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Determining the glycaemic responses of foods: conventional and emerging approaches

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Abstract

A low-glycaemic diet is crucial for those with diabetes and cardiovascular diseases. Information on the glycaemic index (GI) of different ingredients can help in designing novel food products for such target groups. This is because of the intricate dependency of material source, composition, food structure and processing conditions, among other factors, on the glycaemic responses. Different approaches have been used to predict the GI of foods, and certain discrepancies exist because of factors such as inter-individual variation among human subjects. Besides other aspects, it is important to understand the mechanism of food digestion because an approach to predict GI must essentially mimic the complex processes in the human gastrointestinal tract. The focus of this work is to review the advances in various approaches for predicting the glycaemic responses to foods. This has been carried out by detailing conventional approaches, their merits and limitations, and the need to focus on emerging approaches. Given that no single approach can be generalised to all applications, the review emphasises the scope of deriving insights for improvements in methodologies. Reviewing the conventional and emerging approaches for the determination of GI in foods, this detailed work is intended to serve as a state-of-the-art resource for nutritionists who work on developing low-GI foods.

Keywords: **Glycaemic index: Low GI foods: Diabetes: Food digestion: Glycaemic responses**

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Introduction

Carbohydrate is the major source of energy and regulator of appetite in the human diet; satiety follows the order: fat > carbohydrates > proteins. Ketosis refers to a condition in which the liver starts producing ketones owing to the lack of sufficient energy supply to the brain. Sometimes ketosis is induced by lowering the carbohydrate intake (20–50 g/d) to counter obesity. Prolonged ketosis may also cause short-term effects such as dizziness and vomiting[1]. American Diabetes Association has recommended a carbohydrate intake of 130 g/d, the minimum practical requirement[2]. While the dietary role of carbohydrates is indispensable, millions around the world suffer impaired glucose tolerance, and it is estimated that around 10.2% of the world population will be diabetic by 2030[3]. A thorough understanding of carbohydrates in the diet is crucial for the management of diabetes and cardiovascular diseases (CVD), and this explains the emergence of the concept of carbohydrate counting for diabetic people taking insulin. Beyond carbohydrate counting, continuous glucose monitoring, which relates the aspects of glucose concentration with time, body weight, and glucose and insulin clearance, can be a valuable tool[4].

The biological value of dietary glucose is quantified in terms of the glycaemic index (GI). GI represents the blood-glucose-raising potential of a food compared with that of the same quantity of a reference food material (such as white bread/pure glucose)[5]. Another closely related term is the glycaemic load (GL), also considering the amount of carbohydrate in a portion of food. The concept of GL better explains glycaemic responses when mixed meals containing components with varying GI values are consumed. Theoretically, a carbohydrate-rich meal with a large serving size tends to increase the GL. In other words, GL is directly linked with the serving size and carbohydrate content[6]. Based on differences in GL, foods can be classified as high ($GL \geq 20$), medium ($11 \geq GL \geq 19$) and low ($GL \leq 10$)[7].

Another important terminology is the glycaemic response. GI relates to the intrinsic characteristics and is an index representing the carbohydrate quality of a food, whereas glycaemic response relates to the variations in glucose concentration responses in an individual after consumption of a food[8,9]. Given this, controversies on the legitimacy of GI can be simplified and the concept can be viewed as one that is reliable, provided its methods of determination are standardised and made universal because only a handful of assessment methods have validated their protocols[10].

Foods can be classified as low GI ($GI \leq 55$), medium GI ($56 \leq GI \leq 69$) or high GI ($GI \geq 70$)[11]. However, this classification can be misleading; for example, the GI of white bread is 62.4 ± 15.3. Such high standard deviation values appear ambiguous and do not allow precise conclusions to make food choices[12]. Nevertheless, considering the sampled population (ten human subjects), the authors justified that this error margin is within acceptable limits (less than ±20%), and with >1% probability of misclassification, the results can be used for nutritional labeling. It is important to note that many GI certification agencies use a specific GI symbol for low-GI foods[13].

Understanding the GI is important for diet-planning schemes for people with diabetes, dyslipidemia, CVD, and certain types of cancers[14-16]. Meta-analyses have detailed the effect of long-term consumption of low-GI diets on body condition for people with common non-communicable diseases such as type 1 and type 2 diabetes, CVD, and obesity[17]. It establishes that controlling the GI has implications for total glycaemic regulation in subjects with impaired glycaemic response, and reduces serum triacylglycerides in subjects with hypertriglyceridemia[18]. Diet based on low-GI foods showed that reduction in GL by 28 units reduced both systolic and diastolic blood pressure[19]. Importantly, significant improvements in weight loss, lipid profiles associated with blood pressure[20] and glycated hemoglobin (HbA1c) in the blood have been reported[21]. Diets with high GL are associated with risk of coronary heart disease[22]. A study conducted in Wistar rats with prolonged administration of high-GI diet revealed deposition of ectopic fat in liver and pancreas[23], which is linked to insulin resistance[24]. Dieting with low-GI foods helps to promote fat oxidation (by reducing fat storage) even in a sedentary state and minimise fluctuations in post-prandial glucose levels in the blood when compared with high-GI foods[25]. This is because low-GI foods are generally rich in protein or fiber and do not significantly increase calories, but promote satiety[26,27].

Several factors influence GI, including processing conditions of foods, nature of food structure, food groups, maturity of fruits/vegetables, nutrients, chyme viscosity, enzyme inhibitors and starch composition, as shown in Fig. 1. These factors have to be taken into consideration when designing a food product with low GI. For example, due to high temperature and high humidity during cooking, starch granules absorb water and get irreversibly disrupted, losing their crystalline structure, which makes them vulnerable to amylases and glucosidases[28], thus increases their GI. Natural inhibitors of amylases and glucosidases are present in polyphenols and flavonoids. Therefore, a mixed meal combining fruits, vegetables[29] and legumes rich in polyphenols and flavonoids are one such approach to reduce the overall GI of a meal[30]. It is also reported that pasting of starch in wheat flour reduces GI because of the formation of melanoidins due to the Millard reaction; melanoidins inhibit α-glucosidase activity during cooking of wheat flour, resulting in a reduced GI[31]. To give a further example, rice normally has a high GI, and since rice is one of the staple foods, an attempt has been made to reduce the GI by adjusting the cooking temperature and water ratio. Rice cooked under the optimised conditions of 82°C with a water to rice ratio of 1.9 had a lower GI when compared with rice cooked at higher temperature and with lower water content, because the latter condition creates more voids and degrades the starch quickly, making it vulnerable to digestive enzymes[32]. Even the physical state of food (solid/liquid) influences the glycaemic response pattern, i.e. solid starchy foods have sustained glucose release whereas liquid foods cause a sudden drop in glucose response after 30 min, but the overall glycaemic area under the curve is not significantly different for some of the solid or liquid foods because it also depends on nutrient composition[33,34].

GI assessment is in great demand, because of the various health benefits of low GI foods. One of the widely used assessments on the GI and GL of meal composition is capillary human blood sampling for glucose response (*in vivo*)[35]. GI studies have to take into account sampling size, organisation of control groups, population demographics, variation in ethnicity of population, age groups and methodological factors[10].

On the other hand, human trials are costly and time-consuming, and have ethical and subject screening constraints, which in turn discourages the testing of new foods based on carbohydrates for GI[36]. Considering this, some studies have transitioned to the use of animal models, but the suffering, discomfort and death endured by animals during laboratory studies have long been a subject of controversy[37]. Therefore, other predictive testing approaches such as computational modelling have been recently used to conduct GI studies[38]. However, their relevance to real-time data is a big concern. Thus, various digestion models have been developed to achieve better accuracy and precision in predicting GI. The objective of this review work is to critically analyse the conventional GI methods and emerging approaches for GI prediction and to evaluate their relevance with *in vivo* records. This may allow extending the commercialisation of new food products with specific GI values for people with CVD and diabetes.

Food digestion and GI

Digestion starts in the mouth, after which food is further broken down into smaller fragments in the stomach. Then, the intestine absorbs monosaccharides, which enter the bloodstream. Most of the glucose is carried by blood, and the excess of glucose is stored as glycogen by the liver and muscles[39]. The structure of food and composition of foods with high or low GI alters the digestion metabolism which, in turn, is reflected in glycaemic response.

Food digestion involves three important stages: oral phase, stomach phase and intestine phase (Fig. 2).

Oral phase

During mechanical degradation by the teeth, starchy food materials are wetted with saliva during oral processing until a bolus is formed[40]. Carbohydrate digestion begins in the mouth, in which salivary secretions containing salivary α-amylase begin hydrolysis of starch, breaking the starch into different molecular fragments. In the oral phase, food bolus from the mouth can take less than 2 s, but up to 15 s, to traverse the oesophagus[41]. The pH in the oral phase is usually about 6.5–7. Salivary amylase activity is stopped when the pH within the stomach decreases. Depending on the food and the characteristics of each individual, the oral breakdown or destruction of food during mastication is highly variable[42]. Particle size distribution and disintegration of food bolus depends on the texture of the food. For example, bread made of oat flakes has a larger particle size after mastication than bread made out of oat flour. The larger particle size results in less starch hydrolysis, suggesting that the lesser the breakdown, the lower the susceptibility to amylase[43]. Rapid consumption without proper chewing results in an increased glycaemic response[44]. This may be because rapid consumption may

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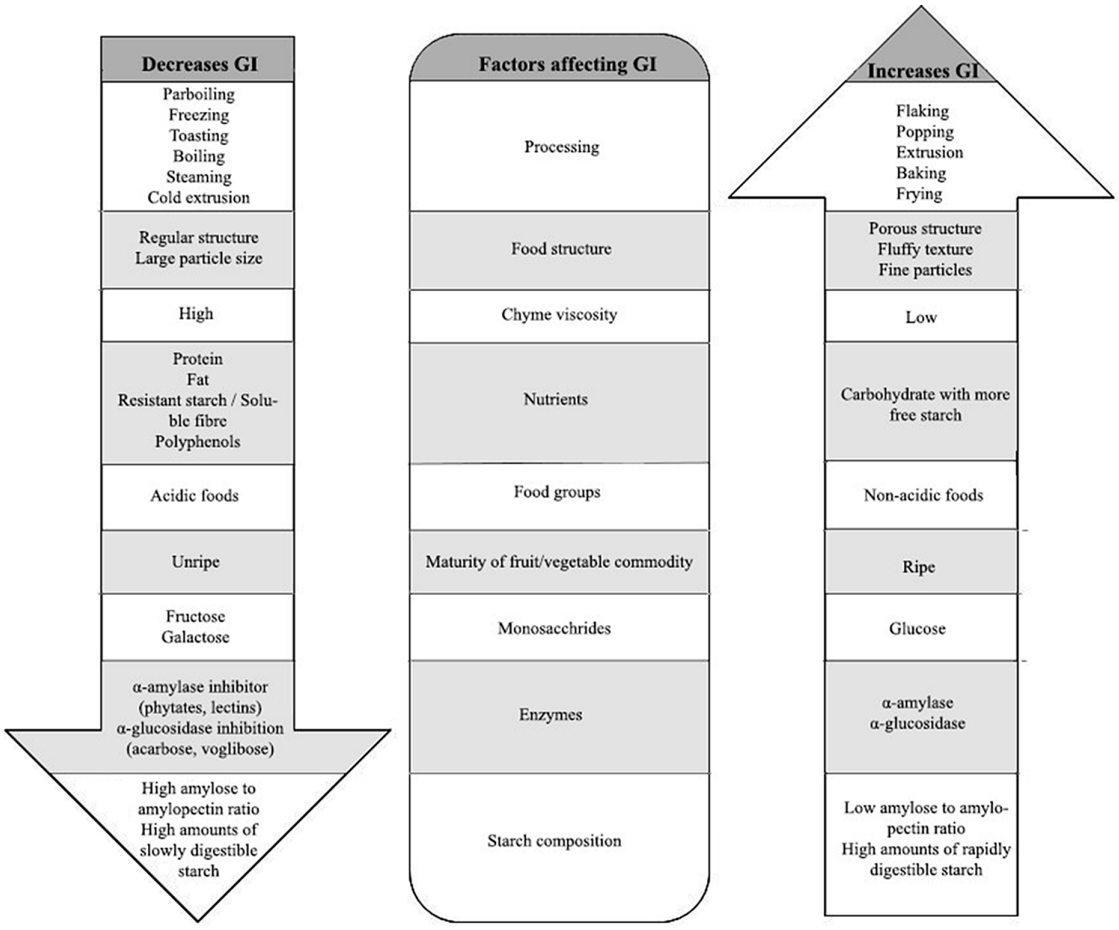

Fig. 1. Factors affecting GI of food products

result in a large volume of food ingestion whereas well-chewed food can decrease food intake by one third; also, when bite sizes are large, oral processing time is less and vice versa[45]. The degradation rate of starch is reported to be dependent on the volume and activity of the α-amylase present in the saliva. This means, because of the exposure of the food to more saliva and the prolonged stay of food in the mouth, greater breakdown of starch occurs but the speed of ingestion is greatly reduced, and therefore the GI is likely to be lower[46]. According to Tan *et al.*[47], greater number of chews within a short period increases the glycaemic response. The higher the number of mastication cycles, the higher the glycaemic response for the same GL, provided the eating rate is higher[48].

