

Computational modeling of drug dissolution in human stomach: effects of posture and gastroparesis on drug bioavailability

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The oral route is the most common choice for drug administration because of several advantages such as convenience, low cost, and high patient compliance, and the demand and investment in research and development for oral drugs continue to grow. The rate of dissolution and gastric emptying of the dissolved active pharmaceutical ingredient (API) into the duodenum is modulated by gastric motility, physical properties of the pill, and the contents of the stomach, but current in-vitro procedures for assessing dissolution of oral drugs are limited in their ability to recapitulate this process. This is particularly relevant for disease conditions, such as gastroparesis, that alter the anatomy and/or physiology of the stomach. In-silico models of gastric biomechanics offer the potential for overcoming these limitations of existing methods. In the current study we employ a biomimetic in-silico simulator based on the realistic anatomy and morphology of the stomach (referred to as “Stomach-Sim”), to investigate and quantify the effect of body posture and stomach motility on drug bioavailability. The simulations show that changes in posture can potentially have a significant (up to 83%) effect on the emptying rate of the API into the duodenum. Similarly, reduction in antral contractility associated with gastroparesis can also be found to significantly reduce the dissolution of the pill as well as emptying of the API into the duodenum. The simulations show that for an equivalent motility index, reduction in gastric emptying due to neuropathic gastroparesis is larger by a factor of about five compared to myopathic gastroparesis.

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I. INTRODUCTION

The oral administration route is a safe, economic, and easy way to administer drugs to patients and one that is known to result in a high degree of patient compliance¹. However, the oral route is actually the most complex way for an active pharmaceutical ingredient (API) to enter and be absorbed by the body. The bioavailability of the drug in the gastrointestinal (GI) tract depends not only on the drug formulation, but also on the dynamic physiological environment in the fed stomach^{2,3}. This environment arises from the complex interplay of factors such as the contents of the stomach, stomach motility, and the gastric fluid dynamics. In particular, stomach contractions induce pressure and shear forces that generate complex pill trajectories. This results in varying rates of pill dissolution and non-uniform emptying of the drug into the duodenum. This sometimes lead to phenomenon such as “gastric dumping” in the case of modified-release dosage forms^{3,4}. These issues pose several challenges to the design of drugs delivery systems in R&D, clinical, and regulatory settings.

One of the important properties to evaluate for oral drugs is the rate of dissolution, which is often the rate limiting step in drug absorption⁵. Existing approaches to assessing/quantifying drug dissolution rely primarily on in-vitro models but recapitulating the conditions experienced by an oral drug formulation in the stomach via these in-vitro models has significant limitations. The US Pharmacopeia (USP) dissolution apparatus (I-IV) are the de-facto standard (particularly, USP II) for assessing and quantifying drug dissolution (Figure 1a), but a variety of studies have shown the significant shortcomings of these devices for mimicking the conditions of the stomach⁶⁻⁸. More advanced in-vitro models^{9,10} have attempted to mitigate these shortcomings but at the cost of increasing device complexity. Furthermore, despite the increased complexity, these in-vitro simulators are still unable to adequately recreate bio-relevant conditions of motility-induced mixing, shear and pressure, the biochemical status associated with food content and gastric secretions^{7,11}.

Another widely used approach to quantifying drug release and absorption in the early phase of drug development is pharmacokinetic/pharmacodynamic (PK/PD) analysis (Figure 1b), which is a technique used to quantify and study the effect of physiological interaction and metabolism of drugs in vivo^{12,13}. PK/PD analysis is robust in that it not only provides “dose-effect” analysis of the drug, but it also gives information on how much of the administered dose is delivered to specific receptors, how much is metabolized, and the variability in drug effect between subjects¹³.

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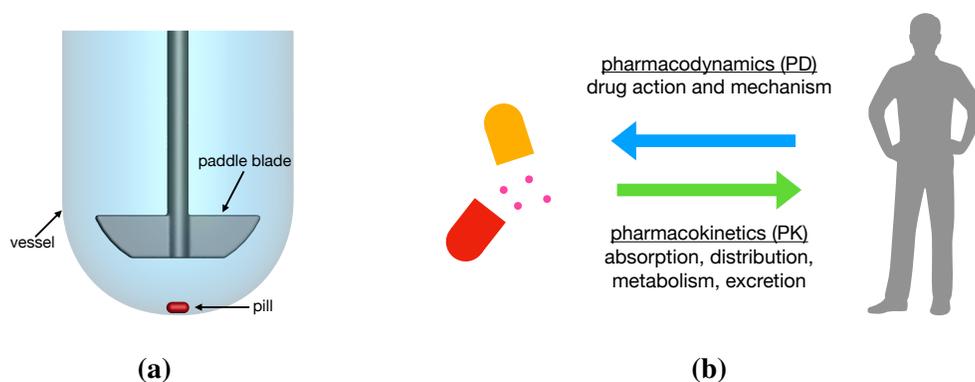


FIG. 1: (a) A schematic of the US Pharmacopeia apparatus type II (USP II: paddle). (b) A schematic of pharmacokinetic/pharmacodynamic (PK/PD) model for dose-effect analysis and assessing physiological interaction and metabolism of drugs *in vivo*^{12,13}.

Despite its advantages and development of more complex PK/PD models, PK/PD analysis is still unable to capture some of the key factors that affect bioavailability of oral drugs, such as posture and gastric motility⁵.

Several studies have shown that differences in posture yield considerable level of variations within and between subjects in gastric mixing and emptying, digestion, and absorption of liquid and solid meals, as well as in drug bioavailability^{14–21}. The effect of posture on drug bioavailability is assessed pharmacokinetically by measuring, for example, time to reach peak plasma drug concentration, maximum plasma drug concentration, and total exposure. However, the exact mechanism and the magnitude of postural effects have not been understood completely¹⁹.

These challenges are particularly relevant for many disease conditions that are associated with alterations in the anatomy and/or physiology of the stomach. For example, gastroparesis is a chronic change in gastric motility caused by conditions such as diabetes, Parkinson's disease, collagen vascular disorders, and Roux-en-Y gastric bypass²². Clinical studies such as PK/PD, however, involve healthy volunteers with an assumption that the inter-individual differences in GI physiology is small²³. Current preclinical and clinical approaches to assess the efficacy of oral drugs are limited in elucidating the relationship between various diseased states that alter gastric motility and also in accounting for other relevant parameters such as the volume, composition, and fluid dynamics of the gastric content⁵. Therefore, the quantitative data that incorporates these

variations in gastric functions, especially in diseased states, are lacking.

Computational fluid dynamics (CFD) is a powerful complement to benchtop experiments that has been widely used in developing and and/or assessing medical devices such as ventricular assist devices^{24–26}, prosthetic heart valves^{27–32}, and blood filters³³. Indeed, in-silico modeling and simulation have become a strategic priority for the U.S. Food and Drug Administration in the recent years in supporting regulatory evaluation of biomedical products^{34–37}. CFD can enable us to obtain full flow information in anatomically realistic stomach to investigate the effect of the interaction between gastric biomechanics and fluid dynamics in drug dissolution and determining the local drug concentrations. Using an in-silico simulator, we can easily test different physiological and other conditions (such as posture) in parallel, and also generate databases that more closely and broadly represent the physiology of different gastric conditions. In this study, we leverage a computational modeling platform to simulate drug dissolution in an image-based human stomach model.

