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Research acticle

MODELING OF ENZYMATIC PROCESSES IN THE DUODENUM TO PREDICT AREAS WITH ELEVATED RISKS OF FUNCTIONAL DISORDERS

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The present work focuses on developing a model of the duodenum considering motility, biochemical reactions occurring under effects produced by secreted digestive juices, and absorption of reaction products in normal conditions and in case of functional disorders. Analysis of literature sources allowed identifying basic bile components and pancreatic and intestinal juice enzymes influencing fats, proteins and carbohydrates that enter the duodenum.

The paper provides a simplified scheme showing how food components are transformed allowing for the neural-humoral mechanism of digestion regulation. Chyme that enters the duodenum is considered a homogenous mixture, which changes its composition during chemical reactions. Mathematical tasking includes mass and momentum conservation equations for a multi-component viscous fluid. The secretion of digestive juices and absorption of components resulting from chemical reactions are described with mass effluents in a pipe in the wall layer. The peristaltic law of the duodenum wall movement was applied to describe the tract motility; the movement characteristics do not depend on the composition of the mixture.

Numeric experiments produced necessary results to describe the hydrolysis of the 5 % starch solution under exposure to pancreatic amylase. Obviously, not all the amount of starch enters a chemical reaction and this is well in line with experimental data. The paper provides data on concentration fields for the components of glucose, amylase, and starch at different moments in time and the fluid velocity field.

The next stage in the model development is expected to consider absorption of food components, functional disorders of secretion / absorption and intestinal motility as well as influence exerted by neural and humoral mechanisms. In future, the developed model can be applied to predict areas with elevated risks of developing functional disorders, ulcer formation, and other defects of the intestinal mucosa. This will help a physician to prescribe personified therapy and diet.

Keywords: *duodenum, multi-component mixture, mathematical modeling, digestive juices, enzymes, secretion, peristalsis, glucose.*

The digestive system is among the most significant parts of the human body. Digestion is a set of biochemical and physiological processes that are involved in physical and chemical processing of consumed food for the subsequent assimilation of nutrients. Physical transformation means that food is reduced to finest particles due to mechanical effects produced by the gastrointestinal tract (GIT) motility. Chemical transformation means that products are transformed under influence exerted by digestive juices[1]. Among the physiological processes, we can spot out secretion of digestive juices and absorption of reaction products.

This paper concentrates on the duodenum as a specific organ in the GIT. It is located between the antral section of the stomach and the small intestine. Its overall length is 25–30 cm and it consists of the superior region (3–6 cm long, the diameter is 3–3.5 cm), descending region (8–10 cm long, the diameter is 4–5 cm), horizontal region (6–8 cm long) and ascending region (the diameter is 4–7 cm)[2]. The major duodenal papilla is located in the descending

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region, 5.5 to 12.8 cm away from the pyloric sphincter; on average, its diameter is 6 mm [1]. The sphincter of Oddi where the common bile duct and the main pancreatic duct open is located in it[3].

Evacuation, motor, secretion and absorption are the basic functions performed by the duodenum. The motor function exists to mix chyme with digestive enzymes. The evacuation function is responsible for transporting chyme to the subsequent sections in the intestines. The secretory function involves secreting digestive juices. Besides, the tract contents are absorbed actively in the duodenum, including elementary food components (amino acids, glycerides, and monosaccharides), water, mineral salts, and vitamins. However, in comparison with the subsequent sections in the GIT, intensity of this absorption is substantially lower in the duodenum, especially when it comes down to food components[4].

The duodenum is a C-shape pipe with typical tonic and pendular peristaltic contractions and non-propulsive segmental activity[5]. Peristalsis plays the leading role in making chyme move into the next section in the tract. Chyme is a pulpy mass that consists of partially digested food, gastric and intestinal juices, secrets of various glands, bile, and microorganisms. Secrets of the intestines and pancreas have an alkaline reaction and this makes for neutralization of the acid medium coming from the stomach. Besides, intestinal and pancreatic juices participate in transforming nutrients into simpler compounds. Secretion of digestive juices is regulated by the neural and humoral mechanism. Hormones make the gall blade contract, induce secretion by the pancreas and bile secretion, and enhance the intestinal motility [2]. Digestion is the most active exactly in this section of the small intestine[6].

Data produced by scientific observations indicate that isolated stomach damage (chronic gastritis) occurs in not more than 10–15 % of patients whereas antral gastritis combined with duodenitis (chronic gastroduodenitis) is the predominant disease [3]. Elevated acidity in the duodenum is among leading factors causing damage to the mucosa [4]. We should note that many aspects associated with proving cause-effect relations between environmental factors and diseases of the duodenum remain unclear so far.

