important progress will soon be made on the modelling of food structure effects on digestion.

3.4. Integration of the microbiota

The lower part of the digestive system hosts the intestinal microbiota. This complex microbial community not only processes non-digestible dietary residues by anaerobic digestion reactions in the colon (Korpela 2018), but also maintains a complex dialogue with the host and plays a very important protective role against pathogenic microorganisms (Guarner & Malagelada 2003).

Some large-scale (whole digestive system or body) digestion models integrating the ecological and metabolic dynamics of microbes have been developed, in order to provide a detailed representation of host-diet-microbe interplays. These models are mainly based on two reductive representations of the intestinal microbiota. The first one focuses on functional traits of

microorganisms and models the microbiota by a small number of functional populations, assuming high functional redundancy in the ecosystem. The second focuses on a few dominant species, whose metabolism is modelled in detail.

A prototypal example of the first category is the model of fiber digestion in the large intestine developed by Muñoz-Tamayo et al. (2010). The colon is divided into compartments corresponding to physiological regions, in which a simplified biochemical reactions network models fiber degradation and short chain fatty acid (SCFA) production. The local microbiota is structured into functional populations that catalyze these reactions. The model includes transport, diffusion, and absorption between compartments or between the colon and the host. Its parameters were drawn from the literature and from *in vitro* culture experiments. This work aimed to synthesize available knowledge in a single model and to qualitatively reproduce simple nutritional scenarios such as variation of the dietary fiber level and its influence on SCFA production and colon transit. Based on the same concept of functional microbial populations, several other models were proposed, for the proximal colon in humans (Motelica-Wagenaar et al. 2014), for an *in vitro* model rumen focused on pH, hydrogen metabolism, and hexose and amino acids utilization (Muñoz-Tamayo et al. 2016), as well as continuous, spatially explicit models coupling microbial metabolism, fiber digestion and fluid dynamics in the colon (Cremer et al. 2017; Labarthe et al. 2019). Another example is demonstrated by Kettle and co-workers (Kettle et al. 2015, 2018). They developed an integrated model for the 10 major bacterial functional groups in the human colon. The growth kinetics and major metabolism of these groups were modelled taking into account their individual traits in term of substrate specificity, metabolic pathways, and pH effects. The model accounts for individual differences in terms of microbiota composition and consists of a large system of differential equations on microbial growth, substrates and metabolites concentrations. Recently, a multicompartment modelling tool was developed in R, called "microPop" (Kettle et al. 2018), to simulate microbiota kinetics in different compartments of the human colon.

Models in the second category result from the rapid and successful development of constraint-based genome-scale metabolic models (GEMs) of microorganisms (Kim et al. 2017; Thiele & Palsson 2010). In these models, the internal metabolic flux partition of each cell is assumed to be at quasi-steady-state and must be computed as soon as the external conditions and uptake rates

change. There are several methods to do this, one of the most popular being flux balance analysis (Orth et al. 2010) for which highly efficient tools such as the MATLAB Toolbox COBRA (Heirendt et al. 2019) can be used. GEMs based microbiota models are recent, an example being the model proposed by Heinken et al. (2013), including 15 prevalent genomes and the host epithelial cells. The model computes the metabolic partition between the different cells given input fluxes of nutrients and can be coupled with compartment models.

Advances in culture-free sequencing techniques in the past 20 years, such as 16SrDNA amplicon sequencing or Whole Genome Shotgun (WGS) allows accessing the taxonomic and functional profiling of large intestine microbiota for human (Li et al. 2014), pig (Xiao et al. 2016) or mouse (Xiao et al. 2015). For both types of models mentioned above, recent efforts have been proposed to integrate the enormous taxonomic and functional diversity in the digestive microbiota, together with the wide variety of indigested dietary fibers (Korpela 2018). A first attempt to link functional population with WGS metagenomics can be found in Raguideau et al. (2016), and a complete MATLAB toolbox to build and simulate GEM models of host and microbiota based on 16S data has recently been released by Baldini et al. (2019).