There have been a few studies that previously developed in silico models of GI tract biomechanics and digestion processes^{20,38–46}. Pal et al.³⁸ developed the first model of the stomach to analyze the fluid behavior during digestion with the presence of antral contraction waves (ACWs). Although it was a two-dimensional model, they were able to show how different motilities affected mixing and the “Magenstrasse” (stomach road) in the stomach³⁹. Ferrua et al.^{40,41} used a simplified three-dimensional model of the human stomach to show the effect of different food viscosity on the flow patterns and also showed limitations of the two-dimensional model in capturing flow structures present in the three-dimensional model. Imai et al.²⁰ used their model to study how the location of gastric content with respect to the antral recirculation affects mixing. Miyagawa et al.⁴² further used the model to study the effect of gastric motility on liquid mixing. Trusov et al.⁴³ developed a model that incorporates the multiphase flow in the antroduodenal portion of the GI tract and showed how the food particle dissolution and biochemical reactions are influenced under pathologic scenarios. Ishida et al.⁴⁴ added the pylorus to their previous model^{20,42} to study the quantify the effect of impaired coordination of the pyloric closure with antral contractions on gastric mixing and emptying. Li and Jin⁴⁵ and Li et al.⁴⁶ developed their CFD model of the human stomach to investigate the effects of gastric motility and addition of food matrix (porous medium) on liquid content mixing and spatial distribution of pH. We note that these previous models focused mostly on the mixing and emptying of only the liquid gastric contents. Seo and Mittal⁴⁷

developed a model of drug dissolution in the stomach that not only considers the flow of gastric contents due to stomach motility, but also resolves the motion of the pill as well as both diffusion and convection of the dissolved API in the gastric flow field. The current model in this study is an extension of this work by Seo and Mittal⁴⁷, which now includes the pyloric opening and closing dynamics that enables us to measure how much of the dissolved API is mixed and transported in the stomach and released into the duodenum. Our model is used to investigate the effect of posture and gastroparesis on drug dissolution in the stomach as well as the release of the drug into the duodenum.

II. MATERIALS AND METHODS

The current model extends the initial model by Seo and Mittal⁴⁷, and the detailed mathematical formulation, governing equations, and implementation of our model can be found in the Appendix section.

A. Stomach model

An anatomical model of human stomach is constructed from in-vivo imaging data available from the Virtual Population library⁴⁸. The database provides high resolution anatomical models created from magnetic resonance image data. For this study, we use the stomach model from “Duke” (Figure 2), who is a 34-year-old male adult. The 3D stomach lumen is segmented and reconstructed from the MRI dataset as unstructured surface mesh with triangular elements.

In our stomach model, we focus on the dissolution, mixing, and emptying driven by antral contractions associated with a fed stomach, and this current model does not include tonic contractions. Antral contractions are modeled as a series of pulse waves called antral contraction waves (ACWs) propagating from the corpus region and all the way down to the terminal antrum. The terminal antral contraction (TAC) is a segmental contraction of the terminal antrum, which is activated when the ACW reaches the terminal antrum⁴⁹. The pylorus is modeled in a similar fashion with a prescribed motion, in which the pyloric closure is controlled by the start-time and duration of the closure. The pyloric sphincter is closed for 65% of the time in one cycle of antral contraction, and the pyloric closure and the TAC begin synchronously as the ACW reaches the distal antrum region, similar to the healthy model described by Ishida et al.⁴⁴. The diameter of the pylorus is

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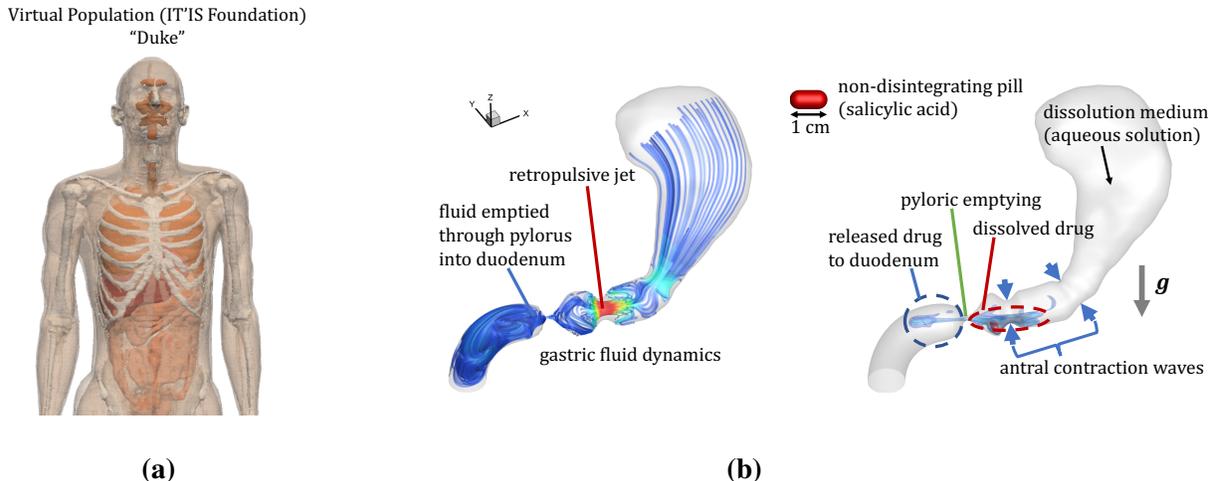


FIG. 2: (a) The anatomy of the human stomach is obtained from the Virtual Population library⁴⁸. For this study, we use the stomach from “Duke”, a 34-year-old male adult. (b) Three-dimensional stomach model is then created by segmenting the stomach lumen.

approximately 2 mm when open during fed state^{50–52}.

The pill is assumed to be made of salicylic acid, with a specific gravity of $\rho_p/\rho = 1.2$, in which ρ_p is the density of the pill and ρ is the density of the fluid medium⁵³ and modeled as a non-disintegrating and non-deformable object, an approximation that is valid for the early stages in the dissolution of the pill. Because the pill is denser than the fluid medium, the pill settles down on the stomach wall due to gravity. Here, we assume that the fluid medium in the stomach is homogeneous (e.g. water, juice, and milk). As the drug dissolves, the dissolved API is transported by the gastric flow that is driven by the antral contractions. The coordination between the antral contraction and the pylorus opening and closing results in a pulsatile release of the stomach contents, including the API into the duodenum. Figure 2b shows the schematic diagram of the features in our model.

