Modeling of Food Digestion
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Food digestion is a complex biological process requiring various interrelated physicochemical actions. Food is broken down in the digestive tube by enzymatic reactions, mechanical forces, and nutrients are transported by advection, diffusion… Limiting steps in such a complex system are difficult to identify and to quantify experimentally, making it necessary to develop models and simulations. In this chapter, historical macroscale modelling based on transport phenomena (mainly mass or momentum transfer) is presented. Then, microscale modelling where the food structural features are considered is introduced. Finally, recent microscale simulations based on multi-agent systems are described. Applications to drug, protein, carbohydrate, and lipid absorption are addressed, with an emphasis on lipid digestion.
introduced to account for the main nutrients and processes. On the other hand, the food features have only recently been taken into account.

In this chapter, the various processes occurring within the digestive tract will be described to set the frame of the basic knowledge. Then, the development of the first models will be reported in their contexts, which were originally the understanding of drug absorption and of animal feed digestion. Finally, the recent microscale modelling approaches focusing on the fate of foods in some parts of the human digestive tract will be detailed.

**14.2. The complexity of food digestion and absorption**

Although digestion may be described as a biological process yielding nutrient and waste from food, it is actually a complex combination of various processes. In this section, the main processes are reviewed within the digestive tract and up to absorption, leaving the biology of hormonal, neural, and electrophysiological regulations out of the focus. The distinct roles of the colon and its microbiota are also not described here. This summary constitutes the basic knowledge, which can be found in any recent volume about gastrointestinal physiology (see for example Johnson, 2014).

**14.2.1. Chemical processes**

The major chemical reaction that converts food into nutrients is hydrolysis. This consists in the rupture of one or several bonds of a molecule by water. The digestive juices comprise various enzymes catalyzing this reaction, with a high selectivity in substrate and bond. The main digestive enzymes are amylases, lipases and proteases, responsible for the hydrolysis of starch (amylolysis), lipid (lipolysis) and protein (proteolysis), respectively.

In saliva produced in the mouth, ptyalin (an \( \alpha \)-amylase) starts the hydrolysis of starch, and lingual lipase, to a minor extent, starts the hydrolysis of triglyceride. Then, in the stomach, the gastric juice contains pepsin, a protease that starts the hydrolysis of protein, and also contains gastric lipase that continues the hydrolysis of triglyceride. Lastly, in the small intestine, the digestive juice from pancreas is secreted into the duodenum to finalize food hydrolysis with pancreatic \( \alpha \)-amylase, pancreatic lipase, and trypsin/chymotrypsin (two proteases). Ultimately, more enzymes from the intestinal brush border are required to complete the hydrolysis of starch and protein before absorption. Note that some vitamins also need specific enzymes to produce their absorbable form. The main end products of hydrolysis are glucose for starch, monoglyceride and fatty acid for triglyceride, and amino acid for protein. The intermediate products of hydrolysis are reported in table 14.1.

**Insert table 14.1**

It is important to note that the activity of all enzymes depends on pH and temperature. The passage of food through the digestive tract modifies pH, which is regulated by the secretion of electrolytes. While pH in the mouth after food ingestion is relatively stable around 7.0 (because the transit time is short), pH in the stomach may vary within the range 6.5 (fed state) to 1.5 (fasted state), and in the small
intestine pH can range from 5.5 (duodenum) to 7.5 (ileum). Temperature in the stomach can also be modified by food, and usually returns to 37°C within 20 minutes. These changes affect the physicochemical conditions in the digestive tract. Temperature, ionic strength and pH modulate the electrostatic charge, conformation and solubility of molecules. Moreover, the various smaller molecules produced by hydrolysis also present specific properties.

14.2.2. Physical processes
As a consequence of the physicochemical conditions, initial food structures tend to alter under the action of physical phenomena such as crystallization, aggregation, flocculation, coalescence, and mass transfer. At the macroscale, this results in phase separation, particle size change, and evolution of rheological properties (elasticity, viscosity). Furthermore, assemblies are created from the association of nutrients and physiological molecules. This is the case for the intestinal mixed micelle composed of bile salts and lipids, or for various micronutrient/protein binding. At the body scale, the muscles of the digestive tract contract and relax in order to separate, mix and propel food. This generates stress, strain, and determines transit times. These fundamental quantities are reported in table 14.2, where the strain rate is characterized in the shear mode. The greatest mechanical breakdown is achieved in the mouth, with high stress and shear rate levels. Shear rate remains high in the pharynx and esophagus regions, whereas pressure decreases markedly (not reported in table 14.2, as not directly related to digestion processes). Then, both pressure and shear rate decrease to lower levels as food progresses through the stomach and the small intestine, where transit times are greatly increased to compensate. Nevertheless, there is still some mechanical breakdown of food in the antrum region (referred to as grinding), linked to a selective gastric emptying based on particle size. Then, mixing is produced by a segmentation process in the small intestine. Throughout the digestive tract, bulk flows are thus generated, constituting the convective part of nutrient transport (by advection).