3.5. Mathematical tools for predictive modelling

Predictive compartmental models are characterized by their ability to cope with uncertainties related to environmental variability (e.g. structure and preparation of drugs or food), inter-individual variability (e.g. age, weight, sex or physical condition of the subject) and finally with the more or less accurate knowledge and representation of the phenomena involved in the digestion and absorption of nutrients. Indeed, the ultimate goal of predictive modelling is to provide prediction intervals in which quantities of interest are located when simulating an uptake scenario, with an associated probability and a modulation by the characteristics of foods and individuals. Models for food digestion and absorption are often large-sized, complex models with limited observations, especially *in vivo*. Moreover, the available information is heterogeneous, in that they may be obtained by very different measurement techniques and come from different experiments or subjects. This is why building predictive models is a major issue in the field and calls for the use of sophisticated mathematical tools. For instance, parameter estimation, in which descriptors of the statistical distribution of the model parameter are estimated, such as the mean,

variance, and covariance, is a crucial step. Many generic or specialized software or programs are available, implementing methods ranging from nonlinear least-squares regression to Bayesian estimation (Balsa-Canto et al. 2016; Haario et al. 2006; Raue et al. 2015). Other aspects, such as interindividual variability, also have to be accounted for when dealing with population studies. This can be done through mixed effect models (Lavielle 2014), which can incorporate covariates.

In establishing a comprehensive food digestion model, we may also insist on the usefulness of conducting Sensitivity Analysis (SA), which is a highly relevant tool for models where several phenomena may interact in a complex way to produce an overall behavior. SA enables highlighting parameters whose variation has a significant influence on the model responses. Hence, parameters distinguished as significant can be estimated experimentally and/or clinically, while the rest can be taken from the literature or approximated. SA may also lead to the total elimination of some model parameters considered insignificant (Manca 2018).

Methods employed for SA can be either local or global. Local methods estimate the effect of small parameter variations on a model response and are primarily used in steady-state models. Global sensitivity analysis (GSA) (Saltelli et al. 2008; Sudret 2008), by contrast, is able to examine the entire parameter space, manage nonlinearities well and provide a complete ranking of parameters by "significance". GSA is a numerical exploration approach based on statistical theory, that aims to understand the influence of parameters on selected model outputs, for which several software tools are available; see for instance Iooss et al. (2019) and Saturnino et al. (2019). For example, an application of SA can be found in Labarthe et al. (2019), where GSA was performed with a model of the spatial repartition of the bacterial population in the human colon, and helped in understanding the influence and relative strength of different factors including peristalsis, fiber intake and mucus viscosity on the total bacterial abundance along the colon.

In GSA, the parameter space is sampled in an appropriate way and the corresponding model outputs are subsequently analyzed with various methods, the most popular of which are the calculation of Sobol indices and Partial Rank Correlation Coefficients (PRCC) (see Iooss & Lemaître (2015) for a complete review). For complex models, low-cost computational screening methods can be used to eliminate insignificant variables prior to employing GSA for the remaining parameters, such as the screening method of Morris (1991).

4. Future challenges

4.1. Towards a more complete model of food transit and absorption

As depicted in section 3, mathematical models related to various aspects of the GI tract have been proposed from different scientific fields (pharmaceutics, nutrition, animal sciences, food sciences, microbiology). A number of pieces are thus available to start building a system model of the functioning of the human GI tract during digestion. Its skeleton could be inspired from the works already undertaken in pharmaceutics and animal sciences, before integrating the most relevant and promising modelling efforts.

For instance, the model proposed by Strathe et al. (2008) for pigs already accounts for all the main nutrients of a meal, with consideration of their transit, their hydrolysis, their absorption kinetics, as well as for nutrient degradation and some aspects of the microbial metabolism in the large intestine. We may, therefore, assume that a comparable model organization, with some adaptations related to human physiology, could constitute a fair starting point before refining and completing the model structure and its underlying hypotheses. It has also been shown that gastric emptying kinetics can be fairly predicted by assuming a nutrient feedback mechanism in the proximal small intestine (Hunt & Stubbs 1975; Moxon et al. 2017), leading to a mean rate of caloric emptying of about 2.5 kcal/min in humans (Hunt et al. 1985). This strategy, therefore, seems much more elegant than empirical equations or mass action laws to predict gastric emptying, as recently proposed in a standardized semi-dynamic protocol for *in vitro* digestion (Mulet-Cabero et al. 2020). However, to the best of the authors' knowledge, this modelling strategy has not been applied yet in published compartmental models of food digestion and absorption. Recent developments in the modelling of enzymatic hydrolysis are also providing new means to take into account some key properties of the main nutrients, with non-empirical relations between the model parameters and the food properties. These mostly rely on the consideration that different rates of hydrolysis can be assumed for different subclasses of the considered nutrient (*i.e.* more or less resistant and/or accessible fractions). Examples have been proposed for lipids (Giang et al. 2016), proteins (Barros & Xavier Malcata 2004; Kondjoyan et al. 2015) and starch (Edwards et al. 2014; Li et al. 2019; Meraz et al. 2019), with promising results. These approaches therefore seem very interesting to integrate the food scientist knowledge, which rapidly increases with the spread of *in vitro* digestion studies in this community. A relevant model of food digestion in the upper