Stomach phase

The stomach serves as grinding, mixing and storing organ which receives the bolus from the oesophagus. As the bolus reaches the gastric phase, the pH changes to 1.5–3.5. The inner walls of the stomach are covered by a glycoprotein called mucin, which protects the internal stomach from the acidic environment[49]. The average amount of time a meal stays inside the stomach is around 1–2 h, depending on the composition of the food. The pepsinogen (precursor of pepsin) released by stomach walls helps in protein digestion[50]. While inside the stomach, there are not many enzymes for carbohydrates. Starch hydrates inside the stomach and increases its intake of bulk and liquids. The physical forces acting on the stomach include peristaltic movements called antral contraction waves, promoting the mixing process, which disperses nearly all the soluble carbohydrates. The antral contraction waves, which appear to push the liquid portion towards the pyloric end, regulate the liquidity of the digested chyme entering the duodenum[51,52]. These contraction waves in the antral region cause a sieving effect, which allows only particles smaller than 2 mm to pass through the pylorus end to the intestine for further digestion. Foods with larger particle size are returned to the stomach for further digestion[53]. This is directly related to the emptying rate of the food from the stomach. High-viscosity meals slow down gastric emptying. The rate at which gastric emptying occurs is the key regulator for digestion and absorption of food entering the small intestine and is essential for regulating post-prandial glycaemic response[54]. The rate of emptying having an exponential effect is determined by the volume, osmolality, acidity and fat emulsion presence[55]. Low-GI foods have greater gastric content and slower gastric emptying when compared with high-GI foods, which is attributed to the higher fiber content of low-GI foods[56]. Delayed gastric emptying lowers the GI[57].

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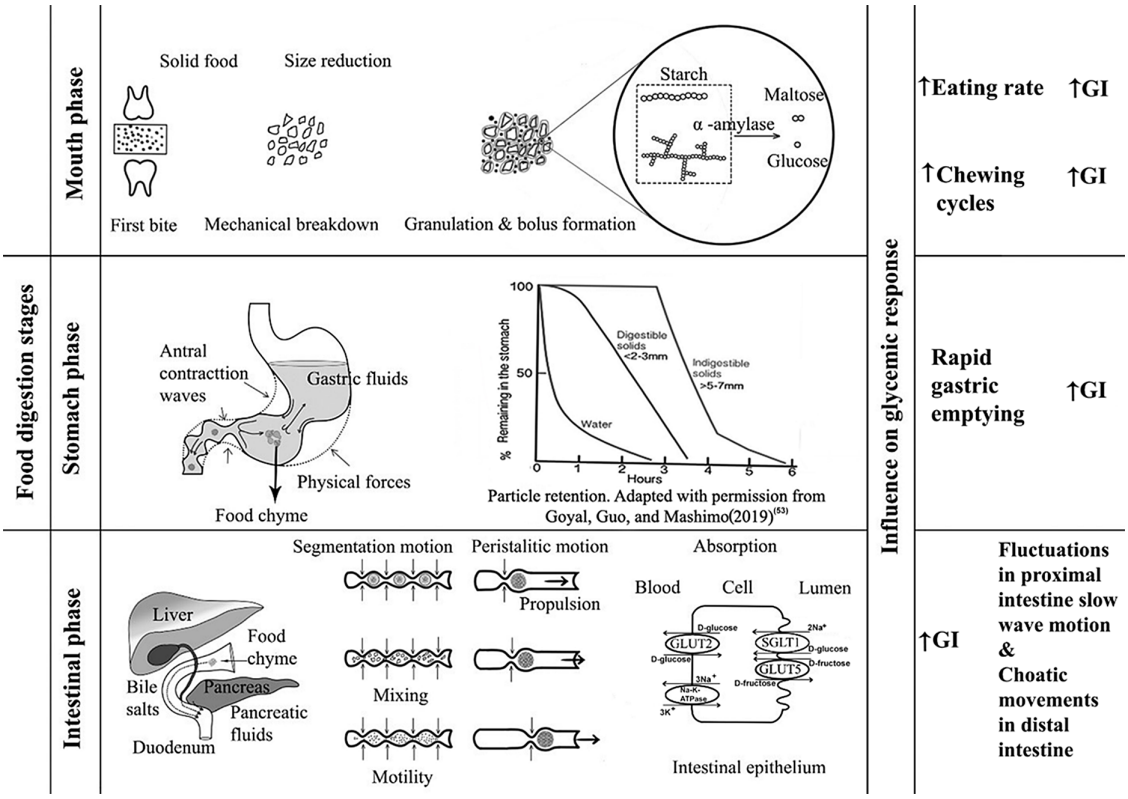

Fig. 2. Digestion stages and their influence on GI

Small intestine

After the stomach, some of the carbohydrates present in the chyme are still in the form of polymers. Starch hydrolysis is completed, and absorption takes place in the small intestine. This mechanism is facilitated by pancreatic α-amylase, which is released into the duodenum as a key component of pancreatic fluid by pancreatic acinar cells[38,58,59]. During this process, amylose in the starch is broken down into maltose and glucose molecules by breaking the α-1,4 glycosidic bonds, and amylopectin is broken down into maltose, isomaltose and dextrins. Among these, glucose is the main carbohydrate entering enterocytes and eventually being distributed to the bloodstream[60]. Absorption of glucose through enterocytes occurs by sodium-dependent carrier-mediated transport, called active transport, whereas absorption of fructose occurs through carrier-mediated facilitated diffusion, but most types of fructose are transported by passive diffusion with cotransporter GLUT5, separated from glucose and galactose mechanisms. Other oligosaccharides are hydrolysed by various brush border enzymes such as maltase, isomaltase, trehalase, sucrase and lactase[61]. Glucose is the main end product of carbohydrate digestion and serves as the primary fuel for normal brain and cell functioning[62]. In addition to enzymes, pancreatic hormones play a crucial role in glucose metabolism and homeostasis in the body. The pancreas has five distinct cell types creating specific endocrine hormones, of which α cells from islets of the pancreas producing glucagon and β cells producing insulin are the focal hormones that are directly involved in glucose control. Amylin is another hormone co-produced with insulin acting as a satiety agent that also functions to inhibit glucagon production. C-peptide is also a similar substance generated in the pancreas as a by-product of insulin, whereas somatostatin and ghrelin function as growth regulators and appetite-inducing hormones, respectively[63]. For the study of glycaemic response, insulin and glucagon are of interest because insulin is the main hormone that tends to reduce blood glucose levels while glucagon raises it, and somatostatin stops the function of both insulin and glucagon[64]. There are also other important sets of hormones apart from insulin and glucagon involved in glucose regulation: incretins (glucagon-like peptide 1 and glucose-dependent insulinotropic peptide, called GLP-1 and GIP, respectively, and produced by L-cells and K cells of the intestine), epinephrine and cortisol. Intake of high-GI foods induces rapid release of GIP, which is largely available in the proximal intestine, increasing glucose absorption compared with low-GI foods. GIP is known to stimulate osteopontin release, a cytokine that is associated with insulin resistance[65], whereas consumption of low-GI foods elicits the release of GLP-1, which is produced in the distal intestine[66]. GLP-1 has been shown to be independent of glucose kinetics and may also be influenced by food characteristics[67]. This incretin helps to promote the feeling of satiety and even delays gastric emptying; it also suppresses glucagon release and increases insulin sensitivity, thereby improving overall glycaemic control[68]. Ingestion of low-GI products causes GIP-producing K cells to decrease the rate of glucose entry into the small intestine, in turn, reducing the secretion of gastric acid and emptying rate. In addition to GIP,

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GLP-1 stimulates insulin and inhibits glucagon release based on glucose kinetics. This will stabilise the post-prandial increase in blood glucose, eventually managing the secretion of incretins (GLP1 and GIP) and the absorption of glucose at a sustained rate[69]. Besides, there are many other complex pathways and hormones in the body that maintain glucose homeostasis[63]. Further, dipeptidyl peptidase-4 (DPP-4) inhibitor, an enzyme that manages incretin hormones, influences glycaemic control. DPP-4 prevents the inactivation of GLP-1, thereby improving blood glucose concentration balance. This aspect requires improved understanding as studies also suggest that DPP-4 inhibitors may not be related to dietary intake of low-GI foods[70].

Apart from enzymes and hormones, another important factor for changes in post-prandial glucose response is intestinal motility. The two major types of motility patterns are segmentation motion and peristalsis. The first type contributes to mixing and chopping the chyme which is formed as smaller segmental contractions and the latter contributes to propelling the digested food towards the large intestine. During both of these processes, absorption of nutrients is enhanced[71]. High-GI foods affect myoelectrical activities by inhibiting proximal intestine (duodenum) contractions and increasing contraction strength in the distal intestine (ileum)[34]. Owing to the complexity of the aforementioned process, determination of glycaemic response due to diet intake requires further understanding. Food composition such as foods rich in soluble dietary fiber tends to reduce GI because dietary fiber forms a gel which protects starch from further degradation even in the small intestine and is finally pushed to the large intestine where it is fermented or excreted[72].

Measurement of glycaemic response

The 34th Joint FAO-WHO Expert Committee Report on Food Additives meeting developed a strategy for considering knowledge on the bioavailability of residues, specifically for their use in nutritional intake estimates[73]. In these situations, after consumption of a meal, the GI on dietary intake can be regarded as the bioavailability of glucose; to date, the official method for this measurement involves estimating the GI with human subjects (*in vivo* tests)[11].

In vivo *human glycaemic response*

For a long time, human blood glucose was measured using devices such as self-monitoring systems that typically have a small fingerprick needle and an oxidising indicator bio-sensing strip. Also used are other continuous monitoring devices that measure interstitial fluid with a glucose sensor tip inserted underneath subcutaneous tissue below the skin. The accuracy of this continuous monitoring devices is a big concern[74]. Glucose measurement is also done by means of glucose oxidase and peroxidase, which is also used in glucose biosensors[75]. Normally, for conducting *in vivo* human studies, 50 g of available carbohydrates is given to the volunteers within 15 min, along with 250 to 300 ml of water, and blood glucose is assessed during a certain predetermined time frame (usually 2 h). In human *in-vivo* glucose response values, incremental area under the curve method is usually used for the calculation of GI[12].

For the calculation of incremental area under the curve, the general calculation uses the trapezoid rule, which is a widely used method for GI determination from human *in vivo* data. The calculation for the area under the curve was determined using the following methods[76]:

For $x = 1$, the following equation (1) is used:

$$if\ G_1 > G_0, A_1 = (G_1 - G_0) \times \frac{t_1 - t_0}{2}\ ; otherwise\ A_1 = 0 \tag{1}$$

For $x > 1$, any of the equations from (2–5) is used based on specified conditions

$$if\ G_x \geq G_0\ \ and\ \ G_{x-1} \geq G_0\ ,\quad A_x = \frac{(G_x - G_0)}{2} \times \frac{(G_{x-1} - G_0)}{2} \times \frac{t_x - t_{x-1}}{2} \tag{2}$$

$$if\ G_x \geq G_0\ \ and\ \ G_{x-1} \leq G_0\ ,\quad A_x = \frac{(G_x - G_0)^2}{(G_x - G_{x-1})} \times \frac{t_x - t_{x-1}}{2} \tag{3}$$

$$if\ G_x < G_0\ and\ G_{x-1} \geq G_0,\quad A_x = \frac{(G_x - G_0)^2}{(G_{x-1} - G_x)} \times \frac{t_x - t_{x-1}}{2} \tag{4}$$

$$if\ G_x < G_0\ \ and\ \ G_{x-1} < G_0\ ,\ A_x = 0 \tag{5}$$

where G is the glucose released at different time intervals; A is the area under the curve; x is intervals; t is the time.