** Insert table 14.2 **

The other component of nutrient transport is diffusion. It is especially important in the small intestine, where the remaining particles in the digestate will finally reach the molecular size. Although an advection contribution still propels the digestate, the absorption of nutrients and micronutrients is mostly achieved by diffusion. First, molecules have to pass through the mucus layer (or unstirred water layer), which is a highly viscous mucin gel covering the intestinal villi lined with intestinal absorptive cells. As advection is very limited in this layer, this is done by either supramolecular (e.g. lipid mixed micelles) or molecular (e.g. peptides or saccharides) diffusion.

14.2.3. Biological processes
Absorption is the transport across the intestinal cell membrane, which is either passive or active. Passive transport is actually diffusion, which can be either simple for lipophilic small molecules
(passage down the concentration gradient across the membrane) or facilitated for hydrophilic or large molecules (binding to membrane protein that opens a channel). On the other hand, active transport is a process requiring energy, moving molecules against the concentration gradient, contrary to diffusion. Energy is supplied by ATP hydrolysis or electrochemical gradient.

14.3. Development of digestion and absorption modelling

The early modelling efforts in the 1960s were mainly related to oral drug. The first works were compartmental, aiming to deduce drug absorption from blood or urinary concentration data (Nelson, 1961, Wagner and Nelson, 1964, Riegelman et al., 1968, Loo and Riegelman, 1968). While it is out of the scope of this chapter, it should be noted that theoretical studies within the gastrointestinal tract focused on drug release out of various dosage forms (see for example Higuchi, 1967, Siepmann and Siepmann, 2008). Then, derivations for drug absorption from the gastrointestinal tract were established. Because most excipients are not digestible, the modelling of digestion was not undertaken. This was done later by nutritionists and food scientists. In this section, we review the different types of model that were developed.

14.3.1. Drug absorption

The first attempt to use a physical model of absorption in the context of the gastrointestinal tract was published in 1966 for urea, in the form of a macroscale diffusion-convection (or diffusion-advection) equation (Lifson and Hakim, 1966). However, this did not include any physicochemical parameter. Then, a model comprising a lipid phase (for the cell membrane) was derived for drug absorption in 1970, only based on diffusion (Suzuki et al., 1970). The initial aqueous diffusion was supposed to obey Fick’s first law, whereas the succeeding diffusion (within the lipid) was supposed to obey Fick’s second law. A mass balance of the ionized and unionized species for drug, buffer, and water was included based on dissociation constants depending on pH. Only unionized drugs could diffuse in the lipid phase, with a distribution determined by the partition coefficient.

A significant advance was made in 1980 when a more realistic diffusion-convection-absorption equation was derived (Ni et al., 1980), with the possibility to include the above physicochemical parameters (Amidon et al., 1981). The basic equation is now known as the dispersion model (Yu et al., 1996, Huang et al., 2009):

\[
\frac{\partial C}{\partial t} = \alpha \frac{\partial^2 C}{\partial x^2} - \beta \frac{\partial C}{\partial x} - \gamma C
\]

where \( C \) is the drug concentration, \( t \) is the time, \( x \) is the longitudinal distance in the intestine represented as a tube, \( \alpha = D \) is the longitudinal diffusion coefficient, \( \beta \) is the longitudinal velocity, equal to \( Q/(\pi R^2) \), and \( \gamma \) is the absorption rate constant, equal to \( 2P_e/R \), where \( Q \) is the flow rate, \( R \) is the radius of the intestinal lumen, and \( P_e \) is the apparent permeability coefficient. Note that the symbols are harmonized in the equations, so each symbol will be explicated only once in the text.
Starting in the 1980s and completed in 1995, the work in the research group of Gordon Amidon established a steady-state model based on mass balances (Amidon et al., 1995, Yu et al., 1996). It enabled the construction of a biopharmaceutics classification system, based on dimensionless numbers, which are:

The dose number \( D_0 = \frac{C_0}{C_S} = \frac{M_0/V_0}{C_S} \)