parts of the GI tract would also enable better predictions of the unabsorbed meal fraction, and hence be valuable for the modelling of the colon microbiota functioning.

The present review also highlights lacks of knowledge and modelling tools. In particular, new developments would be very welcome to relate more directly the oral and gastric behavior of solid food with their known or measured properties. We may nonetheless be confident that the growing interest of food scientists and modelers for this research area will rapidly bear fruit, without forgetting that empirical relations can be of use while awaiting more mechanistic representations. A great number of pieces are thus already available to start building a framework to test and improve our understanding of food digestion in humans.

In fact, we may even highlight here the ongoing development of a multicompartment model of digestion in humans by one of the authors (van Aken 2020), which considers all nutrients, most of the phenomena listed in Table 1, and even some physiological feedbacks (see section 4.2). As an illustrative example of the capabilities of such a model, Figure 2 compares its predictions with the human data obtained by Eelderink et al. (2012) on blood glucose and insulin excursions after a bread meal and a pasta meal. As observed experimentally, the model could reproduce a slightly lower glycaemic peak and a much reduced insulinemic peak for the pasta meal compared to the bread meal. In the model, the differences between the two meals were predominantly caused by the difference in food structures. Compared to pasta (closed gel-like structure), the model assumes that bread (open sponge-like structure with more accessible starch) requires a longer time of oral processing and more saliva to obtain a swallowable bolus, and is associated to faster starch hydrolysis and slower gastric emptying kinetics. It is not the purpose of the present review to describe the model structure nor to discuss the suitability of these modelling assumptions. Figure 2 is rather intended to provide an illustration of what can be achieved with a physiologically-based compartmental model of food digestion: put hypotheses to the test, simulate different scenarios, etc. It also provides a concrete illustration that the establishment of a comprehensive model of the functioning of the GI tract during human digestion can become a reality in the near future.

4.2. Towards the integration of feedback mechanisms

The conditions effective in the alimentary system are highly influenced by the presence of food in order to acutely adjust the physiological "settings" for optimal performance (van Aken 2010). Although physiological studies have delivered the detailed biological pathways for many of these regulatory mechanisms, mathematical modelling of these processes in relation to food digestion has remained rare. In the fed state, a large range of stimuli, including stomach and intestinal distension, luminal pressure, the presence of particles, acidity, osmotic value, and nutrient degradation products are detected by receptor cells all along the alimentary tract. These activate physiological responses through neural signals, sometimes directly, and sometimes indirectly through the nervus vagus, activated by secreting specific gut hormones, such as cholecystokinin (CCK), gastric inhibitory polypeptide (GIP), glucagon like peptide-1 (GLP-1), peptide tyrosine tyrosine (PYY), gastrin, motilin and secretin (van Aken 2010).

Saliva secretion is stimulated by chewing, the parasympathic pathway, and various food stimuli (Ekström et al. 2012; Froehlich et al. 1987; Gavião & Bilt 2004; Pandey et al. 2019). The secretion of gastric acid is stimulated by stomach distension, the presence of peptides in the stomach, the buffering capacity of the food (Konturek et al. 1974), but is inhibited by a too low pH in the antrum (Wheeler 1974) and in the duodenum (Konturek & Johnson 1971) via the release of secretin and neural signals. Gastric acid secretion is also partly controlled by Ghrelin, the "hunger hormone", of which the blood levels increase due to the cephalic expectation of food (Arosio et al. 2004). Food material entering the small intestine is then detected by specific receptors that stimulate the secretion of pancreatic fluid and bile (Chandra & Lidlle 2015; Chey & Chang 2001). These secretions are also mediated to large extent by CCK (Chey & Chang 2001; Liddle et al. 1985; Thimister et al. 1996), which is released by endocrine I-cells in the gut wall, neurons of the enteric nervous system and of the brain (Johnson 2014) in response to digestible proteins, peptides and certain amino-acids (Buffa et al. 1976; Johnson 2014), as well as fatty acids (Sidhu et al. 2000). Many other adjustments are related to the transition between fasted and fed states. The alimentary system even adjusts to returning dietary patterns by slowly modulating parameters such as receptor sensitivity and transporter presence in the gut (Baggio et al. 2004; Tong & D'Alessio 2014).