Experimental methods are among those applied to examine digestive processes. They provide an opportunity to obtain data on an organ's shape and size; to examine composition of digestive juices; to determine acidity; to detect digestive diseases etc. These methods have certain drawbacks since they rely on expensive equipment and the necessity to involve highly qualified experts. Another disadvantage is that they do not provide any possibility to make quantitative predictions of functional disorders.

Mathematical modeling techniques applied in medicine allow performing multiple examinations and numeric experiments that are impossible to be performed as full-scale ones due to underdeveloped experimental equipment or probable health hazards for human subjects. Full-scale physiological experiments can be replaced with computational ones. The latter have a certain advantage since they give an opportunity to examine influence exerted by both specific factors (including cases involving great loads) and their combinations on the human body, to obtain high volumes of experimental data over a short pe-

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riod, and to make predictions how a disease would develop based on these data [5].

Mathematical modeling considers conditions of digestion, the geometry of internal organs and their functional disorders. It allows analyzing impacts exerted by specific factors on the digestive organs. At present, experts are concentrating on developing approaches to numeric modeling of the flow in various GIT sections. They predominantly develop two-dimensional models and three-dimensional ones have been introduced into practice mostly over the last decade [6–8]. Researchers have paid more attention to the tract motility and not to digestion in their previously published papers [9–14]. The authors of the work [15] modeled the duodenum as a two-dimensional channel with moving boundaries and with spotting out a boundary layer to describe the permeable tract walls. Chyme was considered a multi-component two-phase mixture; only one reaction, namely hydrolysis of starch under exposure to amylase, was examined. On one hand, development of such models can result in discovering new and previously unknown mechanisms of digestive diseases. On the other hand, this approach is very promising with respect to practical use since it can be applied to develop personified treatment recommendations and a peculiar diet for a given patient. Given that, the authors plan to improve the existing approaches in the model they suggest to consider secretion and absorption of nutrients, their chemical and physical treatment under exposure to digestive juices and the GIT motility, as well as digestive disorders.

The research goal was to develop a mathematical model of the duodenum as a specific section in the gastrointestinal tract; the model would be used for further prediction of areas with elevated risks of functional disorders.

Materials and methods. We consider the duodenum with peristaltic waves typically moving towards the small intestine with considerable contraction of the wall muscles (amplitude) [16]. The duodenum motility is periodic and parameters of peristaltic waves do not depend on food.

A developed mathematical model of the duodenum should describe properties of a fluid; therefore, it is necessary to examine chemical reactions that occur in this section of the intestines and that induce changes in the composition of chyme. The Figure 1 provides a simplified scheme showing how food is transformed due to effects produced by digestive juices and how their secretion is regulated by the neural and humoral mechanism.

According to this simplified scheme, endocrine and exocrine cells start to excrete cholecystokinin and secretin under exposure to introduced fats, proteins and carbohydrates. These two hormones stimulate secretion of bile components and enzymes of intestinal and pancreatic juices. Neural regulation occurs due to irritation of vagal and splanchic nerves that increase or reduce secretion of digestive juices. Therefore, components and enzymes that are necessary to decompose substances into simpler compounds start to be secreted in the duodenum due to neural and humoral regulation. Salts of bile acids and lipase decompose fats into monoglycerides. Hydrolysis of polypeptides down to amino acids occurs due to effects produced by trypsin, chymotrypsin, carcboxypeptidase, and aminopeptidase. Hydrolysis of complex carbohydrates down to monosaccharides occurs due to influence by amylase, maltase, and saccharose. As opposed to pancreatic enzymes, duodenum enzymes influence products of intermediate nutrient hydrolysis.

Therefore, chyme is considered a multicomponent viscous fluid consisting of (the index $i = \overline{0,\mathrm{I}}$) carbohydrates (starch) ($i = 0$), pancreatic amylase ($i = 1$), water ($i = 2$), glucose ($i = 3$), proteins ($i = 4$), polypeptides ($i = 5$), peptides ($i = 6$), aminoacids ($i = 7$), fats ($i = 8$), emulsified fats ($i = 9$), monoglycerides ($i = 10$), lipases ($i = 11$), trypsin ($i = 12$), carboxypeptidase ($i = 13$), salts of bile acids ($i = 14$), amino peptidases ($i = 15$), maltase, saccharose, lactase ($i = 16$). Hormones (cholecystokinin and secretin) are not components in the mixture and produce their effects through the circulatory system. The authors plan to consider their influence on the properties of digestion in further studies.