This in-silico platform enables us to observe and quantify pill dissolution in the stomach and as well as the release of the API into the duodenum. We estimate the emptying rate of the overall liquid content in the stomach, Q_{emptying} , as well as the dissolved mass into the duodenum by calculating the mass transfer rate through the pylorus, \dot{m}_{API} ,

$$Q_{\text{emptying}} = \int_{S_p} \mathbf{u} \cdot \mathbf{n} dA, \quad \dot{m}_{\text{API}} = \int_{S_p} C_{\text{API}} \mathbf{u} \cdot \mathbf{n} dA, \quad (1)$$

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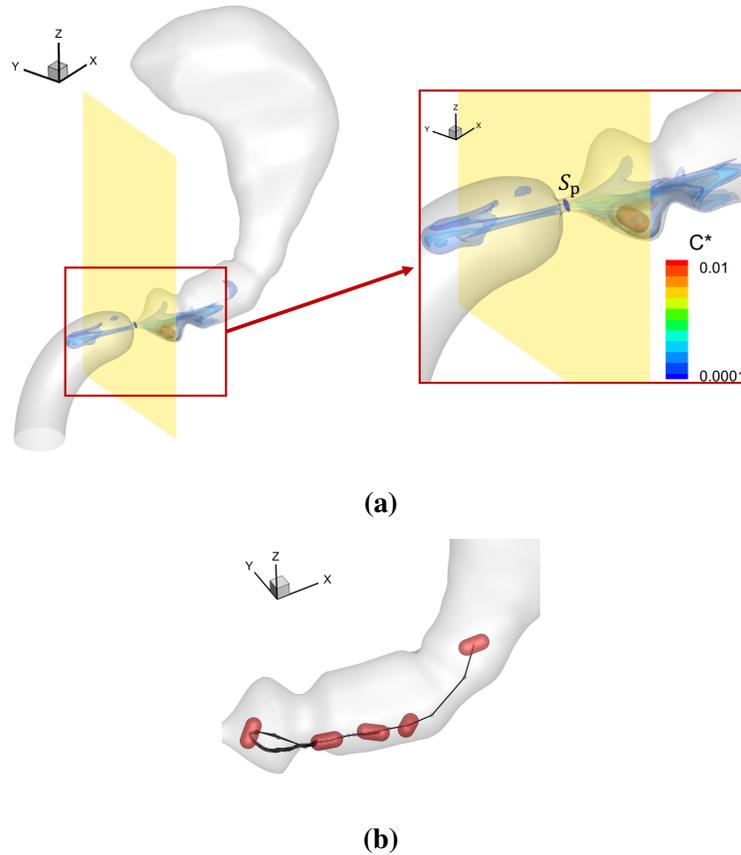


FIG. 3: (a) Computational model of the human stomach and duodenum system in this study. The cross-section of the pylorus (purple circular plane in the pylorus denoted as S_p) formed with the plane shown is where the rate of gastric emptying and the dissolved active pharmaceutical ingredient (API) concentration into the duodenum through the pylorus are measured. For this study, we use the stomach from “Duke”, a 34-year-old male adult. (b) Our computational model includes free motion of the pill induced by the motility of the stomach, the gastric fluid dynamics, and gravity. The trajectory of the pill can be traced (black line).

in which C_{API} is the concentration of the dissolved API, S_p is the cross-section of the pyloric opening, and \mathbf{n} is a unit normal to the plane shown in Figure 3a. Our model also allows us to trace the exact trajectory of the pill motion (Figure 3b), which is induced by a complex interplay of stomach motility, gastric fluid dynamics, and gravity.

Another quantity that we can look at is the total amount of API released into the duodenum

TABLE I: Different postures considered in this study. Here, the stomach geometry is fixed in space, and the direction of gravity is changed. The unit vectors indicate different directions of gravity considered.

	upright	posture 1 (leaning right)	posture 2 (leaning left)	posture 3 (leaning back)
direction of gravity	$(0, 0, -1)$	$(-\sqrt{2}/2, 0, -\sqrt{2}/2)$	$(\sqrt{2}/2, 0, -\sqrt{2}/2)$	$(0, \sqrt{2}/2, -\sqrt{2}/2)$

every cycle of antral contraction. We can use this data to fit a modified Elashoff’s model^{52,54}, a sigmoid-shape function that has been used to describe gastric emptying rate. This model can provide insight into the long-term behavior for different conditions. In this model, the amount of API being emptied per cycle, $API(t)$, is described as

$$API(t) = API_{\infty}(1 - e^{-\alpha t})^{\beta}, \quad (2)$$

in which API_{∞} is the predicted amount of API released per cycle at steady-state (in mg), and α and β represent emptying rate and initial delay in emptying, respectively.

B. Modeling the effect of posture on drug dissolution and release

An advantage of using an in-silico simulator is that we can tightly control the operating conditions, eliminating variations other than the variable of interest between different cases. To compare the effect of posture on the bioavailability of the drug, we consider four different postures: upright, leaning right, leaning left, and leaning back with the rest of the parameters kept constant. To model postural effects, we keep unchanged the stomach geometry, the initial position of the pill, and the gastric biomechanics, and instead of actually rotating the stomach as shown in Figure 4, we just change the direction of the gravitational force as described in Table I. Because the pill is denser than the dissolution medium, the effect of the direction will significantly affect the pill motion, and thereby the rate of dissolution and release of the API. Figure 5 shows the time-dependent volumetric distributions of the dissolved API concentrations in the antral and duodenal regions for different postures.

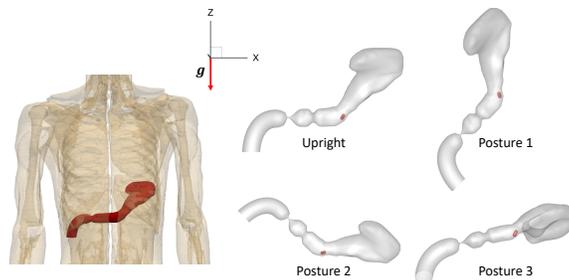


FIG. 4: Diagram showing the original position of the stomach relative to the body and different relative positions of the stomach with respect to the direction of gravity considered in this study.

C. Modeling the effect of gastroparesis on drug dissolution and release

Gastroparesis is typically identified with neuropathic and/or myopathic abnormalities that decrease the number and/or the amplitude of contractions, respectively^{55–60}. Antral motility is often assessed quantitatively via a motility index (MI), which is defined as

$$\text{MI} = [\text{mean amplitude}] \times [\text{number of contractions every 3 minutes}], \quad (3)$$

and gastroparesis is identified with a decrease in MI ^{55,57,61,62}. Gastroparesis can be then further categorized into neuropathy (damaged vagus nerve), myopathy (increased fibrosis or degeneration of smooth muscle cells), or both⁶³. In our simulations, we characterize different types of gastroparesis as listed in Table II, in which the frequency of ACW is reduced to model a case of neuropathy ($T_p = 40$ sec; $\text{MI} = 2.0$) and the amplitude of ACW is reduced to model myopathy ($\lambda_{a,\text{max}} = 0.2$; $\text{MI} = 1.8$), and both ($T_p = 40$ sec and $\lambda_{a,\text{max}} = 0.2$; $\text{MI} = 0.9$), as opposed to the normal stomach ($T_p = 20$ sec and $\lambda_{a,\text{max}} = 0.45$; $\text{MI} = 4.0$). In the cases we consider, we fix the posture of each case to be upright, so the healthy normal case is the same as the upright case in Section II B.