Attempts to model some of these control mechanisms have been proposed in the literature, for instance by Joseph et al. (2003) for the regulation of gastric acid secretion, by Shiang & Kandeel (2010) and Jelic et al. (2009) for the insulin regulatory system for blood plasma glucose and non-esterified fatty acids, respectively. As previously evocated, models of the physiological regulation of gastric emptying have also been proposed by Hunt & Stubbs (1975) and Moxon et al. (2017). It is noteworthy that these models can remain rather simple mathematically despite the high complexity of the biological mechanisms involved. For instance, the *in vivo* regulation of gastric emptying is mediated by many receptors (Minami & McCallum 1984), neural signals, and the release of intestinal hormones such as CCK, GLP-1, and Ghrelin (Marathe et al. 2013; Minami & McCallum 1984). Notwithstanding, Moxon et al. (2017) showed that the gastric emptying patterns observed between low and high nutrient liquid meals could be accurately predicted by assuming an initial emptying rate followed by a maximal caloric flux into the duodenum. However, models of regulatory mechanisms remain scarce and can also be quite complex mathematically, as in Joseph et al. (2003). Much more work is therefore needed to hierarchize the importance of control mechanisms, to determine those which should be considered to reproduce the trends observed *in vivo*, and if and how they may be reproduced with simple modelling assumptions.

4.3. Mathematical and computational challenges

Preceding sections highlight promising first steps in establishing a mathematical modelling framework for food digestion and absorption, built on compartmental approaches that have been so successful in pharmacokinetics. These initial models typically focus on single nutrients, food structure, or microbiota, with a few more comprehensive models in animal feed science. However, to the authors' knowledge, no sustained attempt has been made to link these models together into a whole-body all-nutrients model for human digestion and absorption incorporating food structure information and microbiota; this is some indication of the mathematical challenges this task poses.

Table 1 gives insight into those challenges, with a list of 6 physiological compartments and 31 phenomena which the authors think should be modelled. Each of these phenomena adds its own set of equations and parameters to the modelling framework, leading to a multi-parameter complex model. As noted at the end of section 3.2, incorporating the modelling of postprandial

metabolic responses to the absorption of just one nutrient can already lead to the explosion of physiological compartments and model parameters. For each nutrient and at various sections of the alimentary canal, there would be a diverse range of phenomena to model, and one, therefore, sees that any model of digestion and absorption in humans would be complex.

This complexity generates several mathematical challenges, beginning with ensuring that appropriate equations are used to model the different phenomena. The task of translating information about digestion processes into appropriate equations where such equations do not yet exist, requires excellent communication and collaboration between a variety of expert groups. Another mathematical challenge is the appropriate and physiologically sound determination of parameter values. Where experimental or otherwise reliable values are not readily available, more empirical techniques may have to be employed to set parameters, possibly leading to model inaccuracies. For example, in coupled differential equations with many parameter values to determine simultaneously, a common danger would be finding a solution that is not the physiologically relevant optimum. Thus the key challenge regarding parameters is how to determine physiologically correct values for those which cannot be determined easily and reliably experimentally or otherwise.

Moreover, a computational challenge related to the complexity of human food digestion and absorption model would be its likely computational expensiveness and inefficiency. If existing software tools are linked to enact such a model, they would independently perform sometimes similar tasks without sharing efficiencies with other linked tools, and ultimately the efficiency of the whole process would be determined by the least efficient tool. It would moreover be difficult to manage different software tools working together in a properly inter-connected manner. It is therefore likely that such a model should be developed from scratch to alleviate some of the computational complexity and efficiency issues. However, the time required to build and test such a model into a reasonable state for an application would likely be significant.

In this review, we have assumed that compartment models would be the framework for future human digestion and absorption model. Although the authors strongly believe this, there is the possibility that this may prove a major mathematical and computational challenge, and that one may need to rely partially on other mathematical modelling paradigms, such as fluid dynamic models which are not as easily linked to compartment models.