The dissolution number \( D_n = \frac{t_{res}}{t_{diss}} = \frac{\pi R^2 L/Q}{r_0^2 \rho/(3DC_S)} \)

The absorption number \( A_n = \frac{t_{res}}{t_{abs}} = \frac{\pi R^2 L/Q}{R/(2P_e)} = \frac{2P_e \pi RL}{Q} \)

where \( M_0 \) is the starting drug mass (dose), \( V_0 \) the starting dilution volume, \( C_S \) is the solubility of the drug, \( L \) is the tube length, \( r_0 \) is the starting radius of the drug particle, and \( \rho \) is the density of the particle. Note that the dose number is a concentration ratio, while the dissolution and the absorption numbers are time ratios, relative to the intestinal residence time \( t_{res} \).

The dimensionless mass balance equations for particle radius and drug concentration are:

\[
\frac{dr^*}{dx^*} = -\frac{D_n(1-C^*)}{3r^*} \quad (14.2)
\]

\[
\frac{dC^*}{dx^*} = D_n(1-C^*)r^*D_0 - 2AnC^* \quad (14.3)
\]

where \( C^* = C/C_S, r^* = r/r_0 \), and \( x^* = x/L \).

Compared to the dispersion model, we see that other parameters are included, namely drug solubility, drug particle size and density. Solubility and permeability can be made pH-dependent.

Finally, another type of approach was used in the 1990s, based on compartments, resulting in the CAT (compartmental absorption and transit) model (Yu et al., 1996, Yu and Amidon, 1999). One of its advantages is to describe the whole gastrointestinal tract. The transit is defined as:

\[
\frac{dM_{n}}{dt} = -K_sM_s \quad (14.4)
\]

\[
\frac{dM_{n}}{dt} = K_iM_{n-1} - K_iM_n \quad \text{for } n = 1, 2, \ldots, 7 \quad (14.5)
\]

\[
\frac{dM_{n}}{dt} = K_iM_7 \quad (14.6)
\]

for stomach, small intestine (7 compartments), and colon, respectively. \( K_s \) and \( K_i \) are the rate constants for gastric emptying and small intestinal transit. Absorption is assumed to occur only in the small intestine, which is divided in seven compartments, such that:

\[
\frac{dM_n}{dt} = K_a \sum_{n=1}^{7} M_n \quad (14.7)
\]

where \( K_a \) is the absorption rate constant.

Nowadays, simulation programs are available, using mainly dispersion or compartmental models. They include the parameters of the dimensionless numbers, and others related to release, degradation, food effect (fasted or fed physiology), active transport, metabolism, etc. (Huang et al., 2009).

14.3.2. Animal feed digestion and absorption
Although there were early attempts to model feed digestion and absorption in pigs (Tomassone and Laplace, 1973, Usry et al., 1991), a complete description of a compartmental model was published only in the 1990s, around the same time as the CAT model (Bastianelli et al., 1996). Hydrolysis of all nutrients (proteins, lipids, carbohydrates) was accounted for and it was assumed to take place only in the intestines. Absorption of hydrolysis products and minerals was also assumed to take place only in the intestines. Secretion of endogenous proteins, lipids, and minerals was taken into account. A fermentation model was used for the colon. This simulation was further refined by Strathe et al. in 2008, with the description of hydrolysis and absorption as saturable processes (enzymatic reaction and active transport, respectively). An inhibitory effect of dietary fiber on proteolytic enzymes was implemented. Notably, the exogenous and endogenous proteins were treated separately, as they follow different hydrolysis and absorption kinetics. Note that this last point was developed in an intermediate model of the same nature but focusing only on protein digestion and absorption (Rivest et al., 2000). Recently, a similar model was applied to the digestion and absorption of proteins from milk gels, with the goal to understand the physiologic role of gel structure (Le Feunteun et al., 2014). Most parameters of the previous works were accounted for, except for hydrolysis which was not represented. The stomach was divided into two compartments. In the first compartment, milk clotting due to acidity and aggregation depending on protein processing (native vs. denatured) was included. In the second compartment, endogenous secretions and gastric emptying were simulated. Blood amino acid concentration resulting from intestinal absorption was successfully matched for mini-pig data, shown to be highly dependent on the gel structure.