TABLE II: Different gastric motility parameters that model different types of gastroparesis considered in this study. Gastroparesis is identified with neuropathic and/or myopathic abnormalities that decrease the number ($\propto 1/T_p$; T_p is the pulse interval) and/or the amplitude of contractions ($\lambda_{a,max}$), respectively. We then calculate the motility index (MI) for each corresponding case.

	normal	neuropathy	myopathy	neuropathy + myopathy
$\lambda_{a,max}$	0.45	0.45	0.2	0.2
T_p	20 sec	40 sec	20 sec	40 sec
MI	4.0	2.0	1.8	0.9

III. RESULTS

A. Effect of posture on drug dissolution and release

The upright position (Figure 5a) shows a typical behavior in which the pill is carried by the ACWs toward the pylorus and moved away from the pylorus by the combination of the retropropulsive jet⁴¹ and the antral relaxation⁴⁴. When the body is leaning right by 45°(Figure 5b), we see a significant increase in the dissolved API in the stomach and the duodenum. We know that the emptying of the dissolved API into the duodenum is proportional to the API concentration at the pylorus (Eq. (1)), and the concentration at the pylorus is high in this case. The reason for this increased concentration at the pylorus is that the pill resides close to the pylorus throughout the duration of the simulation because the gravity is now pulling the pill along the antrum toward the pylorus. On the other hand, when leaning left by 45°(Figure 5c) the pill is kept in a position away from the antrum and the large contractions from the traveling ACWs. This results in the dissolved API concentration at the pylorus and in the duodenum being close to zero. Lastly, when the body is leaning back by 45°(Figure 5d), a larger amount of API is released because the pill is closer to the core of the jet and experiences stronger retropropulsive jet. The retropropulsive jet is known to be responsible for rapid gastric mixing⁵², which accelerates the release of the API from the pill. The direction of gravity also pulls the pill slightly more towards the distal antrum region more than the upright position does. This eventually results in larger amount of API concentration dissolved in the pylorus region and thereby increase in the dissolved API released into the duodenum

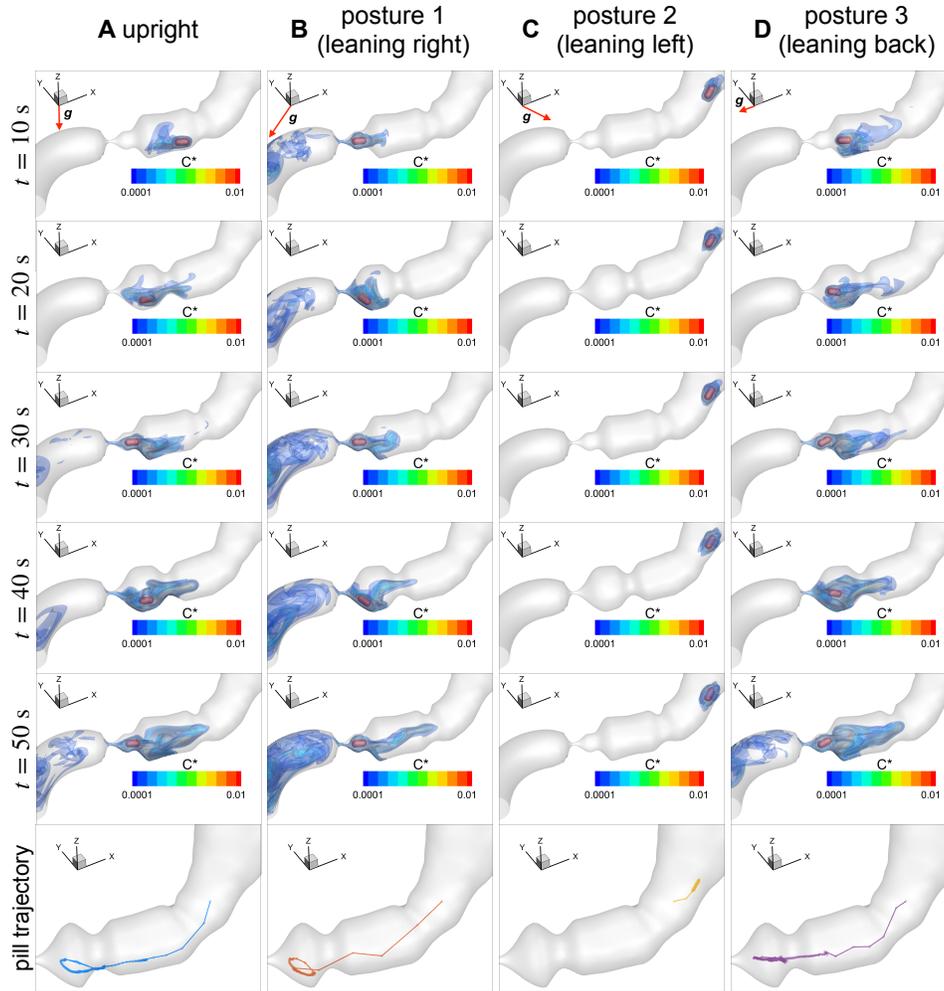


FIG. 5: Volumetric distributions of the dissolved active pharmaceutical ingredient (API) concentrations in the antrum and duodenum regions for different postures ($C^* = C_{\text{API}}/C_s$ is the normalized concentration, C_{API} is the concentration of the dissolved API, and C_s is the solubility concentration of the pill). Red arrows show the relative direction of gravity. The last row shows the pill trajectory for each case.

(Figure 6b).

Figure 6a indicates that gravity does not affect gastric emptying of the liquid content of the stomach, which confirms the clinical findings of Golub et al. that the rate of emptying of the liquid only depends on the volume⁶⁴. Figure 6b shows that leaning right (posture 1) yields significant increase in the dissolved mass released into the duodenum compared to other positions. Leaning

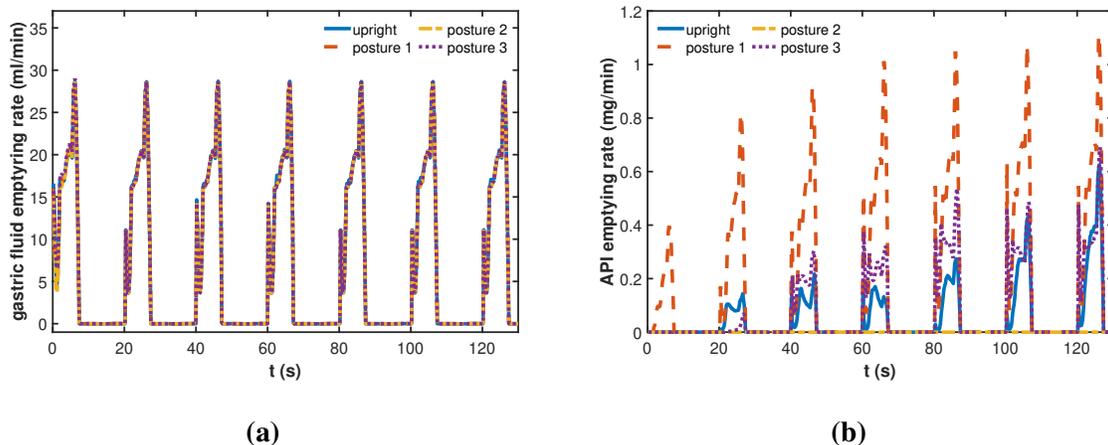


FIG. 6: Comparison for different postures. (a) Quantification of gastric fluid emptying rate into the duodenum measured by calculating the velocity flux through the pylorus. (b) Quantification of the dissolved active pharmaceutical ingredient (API) into the duodenum measured by calculating the concentration flux through the pylorus.

TABLE III: Average dissolved active pharmaceutical ingredient (API) released into the duodenum per cycle for different postures. To calculate the average dissolved API released, the cycle-average of the flux of dissolved API in Figure 6b is calculated, which is then integrated over the duration of one cycle (20 sec).

	upright	posture 1 (leaning right)	posture 2 (leaning left)	posture 3 (leaning back)
average dissolved API released	0.016 mg	0.052 mg	0.0 mg	0.024 mg

left (posture 2) leads to significant decrease.

