Dynamic characteristics of intraperitoneal perfusion

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Perfusion, i.e. the forced flow of a fluid through internal organs of a human body, is an interesting therapeutical method. It still has an experimental character. The paper is devoted to the laboratory investigations of hydromechanical aspects of a physical model of a human peritoneum combined with a hydraulic system, which forces the flow of a liquid through the peritoneal cavity. Main goals of the research were formulated on general and detailed levels. The first one was oriented towards the technical possibility and practical sense of physical modelling of medical procedures, whereas on the second level main hydraulic parameters of the process were investigated. The results of the research presented in the paper give the positive answers to both groups of problems. The method of physical modelling of the considered kind of processes seems to be quite reasonable. It allows us to establish the location of the inlets and outlets from the peritoneum during perfusion.

Key word: intraperitoneal perfussion, process modelling

Notation

c – actual concentration of tracer,
c_K – terminal concentration of tracer,
c_0 – initial concentration of tracer,
c_P – concentration of tracer in auxiliary point,
c_{WI} – concentration of tracer determined for ideal-mixing model,
c_{WR} – real concentration of tracer measured in outlet drain,
c_{WT} – concentration of tracer determined for plug-flow model,
d_D – diameter of drain,
D_M – coefficient of molecular diffusion,
D_T – coefficient of turbulent diffusion,

H – overpressure head,
L_D – length of conduit,
M – mass of injected tracer,
Q – discharge,
t – time,
t_{KC} – time at which $c = c_K$,
t_{KI} – maximal time of tracer flow,
t_{RC} – minimal time of tracer flow,
t_{PS} – mean detention time,
$\mathbf{u}$ – real velocity of flow,
u_D – mean inlet velocity,
V – volume of liquid in model,
Z – source function.

1. Introduction

The medical term *perfusion* denotes a forced flow of a fluid (e.g. blood, lymph or liquid medicaments) through internal organs or through selected regions of a human body. This paper is devoted to the hydromechanical aspects of the perfusion of peritoneum.

Therapeutic procedures, based on the perfusion, are not typical and to some extent still have an experimental character. For this reason it is really purposeful to investigate this basic process. The results of such a research should make it possible to find the most efficient method of the treatment.

The intraperitoneal perfusion considered is a method of chemotherapy applied in some cases of malignant tumours [1], [3], [4], [5], [9]. The method consists in rinsing the peritoneum with the liquid content of the system, which circulates in a closed circuit driven by a peristaltic pump. This content is a mixture of a saline (0.9% solution of NaCl, which is a main carrier of dissolved pharmaceuticals), small amount of natural body fluids and a prescribed dose of medicaments.

The circuit is created by an elastic conduit made of silicone (total length $L_D =$ 1.20 m, internal diameter d_D = 7.0 mm). Both ends of this conduit are divided (using distribution tees) usually into two tips, which are introduced into the peritoneum through incisions and serve as drains (two inlets and two outlets).

The dose of pharmaceuticals is injected into the system when the circulation of the working liquid is steady and stable. The essential condition of the proper course of this perfusion-based treatment is a possibly quick mixing of this dose with the circulating carrier. Denoting the total mass of the active agent by M and the total volume of the liquid by V, we can calculate the terminal concentration of this agent c_K using the following relation:

$$c_K = M/V . \qquad (1)$$

Real concentration of the medicament in the system $c(t)$ changes in oscillating manner from its initial value c_0 (in the dose injected into the circuit) up to the terminal

value c_K, as it is schematically shown in figure 1. The less the number of such cycles and the shorter the terminal time t_{KC}, the more acceptable the parameters of this therapy. t_{KC} should be several times shorter than the total time of the therapy (usually 90 minutes).
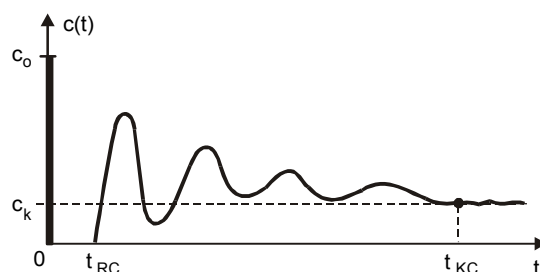

Fig. 1. The schematic of mixing of pharmaceuticals with circulating liquid

From the technical point of view the process described above can be reduced to the problem of distribution of the mass injected into the reactor. Such a reactor works in a closed system. Its shape is irregular and can change, as is bounded by a deformable coat. Because of the origin and functions of this "reactor" (human organism), it is impossible to intervene in its characteristics. So, the only possibility of regulating the system functioning is to match the technical parameters of the process under consideration. Especially important parameters are: localisation of drains (inlets and outlets) and discharge of the circulating liquid.