An engineering approach based on chemical reactors was also developed. It initially focused on colonic hydrolysis and fermentation, represented by enzymes-catalyzed and microbes-autocatalyzed reactions, respectively (Penry and Jumars, 1987). These were modelled by Michaelis-Menten equations. Later, the same approach was applied to hydrolysis and absorption in the small intestine (Jumars, 2000a, Jumars, 2000b). More recently, a generalization was conducted, using an advection-reaction equation, thus implementing a convective term (Logan et al., 2002). Its form is:

\[
\frac{\partial n}{\partial t} = -\theta \frac{\partial n}{\partial x} - \nu(x, t, n)
\]  \hspace{1cm} (14.8)

where \( n \) is the nutrient concentration, \( \theta \) is the velocity, and \( \nu \) is the consumption rate (by hydrolysis and absorption), set to obey either first-order, Michaelis-Menten, or sigmoid kinetics. Furthermore, this model was extended to saccular organs, e.g. the stomach (Logan et al., 2003).

A recent effort has been proposed to implement most processes in the small intestine, including pulsed flow, water proportion, secretion of digestive juices, brush border enzymatic reactions, and indirectly accounting for processes in the stomach (Taghipoor et al., 2012, Taghipoor et al., 2014). The transport equation is:

\[
\frac{d^2 x}{dt^2} = \tau \left(1 - \frac{1}{c} \frac{dx}{dt} \right) c_0 + c_R \frac{dx}{at + bx} - \frac{K_{visco} \omega(t)}{W(t)} \frac{dx}{dt}
\]  \hspace{1cm} (14.9)
where $\tau$ is the mean effect of the pulses by unit time, $c$ is the mean velocity of the waves, and $[W]$ is the water mass proportion. The other constants are the parameters of the model, estimated from biological data. Hydrolysis and absorption were supposed to obey first-order kinetics. A distinction was made between non-solubilized and solubilized species.

Note that all these macroscale models represented flow using advection or a mass balance, and none of them included diffusion. Most of them were developed in the pig, because large sets of physiologic data are available. Some equivalent models exist in the ruminant, but are less transposable to the human, as the rumen system considerably differs from the human stomach.

14.4. Microscale modelling of food digestion and absorption

Currently, there is no complete model of food digestion and absorption in humans. The efforts consist in the description of specific processes, usually within one organ. These models are generally food-oriented, accounting for detailed structures at the microscale.

14.4.1. Mastication

The first step of food digestion is oral processing. Models exist concerning sensory features, which are important but only indirectly related to digestion (Taylor, 2002, Chen, 2009, Chen, 2014). Other crucial aspects are the saliva incorporation and the breakdown of solid foods into small pieces, essential for further processing. Early models were developed to predict the particle size reduction during food mastication (Lucas and Luke, 1983, Prinz and Lucas, 1997) or the maximum force during artificial (non-food) biting (Koolstra et al., 1988). Recently, the use of finite element or smoothed particle hydrodynamics methods allowed realistic simulations of food mastication (Röhrle and Pullan, 2007, Harrison et al., 2014a, Zhang and Hui, 2015). An example is given in Fig. 14.1, where the mastication of a 5% agar gel was simulated by smoothed particle hydrodynamics (SPH). The von Mises stress for each particle was calculated, and the resulting fragment size distribution was compared to experiments. Figure 14.2 shows that the predictability depends on the system studied (2% vs. 5% agar gels). Such simulations can reach a high degree of detail. The most achieved simulation already includes the mechanical effect of saliva (Harrison and Cleary, 2014), and further efforts could account for the release of taste, aroma, and the catalytic role of enzymes in saliva (Harrison et al., 2014b).

** Insert figures 14.1 and 14.2 **

14.4.2. Gastric flow and mixing

Similarly to the oral cavity, the human stomach was only modelled for mechanical purposes so far. The first simulation, presented in 2004 by the research group of James Brasseur, was based on a lattice Boltzmann method to characterize the velocity and pressure fields in a realistic 2D reconstruction of the stomach (Pal et al., 2004, Pal et al., 2007). Later, a similar approach was undertaken in 3D, using a...
computational fluid dynamics solver to simulate the velocity and pressure fields (Ferrua and Singh, 2010, Ferrua et al., 2014). Different types of fluid were simulated, namely Newtonian and shear thinning fluids. The resulting velocity fields are shown in Fig. 14.3 to illustrate the role of food rheology on the laminar flow and recirculation flow (vortices). In parallel, a simulation based on a finite-volume method was developed for the prediction of the velocity fields in a 2D idealized geometry of the antrum, where the secretion and mixing of pepsin were included, but not its catalytic action (Kozu et al., 2010). Note that all these models were only developed in the case of liquid food, so no breakdown could be investigated. In the future, the catalytic effect of enzymes as well as the behaviour of solid food should be included for further realism.