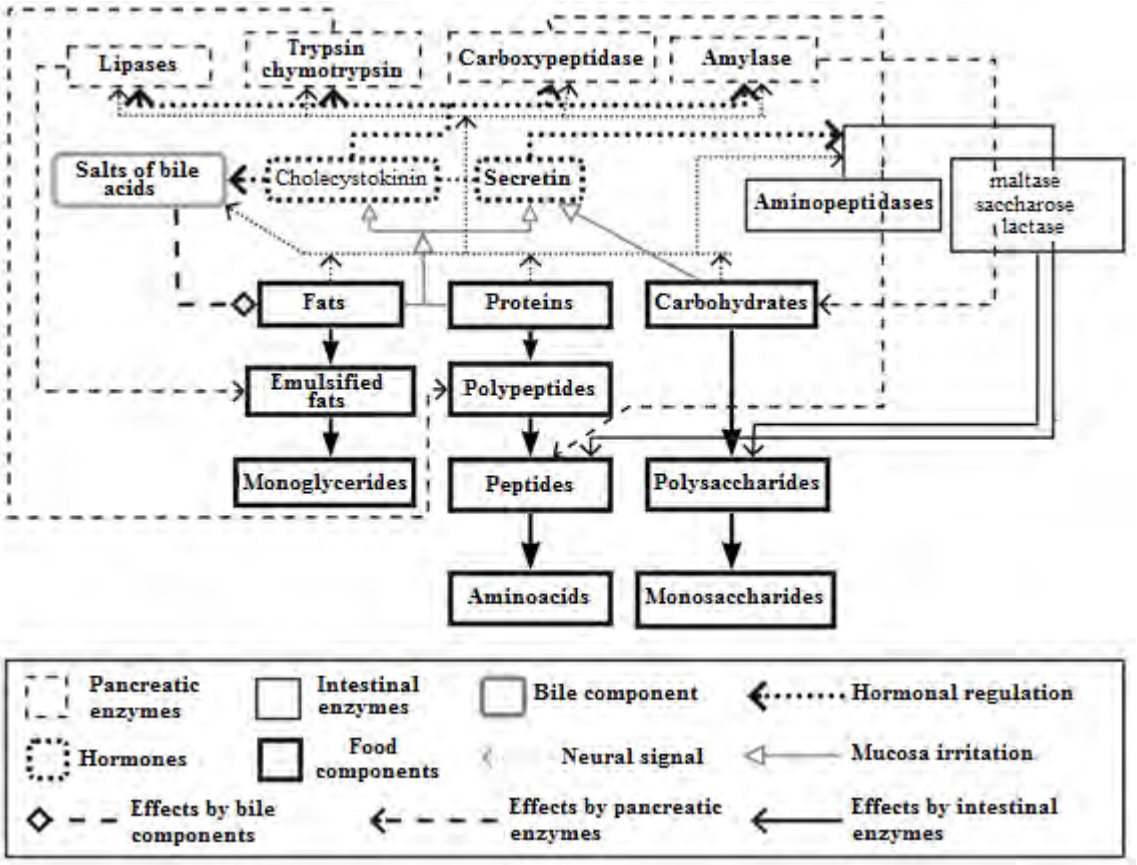

Figure 1. The scheme showing how food components are transformed in the duodenum

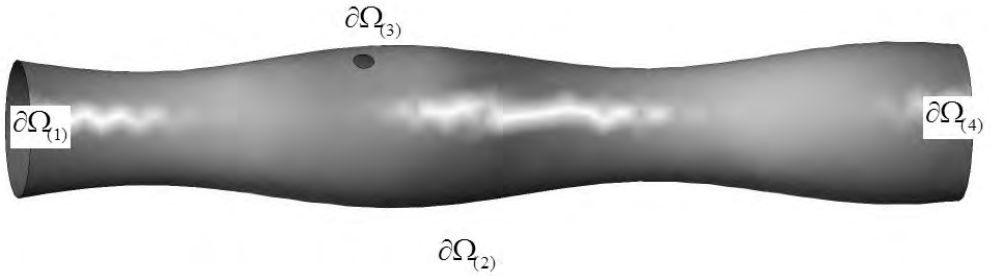

Figure 2. Sub-areas selected as per functional characteristics

The duodenum is divided into L areas where $\partial\Omega_{(1)}$ is the inlet section, $\partial\Omega_{(2)}$ is the area where intestinal juices are secreted and components are absorbed, $\partial\Omega_{(3)}$ is the area where bile and pancreatic juices are secreted (the major duodenum papilla), $\partial\Omega_{(4)}$ is the outlet section where the fluid leaves the duodenum (Figure 2).