As was already mentioned, the method of perfusion is not a standard one. Besides, one has to remember that the laboratory investigations of the fluid-flow medical methods are not typical either. For this reason the purpose of this paper should be formulated on two levels:

1. *General level* – to show that the model testing in a technical laboratory gives possibility of simulating (with a medically accepted precision) the main elements of selected therapeutic procedures and can be applied in some situations (in this case, to the intraperitoneal perfusion).

2. *Detailed level* – determination of the dynamic characteristics of the investigated process and discussion of basic parameters of this method.

2. Description of the model tested

In order to identify the basic dynamic parameters of the object under consideration, the experiments described below were carried out in the open system (i.e. when liquid, leaving the system, was not turned back to the circuit and the model was continuously fed with a fresh liquid). Owing to such a decision it was possible to discuss the results comparing them with the results of classical methods of the theory of fluid-flow reservoirs and reactors (see point 4).

The model was made in a natural scale (1:1). The abdominal walls, glued with rubber (sheet thickness − 2.0 mm), were put in a rectangular plastic container (0.46 × 0.30 m). The bottom of this container was shaped in a form of the lower segment of the vertebral column, together with bulges of kidneys.
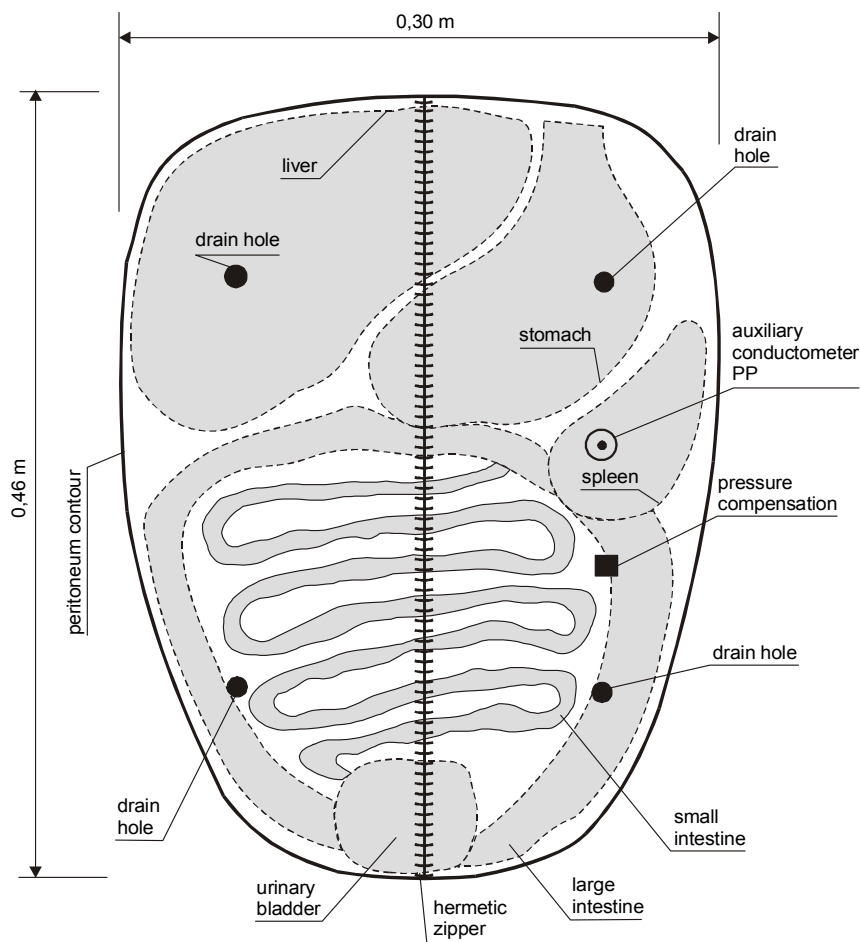

Fig. 2. The model of the peritoneum

Models of the internal organs, which are inside the peritoneal cavity (liver, stomach, spleen and intestines), were made of thin plastic foil filled with the mixture of granulated PVC and oil (figure 2). The mean density of these organs was the same as that of water, which secured their neutral buoyancy as in real human body.