** Insert figure 14.3 **

14.4.3. Intestinal digestion and absorption

Several approaches have been adopted to investigate the small intestine numerically. First, the research group of James Brasseur used a multiscale lattice Boltzmann method to resolve both the macroscale phenomena that occur in the intestinal lumen and the microscale phenomena that occur at the villi, in a 2D idealized geometry (Wang et al., 2010a, Wang et al., 2010b). A luminal bulk flow, a pendular motion for the villi, and absorption of nutrients were modelled at steady state. The results indicated a coupling between the advection in the lumen and the diffusion in the unstirred water layer, both resulting in vortices that enhance absorption. These findings are illustrated in fig. 14.4.

** Insert figure 14.4 **

Later, the microscale part of the model was explored dynamically by another research group (Lentle et al., 2013, Lim et al., 2015). The simulation was focused around the villi, with alternative hypotheses: no luminal bulk flow, a relaxation/contraction motion for the villi. Similar results were reported, showing the formation of vortices around the villi, highlighting the important role of villi motion for optimal absorption. The flow and absorption patterns during a relaxation/contraction cycle are presented in Fig. 14.5.

** Insert figure 14.5 **

Another approach was initiated in the research group of Julian McClements, for the hydrolysis and release of lipid from emulsion droplet (Li and McClements, 2010). Trying to elucidate the role of different physicochemical characteristics of the system, these authors proposed a zeroth order kinetics equation of general form:

\[ \frac{dm}{dt} = kA(t) \]  
(14.10)

where \( m \) is the mass of lipid released from the droplet, \( k \) is the mass transfer coefficient, and \( A \) is the total surface area of the droplets. This equation can be solved analytically to give (Marze and Choimet, 2012, Gaucel et al., 2015):

\[ \frac{\phi}{\phi_{max}} = 1 - max \left\{ 0, \left( 1 - \frac{kMt}{n_{rot}} \right)^3 \right\} \]  
(14.11)
where $\phi$ and $\phi_{\text{max}}$ are the proportion and maximum proportion of lipid released from the droplet, $M$ is the triglyceride molar mass (equal to $3M_s$ in the case of a triglyceride with three identical carbon chains, where $M_s$ is the molar mass of the solubilized digestion products), $r_0$ and $\rho_0$ are the initial droplet radius and density, and $n$ is a coefficient depending on the type of measurement. Note there was an error in the original calculation of the solution of Eq. (14.10) (Li and McClements, 2010), but the correct form was derived afterwards (Marze and Choimet, 2012, Gaucel et al., 2015). Eq. (14.11) was used to analyze the digestion of emulsified triglyceride, which is hydrolyzed to yield two free fatty acids and one monoglyceride, further solubilized in bile salt micelles. Depending on the technique used to evaluate the hydrolysis of triglyceride, only free fatty acids (pH-stat) or all digestion products (HPLC) are measured. The interpretation should then be made with $n = 2$ or $n = 3$, respectively. Equation (14.10) can be modified to express the temporal derivative of the droplet radius, which can be compared to measurements (Marze and Choimet, 2012). Note that $k$ is an effective coefficient, as it represents both hydrolysis and solubilization, but can be used to interpret hydrolysis alone or solubilization alone, depending on the experimental data. A first order kinetics equation was also proposed by Marze and Choimet (2012) in the form:

$$\frac{dm}{dt} = kA(t)(m_{\infty} - m) \frac{1}{V_T}$$  \hspace{1cm} (14.12)

where $m_{\infty}$ is the maximum mass of digestion products that can be solubilized, and $V_T$ is the total volume of the emulsion sample. This equation can be solved with various hypotheses concerning $(m_{\infty} - m)$, either that solubility is infinite, or governed by the Kelvin equation, which is:

$$m = m_{\infty} \exp \left( \frac{2\gamma M/\rho N_A k_B T_k}{3} \right)$$  \hspace{1cm} (14.13)

and can be approximated by:

$$m \approx m_{\infty} \left( 1 + \frac{2\gamma M/\rho N_A k_B T_k}{3} \right)$$  \hspace{1cm} (14.14)

where $\gamma$ is the interfacial tension, $N_A$ is the Avogadro constant, $k_B$ is the Boltzmann constant, and $T_k$ is the temperature in Kelvin. Note that the interfacial tension can be further decomposed using interfacial viscoelastic properties. When using the Kelvin equation, analytical solutions exist only for the temporal derivative of the droplet radius. In all cases, it was shown that the first order form was in better agreement with experimental data than the zeroth order form was, especially when the interfacial viscoelastic properties were accounted for (Marze and Choimet, 2012). This finding is illustrated in Fig. 14.6, where the experimental and simulated droplet mean diameters are plotted as a function of intestinal digestion time.