Secretion of digestive juices and absorption of chyme components are described with mass effluents in a pipe in the wall layer. Functional disorders of secretion influence the intensity of mass effluents.

Mass conservation equations for various components in the mixture are given as follows considering mass effluents due to secretion and enzymatic reactions:

$$\frac{\partial}{\partial t}(\rho Y_{(i)}) + \nabla \cdot (\rho \mathbf{v} Y_{(i)}) = -\nabla \cdot \mathrm{J}_{(i)} + R_{(i)} + S_{(i)}, \quad (1)$$

$$r \in \overline{\Omega}, \quad t \in [0;T), \quad i = \overline{0,I},$$

where r is the radius vector of spatial points, m;

ρ is medium density, kg/m^3;

Ω is the interior of the whole area;

$\partial\Omega$ is the area boundary;

$\overline{\Omega} = \Omega \cup \partial\Omega$ is the closed area (the area interior and its boundary);

$\partial\Omega_{(l)}$ is the l-th boundary of the area, $l = \overline{1, L}$;

$\Omega_{(l)}$ is the area interior adjacent to the l-th boundary, $l = \overline{1, L}$;

$\mathbf{v}$ is velocity of particles in a medium, m/sec;

$Y_{(i)}$ is the mass fraction of the i-th component;

$\mathrm{J}_{(\mathrm{i})}$ is the intensity vector of the i-th component's mass flow due to diffusion processes, kg/(m^2·sec), $i = \overline{0, I}$;

$R_{(i)}$ is the intensity of the i-th component's mass effluent due to reactions between components, kg/(m^3·sec), $i = \overline{0, I}$;

$S_{(i)}$ is the intensity of the i-th component's mass effluent in the area due to secretion, kg/(m^3·sec), $i = \overline{0, I}$.

In a homogenous mixture, each component occupies its whole volume; a mass fraction (or a percent concentration of a substance) is a ratio of a mass of a dissolved substance to the overall mass of a solution. Its difference from a concentration is that this value is dimensionless and the following condition is met:

$$\sum_i Y_{(i)} = 1, \; i = \overline{0, I}. \qquad (2)$$

An impulse conservation equation for a viscous multi-component liquid is given as follows:

$$\frac{\partial}{\partial t}(\rho\mathbf{v}) + \nabla\cdot(\rho\mathbf{v}\mathbf{v}) = -\nabla p + \nabla\cdot\tau + \rho\mathbf{g},$$

$$\mathbf{r} \in \Omega, \; t \in [0; T), \qquad (3)$$

where p is pressure (Pa); τ is the deviatoric part of Cauchy stress tensor (Pa), which can be given as follows for a viscous incompressible liquid:

$$\tau = \eta(\nabla\mathbf{v} + (\nabla\mathbf{v})^T), \; \mathbf{r} \in \overline{\Omega}, \qquad (4)$$

where η is shear viscosity, Pa·sec.

The intensity vector of the i-th component's mass flow due to diffusion processes can be given as follows:

$$\mathrm{J}_{(\mathrm{i})} = -\rho K_{(i)} \nabla Y_{(i)}, \qquad (5)$$

where $K_{(i)}$ is the diffusion factor of the i-th component in the GIT cavity, m^2/sec, $i = \overline{0, I}$. At a first approximation, $K_{(i)}$ is assumed the same for all the components.

Molar concentration $M_{(i)}$ of the i-th component can be given as:

$$C_{(i)} = Y_{(i)}\rho / M_{(i)}. \qquad (6)$$

Enzyme secretion rate in the area l is determined by the following relation:

$$S_{(i)(l)} = s^0_{(i)(l)} + \frac{s_{(i)(l)}[\rho Y_{(i)}]_{(l)}}{s'_{(i)(l)} + [\rho Y_{(i)}]_{(l)}}, \qquad (7)$$

where

$s^0_{(i)(l)}$ is the baseline level of enzyme secretion (when any food is absent) in the area $\Omega_{(l)}$, kg/(m^3·sec);

$s_{(i)(l)}$ is the constant of the enzyme secretion rate in the area $\Omega_{(l)}$, which is equal to the maximum secretion rate, kg/(m^3·sec);

$s'_{(i)(l)}$ is the second constant of the secretion rate in the area $\Omega_{(l)}$, which is equal to the average mass concentration of those components that intensify secretion of a given enzyme at a moment when the secretion rate reaches a value equal to a half of the maximum secretion rate, kg/m^3;

$[\rho Y_{(i)}]_{(l)}$ is the average mass concentration of those components which enzyme secretion depends on near the tract wall, kg/m^3.