Access to the interior of the model was provided with the hermetic zipper and 6 holes fitted out with liquid-sealed glands (4 − for drains, 1 − for auxiliary conductometer, 1 − for pressure compensation reservoir, see figure 2).

Four drain holes give opportunity to investigate six different variants of flow through the peritoneum (see figure 3).
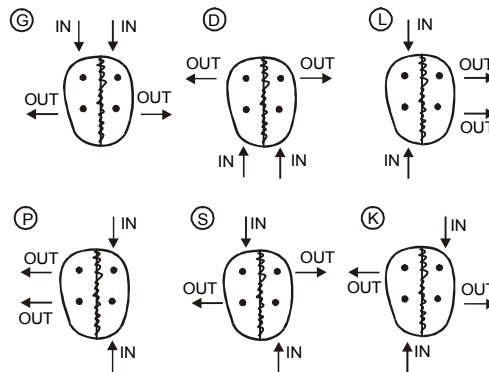

Fig. 3. Variants of the flow directions

The mass-transfer carrier (main component of the circulating liquid), i.e. the municipal water, was taken from the water-pipe network (figure 4). The discharge of flow was measured by means of a water-meter. The distributing tee was foregoing by a dosage device, which gives the possibility of injecting the dose of a tracer (water solution of NaCl, initial concentration $c_0 = 300$ g/dm^3) by means of a syringe. In order to stabilize and measure the pressure in the system, a compensation reservoir (of 2.0 dm^3 maximal volume) was connected with the model of the peritoneum.
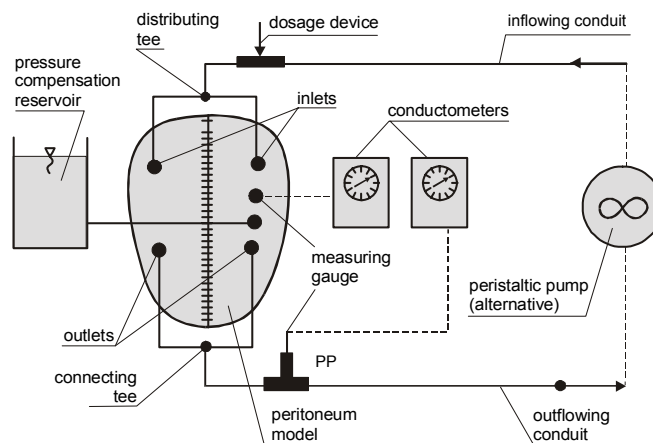

Fig. 4. Schematic view of the installation

Two outlet drains were put together by a connecting tee, and just behind this connector a concentration gauge was placed. This gauge measures the total concentration of the tracer leaving the model. The second gauge, an auxiliary one, was placed directly in the peritoneal cavity (point *PP* in figures 2 and 4).

3. Experimental

The model investigated is rather irregular in shape, which could change during the flow of the working liquid. It was caused both by the deformability of the outer coating and by the limited mobility of the internal organs. As a consequence, the repeatability of measurements was not perfect. However, one has to remember that this is not the defect of the model only, but also a very important feature of the original object (peritoneal cavity of a human body).

The scatter of results can be seen even in the values of the flow discharge. The experiment was carried out at two different intensities of flow. Mean values of these intensities were equal to

$$Q_W = 0.031 \text{ dm}^3/\text{s}, \quad Q_M = 0.018 \text{ dm}^3/\text{s}. \tag{2}$$

The individual discharges in each of 6 investigated variants of drains' positions (figure 3) are presented in figures 6 and 7.

In tests denoted by the symbol W (for the greater discharge Q_W), the overpressure head H_W was equal to 0.15 m above the upper level of the coating. In this case, the system capacity V_W was equal to 7.9 dm^3. In tests M (for lower discharge Q_M), the overpressure head was maintained on the level $H_M = 0.07$ m, which yielded $V_M = 6.8$ dm^3.