4.4. Prospects on the benefits of a more complete physiologically-based food digestion model

The building of a physiologically based model of the GI tract during digestion would first require to gather and carefully organize the available knowledge. This crucial step represents at the same time a challenge (though surmountable) and a real opportunity for researchers from various scientific origins (mathematics, nutrition, microbiology, human medical science, food and feed sciences, pharmacology) to share their knowledge and collaborate. For a widespread knowledge collection and use, this task would preferably be associated with the establishment of a dedicated multidisciplinary network, and lead to a shared modelling platform that could serve as a basis for incremental improvement of the model structure and underlying hypotheses. This would undoubtedly enable identifying lacks, or grey boxes, of knowledge, hence possibly guiding the experimental research. This could even offer a common ground to bridge the gaps between food science and medical, pharmaceutical, human microbiota sciences. Insight from food digestion studies can give a better and quantitative insight in the unabsorbed meal fraction reaching the colon (Beaumont et al. 2017), in how food properties might modulate risk factors of metabolic diseases (e.g. diabetes type 2) and metabolic syndrome, or in the way pharmaceuticals can be optimally delivered orally in conjunction with food intake (Koziolek et al. 2019). In return, the vast knowledge base of the medical field will deliver valuable insight into the development of healthier foods.

A more common hope with the establishment of a physiologically-based model of digestion is that it could allow accurate *in silico* predictions on various aspects (Le Feunteun et al. 2020), probably starting with the effects of food/meal composition and structure on: transit and disintegration kinetics, postprandial plasmatic concentrations in nutrients, the arrival of unabsorbed nutrients and fibers available for the intestinal microbiota. Such a model could also be used to predict the effect of variations such as inter-individual variability, time-of-day, and pre-meal effects, and to support the development of personalized nutrition, targeting different groups of the population. It could even become a central element in all models where the processes taking place in the GI tract play a key role, as for instance for nutritional (e.g. satiety), metabolic (e.g. the fate of nutrients in the host), or colon microbiota (e.g. biodiversity) related

considerations. In the long term, *in silico* predictions could even justify the need for *in vivo* investigations by fast evaluation of expected outcomes, or alternatively offer a substitute to some animal and human studies (van Milgen & Lescoat 2008).

The authors are convinced of the great possibility and benefits of developing a mathematical framework for performing *in silico* human food digestion and absorption experiments. Notwithstanding all the facing challenges, the number of building blocks already existing, the youth of this research field, and the successes observed in the pharmaceutical area clearly support the idea that attempts will be proposed in the future. It is difficult to know how accurate *in silico* predictions can become in the food digestion area, but our general impression is that this research field is mature enough to start building a human physiologically-based food digestion model, should it be only to provide a practical means to bring research communities interested in the functioning of the GI closer.

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788 **Table 1.** Overview of the phenomena and the important food properties that should be
789 considered when developing a multicompartment model of food digestion and absorption.

Physiological Compartment	Main phenomena to be modelled	Important food properties
Oral	• Mechanical breakdown • Saliva incorporation (amylase, water, mucus) • Enz. hydrolysis of starch	• Mechanical and rheological properties • Structure (mostly macro) • Composition (dry content, pH, nutrients)
Gastric	• Gastric secretion (enzymes, HCl, mucus) • pH drop • Enz. hydrolysis of starch, protein and lipid • Mechanical breakdown • Mixing and sieving • Phase separation (sedimentation, creaming) • Controlled flow into duodenum	• Mechanical and rheological properties • Structure (all scales: particle size and density, emulsion stability, microstructures, state of nutrients…) • Composition • Buffering capacity • Intermolecular interactions
Duodenum	• Multiple secretions (pancreatic enzymes, bile, bicarbonate, water, mucus) • pH increase • Enz. hydrolysis of starch, protein and lipid • Absorption of water and nutrients • Mixing • Residence time	• Structure (all scales) • Composition • Buffering capacity • Intermolecular interactions
Jejunum	• Intestinal secretion (water, bicarbonate, mucus) • Enz. hydrolysis of starch, protein and lipid • Absorption of water and nutrients • Mixing • Residence time	• Structure (all scales) • Composition • Intermolecular interactions
Ileum	• Intestinal secretion (water, bicarbonate, mucus) • Enz. hydrolysis of starch, protein and lipid • Absorption of water, nutrients and bile salts • Mixing • Residence time	• Structure (all scales) • Composition • Intermolecular interactions
Ascending, Transverse and Descending Colon	• Intestinal secretion (water, bicarbonate, mucus) • Microbial growth and metabolism and the way it is affected by material entering the colon • Absorption of water and microbial metabolites such as short chain fatty acids • Mixing • Residence time	• Composition (fibre, polyphenols, polyols…) • Interaction of components with the microbiota