The general calculation was that upon intake of each food, the area under the curve was expressed as the percentage of average area under the curve after the same subject had taken oral glucose, as given in equation (6). The total average of these values is given as the GI of food[77]. Here, the area under the curve is calculated based on the trapezoid rule:

$$GI = \frac{AUC_{test}}{AUC_{pure\ glucose}} \times 100 \tag{6}$$

where AUC is the area under the curve.

Different methods have been suggested[77] for the calculation of area under the curve: $iAUC$ as the incremental area under the curve ignoring the total area underneath the fasting state; AUC_{net} is the net incremental area under curve including the total area underneath the fasting state; AUC_{cut} is the cut area under the curve which includes only the area under which the blood glucose concentration drops below the baseline; AUC_{min} is determined by deducting the lowest blood glucose obtained from any of the other blood glucose concentrations during the last test cycle and adding the region under the curve to the resulting increments.

Similarly, in another study[78], an attempt was made to estimate the GI of mixed food meals. The GI of three different types of food mixes was determined in thirty human volunteers. This study attempted a method (7) which could calculate the GI of mixed meals.

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$$GI\ of\ meal = \frac{\begin{array}{l}[GI\ of\ food\ A\ x\ available\ carbohydrates\ of\ food\ A]+\\ [GI\ of\ food\ B\ x\ available\ carbohydrates\ of\ food\ B] + \ldots\end{array}}{Total\ available\ carbohydrates} \quad (7)$$

Nevertheless, the results of this study showed that, the above calculation equation (7) overestimated the outcome of GI and reported an inconsistency with the GI concept, so there is still a quest for a more accurate model. In disagreement with this conclusion, researchers[79] have pointed out some limitations with the study of Dodd *et al.* (2011)[78], such as the missing consideration of the effects of proteins and fat added to carbohydrates in the reduction of overall GI. They have also called attention to the lack of clarity in some terminologies.

Numerous human *in vivo* studies have been conducted in the development of low-GI foods. Some recent studies include the evaluation of low-GI proprietary food composite[80] called LoGICarb™ blended with white rice; GI reduction was observed when this mixture was provided to healthy volunteers. LoGICarb™ is a combination of anthocyanins from black rice extracts, β-glucans from oatmeal extract, and dietary fibers called resistant dextrin. The reduction in GI was about 23.61% after the addition of LoGICarb™ to white rice. In this study, 15 healthy volunteers were selected with specific exclusion criteria, and the subjects fasted for more than 10 h.

Merits of the human *in vivo* sampling method include the consideration of effects of gastric emptying, osmolality, volume, acidity, sex and age factors. There is no exact replacement for this method because every physiological factor is considered[81].

Though human trials for GI estimation are considered the benchmark method, a major concern of using human trials is the inter-individual variability due to differences in each individual's metabolism[82]. Also, from the aforementioned studies it can be seen that a large number of volunteers are needed for blood sampling. In this situation, screening of volunteers plays a vital role, which requires close monitoring of fasting conditions, and it is also important to pay attention to meals provided the day before to avoid more deviations in blood routine parameters. The trial results are only accurate if the screening is flawless and follows specific guidelines[83]. Human ethical issues are another important impediment to such dynamic studies, such as pain caused by finger prick if glucometer is used or when drawing blood by syringe, cost of the testing apparatus and potential hazard due to possibility of negligence during the use of disposables[84,85]. It is difficult in human studies to unravel the complex dietary associations to identify the mechanisms of GI separately because of the constant nutrient requirements and the enormous expense of delivering regulated meals for a prolonged period[86]. Thus, the need for animal-based predictive models may be an alternative to human clinical trials. Such models reduce the potential risk of testing for any newly developed food products and avoid human discomfort.

In vivo *animal models*

Animal models have long been used to demonstrate therapeutic effectiveness and to assess new-product toxicity before human clinical trials[87]. Genome sequencing facilitates and helps researchers to better identify the key areas of biological similarity between animals and human subjects[88]. The GI in animal *in vivo* models can be calculated using the same procedure as that of human *in vivo* blood sampling tests (incremental area under the curve)[89]. Table 1 presents various *in vivo* animal models and the methods used for the study of glycaemic responses and their comparison with those of human trials. It was inferred that rats and mice are commonly used and have quite similar glycaemic responses to that of human subjects. Pigs also have comparable responses and, recently, zebrafish has emerged as a modern comparative species. The advantage of using rodents in GI determination is that mouse glucose homeostasis metabolism is similar to that of human subjects, i.e. insulin sensitivity and insulin release rate[90]. Mice are used for diabetic studies because of the high degree of similarity between human and mouse DNA sequence. Moreover, mice have short gestational periods, making in-house breeding less expensive[91]. In another study, postprandial responses of human and pig blood metabolomes were found to be identical. Here, the glycaemic response was similar after the consumption of four types of bread despite different basal concentrations between species (human and pig)[92]. In the case of pigs, a variety of pig strains have a phenotype that reflects human type 2 diabetes[93]. Porcine models have various advantages such as the possibility of ethical acceptance; large study groups due to favorable reproduction conditions; and blood volume similar to that of that of human subjects[94]. At the same time, rabbits have similar lipid metabolism, rather than glycaemic profiles, to that of human subjects due to resemblance in lipoprotein profiles. Short-term diabetes in rabbits has limited applications as a model because it fails to consider the long-term complications of human diabetes[95,96]. Few notable glycaemic studies have been performed with rabbit as a model animal for human subjects. The similarity of the glycaemic response of zebrafish and human subjects can be seen in Table 1. Zebrafish express a significant amount of near-human genetic integrity and organ systems. Also, maintenance is quite easy when compared with large animals. Their translucent body has an advantage of non-invasive visualisation and is genetically manageable; also, their functional human disease gene is 70% similar to that of humans[97].

Despite various advantages of using animal models, there are some ethical issues to be considered before using animal models. Nonetheless, well-designed studies can mitigate suffering and provide humane endpoints if the animal studies compromise between acquired expertise and less possible damage to the animals[98]. However, particularly in research associated with glycaemic response, mechanisms should be in place to determine complications associated with diabetes and to avoid or mitigate the negative effects of these complications. Suitable support must be provided to induce and sustain diabetes in animal models[99]. The suffering, discomfort and death experienced by animals during laboratory experiments have long been a subject of discussion. In addition to the main ethical issues, there are

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Table 1 *In vivo* animal models for determination of glucose response testing and its comparison with human *in vivo* clinical trials

Animal model	Diet	Experimental design	Results	Comparison with human *in vivo* trials	References
Mouse	Algal extracts from *Ascophyllum nodosum* and *Fucus vesiculosus*	Mice with mean age of 8 years, in agreement with European guidelines; two experimental groups: standard and high fat subdivided into two sub-categories: fed with control and algal extracts	The diet with algal extracts reduced postprandial glycaemia due to its phyto-complex property rather than dietary fiber; presence of phlorotannins and fatty acids in the algal extracts inhibits digestive enzymes of α-amylase and α-glucosidase	NA	(176)
	Fiber blends, polydextrose, dextrose	Randomised, four-arm cross-over design as per Institutional Animal Care and Use Committee protocols; male mice; 2 g/kg of feed with 10 ml/kg of water after 6 h fasting	Incorporation of α-(1,2)-branching in glucose oligomers increases resistance to digestion, an important characteristic of dietary fiber	Large difference in iAUC between mice and human trials but both humans and mice have been reported to be able to digest α-(1,6)-linked and α-(1,3)-linked glucose oligomers	(177)
	Eight different diets (cornstarch, maltodextrin, glucose, sucrose, fructose, isomaltulose, calcium caseinate, safflower oil, wheat bran, gelatine, mineral mix, vitamin mix, choline bitartarate, methionine)	Cross-over design with 10 female mice fed standard chow diet at a specific time, for GI testing 0.3 g carbohydrates are given	A suitable controlled mice training protocol was established, and the diets were selected in such a way that the carbohydrates varied only in terms of starch and sugar type and not fiber or other macronutrients	Reported as a suitable alternative protocol for human trials	(86)
	Dietary fiber fractions from enzymatically treated bamboo shoot shells	Male Kunming mice; experimental design according to EU directive protocol; induced diabetes using high-fat diet and streptozotocin and effect of dietary fiber fractions from bamboo shoot shell on glucose-lowering property was analysed	Administration of bamboo shoot shell for 4 weeks significantly improved oral glucose tolerance; soluble dietary fiber considerably absorbed glucose and increased insulin levels when compared with insoluble and total dietary fibers from bamboo shoot shells	NA	(178)
Rat	Carbohydrates: fructose, lactose, sucrose	Male Wister rats administered with mixture of 0.8 g/kg carbohydrate dissolved in 2 ml water, 0.4 g/kg sucrose + 0.4 g/kg lactose and 2 ml water for control; one group fasted for 6 h fasting and another for 15 h	Rats fasted for 15 h are more suitable for the preclinical model to evaluate glycaemic response; can be used as a functional food ingredient for human consumption	NA	(179)
Porcine	Minipig fodder and glucose 2 g/kg	Gottingen adult minipigs with mean weight of 26 kg; 12-h day and dark cycles; oral glucose tolerance test, insulin test and histological examination of pancreas for β-cell inspection	Reduction in β-cells on dosing of nicotinamide and streptozotocin	β-cell mass (mg/kg body weight) is higher in minipigs when compared with human subjects; correlation of functional tests based on β-cell mass between minipigs and human subjects was not effective	(180)
	Individually prepared bread with wheat, rye, arabinoxylan and β-glucan, respectively	Female pigs, six crossbreeds; 15 human subjects	Similar glycaemic response in both pigs and humans despite different basal concentrations	Significant difference in metabolism response to bread but comparable glycaemic response between human and pig	(92)
Zebrafish	Glucose 25% in dimethyl sulfoxide with and without 1.5 mg/kg of oral diabetes medicine (glipizide)	Fish maintained in recirculation system with 14-h/10-h light/dark cycles; glucose levels monitored by drawing blood from tail vein	Response to anti-diabetic drug of adult zebrafish was similar to that of mammalian models	Zebrafish contains the transporter GLUT1 orthologue to human glucose transporter	(181)
	Fed dry meal; dissolved glucose in Cortland saline solution	4 d of fasting; zebrafish of multiple transgenic lines AB wild type line	Devised methodology for blood sampling in zebrafish for blood glucose measurement and standardised method for oral glucose tolerance test	Method can be used to analyse blood glucose in glucometers used by humans	(182)
	Processed fish feed containing algae	Type 2 diabetes induced by administering Otohime B2 for 4 weeks	Aminoacid pathways for host–bacterial interaction were studied	Gut microbiome similar to humans	(183)

few other drawbacks to animal experimentation, such as the need for professional personnel, time-consuming procedures, high training and housing costs involved[37]. Moreover, technical issues such as the size of the animal, monogenic inheritance and the possibility of quick cytotoxic conditions during the study can become challenges. For example, rats have very small body parts, and total resection of pancreas would be very difficult for the operator to perform, in turn, resulting in large inter-animal variations during diabetic studies. Post-operation anagesis, supplementation to mitigate pancreatic malabsorption, and animal infections should also be carefully considered by technical experts[100]. Besides, a non-invasive alternative to killing animals for the benefit of humans must be found, in particular for well-established glycaemic studies. Thus, the use of cultures of *in vitro* cells and tissues that require cell growth outside the body in the laboratory setting may be a less invasive alternative to *in vivo* animal experiments. Tissues and cells separated from an animal can be stored outside the body for a few days to several months or even for a few years, in adequate growth medium[37,101].

Ex vivo *models*

Ex vivo models are developed outside an organism but include active biological tissues with *in vivo* complex cellular surroundings. In these models, the structural integrity of the target tissues is preserved using an appropriate environment[102]. These *ex vivo* models can be isolated tissues or cultured tissues/cells in a growth medium.