Table III summarizes our findings in terms of average dissolved API released into the duodenum per cycle for each posture. To calculate this, we first obtain the cycle-average of the flux of dissolved API shown in Figure 6b, which is then integrated over the duration of one cycle (20 sec). We note that for the upright position, 0.016 mg of API is released into the duodenum per cycle, 0.052 mg for posture 1 (leaning right), 0.0 mg for posture 2 (leaning left), and 0.024 mg for posture 3 (leaning back). Here, the mean dissolved API is 0.023 mg and the root mean squared deviation

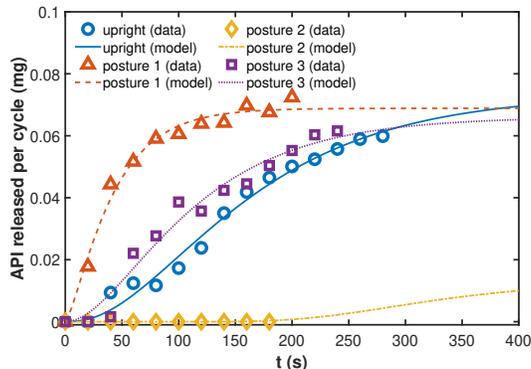


FIG. 7: Comparison of fit for a modified Elashoff model against simulation data for the amount of active pharmaceutical ingredient (API) emptied into the duodenum every cycle for different postures.

TABLE IV: Parameters obtained by fitting the modified Elashoff model (Eq. (2)) against the simulation data for the amount of active pharmaceutical ingredient (API) emptied into the duodenum every cycle for different postures (Figure 7). API_{∞} is the predicted amount of API released per cycle at steady-state, and α and β represent emptying rate and initial delay in emptying, respectively.

	upright	posture 1 (leaning right)	posture 2 (leaning left)	posture 3 (leaning back)
API_{∞} (mg)	0.0735	0.0689	0.0131	0.0661
α	0.0096	0.0284	0.0116	0.0126
β	2.6004	1.4225	27.7228	2.1235

(RMSD) among the four simulated cases is 0.019 mg.

Figure 7 compares the simulation data for the amount of API emptied into the duodenum every cycle for different types of gastroparesis. The data is then used to fit the modified Elashoff model (Eq. (2)). The fitted parameters API_{∞} , α , and β are listed in Table IV. The predictions from the model shows that the difference in the amount of API being emptied per contraction between the upright, leaning right, and leaning right positions are eventually similar in long-term (API_{∞}). However, it is clear that depending on the posture there are significant differences in the rate of emptying and initial delay in emptying.

B. Effect of gastroparesis on drug dissolution and release

Figure 8 shows time-dependent volumetric distributions of the dissolved API concentrations in the antral and duodenal regions for different types of gastroparesis. The neuropathic case (Figure 8b) shows that the dissolved API concentration is distributed further up away from the pylorus although the strength of the retroulsive jet is unchanged. This is because of a delay in the arrival of the next ACW to push the API concentration back toward the pylorus against the increased duration of retroulsive jet. Although the dissolved mass is still well-mixed despite the delayed arrival of successive ACWs with the help of sustained strong antral contraction, this delay results in reduced transport of the dissolved API into the duodenum. In the case of gastric myopathy (Figure 8c), the amplitude of the antral contraction is reduced to less than half that of the normal case. The dissolved API is pushed toward the pylorus as frequently as that in the normal case. However, the strength of the retroulsive jet is decreased and most of the API concentration therefore resides closer to the pylorus compared to the normal and the neuropathic cases. Despite this increased API concentration residing closer to the pylorus, the API is not transported to the pylorus and released into the duodenum as efficiently as it did in the normal case. In the stomach with combined neuropathy and myopathy (Figure 8d), the effect of gastric motility is significantly reduced. Therefore, the dissolution and transport of the API is driven primarily via diffusion, with some mixing induced by the retroulsive jet.

Figure 9 summarizes the effect of altered gastric motility on dissolution and release of the API. Figure 9a indicates that reductions in either the amplitude of the antral contraction or the frequency of antral contractions yield considerable decrease in gastric emptying rate. Moreover, Figure 9b shows that there is also a delay in release of the dissolved API into the duodenum, as well as a significant reduction in the total amount of API in the duodenum.

Table V summarizes our findings in terms of average dissolved API released into the duodenum per cycle. To calculate this, we first obtain the cycle-average of the flux of dissolved API shown in Figure 9b and then integrate this over the duration of one cycle that corresponds to the condition. We note that for the normal condition, 0.016 mg of API is released into the duodenum per cycle (20 sec), 0.00092 mg every 40 sec for neuropathy, 0.0051 mg every 20 sec for myopathy, and 0.0022 mg every 40 sec for both neuropathy and myopathy.

Figure 10 compares the simulation data for the amount of API emptied into the duodenum every

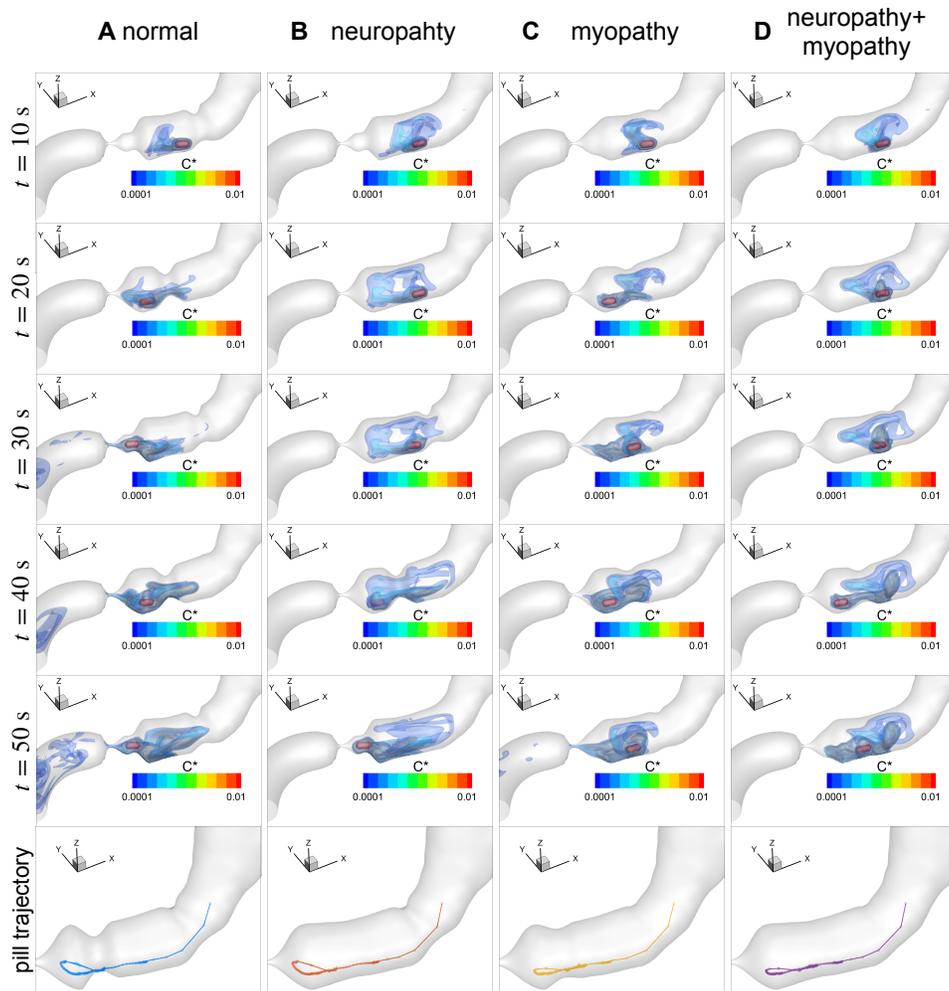


FIG. 8: Volumetric distributions of the dissolved active pharmaceutical ingredient (API) concentrations in the antrum and duodenum regions for different types of gastroparesis