The measurements of the time-dependent distribution of concentration in the outlet and in the auxiliary point, recorded automatically, were repeated three times for each of 12 combinations investigated (6 positions of drains, each for two discharges). These three repetitions were averaged and the discussion was conducted on the basis of the mean functions $c_{WR}(t)$ and $c_P(t)$.

The volume of the tracer being injected into the system in each test was equal to 25 cm^3. Remembering that the concentration of the injected dose $c_0 = 300$ g/dm^3 we can state that the total mass of tracer for each test was $M = 7.5$ g. Computational terminal concentrations (figure 1, equation (1)) are:

$$c_{KW} = 0.95 \text{ g/dm}^3, \quad c_{KM} = 1.10 \text{ g/dm}^3. \tag{3}$$

4. Methods of the result analysis

The transformation of the dispersed mass concentration (figure 5) during the flow of mass-transfer carrier through the system (reservoir, reactor) can be described by means of the equation of unsteady advection–diffusion. In practice, almost always we have to do with turbulent conditions of flow, so the equation under consideration has the following form [8]:

$$\frac{\partial c}{\partial t} + \text{div}(c\mathbf{u}) = \text{div}[(D_M + D_T)\, \text{grad}\, c] + Z\,. \tag{4}$$
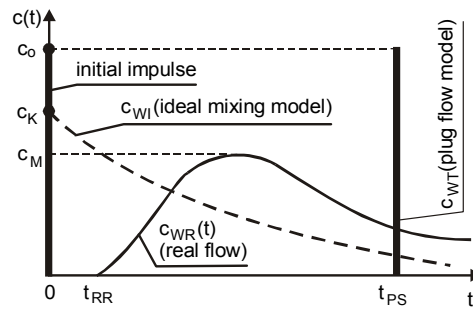
Fig. 5. Classical models of flow through reactors

When the velocity and concentration fields are regular enough to be partly averaged (with respect to one or two spatial variables), one can use the equation of dispersion [2], [8].

However, the shape of the object considered in this paper is so complex that this kind of mathematical tools is not suitable. So, as a level of reference for the discussion of results, two classical models were accepted – *the plug flow model* and *the model of ideal mixing* [6], [7]. Both these attitudes are of a limiting character – the first one completely neglects the relative mixing of the dissolved mass, whereas the second one assumes the immediate and full mixing of this tracer with a mass-transfer carrier.

In the case of the plug flow model, the transformation of the initial concentration c_0 into its terminal value c_{WT} is given by the following relation (see figure 4):

$$c_{WT}(t) = c_0(t - t_{PS}), \tag{5}$$

where the mean detention time is defined by the quotient

$$t_{PS} = V/Q. \tag{6}$$

The terminal concentration of the tracer in the outlet of the system with ideal mixing is described by the followingexpression [6], [7]

$$c_{WI}(t) = c_K \exp(-t / t_{PS}), \tag{7}$$

where the value c_K is given by equation (1).

With regard to the main goal of the process under consideration (quick and uniform distribution of pharmaceuticals in the peritoneum) the investigated object should behave as a reactor with ideal mixing. Any similarity with the plug flow model should be excluded.