Isolated tissues. The everted gut sac technique is a very common technique used for nutrient transport studies, especially in drug absorption research, dating back to the 1900s. Glucose absorbed into the bloodstream is directly proportional to GI. Therefore, permeability is an important factor to be considered in models. The intestinal effective permeability for passive transcellular diffusion is supposed to represent the diffusion of ions through the complex apical intestinal barrier[103]. Permeability of ions/nutrients is related to the rate of transportation through intestinal mucosa, a rate-limiting barrier, and can be studied irrespective of the mechanism of transportation. The permeable ions can also be utilised by the passive component during glucose absorption by the intestinal epithelium[104]. The permeability of drugs through the intestinal segment can be investigated. Apparent permeability is given by equation (8)[105]:

$$\begin{aligned} \textit{Apparent permeability} &= \frac{dQ}{dt} \times \frac{1}{(A \times C_0)} \\ &= V \times dt \times (A \times C_0) \end{aligned} \quad (8)$$

Where $\frac{dQ}{dt}$ is the amount of drug accumulation at the serosal region of intestinal tissue; C_0 is the initial concentration of drug (μg/ml); is the intestinal surface area (cm^2); V is the sample volume (ml). The aforementioned equation is Fick's law of diffusion. This apparent permeability is an important parameter illustrating the quantity of glucose that crosses the intestinal barrier and is available for absorption into the bloodstream after digestion.

Glucose absorbed by the everted intestinal segment was calculated[106] using equation (9):

$$\textit{Absorbed glucose} = \frac{(\textit{Glucose concentration before incubation} - \textit{Glucose concentration after incubation})}{\textit{length of the intestinal segment}} \quad (9)$$

whereas, muscle glucose uptake per g of muscle tissue is calculated[106] using equation (10):

$$\textit{Muscle glucose uptake} = \frac{(\textit{Glucose concentration before incubation} - \textit{Glucose concentration after incubation})}{\textit{weight of intestinal segment}} \quad (10)$$

Glucose absorption index is another parameter that gives the amount of glucose that is absorbable by a given intestinal segment. Here, phenol red (0.05%) was used as a recovery marker[107].

$$\textit{Glucose absorption index}\ (\%) = \frac{\textit{amount of glucose recovered from the intestinal segment}}{\textit{amount of phenol red recovered from theintestinal segment}} \quad (11)$$

Dixit *et al.* fitted an isolated intestinal segment of rat to a J-shaped tapering glass apparatus. The glass apparatus consisted of two cylinders with varying diameters, and the lower ends were made suitable for attaching the everted intestinal segment to it[105]. The results of this study showed good absorption kinetics and are reported to be validated. The author suggests that this technique can be used for all types of studies related to the transport of nutrients across the interstitial epithelium. A similar work studied the absorption of glucose fractions through an isolated jejunal part of rat intestine after digestion of mannitol (a low-calorie sugar). The study also investigated the effects of mannitol on intestinal enzymes such as α-glucosidase and α-amylase activities during digestion of sugar. For this, the gastrointestinal tract of healthy and normal rats were carefully isolated after anesthesia. The isolated jejunum was everted and incubated in buffer solution. Suitable conditions of gas composition were given to maintain the integrity of the tissue. The buffer solution was infused with mannitol at different concentrations along with glucose. The results indicated that the addition of mannitol significantly reduced the absorption of glucose, indicating that mannitol can be used as a dietary supplement for reducing post-prandial glycaemia[108]. The Ussing chamber is another powerful apparatus to measure ion transport which also uses *ex vivo* intestinal tissue for determining intestinal permeability. This apparatus dates back to 1951, though upgrades have been made since then[109]. The *ex vivo* animal intestinal segment is mounted by a slit in the small intestine at the conjunction between the duodenum and jejunum where the segment is removed about 30 cm in length. Then, each portion removed

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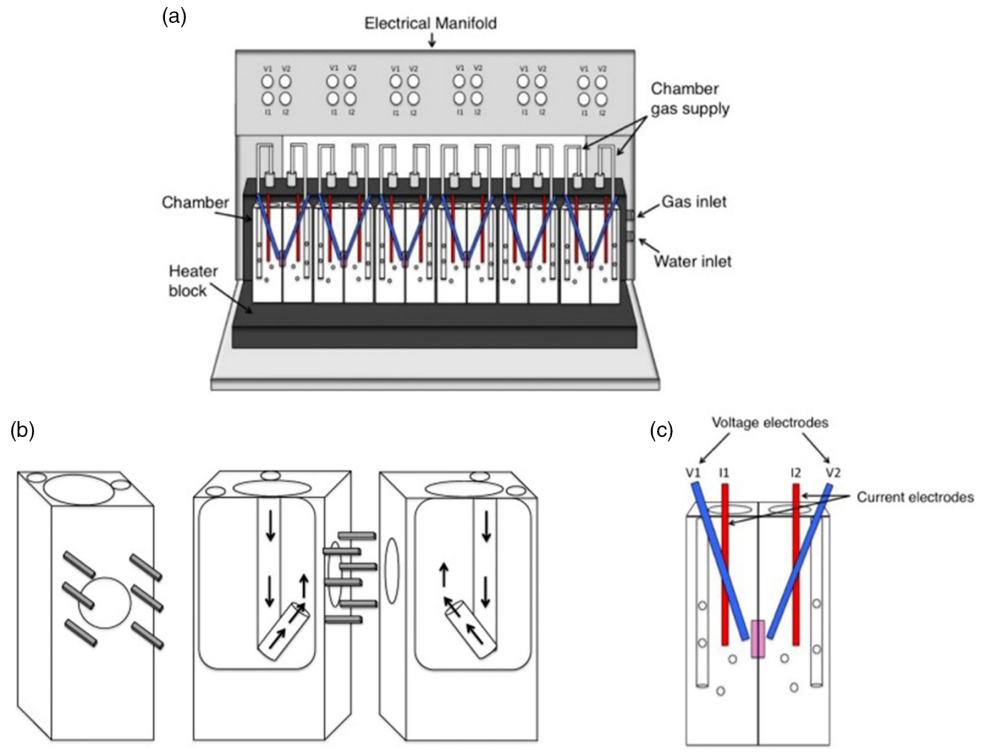

Fig. 3. Ussing chamber[111]; **(a)** schematic diagram of Ussing apparatus; **(b)** halves of chamber displaying the pins keeping tissue in place. Arrows show path of gas flow to agitate buffer; **(c)** Ussing chamber with electrodes

along the mesenteric border with a length of 3 cm, containing no patches of Peyer, is immediately placed in an Ussing chamber. Krebs solutions and test solutions are used for ion transport, and temperature is maintained at 37°C. The outcome of the analyte is collected and tested separately. This *ex vivo* process helps to study absorption mechanisms relating to humans. On the downside, this method is not suitable for higher animal tissues (e.g. pig, rabbit, dog, monkey) whose intestinal tissues are too dense for diffusion chambers; moreover, trickles were observed[110]. The setup of the Ussing chamber is shown in Fig. 3, where the electrodes are placed to measure the resistance created by buffer[111]. InTESTine™ was developed by TIM to investigate drug delivery. This uses *ex vivo* porcine intestinal tissue which is punched and mounted in a chamber[102,112].

The cut portions of tissues can be considered as the intestinal barrier because these isolated tissues are mostly derived from the intestinal portions of animals that can mimic the gut mucosa. Both the everted gut sac apparatus and Ussing chamber can be successfully used to determine the absorption kinetics of glucose after carbohydrate digestion by following any one of the well-established protocols provided by Englyst *et al.* (1996), Jenkins *et al.* (1982) and Wolever *et al.* (1991)[113-115] especially for GI, provided every factor affecting glucose metabolism is taken into consideration. The isolated intestinal segments possess multiple cell types, and even the hormones, microbial load, and cell-to-cell communications can be kept intact if maintained carefully in a buffer solution with gas supply[112].

The challenge lies in carefully isolating the tissues without damage and maintaining the integrity of the tissues. Biological variation is another important challenge to be addressed in selecting the animals from which the tissues are separated. Multiple replications have to be carried out to attain a reliable result. Apart from these factors, even small changes in harvesting time, age, sex, diet, stress level and method of killing influence the outcome of the study[116]. Further, technical limitations such as those in the identification of individual rate-limiting factors, constant monitoring of luminal hydrostatic pressure, and screening of tissues without cancerous origin are concerns in the use of isolated tissues for drug/glucose transport or absorption studies[117].

Cultured tissues. Another set of *ex vivo* studies used cultured tissue/cells to measure glucose transport. Advanced tissue-engineering systems have evolved, such as self-assembling 3D aggregates called organoids, in contrast to 2D cultures which present as monolayers. Recently, microfluidic lab-on-chip models have been progressing with the ability to successfully mimic intestinal epithelial tissues[118]. To study nutrient/ion transport in the intestine, a 3D villi structure on Caco-2 cells combined with fluidic technology has been developed[119]. This 3D villi scaffold was used to assess nutrient absorption at the molecular level using the permeability model indicating passive absorption. A gut microchip was mounted on three layers of polymers, and using the photolithography technique a wafer mold was made with the inverse configuration of the villi. Molecular flux, representing the rate of nutrient/ion transport through the scaffold, was determined using equation (8) as given above. The results showed that the presence of fluidic stimuli in the chip and 3D culture reduced efflux transport and may theoretically act as a platform with enhanced physiological relevance to the human gut[120].

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Similarly, intestinal epithelial cells cultured and integrated on microchips had villi-like protrusions, multi-lineage differentiation and brush boundary enzyme activity. In addition, mucin secretion has also been demonstrated under cyclic motion and flow conditions similar to intestine constructed by using cell lines[121]. There are also many gut scaffolds mimicking the entire intestinal dynamic environment including the microbiome. Yet, cell lines have to be constantly screened for cross-contamination to avoid misleading results.

Time commitment presents the greatest challenge of this model, as precision and repeatability are required[122]. *In vitro* approaches are therefore used to address these obstacles, in particular for ethical dominance, reduced time usage and readily analysable outcomes.

In vitro *models*

In vitro digestion assays are models that mimic *in vivo* digestion physiological conditions and are valuable methods to test and interpret modifications, associations and bio-availability of nutrients and medications. In the beginning, *in vitro* methods were used to determine availability of carbohydrates[123] and non-starch polysaccharides[124]. The *in vitro* method for GI determination started with Jenkins *et al.* (1984)[125], where a dialysis bag was used in a restricted method. Here, the digesta along with digestive enzymes were placed inside the bag, and the glucose from the digested carbohydrates was allowed to diffuse to the buffer environment over time. Because of a prolonged incubation period and an excess of amylolytic enzymes in the previous methods, Berry (1986)[126] made a few modifications to the previous method to more closely mimic digestion physiology. The study aimed to show how resistant starch survives during digestion, but the yields of resistant starch remained higher. Granfeldt & Björck, (1991)[127] included pepsin along with amylase enzyme in a dialysis bag. The concept of carbohydrate foods as "eaten" was introduced here. Englyst *et al.* (1992)[128] introduced a method that is widely used to this day. This method overcame the previous lacuna by including separate stomach and intestinal phases. This method also clearly classified the fractions of starches as rapidly digestible starch, slowly digestible starch and resistant starch. This is an unrestricted method that does not use any dialysis constraints. Later, Muir and O'Dea (1993)[129] employed α-amylase and amyloglucosidase in shaking water bath whereas Brighenti *et al.* (1995)[130] devised an *in vitro* method to investigate resistant starch digestion which used pancreatin and glass balls to mimic the digestion process. This method had a limitation in determining the effects of digestion of molecules other than glucose. Though Brighenti *et al.* developed the practical method, the well-defined calculation based on starch hydrolysis was clearly defined by Goñi, Garcia-Alonso and Saura-Calixto (1997)[131], which is used to this day. It was concluded that GI is also determined by the rate of digestion and absorption of glucose in the small intestine[132]. Another method was devised[133] to determine the starch fractions, but this method used maltose as standard and is not able to predict the digestibility of glucose-containing polymers such as pullulan, and it uses only α-amylase. There were also other protocols for GI, which used rapid glucometry for analysis and also determined the rheological properties of carbohydrate foods[134,135]. The absorption due to the influence of viscosity on the release of bile acid also needed to be considered. A modified method based on a dialysis diffusion-based approach estimating the influence of bile acid release on high-fiber barley was devised by Naumann *et al.* (2018)[136]. To this day, both restricted (dialysis bag) and unrestricted methods (without dialysis bag) are used. A protocol was devised based on the restricted *in vitro* method to determine GI, and this GI was correlated with the mass transfer of glucose from the dialysis membrane. The study showed that variations in the mass transfer of glucose were directly proportional to the GI with different food composition[137].The use of dialysis bag to designate the intestinal membrane as a boundary for diffusion has the advantage over the unrestricted method because starch hydrolysis is a rate-limiting process and changes in viscosity of incubated dialysate can be predicted by this membrane[127,136].

As time progressed, researchers viewed *in vitro* models as static and dynamic; the static *in vitro* model depicts the cycle of digestion (oral, gastric and intestinal) represented in separate compartments, while the dynamic *in vitro* model characterises the automatic, interconnected multi-compartments for ingested food similar to the human digestive system.