($C^* = C_{API}/C_s$ is the normalized concentration,

C_{API} is the concentration of the dissolved API, and C_s is the solubility concentration of the pill). The last row shows the pill trajectory for each case.

cycle for different types of gastroparesis. The data is then used to fit the modified Elashoff model (Eq. (2)). The fitted parameters API_∞ , α , and β are listed in Table VI. The predictions from the model confirms the earlier results that reductions in the amplitude or the frequency of the antral contractions yield significant decrease in the emptying of the API in long-term (API_∞) by up to 89%. Different gastric motilities also result in either decrease in the emptying rate or increase in

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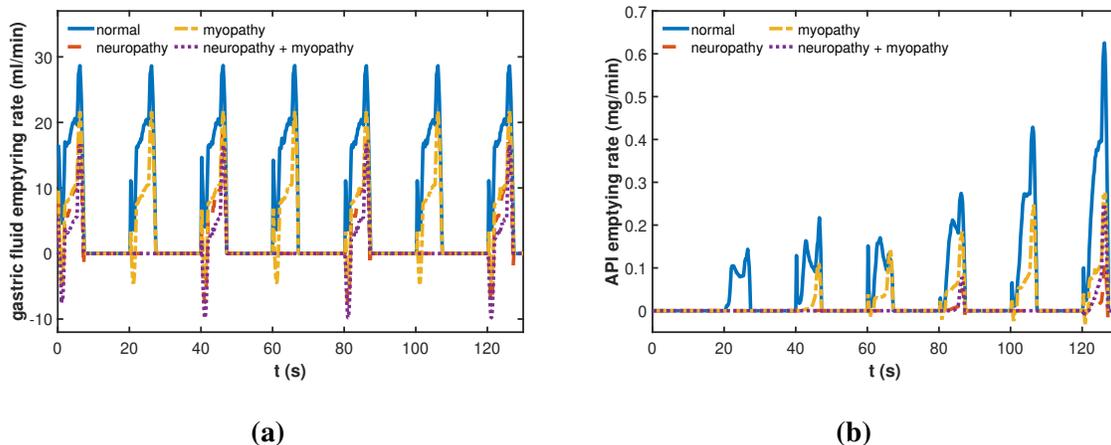


FIG. 9: Comparison for different types of gastroparesis. (a) Quantification of gastric fluid emptying rate into the duodenum measured by calculating the velocity flux through the pylorus. (b) Quantification of the dissolved active pharmaceutical ingredient (API) into the duodenum measured by calculating the concentration flux through the pylorus.

TABLE V: Average dissolved active pharmaceutical ingredient (API) released into the duodenum per cycle for different gastric conditions. To calculate the average dissolved API released, the cycle-average of the flux of dissolved API in Figure 9b is calculated, which is then integrated over the duration of one cycle that corresponds to the condition.

	normal	neuropathy	myopathy	neuropathy + myopathy
average dissolved API released	0.016	0.00092	0.0051	0.0022
	mg	mg	mg	mg
	every 20 sec	every 40 sec	every 20 sec	every 40 sec

the initial delay in emptying.

IV. DISCUSSION

In this study, we demonstrate a computational model of drug dissolution in the human stomach and investigate the effect of posture and gastroparesis on drug dissolution and the emptying rate of the API into the duodenum. To the best of our knowledge, this is the first model that couples gastric

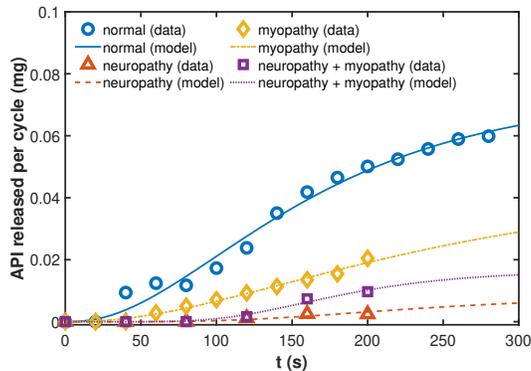


FIG. 10: Comparison of fit for a modified Elashoff model against simulation data for the amount of active pharmaceutical ingredient (API) emptied into the duodenum every cycle for different types of gastroparesis.

TABLE VI: Parameters obtained by fitting the modified Elashoff model (Eq. (2)) against the simulation data for the amount of active pharmaceutical ingredient (API) emptied into the duodenum every cycle for different types of gastroparesis (Figure 10). API_{∞} is the predicted amount of API released per cycle at steady-state, and α and β represent emptying rate and initial delay in emptying, respectively.

	normal	neuropathy	myopathy	neuropathy + myopathy
API_{∞} (mg)	0.0735	0.0083	0.0431	0.0165
α	0.0096	0.0106	0.0064	0.0169
β	2.6004	7.6065	2.4855	13.8995

biomechanics with pill movement and drug dissolution, and quantifies the API passing through the pylorus into the duodenum. With our model, we are able to calculate and compare the emptying rate and the release of dissolved API into the duodenum for a variety of physiological situations.

Previous studies have shown that the right lateral position leads to faster gastric emptying and that the left lateral and supine positions generally lead to slower mixing and gastric emptying of food^{14,16–20}. It has been also known that sitting, standing, and recumbent right postures that accelerate emptying of the food also accelerate the absorption of orally administered drugs and thus the plasma drug concentration¹⁹. This study provides further insights into how posture impacts

bioavailability of oral drugs. Our results agree with previous findings from clinical studies^{65–73} that showed that the release of gastric content into the stomach and the bioavailability of oral drugs is maximized when the direction of gravity aligns with the antrum and the pylorus. Our results suggests that the location of the pill with respect to the core of the retroulsive jet is also an important factor in the dissolution and release of the API. These insights have important implications for accounting for posture in clinical studies of drug dissolution and to consider posture as a way of modulating the release of API concentration into the duodenum. This is particularly relevant for narrow absorption window (NAW) drugs, which are absorbed mainly in the upper part of the GI tract and require that pills be retained in the stomach longer compared to other oral drugs⁷⁴. Moreover, our results show that the mean dissolved API released into the duodenum (0.023 mg) is of the same magnitude as the root mean squared deviation (0.019 mg) for the various postures. Indeed, we observe that certain postures can potentially reduce API bioavailability to a degree similar to that caused by a severe gastroparesis. Our long-term prediction using the Elashoff model shows that the amount of API being emptied can eventually be similar for three of the cases, different postures can lead to different rate at which enough API reaches the duodenum (Figure 7). This has an important implication especially for the rate of drug absorption for bedridden patients or elderly adults^{19,75}.