A mass effluent due to an enzymatic reaction is given as:

$$R_{(i)} = \frac{k_{(j)(k)} \rho^2 Y_{(j)} Y_{(k)} / M_{(k)}}{k'_{(j)(k)} + \rho Y_{(j)} / M_{(j)}}, \quad (8)$$

where $k_{(j)(k)}$, $k'_{(j)(k)}$ are the constants of the enzymatic reaction rate, 1/sec, kmol/m^3, $R_{(i)}$ takes a negative value for a reagent and a positive one for a reaction product;

$Y_{(j)}$, $Y_{(k)}$ are mass fractions of a substance and an enzyme;

$M_{(k)}$, $M_{(j)}$ are molar masses.

This formula is a Michaelis – Menten equation for describing the enzymatic reaction rate. The constant $k_{(j)(k)}$ is the limit of this rate; the second constant $k'_{(j)(k)}$ is equal to a concentration of a substance that enters the reaction at a moment when the reaction rate reaches a value equal to a half of its maximum rate.

The absorption rate for components in the mixture is determined as follows:

$$S_{(i)(l)} = -s_{(i)(l)} \left\langle [\rho Y_{(i)}]_{(l)} - h_{(i)} C^b_{(i)} \right\rangle, \quad (9)$$

where $s_{(i)(l)} > 0$ is the constant of the rate at which the *i*-th component is absorbed in the area $\Omega_{(l)}$, 1/sec;

$[\rho Y_{(i)}]_{(l)}$ is the average mass concentration near the tract wall *l*, kg/m^3;

$C^b_{(i)}$ is the mass concentration of the *i*-th chemical in blood, kg/m^3;

$h_{(i)}$ is the factor of proportionality that shows what ratio of concentrations is required to start diffusion.

In the developed model, it is assumed at this stage that particles in the mixture do not stick to the tract walls:

$$\mathbf{v}(t,\mathbf{r}) = \frac{d\mathbf{r}(t)}{dt},$$

$$t \in [0;T),\ \mathbf{r}(t) \in \partial\Omega_{(l)},\ l = 2,3, \quad (10)$$

where $\mathbf{r}(t) \in \partial\Omega_{(l)}$ is the radius vector of a material point on the duodenum wall. Values of mass fractions for components in the mixture $Y_{(i)} = Y^{\partial\Omega}_{(i)}$, the flow rate, and the conditions under which tangent components in the stress vector are equal to zero are set at the boundary $\partial\Omega_{(1)}$:

$$\mathbf{v}(t,\mathbf{r}) = \mathbf{v}_{in},\ \mathbf{t} - (\mathbf{n}\cdot\boldsymbol{\sigma}\cdot\mathbf{n})\mathbf{n} = \mathbf{0},\ \mathbf{t} = \mathbf{n}\cdot\boldsymbol{\sigma},$$
$$t \in [0;T),\ \mathbf{r} \in \partial\Omega_{(l)},\ l = 1,4.$$

The equation system is completed with the following initial conditions:

$$Y_{(i)}(t,\mathbf{r}) = Y^0_{(i)},\ \mathbf{v}(t,\mathbf{r}) = \mathbf{v}^0,\ \mathbf{r} \in \overline{\Omega},\ t = 0.$$

Results and discussion. This study involved performing a numerical experiment to describe hydrolysis of starch under exposure to amylase. The duodenum is considered a pipe, which is 0.28 m long and has a diameter equal to 0.04 m. Peristaltic waves typical for it have the following preset parameters: the period is 20 sec; the amplitude, 0.0035 m; the velocity, $5 \cdot 10^{-3}$ m/sec [17]. In case the motor function is deranged, these parameters may vary.

Chyme is considered a multi-component viscous liquid consisting of (the index $i = \overline{0,I}$) a carbohydrate (starch) (i = 0) and water (i = 2). As the mixture moves along the pipe, its composition starts to change due to effects produced by pancreatic amylase (i = 1); as a result, glucose is formed (i = 3).

The amylase secretion is described with a mass effluent in the pipe in the wall layer at the boundary $\partial\Omega_{(3)}$. The effluent is located 0.1 m away from the inlet section; the diameter of the opening is 0.006 m. The effluent intensity does not change over time.