To closely replicate digestion dynamics, each stage of food digestion has to be carefully considered. In digestion, food, as described in the introduction, gets transported from the oral phase, enters the gastric phase, and finally reaches the intestinal phase, where the absorption takes place[138]. The oral phase involves various motor responses of break-down of food particles into smaller size. The size distribution of particles after the oral mastication process is given by equation (12):

$$\overline{Q}(X) = 1 - 2^{-\left(\frac{X}{X_{50}}\right)^{b}} \tag{12}$$

where, $\overline{Q}$ is the particle fraction, X is the particle size, X_{50} is the median particle size and b represents the extent of the distribution[139].

It has been reported that the effect of oral processing influences GI. Also, the speed and eating method has a major impact on GI according to researchers[140], which is due to variations in chew cycles and bite size. The bolus formed in the mouth enters the stomach, and digestion in the gastric phase is quantified in terms of gastric emptying. Gastric emptying can be calculated by equation (13):

$$y(t) = 2^{-\left(\frac{t}{T}\right)^{\beta}} \tag{13}$$

where, $y(t)$ is the chyme remaining in the stomach at time t; β is the shape factor; $T/2$ is the half time of gastric emptying [54].

Gastric emptying is an important determinant for the glycaemic response; the slower the emptying rate, the lower is the GI for starchy meals[55]. Though all these factors affect GI, it is the intestine which absorbs the glucose into the blood. GI, as discussed in the previous sections, can be calculated using the incremental area under the curve. However, for GI calculation using the *in vitro* method, the formula based on starch hydrolysis

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is widely used[131]. The kinetics of starch digestion follow a first-order non-linear trend. Based on the percentage of starch hydrolysed, the GI is calculated by using equations (14) and (15):

$$C = C_\infty\left(1 - e^{kt}\right) \tag{14}$$

$$GI = 39{\cdot}71 + 0{\cdot}549HI \tag{15}$$

where C is the concentration of hydrolysed starch at any time, C_∞ represents the concentration attained at equilibrium and k is the rate constant; HI is the hydrolysis index. All these parameters can be replicated and simulated by reproducing the digestion conditions. In a study, the *in vitro* starch hydrolysis of bread at the termination of oral, gastric and intestinal phase was found to be 9·5%, 49% and 68% respectively[141]. Some of the most recent *in vitro* models are presented in Table 2 and the illustrations are provided in Fig. 4.

In vitro models are successful alternatives to other models as they save time because *in vivo* animal, *in vivo* human clinical trials and cell and tissue models require lots of training time. To date, numerous *in vitro* models are being developed that aim to replicate the physiological conditions of humans, but accuracy remains a challenge. In the case of GI, there are a wide variety of existing models (Table 2). GI is a delicate parameter unlike other parameters of absorption and digestion because the response to glucose is subjected to hormonal effects that need to be considered carefully[64]. As we can see in Table 2, if all demerits in each models are resolved by considering all the parameters affecting glucose homeostasis, GI replication can be strongly correlated. Validation with more food products and human clinical trials will be a vital step and must be performed carefully in coherence with ethical clearance[11]. When thoroughly standardised, the prototype can then be used everywhere consistently. GI prediction is not possible without the aid of *in silico* combination because, as stated in the introduction, the individual glucose response requires the involvement of hormones and transporters. Moreover, the movement of the intestine across the digestive cycle and the mass distribution throughout the intestine must be properly reflected in addition to *in vitro* digestion, which is only possible with the inclusion of *in silico* approaches.

In silico *models*

Computer-generated models are used to predict various potential nutrient biological effects without animal dissection. Wessel *et al.* (1998)[142] developed the model and validated it with the *ex vivo* intestinal method. Boundary conditions were fixed with the partition coefficient. The partition coefficient determines the affinity of a bioactive molecule in the lipid phase and aqueous phase. The overall mass balance around the intestine can be elucidated with the following equations:

$$M_0 = V_dC_d + V_rC_r + V_pC_p + \int C(r)2\pi Lr.dr \tag{16}$$

where V and C are volume and concentration respectively, suffixes d, r and p are donor, receptor and particle, respectively, and L is the intestinal length. The equation was validated with the experimental *ex vivo* intestinal method; predicted values agreed with the experimental results.

The degree to which a bioactive molecule can move freely in the intestinal lumen is described by the diffusion coefficient (D). Ogston, Preston and Wells (1973)[143] discussed two approaches to determine the diffusion coefficient, and both being notable contributions of Einstein: (i) phenomenological approach (hydrodynamic drag on the molecule), and (ii) stochastic/random walk approach. In the phenomenological approach, the diffusion coefficient can be calculated from the hydrodynamic drag force of a species:

$$D_0 = \frac{K_BT}{6\pi\mu} \tag{17}$$

where the hydrodynamic radius of the diffusing molecule is r and μ is the medium viscosity, T is the absolute temperature and K_B is the Boltzmann constant. In the random walk approach, average molecular displacement (χ) due to the Brownian motion is accounted for, and the diffusion coefficient can be calculated by the following equation:

$$D_0 = \frac{\chi^2}{2t} \tag{18}$$

where D is the coefficient of diffusion, χ is the average molecular displacement and t is the time.

The mass balance approach[144] was developed at a macroscopic level for estimating the absorption by assuming the small intestine to be a cylindrical tube and the stomach with constant output rates an infinite storage tank. Mass balance around the intestine can be elucidated as

$$-\frac{dm}{dt} = Q(C_{in} - C_{out}) = \iint J_w dA \tag{19}$$

where M is the compound mass, Q is the flow rate, C_{out} is the concentration at the outlet, C_{in} is the concentration at the inlet, A is the absorptive surface area and J_w is the flux at the intestine wall. The dose fraction transferred in the intestine at steady-state condition can be elucidated as

$$F_a = 1 - \frac{C_{out}}{C_{in}} = 2A\int C'dz' \tag{20}$$

where dz' and C' are the variables of position and concentration, $C' = C/C_0$, $z' = z/L$. The authors considered three cases (based on solubility in the intestinal lumen) to integrate the above equation. The dissolution factor of the bioactive compound in the intestinal lumen is not accounted for in this approach, which is the main drawback of this model. However, this macroscopic mass balance approach is suitable for compounds in solution form or with high solubility.

The main disadvantage of the aforementioned approach was that it failed to describe the dissolution/absorption processes in the intestine. To overcome this problem, Oh and Marshall (1993)[145] developed a microscopic model for intestinal absorption, considering the dissolution of the bioactive compound in the

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Table 2. Dynamic *in vitro* digestion models

Model	Food	Mouth phase	Stomach phase	Intestinal phase	Findings	Merits	Demerits	References
SIMGI (Simulator Gastro-Intestinal) (Fig. 4a)	Solid and liquid foods	—	Flexible silicone compartment with physical force simulation; gastric juice is simulated; changes in pH are computer controlled	Five compartments of simulated small intestine and three compartments for large intestine; intestinal juice; temperature is maintained	Ability to reproduce dynamic environment of human *in vivo* system including colonic microbiota	Automated working conditions with microbial colonic studies; peristaltic movement and controlled gastric emptying	Gut microbiota and host interactions are yet to be studied; formation of microbial biofilms in colonic region	(168)
Dynamic gastrointestinal digester (DIDGI®) (Fig. 4b)	Dairy, meat, fruits and vegetables, emulsions	—	Gastric juice, pepsin enzyme, pH and temperature controllers are present; emptying time can be determined	Intestinal secretions are automised (bile and pancreatin)	Comparable data with *in vivo* piglets	Modifiable gas conditions during digestion; works well for liquid and masticated foods	Does not mimic anatomy of gut; no nutrient absorption simulation	(169)
HDM (Human Duodenum Model) (Fig. 4c)	Starch solution (2% w/v) guar gum used for viscosity variation	—	—	Intestinal and pancreatic juice simulated; temperature maintained similar to *in vivo* humans; dialysis membrane to act as intestinal barrier	Simulates duodenum segmentation motion. Contraction rings connected with rubber finger cuttings provide segmentation motion in this prototype. Dynamic intestine sigmoidal shape reflects real duodenum shape.	Effect of segmentation, orientation, flow rate, viscosity changes are successfully studied	Oral and gastric phase is missing here; digestion of solid foods needs these two phases	(170)
Model of an Infant Digestive Apparatus – MIDA (Fig. 4d)	Rice-based starchy liquid food	Salivary α-amylase; pH of 7; Simulated salivary fluid at 37°C for 2 min	Bolus is pushed through esophageal compartment where pepsin and simulated gastric fluid are added and digested for 120 min	Digested chyme is passed to an intestinal compartment; pH 6.5–7; pancreatic α-amylase and lipase in simulated intestinal fluid for 120 min, and glucose released at definite intervals is observed	Digestion pattern obtained in terms of percentage of starch hydrolysis during different stages of digestion. Digestion of both simple starch and fermented starch in infants were predicted	Only known *in vitro* model for infant digestion	Peristaltic motion in intestine is not mechanised; No mechanised physical forces on stomach digestion; human microbiome of intestinal colon is not considered	(171)
Dynamic *in vitro* rat stomach–duodenum model (Fig. 4e)	Hydrated diets made of pectin and mango containing starch, protein, cellulose, casein, whey, egg powder and fat	Artificial saliva in which food sample is vortexed for 30 s and 37° C is maintained	Elastic silicone rat stomach model with real rat stomach turned inside out; mechanical forces given by electrical compression rolling rig; 9 ml capacity; artificial gastric digestion is simulated	Silicone duodenum model with mechanised peristaltic movements; intestinal digestive juice with bile acids and enzymes are present	Starch hydrolysis and gastric emptying decreased with increase in dry matter content of food sample due to increase in viscosity of tdigesta. Significant difference found due to pectin which increased viscosity	Automatic secreting and emptying system with temperature controller	This model mimics only the rat digestive model, which needs further validation studies to scale up for comparison with human digestion models	(165)

Table 2. (*Continued*)

Model	Food	Mouth phase	Stomach phase	Intestinal phase	Findings	Merits	Demerits	References
TIMCarbo using tiny TIM system (Fig. 4f)	Bread, drink formula	Artificially masticated using food processor in simulated salivary fluid with amylase enzyme for 5 min at 37° C	Gastric fluids and pepsin; automated injection of enzymes and balance of pH	Automated secretion of brush border enzymes and pancreatic juice; mechanised peristaltic movement; intestinal chyme dialysed over hollow fibers semi-permeable cartridge; output is combined with *in silico* modelling	GI was nearly comparable with human *in vivo* data	Only known single-pass *in vitro* dynamic model to mimic nearly exact human *in vivo* GI	Glucose absorption from intestine is not considered at villus level and, microbiota factor is ignored here	(172,175)
Engineered small intestine system (Fig. 4g)	Vitamin E and gallic acid	—	—	Small intestine from Wister rats was carefully isolated and attached; intestinal enzymes were simulated; the temperature was maintained; buffer oxygenated with carbogen was given to maintain integrity of intestine	Intestinal permeability of bioactive compounds was studied at nanoscale levels	Absorption at villus range was studied; intestinal microbiota was considered; successful for passive diffusion of bioactive components	Active diffusion through energy transporters simulated using a correction factor since it is available only in *in vivo* environment	(103)
3D-printed stomach dynamic digestion model ARK®(Artificial-stomach Response Kit) (Fig. 4h)	Solid and liquid foods; nano foods	Oral phase using salivary amylase and salivary fluids is simulated	3D-printed stomach designed from stomach MRI scan of healthy subjects; physical forces simulated using pistons	Small intestinal section designed to be fitted with isolated animal intestinal section	System can study intestinal permeability of bioactive components and glycaemic responses, coupled with *in silico* model	Absorption at villus and microvillus levels can be studied; exact mimic of human stomach and small intestinal section	Colonic microbiota not simulated	(103,173)
DIVRSD-II dynamic *in vitro* digestion model (Fig. 4i)	Soy milk	Standard oral digestion	Stomach gastric fluid fed constantly with syringe pump; physical forces given using rolling extrusion plate and compression plate	Artificial duodenum compressed by 6 rollers mimicking *in vivo* model	Different degrees of satiety simulated by altering quantity of food intake, full satiety, semi satiety and limited satiety; digestive pattern and antigenicity of food sample varied with various satiety levels	Study with varying satiety level using dynamic rat model is a new approach	Validation with human *in vivo* data is not mentioned	(174)
Bionic gastrointestinal reactor (BGR) (Fig. 4j)	Newtonian fluids: glycerin solution and non-Newtonian fluids: xanthan solution	—	Silica gel model of fundus and gastric body have folds mimicking mixing mechanism of stomach; movement of gastrointestinal wall, i.e. peristalsis and gastric diastole, simulated by varying water pressure	Villus structure constructed to increase surface area of small and large intestine	Gastric pressure was maintained depending on real gastric action; surface area of small intestine was increased by 112% and that of large intestine was increased by 52%	First dynamic *in vitro* model known to mimic foldings of stomach and villus structures of intestine	Detailed validation needed in comparison with human clinical trials; nutrient absorption not justified	(164)

small intestine and permeation from the small intestine to the bloodstream. Considering the small intestine as a cylindrical tube, the rate of change of particle radius can be elucidated by the microscopic approach as

$$\frac{dr}{dz} = \frac{-D_r}{3} \cdot \frac{(1-C)}{r} \tag{21}$$

$$\frac{dC}{dz} = D_n D_0 \cdot r(1-C) - 2A_n \cdot C \tag{22}$$

where D_n is the number denoting the dissolution, D_O is the dose number, A_n is the absorption number, C is the dimensionless concentration ($C = C_L/C_S$), C_L is the concentration of the compound at the lumen, C_S is the compound solubility, r is the dimensionless radius of the particle ($r = r_p/r_O$), r_O is the initial particle radius, r_p is the radius of the particle at distance z, and z is the axial intestinal coordinate. Further, four dimensionless parameters like A_n (absorption number), D_n (dissolution number), and D_o (dose number) were developed to estimate the transported fraction in the intestine. Absorption number (A_n) gives the effective permeability of a compound to the flow rate in the intestine volumetrically (equation 23). Maximum absorption of 87% was observed for a compound with $A_n = 1$, and complete absorption could be achieved for the absorption number (A_n) larger than 1.