Our simulation results recapitulate what has been observed clinically for patients with gastroparesis and provide additional support for the utility of this in-silico modeling approach. In fact, our models of gastroparetic stomachs capture duodenogastric reflux, which has been known clinically to be associated with decreased MI^{57,61,62,76–78}. The results also provide insights regarding the concept of the motility index (MI) and its clinical implications. For example, the neuropathic and the myopathic cases have similar values for MI, with the myopathic case being slightly smaller. However, in our simulations the myopathic case showed more efficient emptying of the dissolved API into the duodenum, indicating that MI does not fully encapsulate the functional severity of gastroparesis. Using the Elashoff model, we predict that this trend may continue long-term, owing to a significant increase in the initial delay in emptying for the neuropathic case. Another interesting example in which we show that our results may provide more mechanistic insights is the comparison between the neuropathic case and both neuropathic+myopathic case. Although MI for the neuropathic case is twice as large, we observe that the emptying of API is less efficient in this case, which is counterintuitive. This is explained by looking at the interplay between the strength

of the ACW and the strength of retroulsive jet, and it is evident in our simulations that this balance is necessary in optimal emptying of API. We also use our model can predict that unlike being in different postures that showed more differences in the rate of emptying, gastroparetic stomachs have long-term effects on the actual amount of API emptied into the duodenum (Figure 10). Figure 9 also shows that improving just one of the conditions may not eliminate the duodenogastric reflux and sufficiently increase the release of API concentration into the duodenum. Other approaches to improving gastric emptying without modifying the antral motility such as pyloroplasty and pyloromyotomy widen the opening at the pylorus but also increase the possibility of duodenogastric reflux^{79,80}. The in-silico platform developed here could be used to compare different options for the treatment of gastroparesis in a patient-specific manner.

One of the limitations of our model is the absence of tonic contraction, although we expect that only the overall emptying rate will change, and that the general behavior will be similar to our results. Due to the computational expense, the current simulations are limited to modeling a short duration of the dissolution process (about 3 minutes) which is quite short given that drug dissolution might occur over many hours. Methods to speed up the simulations are currently under development and these should allow for simulations that extend over O(1 hour). Despite these and other limitations, we have demonstrated that computational models and simulations of gastric fluid mechanics can provide useful and unique insights into the complex physiological processes that underlie drug dissolution. Further extensions of this modeling framework include coupling with physiologically-based pharmacokinetics to predict the absorption of the API in the duodenum, and multiphase flow modeling in the stomach to model more complex gastric contents.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A: Computational modeling of drug dissolution in the stomach

1. Gastric motility model

The motility of the stomach is modeled as the radial motion of the stomach lumen with respect to the centerline along the stomach,

$$\mathbf{x}_w = \mathbf{x}_{w,0} + \lambda_a \mathbf{r}, \quad (\text{A1})$$

in which \mathbf{x}_w is the position vector of the lumen wall, $\mathbf{x}_{w,0}$ is the initial position vector of the lumen wall, \mathbf{r} is the vector from the wall to the antrum centerline, λ_a is the wall strain, s is the distance along the centerline of the stomach. See Figure 11 for the schematic diagram of the implementation of gastric motility. Here, the centerline is divided into different regions; $s < s_1$: no antral contraction wave (ACW), $s_1 - s_2$: ACW amplitude grows, $s_2 - s_3$: ACW amplitude is constant, $s_3 - s_4$: ACW amplitude increases (terminal antral contraction (TAC)), $s_4 - s_5$: ACW amplitude diminishes + segmental contraction of the distal antrum, and $s_4 - s_6$: TAC + pyloric closure and opening. This overall motion of the stomach lumen can be further divided into two motions,

$$\lambda_a = \lambda_{a,\text{ACW}} + \lambda_{a,\text{pyl}}, \quad (\text{A2})$$

in which $\lambda_{a,\text{ACW}}$ is the wall strain from the ACW and $\lambda_{a,\text{pyl}}$ is the wall strain from the pyloric opening and closing.

The antral contraction consists of three phases: peristaltic contraction, terminal antral contraction (TAC), and antral relaxation⁴⁴. The peristaltic contraction is modeled as the motion of the

stomach lumen, which is prescribed by the propagation of the antral contraction wave (ACW),

$$\lambda_{a,ACW}(t,s) = \lambda_{a,max} \sum_n \frac{1}{2} \left[\cos \left(\frac{2\pi(s - V_p t - nT_p V_p)}{W_p} \right) + 1 \right] h(s), \quad (A3)$$

$$h(s) = \begin{cases} 0, & s \leq s_1 \\ \frac{1}{2} \left(1 - \cos \left(\frac{s-s_1}{s_2-s_1} \pi \right) \right), & s_1 < s \leq s_2 \\ 1, & s_2 < s \leq s_3 \\ 1 + \frac{h_{max}-1}{2} \left(1 - \cos \left(\frac{s-s_3}{s_4-s_3} \pi \right) \right), & s_3 < s \leq s_4 \\ \frac{h_{max}}{2} \left(1 + \cos \left(\frac{s-s_4}{s_5-s_4} \pi \right) \right), & s_4 < s \leq s_5 \\ 0, & \text{otherwise} \end{cases}, \quad (A4)$$

in which $\lambda_{a,max}$ is the maximum diameter contraction ratio, n is the pulse count, V_p is the pulse propagation speed, T_p is the pulse interval, W_p is the pulse width, and $h(s)$ is a spatial damping function. For a healthy case, we use $V_p = 2.3$ mm/sec, $T_p = 20$ sec, $W_p = 20$ mm, and $\lambda_{a,max} = 0.45^{41,82,83}$.

The opening and closing of the pyloric sphincter is prescribed by radial contraction and relaxation of the pyloric wall strain,

$$\lambda_{a,pyl} = p(s)gate(t), \quad (A5)$$

in which $p(s)$ defines the shape of the terminal antrum and the pylorus and $gate(t)$ deforms $p(s)$ to open and close the pylorus. Note that because here we also model the terminal antrum as well, so $gate$ also deforms that region, which plays part in TAC. In our model, $p(s)$ and $gate(t)$ are defined as

$$p(s) = \begin{cases} \frac{1}{2} \left(1 - \cos \left(\frac{s-s_4}{s_5-s_4} \pi \right) \right), & s_4 \leq s \leq s_5 \\ \frac{1}{2} \left(1 - \cos \left(\frac{s-s_5}{s_6-s_5} \pi \right) \right), & s_5 < s \leq s_6, \\ 0, & \text{otherwise} \end{cases}, \quad (A6)$$

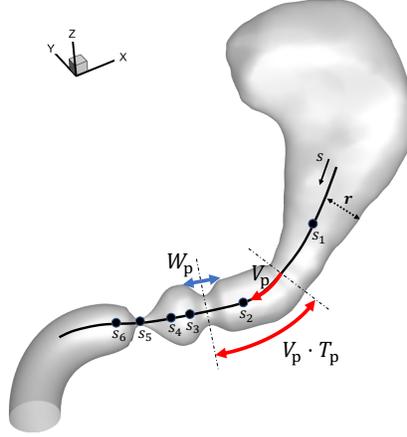


FIG. 11: Schematic diagram of the implementation of gastric motility. s is the coordinate along the centerline, and the centerline is divided into different regions; $s < s_1$: no antral contraction wave (ACW), $s_1 - s_2$: ACW amplitude grows, $s_2 - s_3$: ACW amplitude is constant, $s_3 - s_4$: ACW amplitude increases (terminal antral contraction (TAC)), $s_4 - s_5$: ACW amplitude diminishes + segmental contraction, and $s_4 - s_6$: TAC + pyloric closure and opening. V_p is the pulse propagation speed, T_p is the pulse interval, W_p is the pulse width.

and

$$\text{gate}(t) = \begin{cases} A_c - \frac{A_c - A_o}{2} \left(1 - \cos \left(\frac{\tau}{T_{\text{opening}}} \pi \right) \right), & \text{opening} \\ A_o, & \text{open} \\ A_c - \frac{A_c - A_o}{2} \left(1 + \cos \left(\frac{\tau - T_{\text{open}} - T_{\text{opening}}}{T_{\text{opening}}} \pi \right) \right), & \text{closing} \\ A_c, & \text{closed} \end{cases}, \quad (\text{A7})$$

in which $\tau = (t \bmod T_p) / T_p - T_0$ is the fractional time in antral contraction cycle starting from when the pylorus begins to open (T_0), $T_{\text{opening}} = 0.09$ is the fraction of time in one antral contraction during which the pylorus start to open (or close), $T_{\text{open}} = 0.17$ is the fraction of time during which the pylorus is kept open, and $A_c = 0.91$ and $A_o = 0.819$ are parameters that determine the closed and open configuration of the pylorus, respectively.