5. Results of measurements

The averaged (for three repetitions) distributions of the outlet and auxiliary concentrations obtained during the experiments are shown in figure 6 (for the higher discharge Q_W) and in figure 7 (for the lower discharge Q_M).
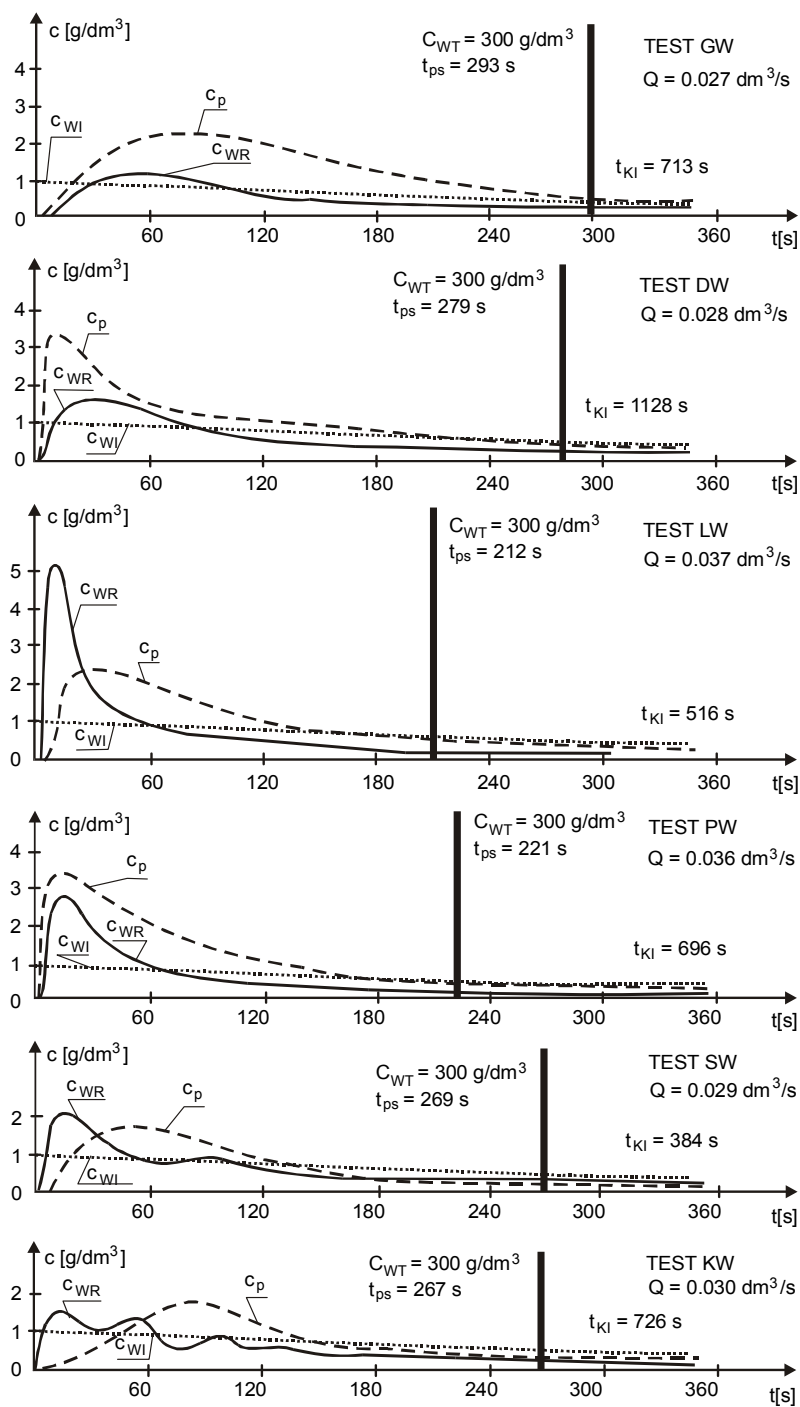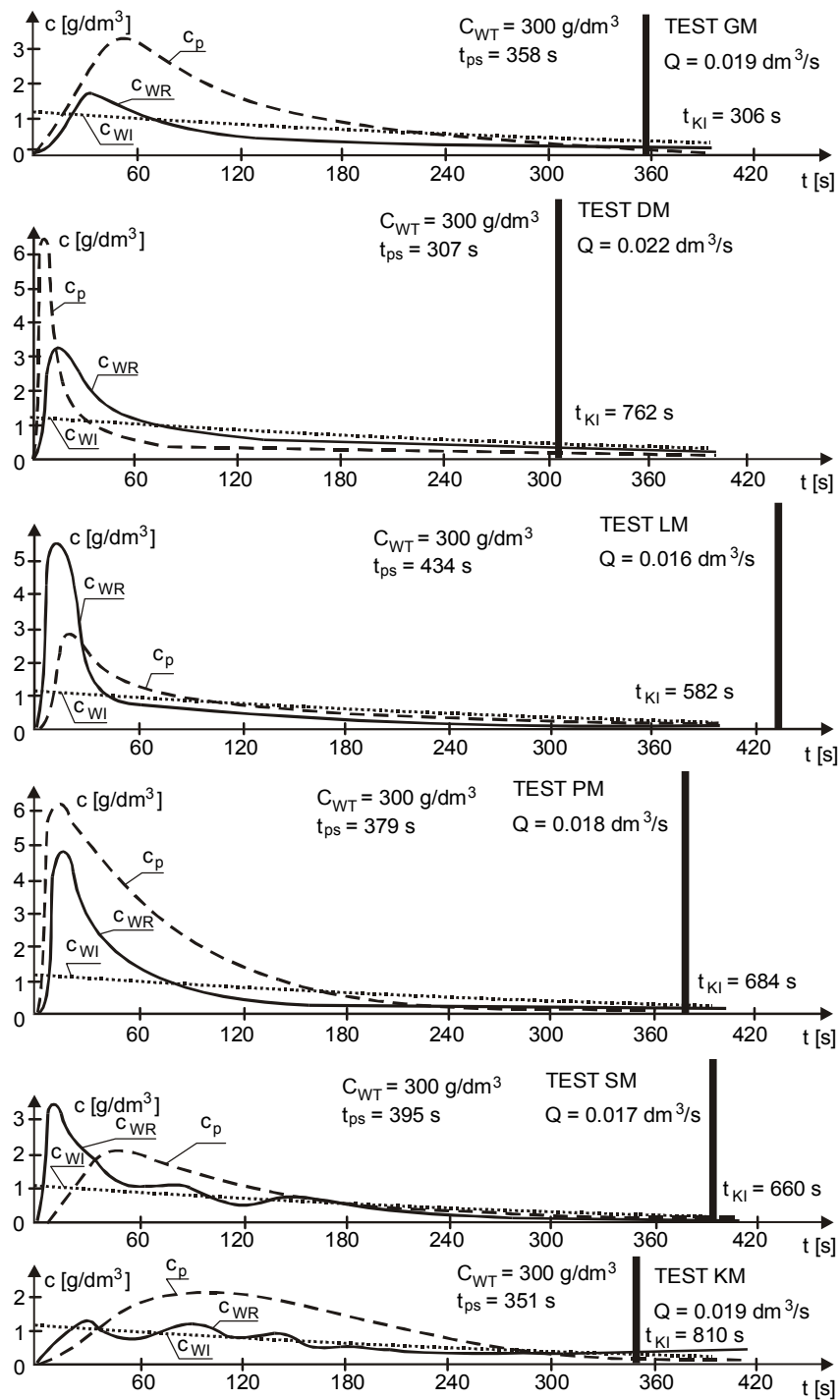
Fig. 6. Measured concentrations of tracer for discharge Q_W