$$A_n = \frac{k\pi RL}{Q} = \frac{Radial\ absorption}{Axial\ convection\ rate} \tag{23}$$

Dose number (D_O) can be elucidated as

$$D_0 = \frac{M_0 V_0}{C_s} = \frac{Dose\ concentration}{Solubility} \tag{24}$$

and the dissolution number (D_n) is given by the following equation (25):

$$D_n = \frac{\left(\frac{D}{r0} \times C_S \times 4\pi r^2\right) / \left(\frac{4}{3}\right)\pi r^3 \rho}{\frac{Q}{\pi L R_0^2}} = \frac{Transit\ time}{Dissolution\ time} \tag{25}$$

Partitional diffusion and transit model was developed to determine the fraction of the absorbed dose and the rate of molecular absorption for molecules transported passively[146]. Small intestinal segments were divided into a series of compartments, and the rate of mass transfer of drugs from one compartment to the next compartment is directly proportional to the bioactives present in the initial compartment. The number of compartments is determined by comparing the modeled data with experimental results.

The area of interest here is engineering the absorption of glucose from the gut after digestion. The complex, highly orchestrated movement of the intestinal region, known as motility, regulated by electrophysiological, neurological, hormonal and other factors, is essential for nutrient absorption and excretion of undigested food[147]. Polyflow model was used to design specific intestinal contractions to examine computationally how these non-propagating contractions and their combined operation influence the patterns of intestinal flow and their ability to facilitate mixing. Results show that contractions along the length facilitate mixing and transfer of species in the periphery of the wall, while combined operation with a segmental compression increases these fluid flowing properties in the intestinal region[148]. Fig. 5 shows how intestinal contractions occur with different fluids of varying viscosity (water and honey). Research employed rigid particles suspended in a Newtonian fluid to imitate the viscous digesta to model the peristalsis in the duodenum shown in Fig. 6. The duodenum is perceived as a thin visco-elastic tube-like structure combined with numerical methods based on particles. The smooth hydrodynamics of particles and the discrete methods of components are coupled with solid and fluid motion. Because of the development of high pressures and radial velocity which is critical for advective nutrient absorption, the complete liquid content is found to dilate the walls of the gut[60]. The first model that was devised by Moxon, Gouseti and Bakalis (2016)[149] emphasises the transport of glucose taking place in the small intestine using the concept of the mass transfer process, given as the 1D advection reaction equation. The overall idea of this process is given in equation (26):

$$\begin{aligned} &Change\ in\ glucose\ mass\ with\ time \\ &\quad = movement\ along\ small\ instestine\ due\ to\ advective \\ &\qquad - Absorption\ of\ glucose \end{aligned} \tag{26}$$

The diffusion coefficient in the intestine is determined by two factors: molecular weight and solubility. A change in concentration with time is given by modified Fick's law, also called the second law of Fick (expressed as a vector quantity), at a defined location:

$$J = -D \cdot \nabla C \tag{27}$$

where ∇ is the gradient function $\nabla = i\frac{\partial}{\partial x} + j\frac{\partial}{\partial y} + k\frac{\partial}{\partial z}$; and the direction vectors (i, j, k) represent the x, y, z directions. Absorptive flux (J) is a permeability function of a compound through the intestinal membrane, which determines rate and extent of nutrient absorption in the intestine, and the flux can be represented by:

$$J = P_{eff} \times SA \times C \tag{28}$$

where P_{eff} is the permeability, SA is the surface area (intestinal surface accessible for absorption), and C is the concentration gradient of bioactive compounds across the intestinal mucosa[150]

The post-prandial glycaemic response of different types of foods and mixed meals have been quantified in terms of the model-based approach by Rozendaal *et al.* (2018)[151], whose model was devised based on the kinetic constants of the blood glucose response curves after ingestion of food. Similarly, Flint *et al.* (2004)[152] predicted GI using literature values for composite breakfast meals. The equation was devised as a function of other macronutrients as follows:

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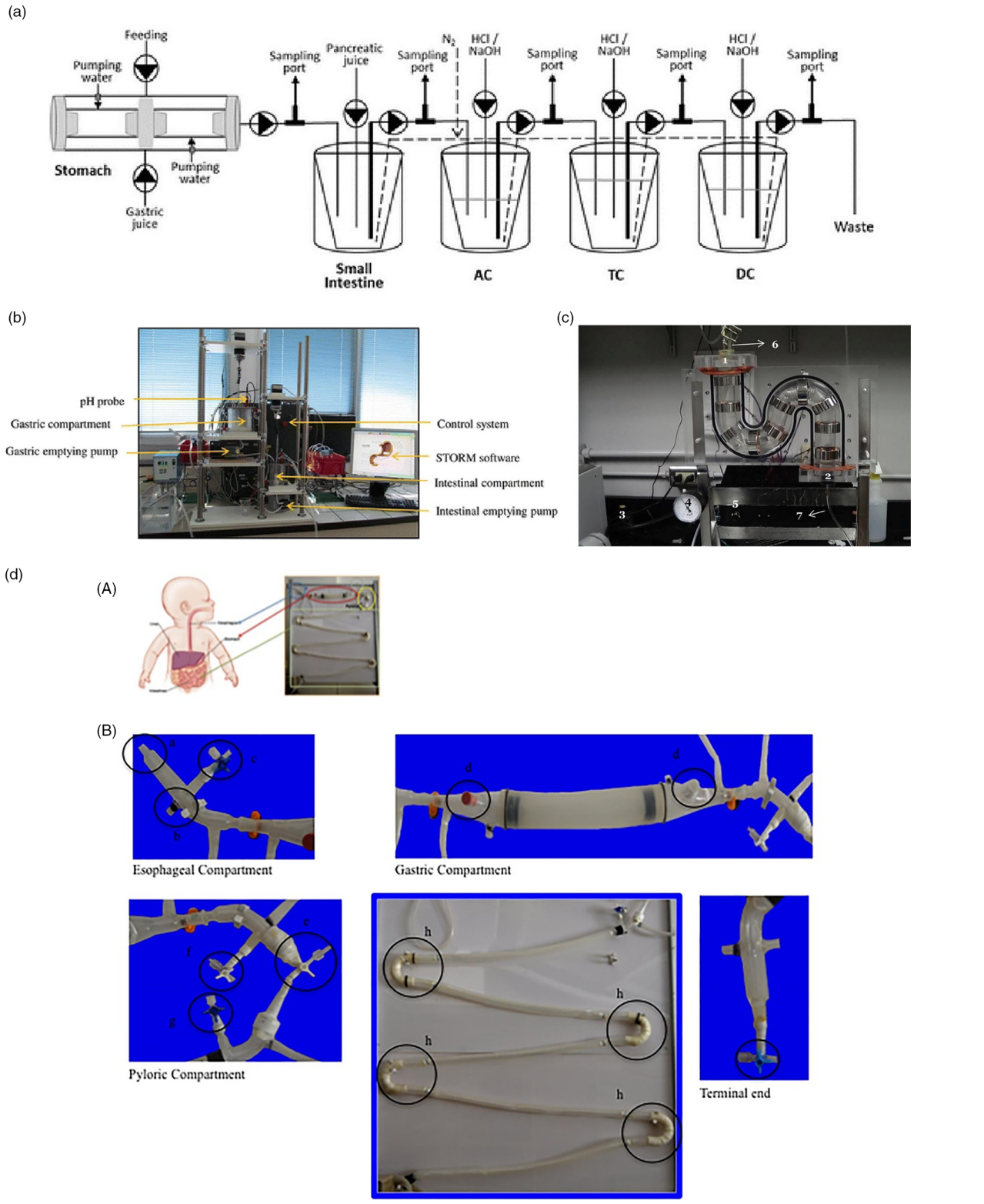

Fig. 4. Various *in vitro* dynamic digestion models; **(a)** SIMGI (Simulator Gastro-Intestinal)[168]; **(b)** dynamic gastrointestinal digester (DIDGI®)[169]: (1) gastric emptying pump, (2) gastric compartment, (3) pH probe, (4) intestinal emptying pump, (5) intestinal compartment and (6) control system. **(c)** HDM (Human Duodenum Model), adapted with permission[170]: (1) inlet ports for digesta, enzymes and sampling, (2) outlet tube (3), source for vacuum, (4) pressure gauge, (5) regulator, (6) inlet, (7) emptying port; **(d)** model of an infant digestive apparatus (MIDA)[171]: (A) view of complete system, (B) oesophagal, gastric, pylorus and intestinal compartments: (a) bolus inlet, (b) port for water bath at 37°C, (c) inlet for simulated gastric fluid, (d) connection to pH meter, (e) pylorus stimulus, (f) sampling port for gastric content, (g) inlet port for simulated intestinal fluid, (h) connecting loops, (i) chyme sampling; **(e)** dynamic *in vitro* rat stomach–duodenum model, adapted with permission[165]: (1) silicon stomach, (2) plate, (3) eccentric wheel, (4) shaft; **(f)** TIMCarbo using tiny TIM system[172]: (A) gastric chamber, (B) pyloric sphincter (C), duodenal chamber, (D) gastric juices, (E) duodenal secretion, (F) filter, (G) pH electrodes, (H) dialysis membrane, (I) dialysis system (J), pressure sensor, (K) level sensor; **(g)** engineered small intestine system, adapted with permission[103]; **(h)** 3D-printed stomach dynamic digestion model ARK®(Artificial-stomach Response Kit)[173]: (1) stomach geometry, (2) meshed geometry, (3) simulated fluid flow; **(i)** DIVRSD-II dynamic *in vitro* digestion model[174]; **(j)** bionic gastrointestinal reactor (BGR), adapted with permission[164]