2. Flow solver

In this study, we use a sharp–interface immersed boundary solver ViCar3D^{84,85} to simulate gastric fluid-structure interaction (FSI), which has been used and extensively validated for cardiovascular flows^{86–88}. Here, we model the liquid content in the stomach as a Newtonian fluid, and we simulate the gastric flow by solving the incompressible Navier-Stokes equations,

$$\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} = -\frac{1}{\rho} \nabla p + \nu \nabla^2 \mathbf{u} + \mathbf{g}, \quad (\text{A8})$$

$$\nabla \cdot \mathbf{u} = 0, \quad (\text{A9})$$

in which \mathbf{u} is the flow velocity, p is the static pressure of the fluid, ρ is the fluid density, ν is the fluid kinematic viscosity, and $\mathbf{g} = -G\hat{z}$ ($G = 9.8 \text{ m/s}^2$) is the gravitational acceleration.

3. Pill motion

The motion of the pill is obtained by solving 6-DOF equations of motion^{89,90}

$$m \frac{\partial \mathbf{u}_p}{\partial t} = \mathbf{F}_f + \mathbf{F}_c + m\mathbf{g}, \quad (\text{A10})$$

$$I \frac{\partial \boldsymbol{\omega}_p}{\partial t} = \mathbf{M}_f + \mathbf{M}_c, \quad (\text{A11})$$

in which m is the mass, I is the moment of inertia, \mathbf{u}_p is the translational velocity, $\boldsymbol{\omega}_p$ is the angular velocity of the pill, and \mathbf{g} is the gravitational acceleration. \mathbf{F}_f and \mathbf{M}_f are the force and moment induced by shear stress and pressure of the surrounding fluid, which are computed by

$$\mathbf{F}_f = \int_{\partial\Omega_p} -p\mathbf{n} + \boldsymbol{\tau} \, dS, \quad (\text{A12})$$

$$\mathbf{M}_f = \int_{\partial\Omega_p} \mathbf{r} \times (-p\mathbf{n} + \boldsymbol{\tau}) \, dS, \quad (\text{A13})$$

in which $\partial\Omega_p$ is the surface of the pill, $\boldsymbol{\tau}$ is the viscous shear stress, and \mathbf{r} is the displacement from the center of mass of the pill to the point on the pill surface. \mathbf{F}_c and \mathbf{M}_c are the force and moment

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from contact with the stomach wall, which are computed by

$$\mathbf{F}_c = \int_{\partial\Omega_p} \mathbf{f}_c dS, \quad (\text{A14})$$

$$\mathbf{M}_c = \int_{\partial\Omega_p} \mathbf{r} \times \mathbf{f}_c dS, \quad (\text{A15})$$

Here, \mathbf{f}_c is the contact stress between the pill and the stomach lumen, which is described using a non-linear spring-based model:

$$\mathbf{f}_c = \begin{cases} -(k_{\max} + k_d \dot{\delta}) f_b \mathbf{d} / |\mathbf{d}| & \text{for } \mathbf{n} \cdot \mathbf{d} > 0 \\ 0 & \text{otherwise,} \end{cases} \quad (\text{A16})$$

$$\delta = |\mathbf{d}|, \quad \dot{\delta} = (\mathbf{v}_p - \mathbf{v}_w) \cdot \mathbf{d} / |\mathbf{d}|, \quad f_b(\delta) = \exp(-(\delta/\delta_{\min})^4), \quad (\text{A17})$$

in which k_{\max} is the spring constant, k_d is the damping constant, \mathbf{v}_p is the pill surface velocity, \mathbf{v}_w is the wall velocity, f_b is a non-linear function, \mathbf{d} is the displacement between each point on the pill surface and the contact point on the stomach wall, and δ_{\min} is the minimum distance parameter, which is set to 1.5 mm in our simulations. To satisfy the no-penetration condition, the maximum contact stress is written based a scaling analysis as

$$k_{\max} = C_k \Delta\rho g L_p, \quad (\text{A18})$$

in which $\Delta\rho$ is the density difference between the body and the surrounding fluid, L_p is the length scale of the body obtained by dividing the volume by the frontal area of the body, and C_k is a constant, which is set to 2.5 in this study. The damping constant is set to suppress unphysical rebound after the contact by using a relaxation time scale, t_R ,

$$k_d = \rho_p L_p / t_R, \quad t_R = C_d \Delta t, \quad (\text{A19})$$

in which C_d is the ratio between the relaxation time scale to the simulation time step size, which is set to 5 in our simulations.

4. Pill dissolution

The pill dissolution and release of API (denoted as C_{API}) is treated as a scalar, and we compute it by directly solving the convection-diffusion equation

$$\frac{\partial C_{\text{API}}}{\partial t} + (\mathbf{u} \cdot \nabla) C_{\text{API}} = D \nabla^2 C_{\text{API}}, \quad (\text{A20})$$

in which D is the diffusion coefficient. For the salicylic acid pill, the Schmidt number for the mass diffusion, ν/D is about 400^{53} , in which ν is the kinematic viscosity of the water. Here, the local API concentration at the surface of the pill is equal to the solubility concentration of the pill ($C_{\text{API}} = C_s$).

5. Fluid-structure interaction

In this study, the density ratio between the pill to the fluid medium is close to 1, we solve the coupled fluid and solid equations (Eqs. (A8)–(A11)) using an implicit coupling scheme:

$$\left\{ \begin{array}{l} (\mathbf{u}^{k+1}, p^{k+1}) = q(\mathbf{x}^k, \mathbf{v}^k, \mathbf{u}^k, p^k) \\ \mathbf{F}^{k+1} = f(\mathbf{x}^k, \mathbf{v}^k, \mathbf{u}^{k+1}, p^{k+1}) \\ \frac{\mathbf{v}^{k+1} - \mathbf{v}^k}{\Delta t} = \mathbf{g} + \frac{1}{M} [\gamma \mathbf{F}^{k+1} + (1 - \gamma) \mathbf{F}^k] \\ \frac{\mathbf{x}^{k+1} - \mathbf{x}^k}{\Delta t} = \mathbf{v}^{k+1} \end{array} \right. , \quad (\text{A21})$$

in which q represents the Navier-Stokes equations, f represents the force calculations governing the pill motions, k is the iteration index, γ is a relaxation parameter used to improve stability and convergence ($\gamma = 0.5$ in this study), and \mathbf{x}^k and \mathbf{v}^k are the position and velocity of the pill, respectively.

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