The reaction rate constants are set as follows: $k_{(0)(1)} = 408$ 1/sec, $k'_{(0)(1)} = 10^{-3}$ kmol/m³ [18]. Molar masses of starch and amylase are taken from literature sources: $M_{(0)}$ = 828.7, $M_{(1)}$ = 54,000 g/mol [19]. The intensity of the

amylase effluent is considered equal to 0.01 kg/(m^3·sec) and it is 0.1 kg/(m^3·sec) for water, which corresponds to an active phase in intestinal digestion. The flow rate for the mixture at the inlet was taken as 0.001 m/sec and the starch molar fraction was considered equal to 0.05.

The previously formulated system of equations to describe digestion in the duodenum was solved using Ansys computation package. A time step was equal to $\Delta t = 0.1$ sec. A mixture of starch and water components was set at the initial moment. Figures 3–5 show how the mixture components are distributed in the pipe.

Figure 3 shows the mass fraction of starch at different moments. Obviously, as time passes, starch is distributed along the pipe, and its maximum concentration does not exceed 0.036; that is, not all the amount of starch enters a chemical reaction. The authors of the work [20] performed an experiment that produced the following results. Not more than 25 % of a 5 %-starch solution was transformed into glucose due to effects produced by amylase over a period equal to 11,000 sec. In our study, the numeric experiment lasted up to 600 sec since our goal was to analyze how the concentration of substances would be distributed allowing for a chemical reaction and components being mixed up due to the moving pipe walls.

Figure 4 shows a situation when glucose is formed due to effects produced by the moving walls that make the components mix and by amylase secreted in the area $\partial\Omega_{(3)}$. It occurs when the reaction time reaches 100 sec and the maximum concentration field for glucose is equal to $9.5\cdot10^{-6}$. Its value grows over time and reaches $2\cdot10^{-5}$ when the reaction time is 600 sec. An area where the concentration of the reaction product is higher is located near to the mass effluent but the concentration of the substance goes down closer to the outlet from the duodenum. This is probably due to time scales of the reaction rate being greater than the scales of the medium transfer; besides, water is pushed back into the pipe due to preset movement of its walls.

Figure 5 shows how amylase is distributed in the pipe. It induces a chemical reaction with glucose being its product. Obviously, as the reaction proceeds, amylase starts to fill in the channel. Its maximum concentration is equal to $3.3\cdot10^{-8}$. This secreted amount is enough to form glucose and its concentration is higher than the amylase concentration in the analyzed area when the reaction time reaches 600 sec.

According to the results shown in Figure 6, we can assume that, given the present peristaltic movement, there are areas where the velocity direction is inverse to the direction of the wave