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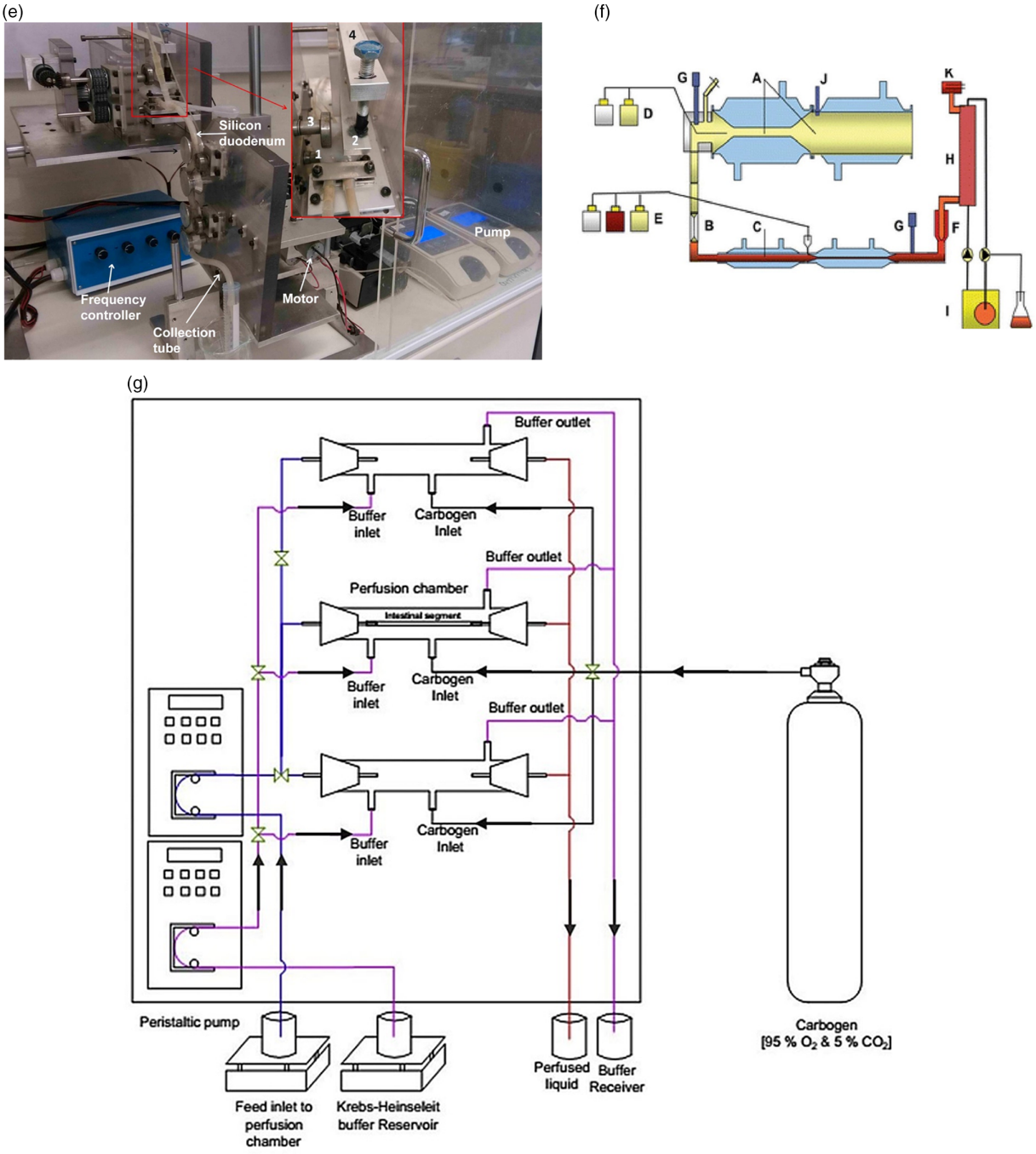

Fig. 4. (Continued).

$$GI_{meas} = 1/0{\cdot}0057 + 0{\cdot}0005 \times fat(g) + protein(g) \quad (29)$$

This equation was unable to predict the GI, and its correlation with *in vivo* data was very poor ($R^2 = 0{\cdot}25$).

Some of the other mathematical algorithms were also developed based on glucose absorption through the intestinal walls and insulin release as follows[153,154]. Equations (30–32) were devised for people with diabetes, and equation (33) represents glucose released based on mass equivalents[154]. The limitations of these models are that these are developed based on human clinical trials and the physical activity and stress levels are not taken into consideration.

$$\frac{dG}{dt} = -k_i \times G(t)I(t) + \frac{T_{GH}}{V_G} \quad (30)$$

Where k_i is glucose absorption rate by insulin-dependent tissues; T_{GH} is total equilibrium between insulin-independent zero-order glucose uptake by the brain and hepatic glucose output and V_G is apparent dispersal for glucose volume.

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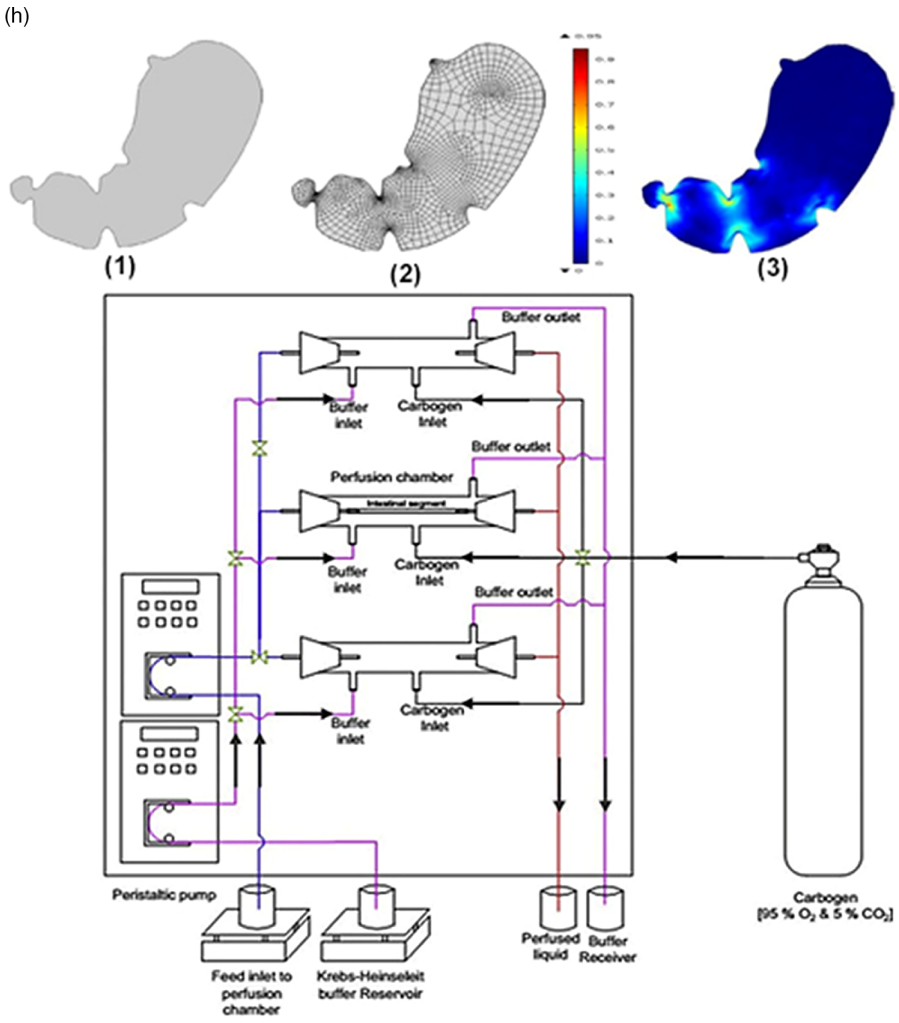

(i)

Fig. 4. (Continued).

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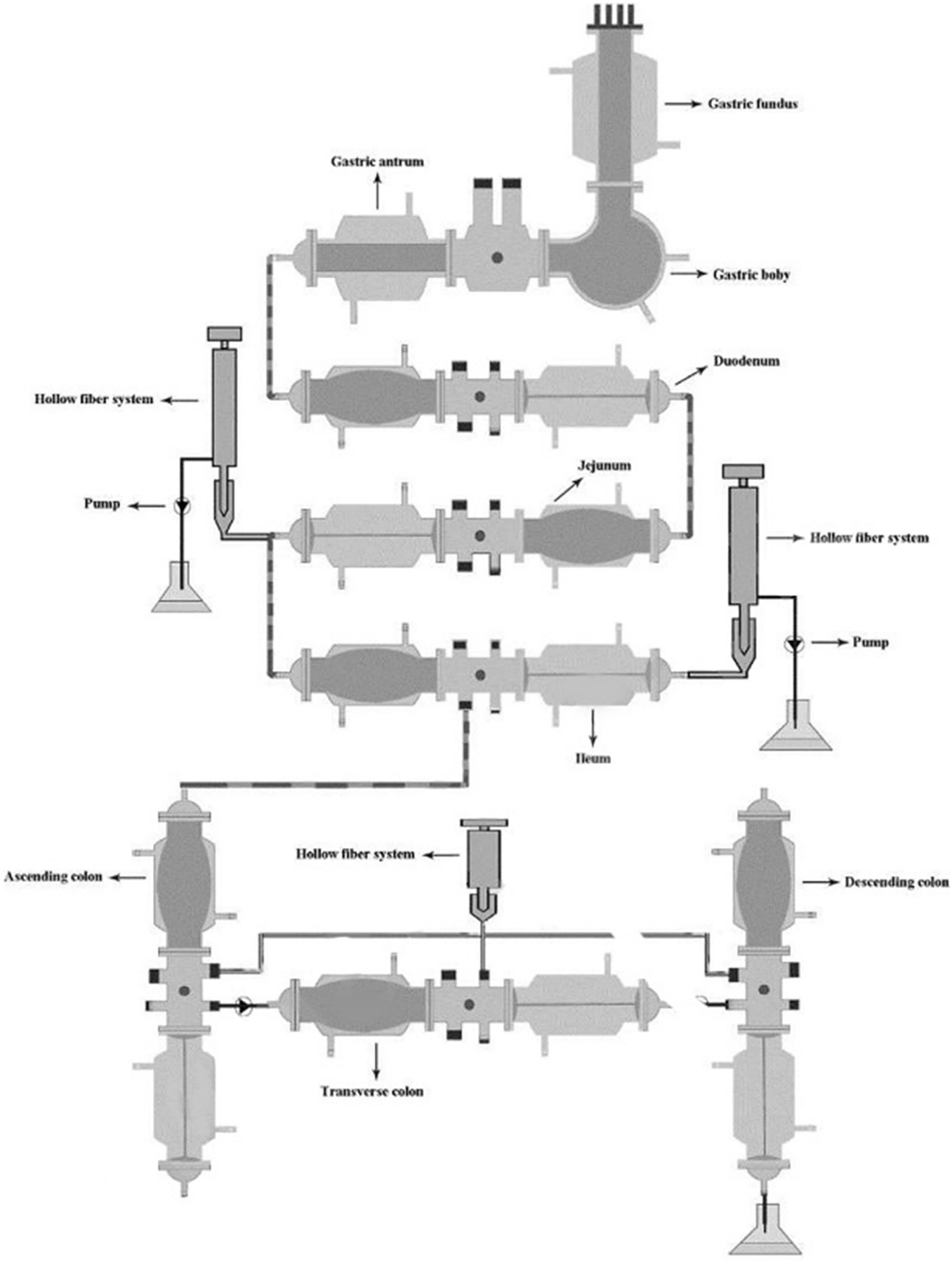

Fig. 4. (Continued).