** Insert figure 14.6 **

Recently, increasingly complex models for starch digestion in the gastrointestinal tract were developed (Moxon et al., 2016). The most complete model was in the form of advection-reaction-absorption equations:

$$\frac{\partial S}{\partial t} = \gamma S_S - \theta \frac{\partial S}{\partial x} - \frac{v_{\text{max}}}{k_m + S}$$  \hspace{1cm} (14.15)
\[
\frac{\partial G}{\partial t} = -\gamma \frac{\partial G}{\partial x} + \frac{V_{\text{max}}}{K_m+S} S - \frac{2fK}{R} G \tag{14.16}
\]

where \( S \) and \( S_S \) are the starch concentrations in the small intestine and in the stomach, \( \gamma \) is the decay constant for stomach emptying, \( V_{\text{max}} \) is the maximum hydrolysis rate, \( K_m \) is the Michaelis constant, \( G \) is the glucose concentration in the small intestine, \( f \) represents the increase in absorptive surface area due to the folds of the intestinal wall, and \( K \) is the mass transfer coefficient for absorption, expressed as
\[
K = 1.62 \left( \frac{\theta D^2}{2\pi R L} \right)^{1/3},
\]
with all other parameters already defined previously, the diffusion coefficient \( D \) being calculated using the Stokes-Einstein equation.

### 14.4.4. Multi-agents simulation

This type of modelling was first developed in ecology and social sciences, to investigate the interactions between various actors. This was applied to swarm, migration, or predation behaviours, but also to entire organizations such as ant or bee colony. Then, it was enlarged to humans for the study of crowd behaviour, as well as cultural, political, social, or economical interactions. In these fields, the applications are abundant, such as diffusion of ideas or values, decision-making processes, business or industrial organizations (Bonabeau, 2002). More recently, it was developed at the microscale for biology, chemistry, and physics (Hunt et al., 2009). Whatever the application is, the basic principle is the use of different agents (particles) that have specific behaviours (properties), and interaction rules. As the type or number of agents changes, the response of the whole system is expected to change, in a deterministic or in a stochastic manner, owing to the possibility of emergent phenomena.

Recently, the use of a 2D multi-agents simulation was proposed to study lipid digestion (Marze, 2014, Marze, 2015). Each type of molecule was represented as a particle of given mass, with specific physicochemical properties and interaction rules. The model consisted in a square droplet containing triglyceride and lipophilic micronutrient particles, and lined with interfacial particles (emulsifier stabilizing the interface). It was immersed in a digestive fluid aqueous environment containing a single type of particle, representing enzymes or enzymes/bile salts.

** Insert figure 14.7 **

All the simulation rules are outlined in Fig. 14.7. Briefly, all the lipophilic particles were set to diffuse with a relative diffusion coefficient based on the Stokes-Einstein equation, thus depending on their molar mass and on the lipid phase viscosity. The digestive fluid particles (IDF in Fig. 14.7) were set to diffuse faster using position randomization, reflecting their much higher diffusion coefficient, and the possible advection of the whole droplet relative to the aqueous phase. Interfacial particles were set to remain located at the interface, where hydrolysis and solubilization generally occur. When a contact was established between a digestive fluid particle and an interfacial particle, the first was either removed or kept in the simulation, and the second was activated. In this state, a contact with a lipophilic particle resulted in hydrolysis or solubilization, the interfacial particle returning to the
inactivated state. This rule was set to account for the interfacial competition between digestive molecules (enzymes, bile salts) and digestion products. The contact rules for hydrolysis and solubilization were derived from experimental data on lipolysis rate and solubilization ratio (mass of solubilizate per mass of bile salt) respectively, the number of contacts required being inversely proportional to these quantities. As seen in Fig. 14.7, triglyceride is hydrolyzed to a fatty acid and a diglyceride, the latter being hydrolyzed to a fatty acid and a monoglyceride. Only fatty acids, monoglycerides, and lipophilic micronutrients can be solubilized in bile salts. Note that the solubilization or micellization concepts are mostly used in pharmacology, while the concept of bioaccessibility (percentage of (micro-) nutrient transferred in bile salt micelles) is preferred in food science, but all refer to the same notion. The droplet size was set to decrease in proportion to the number of solubilized fatty acid and monoglyceride. The simulations where the digestive particles were removed or kept were called the saturated bile or the recycled bile cases, respectively. These represented the in vitro or the in vivo cases, respectively. The simulations were stopped when there was either no more digestive particles or no more lipids. Pictures in Fig. 14.8 show the evolution of a typical simulation in the saturated bile case.