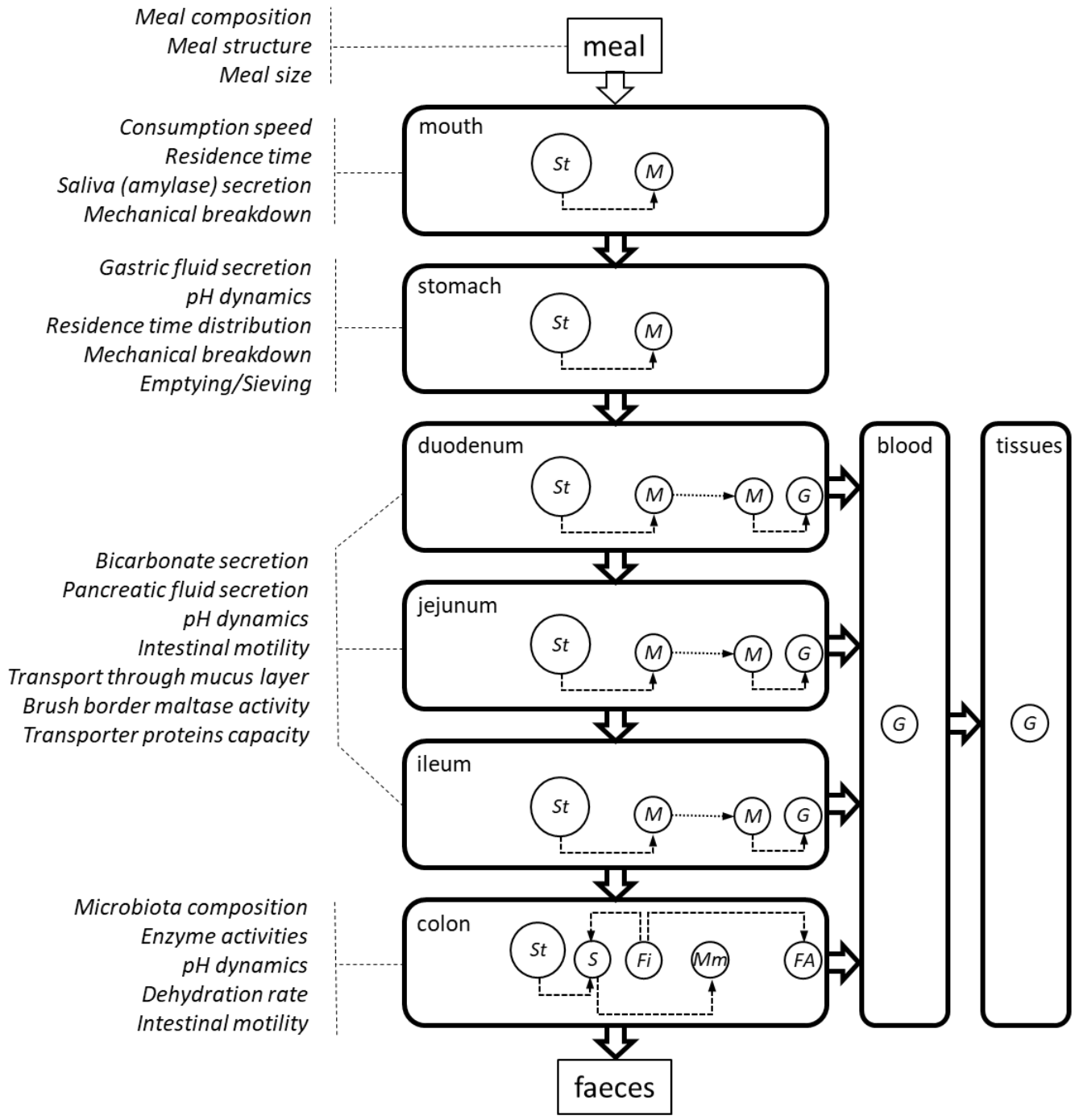
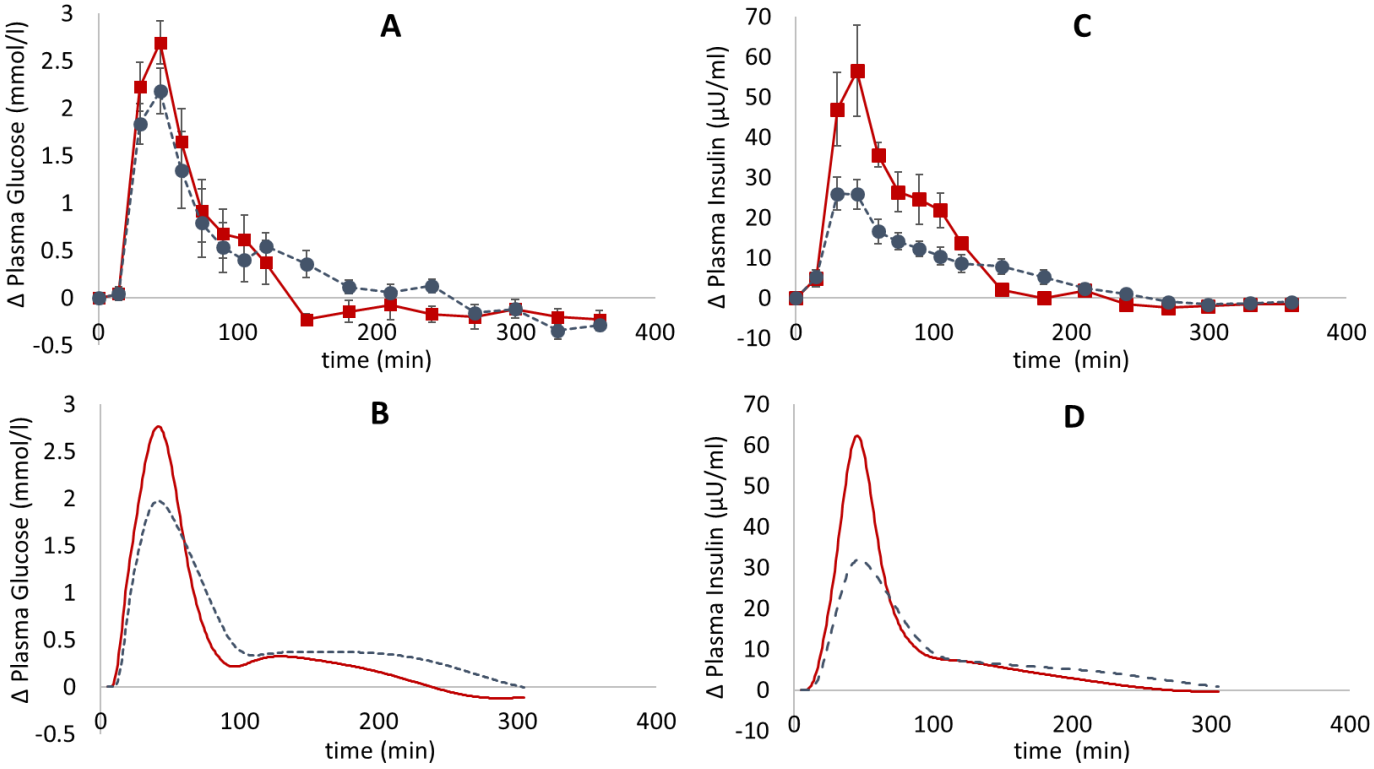


Figure 1. Schematic representation of starch digestion and important processes to be included in a multicompartment model (omitting proteins and lipids to keep the figure simple). Dashed arrows: transformations, dotted arrows: transport from lumen to brush border through mucus layer; St: starch; Fi: fibre; FA short chain fatty acids; G: glucose; M: end products of amylolytic reactions (maltose, maltotriose and α-limit dextrins); Mm: microbial mass; S: various sugars.



796

797 **Figure 2.** Example of digestion modelling by a program in development by one of the author (van
798 Aken 2020): Experimental (A, C) and simulated (B, D) blood glucose and insulin excursions
799 following a bread meal (plain line) and a pasta meal (dotted line). Experimental results have been
800 extracted from study performed by Eelderink et al. (2012), who investigated a bread meal and a
801 pasta meal both consisting of 50 g available carbohydrates, 9 g fat, 6 g protein and 250 mL tap
802 water.

803