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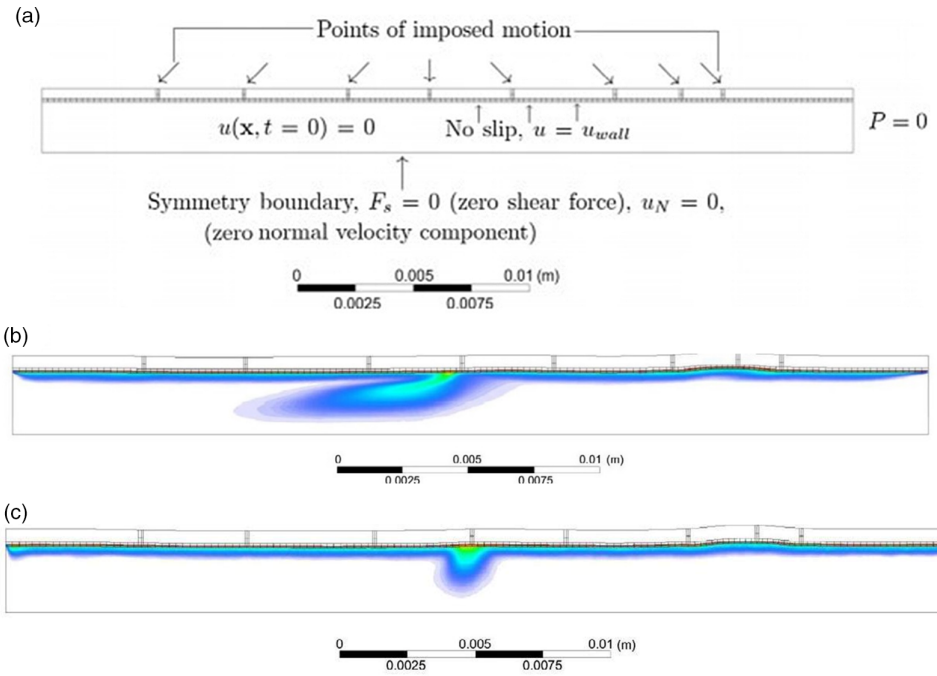

Fig. 5. **(a)** Boundary conditions imposed in an ileum part of model rabbit intestine; **(b)** contour plot of intestinal contraction when water is used as fluid; **(c)** contour plot of intestinal contraction when honey is used as fluid, adapted with permission[148]

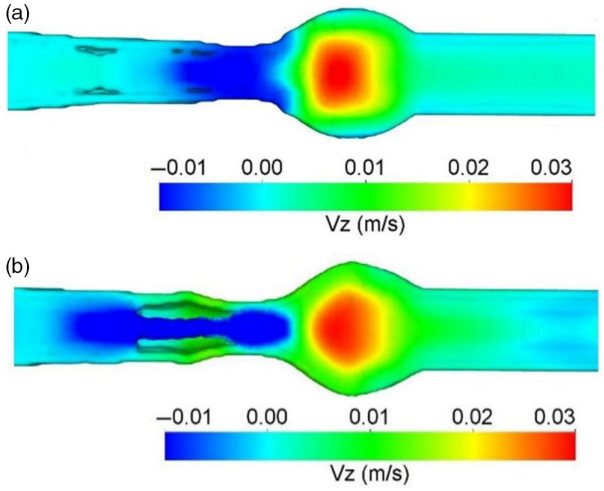

Fig. 6. Longitudinal velocity profile due to peristaltic wave of duodenum after 3 s of ingestion; **(a)** only fluid; **(b)** with 20% solid content, adapted with permission[60]

$$\frac{dG}{dt} = -k_i \times G(t)I(t) + \frac{T_{GH}}{V_G} + aMonosaccharide(t) \quad (31)$$

$aMonosaccharide(t)$ is absorption of the monosaccharides through the intestine wall estimated from the digestion model

$$\frac{dI}{dt} = -k_x \times I(t) + \frac{T_{iGmax}}{V_I} \times f(G(t - \tau_G)) + \frac{1}{V_I \times t_{max,I}} \times S_2(t) \quad (32)$$

where k_x is a rate constant for apparent first-order disappearance of insulin, T_{iGmax} is second-phase insulin release at the maximal rate, V_I is insulin distribution volume, τ_G with respect to varying plasma glucose concentrations is the time delay with which the pancreas initiates secondary insulin release and $t_{max,I}$ is the maximum time taken for insulin uptake.

$$G(t) = \frac{G_m(t)}{2.2 \times bm} \quad (33)$$

where G is glucose concentration in blood (mg/dL), G_m is mass of glucose in blood (mg), bm is body mass (kg) and t is the time (min). The absorption variation of about 25% was found in reaction kinetics of starch hydrolysis when model (33) was used[154].

Slow-wave propagation is also included in addition to peristaltic motility in the model of gut electromechanical coupling. Through computational fluid dynamics models, the mechanical deformations and generations of force could then be used as boundary conditions to enlighten the combined multi-scale models of full motility and the intestinal luminal mixing for which more anatomical details are required. New mechanical models coupled with a dye tracing process would also provide a clear way for simulation findings to be tested against analytical and imaging data. Spatiotemporal imaging experimentations can also be tested using computational fluid dynamics simulations. Various diseases, including chronic mesenteric ischemia, diabetic intestinal dysfunction and irritable intestinal syndrome, can be understood with the help of these integrated models. Signal processing and analytical techniques must take these variations into account when using methods for quantifying data for physiological applications and clinical interpretation[155,156].

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TIMCarbo has simulated the GI by combining *in vitro* and *in silico* methods. This method considers the insulin component of glucose homeostasis, which differentiates it from the other studies. Though we also require further investigations that consider other hormones involved in glycaemic response such as glucagon and incretins, as discussed previously, for a comprehensive and accurate prediction of *in silico* GI. The organisation of slow waves in the intestine and the interaction between interstitial cells and wave propagation is challenging to investigate experimentally but can be easily assessed using the *in silico* technique. These models, once established, may also be used to forecast the effects of neural input into intestinal motility disorders or intestinal slow-wave dysrhythmias, and also the succeeding effects using computational fluid dynamic studies on mixing and movement, which would allow the prediction of glucose responses in individuals with intestinal disorders.

Relevance to *in vivo* records

Digestion is a complex process, and in attempting to replicate the process it is necessary to consider the complementary contributions of different methodologies. A significant aspect of *in vivo* studies, particularly human studies, is the strong correlation of the findings, as the population of this research is also the real end-user of the food product. Though there are issues such as ethical constraints and inter-individual variabilities, the *in vivo* human method is the foremost important technique, especially for validation of glycaemic studies. Methods used in animal studies correlate highly with human *in vivo* protocols. Animal studies are typically less expensive and less laborious compared with human studies, and they can offer a degree of moral adaptability that is forbidden for human subjects[157]. Animal selection must be considered carefully based on the target study. The selection of animals for glycaemic studies can focus on the similarity of types of receptors associated with a glycaemic response, such as GLP-1 and GLUT-4. For example, the homology of glucagon and GLP-1 in humans with those of the mouse (humanised mouse) and rat is more than 90%[158] whereas zebrafish shares 50% homology[159]. Though gene similarity can be one of the factors to consider when selecting an animal model, other factors such as maintenance, total time invested, easy handling and cost should also be considered[160]. Similarly, the *ex vivo* rat intestine has been closely correlated with the human intestine in permeability studies because of the expression patterns of similar transporters[161]. The selection process in *in vivo* animal studies should also be carefully considered for isolating or culturing *ex vivo* and culture tissues. *In vitro* procedures are useful to reduce the time and cost of the analytical process.

The GI of different foods found a strong association ($r > 0{\cdot}86$) of static *in vitro* digestive kinetics with *in vivo* data in the presence of human saliva and intestinal juice in dialysis bags[115]. Since then, attempts have been made to standardise the static *in vitro* protocols. Research conducted by Englyst *et al.* (1992)[128], highlighted the importance of rapidly digestible starch (RDS), slowly digestible starch (SDS) and resistant starch (RS) which is sampled throughout the *in vitro* digestion process. These parameters and the GI values had a better correlation ($r = 0{\cdot}76$) with the *in vivo* values obtained from the literature. After this, Goñi *et al.* (1997)[131] obtained an even better correlation ($r = 0{\cdot}91$) with *in vivo* data. Monro and Mishra (2010)[162] devised a method for estimating glycaemic response based on relative glycaemic impact, which depends on grams of glucose equivalent clearance rate that can subtract the estimated glucose from the cumulative glucose released. This was developed to mimic the curve of the *in vivo* glucose response. This method was successful in obtaining a correlation of $r = 0{\cdot}88$ with experimental *in vivo* values and $r = 0{\cdot}90$ with literature *in vivo* values. To mimic the exact human digestion conditions and to exactly predict the *in vivo* glycaemic response, dynamic models were employed in which the TIM-1 and TIM-2 provided consistent results for the human *in vivo* condition with the replication of modelling the gastro-intestinal digestion including colonic fermentation of carbohydrates and dietary fibers. By integrating TIM digestion studies with insulin response using *in silico* methods, the human glycaemic response curve following carbohydrate intake can be predicted much more closely[163]. The correlation of the TIM model with that of *in vivo* human records is shown in Fig. 7, achieving a correlation of $r = 0.94$. To date, this model has been successful in predicting human glycaemic response curves of different foods with strong correlation. When comparing all the models, animal models correlate perfectly with *in vivo* human trials. This is due to the proximity of animal genes to humans in the glucose homeostatic condition. In *in vitro* models, replication of motor responses from the mouth during chewing must be carefully programmed to replicate the oral phase. Since the dependency of the glycaemic response starts from oral disintegration itself, the physical forces in the stomach and absorption level at intestinal villi must be exactly mimicked. The *in vitro* model designed by Bionic gastrointestinal reactor (BGR) has nearly the same morphology as the real *in vivo* model, which increased number of folding and surface areas of the intestine[164], whereas in Dynamic *In-vitro* Rat Stomach-Duodenum (DIVRSD) model, the enzyme secretions are automated similar to humans[165]. The engineered small intestine system, which is a part of the 3D-printed stomach dynamic digestion model ARK®(Artificial-stomach Response Kit), could simulate computational gastric movements[52]. The human oral glucose tolerance test was mimicked using the engineered small intestine system and was validated with *in vivo* data. The limits of agreement were within −24·52 and 22·63, corresponding to the lower and upper limits, respectively (Fig. 8)[166]. This system combines *in vitro*, *ex vivo* and *in silico* approaches. The *in silico* approaches are very useful in substituting the factors that are missing such as transporters, hormones and diseases. Also, the mass transfer phenomenon due to changes in food properties and the glycaemic response can be well projected using *in silico* models[167].

The human *in vivo* method is the standalone approach that is used for testing purposes generally. If successfully validated and if a particular procedure has a strong correlation, then the protocol will be repeated and a complete ethical replacement may occur. For this scenario to be successful, a device can be formulated like the gut-on-a-chip[120], with villi structures cultured carefully from the most relevant animal tissues based on desired selection criteria (homology, cost, maintenance and handling) or with artificially fabricated gastro-intestinal tissues analogues to the cultured tissues. This can also be automated for digestive and hormonal secretions supplementing with mass transfer parameters. Understandably, one single method cannot

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Fig. 7. Predicted glycaemic response in TIMCarbo against human glycaemic response where the correlation ($r = 0.94$), adapted with permission[175]

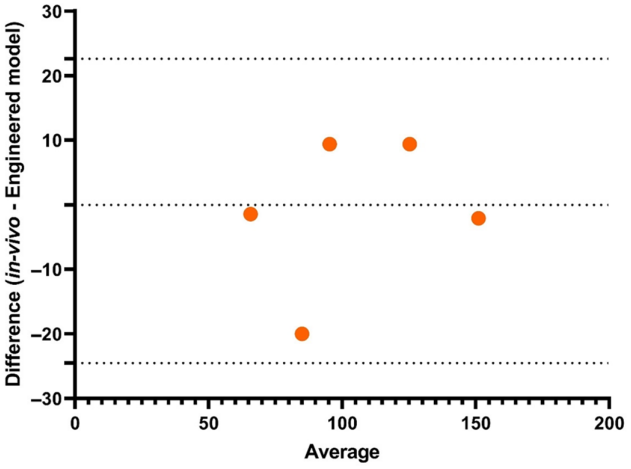

Fig. 8. Validation of predicted oral glucose tolerance test using engineered small intestine system[166]

reproduce the exact glycaemic response. Each method has its own merits and demerits; starting from conventional GI methods (restricted and unrestricted) to emerging methods (dynamic models and gut-on-a-chip) improvements have been made to date to achieve accuracy. The *in vivo* animal models and *ex vivo*, *in vitro* and *in silico* methods can complement each other to achieve the best results. A judicious way to move forward is to have combined understanding of computational, mechanistic and omics data to deliver precise prediction for nutrient absorptivity and cytotoxicity with improved interspecies translation. This can also aid in the research and development of new food products and health supplements, in addition to providing an improved understanding of food–drug interactions, disease-related diet frameworks and personalised nutrition.

Conclusion

Digestion is a complex phenomenon, especially when it comes to glycaemic response, due to factors that affect glycaemic response such as food composition, eating rate, amylase activity, gastric emptying and intestinal motility. GI is influenced by various factors such as processing and nutrient composition. Estimating certain criteria using human trials, however, has several ethical issues. Different models such as animal models, static and dynamic *in vitro* models, isolated tissue models and *in silico* models have been developed to date, and the ability of these models to predict the glycaemic response has been reported in this work. The relevance of these models to *in vivo* records has also been compared. Each method has its own merits and demerits; starting from conventional GI methods (restricted and unrestricted) to emerging methods (dynamic models and gut-on-a-chip), improvements have been made to date to achieve accuracy. Nevertheless, it must be emphasised that every system mentioned in this analysis cannot be employed at the same implementation level. To achieve replication of the exact human glycaemic response to foods with different GI, we need to make complementary use of *ex vivo, in vitro,* and *in silico* models.

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Conflict of interest

There are none to declare.

Author contributions

Priyadarshini S R: data curation, original draft; Moses J A: review and editing, resources; Anandharamakrishnan C: conceptualization, review and editing, supervision.

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