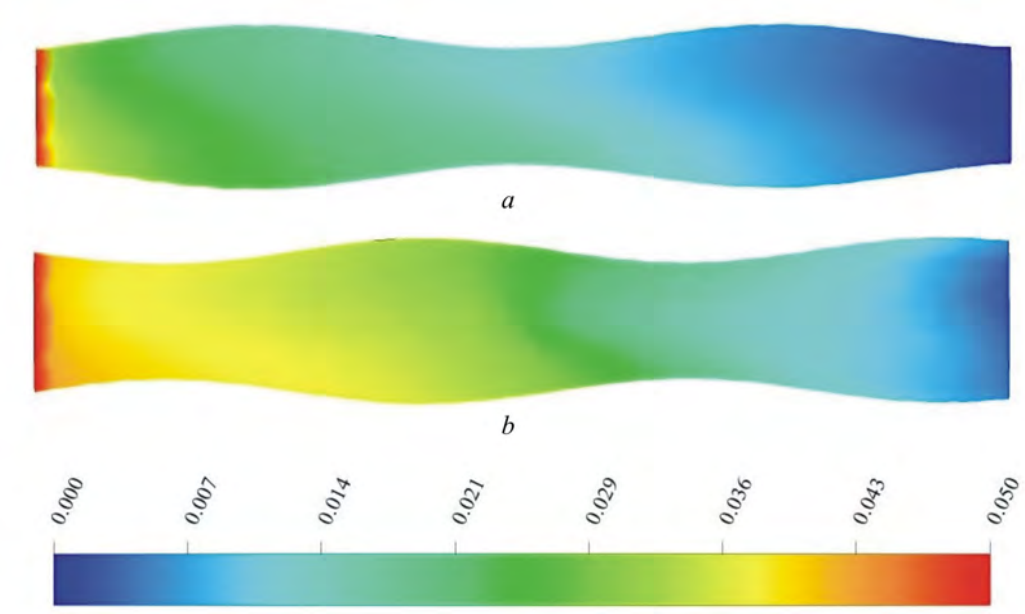

Figure 3. The mass fraction of starch at the moments a) 100 sec, b) 600 sec

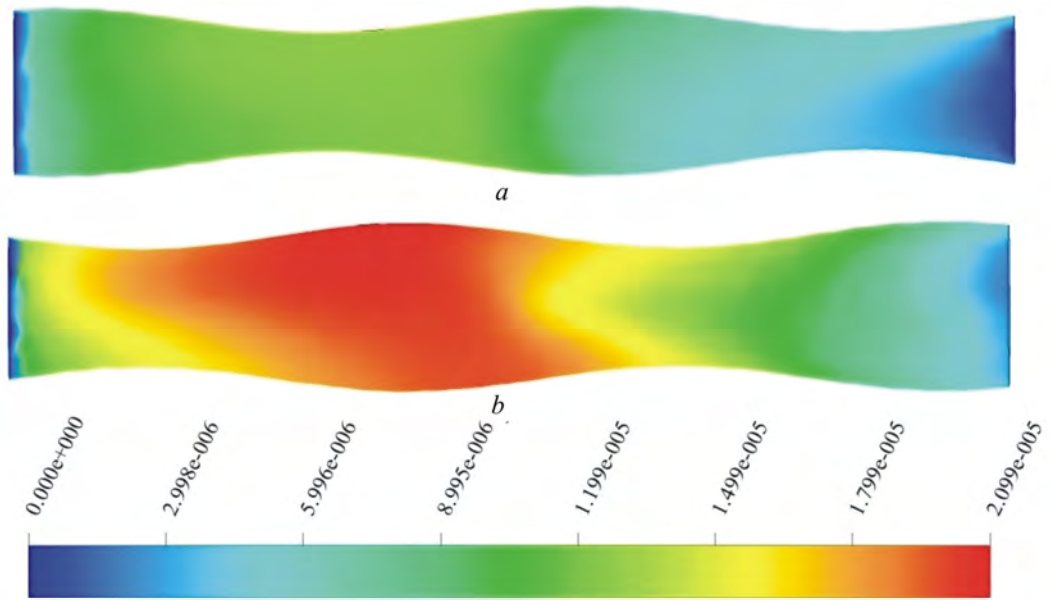

Figure 4. The mass fraction of glucose at the moments a) 200 sec, b) 600 sec

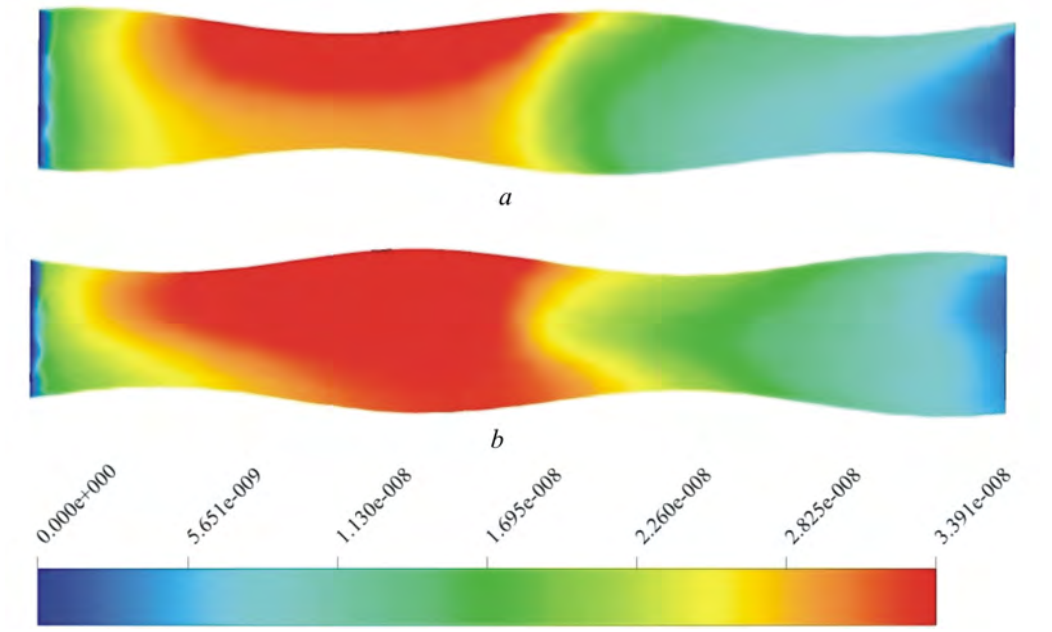

Figure 5. The mass fraction of amylase at the moments a) 200 sec, b) 600 sec

spread (at the points where the pipe contracts). Due to this effect, the components are mixed and the mixture itself is sent back into the pipe at 0.023 m/sec. The maximum flow rate is detected at the area where amylase is secreted (the wall effluent) at the moment when the wall contracts; this rate is equal to 0.07 m/sec. These results are in line with those described in the work [15] where the duodenum was modeled as a two-dimensional channel with moving boundaries; the velocity at the contraction area was the highest and equal to 0.05 m/sec.

Conclusion. The present work focuses on developing a mathematical model to describe the duodenum. The model considers conditions under which substances are being transformed, a shape and a size of an organ, typical features of intestinal peristalsis, and functional disorders in case there are any. It also covers absorption of substances and changes in the composition of a liquid when it moves along a pipe.

By now, mathematical and conceptual tasking has been developed; the section covering

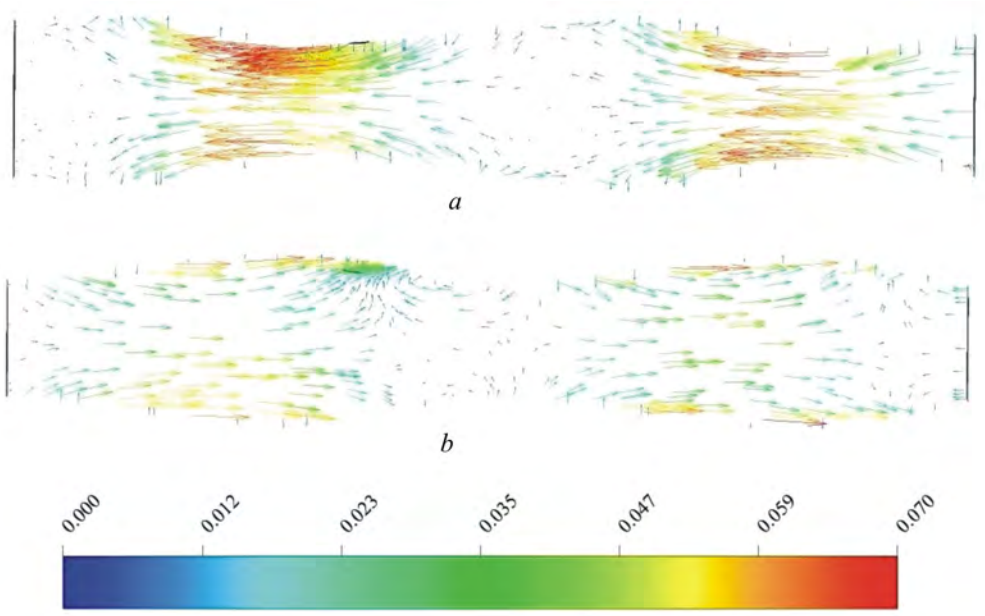

Figure 6. The velocity field (m/sec) at the moments a) 533 sec, b) 550 sec

the results describes an example how the model can be applied in a numeric experiment. To be exact, the experiment involves examining hydrolysis of starch in the duodenum allowing for peristaltic movement of the tract walls that make for the components in the mixture intermingling with incoming amylase. The study provides data on determined concentrations of the substances at different moments as well as the velocity field. As planned, the further studies will consider all the components and chemical reactions shown in Figure 1.

Another vital issue is to examine changes in physical and mechanical properties of a mixture during its flow. The next stage in the model development is expected to consider absorption and examine various scenarios with functional disorders of the secretory / absorption function and intestinal motility. Attention will also be paid to influence exerted by hormonal regulation through such hormones as secretin and cholecystokinin.

Results produced by examining how acidity is distributed in various parts of the duodenum are going to be of primary theoretical and practical importance. In future, the developed model can be applied as a noninvasive diagnostic method in clinical practice. Personal data may be used as a basis for predicting areas with elevated risks of functional disorders, ulcer formation and other defects in the tract mucosa. In addition, results produced by numeric modeling will facilitate detecting what disorders influence abnormal acidity in the duodenum thereby helping a physician to prescribe personified therapy and a diet.

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Competing interests. The authors declare no competing interests.

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