** Insert figure 14.8 **

The main finding reported in the first study (Marze, 2014) was the generic relationship between vitamin bioaccessibility and fatty acid bioaccessibility (Fig. 14.9), even though the solubilization enhancement by digestion products was not taken into account. This aspect as well as other ones were accounted for in a second study (Marze, 2015). First, the incorporation of digestion products into bile salt micelle resulted in a higher final vitamin A bioaccessibility. The final bioaccessibility of vitamin A was also increased by its ability to remain at the interface (in the form of retinol). On the other hand, the addition of a gastric step only had a minor effect. Triglyceride mixtures as well as triglyceride-limonene mixtures were also investigated as the oil phase, using the Kendall-Monroe equation to calculate the mixture viscosity. The final bioaccessibilities and their kinetics were significantly affected compared to the pure compounds. The results for the triglyceride-limonene mixtures are presented in Fig. 14.10. For a given digestion duration, it shows that the more limonene in the mixture, the lower the fatty acid and the vitamin A bioaccessibilities are. Although not quantitative in terms of time, this approach is interesting to compare the effects of various physiological, structural, and formulation parameters on lipid digestion.

** Insert figures 14.9 and 14.10 **

14.5. Conclusion

Modelling of food digestion developed in parallel to modelling of oral drug absorption, yet in a scarcer way. Thus, this field is more fragmented, most models being established for a specific nutrient, a specific process, or a specific part of the digestive tract. Nevertheless, descriptions tend to be much more detailed. For example, the geometries of the oral cavity and of the stomach are reproduced with
high fidelity to investigate mechanical aspects. Another example is the inclusion of the villi for the study of intestinal flow, mixing, and absorption. Overall, these microscale models are very useful to highlight the parameters and mechanisms controlling specific processes. As already initiated recently, some future models will try to include most nutrients, compartments, and processes. Nevertheless, the ultimate goal to simulate digestion comprehensively is still far ahead, as food is a complex mixture of nutrients with multiscale structures. Some of their interactions occurring during digestion are not precisely known. Moreover, the succession of processes throughout the digestive tract likely plays an important role and needs to be accounted for. Finally, micronutrients such as minerals and vitamins were scarcely included in the models, although they play an essential metabolic role.

References


### Table 14.1: The main products of hydrolysis at each step of the digestive tract.

<table>
<thead>
<tr>
<th>Location</th>
<th>Starches</th>
<th>Triglycerides</th>
<th>Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth</td>
<td>Dextrins</td>
<td>Diglycerides</td>
<td>Polypeptides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatty acids</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td>Diglycerides</td>
<td>Polypeptides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatty acids</td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>Maltose</td>
<td>Monoglycerides</td>
<td>Tripeptides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatty acids</td>
<td>Dipeptides</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amino acids</td>
</tr>
<tr>
<td>Intestinal brush border</td>
<td>Glucose</td>
<td></td>
<td>Amino acids</td>
</tr>
</tbody>
</table>

Table 14.1: The main products of hydrolysis at each step of the digestive tract.
<table>
<thead>
<tr>
<th></th>
<th>Pressure or stress (kPa unless otherwise specified)</th>
<th>Shear rate (s⁻¹)</th>
<th>Transit time (min unless otherwise specified)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mouth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teeth</td>
<td>4-17 MPa (a), 8-86 MPa (b), 4-16 MPa (c), 40-440 (d), 23-55 (e)</td>
<td></td>
<td>Liquid 2-3.2 s (t)</td>
</tr>
<tr>
<td>Tongue-palate</td>
<td></td>
<td>10-1000 (m)</td>
<td>Solid 6.6-12 s (t)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Soft solid 3.8-11.6 s (u)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hard solid 15.2-23 s (u)</td>
</tr>
<tr>
<td><strong>Stomach</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antrum</td>
<td>5.9 (g), 0.8-1.6 (h), 0.9-2.1 (i), 3.5 (j), 1.3-1.7 (k), 0.7-1.1 (l)</td>
<td>0.02-0.8 (n), 0.01-0.04 (o)</td>
<td>Solid 150-270 (average 210)</td>
</tr>
<tr>
<td>Pylorus</td>
<td>0.8-4.3 (h), 7.1-8.1 (k)</td>
<td>0.27-0.45 (o)</td>
<td>Liquid 60-180 (average 110)</td>
</tr>
<tr>
<td><strong>Small intestine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>3.9 (g), 4.8 (j)</td>
<td>0.7-5.8 (p), 0.02-0.9 (q), 0.02-1.2 (r)</td>
<td>Solid 160-320 (v), 150-290 (w), 180-210 (x), 260-300 (y), 180-230 (z)</td>
</tr>
<tr>
<td>Villi</td>
<td></td>
<td></td>
<td>Liquid 270-320 (y), 120-250 (z)</td>
</tr>
</tbody>
</table>

Table 14.2: Ranges for some mechanical and temporal quantities in the digestive tube. The stomach transit times were evaluated from the literature, being too abundant to be cited systematically. The references are: (a) Anderson (1956), (b) Dejak et al. (2003), (c) Zhang and Hui (2015), (d) Harrison et al. (2014a), (e) Harrison and Cleary (2014), (f) Ono et al. (2004), (g) Haruma et al. (1994), (h) Indireshkumar et al. (2000), (i) Hveem et al. (2001), (j) Hausken et al. (2002), (k) Desipio et al. (2007), (l) Kwiatek et al. (2009), (m) Shama and Sherman (1973), (n) Ahmed et al. (2009), (o) Ferrua et al. (2014), (p) Ehrlein and Stockmann (1998), (q) de Loubens et al. (2013), (r) Lentle et al. (2013), (s) Lim et al. (2015), (t) Palmer et al. (1992), (u) Hiiemae (2004), (v) Read et al. (1986), (w) Camilleri et al. (1991), (x) Degen and Phillips (1996), (y) Bennink et al. (1999), (z) Graff et al. (2001).
Figure 14.1: Simulation of agar gel chewing, displaying the breakdown into particles and their von Mises stress. Reproduced from Harrison et al. (2014a) with permission from John Wiley and Sons.

Figure 14.2: Experimental and simulated fragment size distributions of agar gels after two chewing cycles. Reproduced from Harrison et al. (2014a) with permission from John Wiley and Sons.

Figure 14.3: Simulated velocity field in the stomach for liquids with different rheological properties, coloured by velocity magnitude (cm s$^{-1}$). Reproduced from Ferrua et al. (2014) with permission from Elsevier.

Figure 14.4: Simulated instantaneous streamlines in the intestinal lumen (a), with an expanded view near the villi (b). Reproduced from Wang et al. (2010b) with permission from Springer.

Figure 14.5: Simulated velocities and concentrations of a tracer nutrient near the intestinal villi. Reproduced from Lentle et al. (2013) with permission from John Wiley and Sons.

Figure 14.6: Mean droplet diameter during in vitro intestinal digestion of various emulsions. The graph on the top-left reports the experimental results. The other graphs report the simulated results using various models. The simple first and zeroth order kinetics correspond to graphs on the top. The first order kinetics integrating the Kelvin equation, the interfacial viscosity or elasticity correspond to graphs on the bottom, from left to right, respectively. Reproduced from Marze and Choimet (2012) with permission from The Royal Society of Chemistry.

Figure 14.7: Diagram showing the rules applied to simulate intestinal lipid digestion. IDF: intestinal digestive fluid, TG: triglyceride, DG: diglyceride, MG: monoglyceride, FA: fatty acid, MN: micronutrient. Reproduced from Marze (2014) with permission from The Royal Society of Chemistry.

Figure 14.8: Pictures from a typical simulation of intestinal lipid digestion in the saturated bile case. Top: first step of the simulation, bottom: step at which half of the bile was saturated. TG: yellow, MN: orange, IDF: red, interface: green, DG: blue, MG and FA: pink. The numbers represent the number of contacts needed to solubilize the products in bile. Reproduced from Marze (2014) with permission from The Royal Society of Chemistry.

Figure 14.9: Results from various simulations of intestinal lipid digestion, plotted as vitamin A bioaccessibility vs. fatty acid bioaccessibility. Triecosapentaenoic and tridocosahexaenoic: red, triolein: green, tricaprylin: blue. Dashed line: recycled bile, full line: saturated bile. Reproduced from Marze (2014) with permission from The Royal Society of Chemistry.
Figure 14.10: Results from various simulations of intestinal lipid digestion where the lipid phase is a mixture of triglyceride and limonene, plotted as the bioaccessibility of fatty acids (square) and vitamin A (circle) for the same digestion duration, with tricaprylin (empty symbol) or triolein (full symbol). Reproduced from Marze (2015) with permission from The Royal Society of Chemistry.