Fig. 7. Measured concentrations of tracer of discharge Q_M

Four functions are drawn in each of 6 diagrams – concentration in the auxiliary point c_P (dashed line), concentration in the outlet c_{WR} (continuous line), theoretical concentration according to the ideal mixing model c_{WI} (dotted line) defined by equation (7) and position of the impulse, according to the plug flow model (for $t = t_{PS}$).

6. Discussion of results

A conservative tracer was used during the experiments (NaCl), so the total mass of this tracer M injected into the system is equal to the mass of the tracer which leaves this system, which can be written in the form of the equation

$$M = \int_0^{t_{KI}} c_{WR}(t) \, Q \, dt . \tag{8}$$

Making use of this expression, for 12 tests the terminal time (t_{KI}) of the rinsing the tracer out of the system was calculated. The integral in equation (8) was determined using the planimeter. The obtained values t_{KI} are shown in figures 6 and 7. As it is seen there, the main part of the tracer mass M leaves the system after the time much shorter than t_{KI}. The order of magnitude of this time is about $(0.2 - 0.3)t_{KI}$. Elongated "tails" of the concentration diagrams (resultant from the retention of the part of dispersed mass in "dead zones" and in boundary layer) are situated in the segment of rather small concentration, so do not significantly influence the mass balance and could be neglected during the analysis of results.

As it was mentioned in the point 4, the basic measure of the dispersion of tracer (which represents the pharmaceutical agents in real human body) in the system is a conformity between the real curve $c_{WR}(t)$ and the theoretical ideal mixing model given by the curve $c_{WI}(t)$. The level of this conformity for the majority of the cases investigated is not very high, although there are not big discrepancies. The lines obtained during the measurements for each case exceed theoretical lines $c_{WI}(t)$ in the initial segment of time, even several times. Obviously it indicates that the total capacity of the model is not fully covered with the flow field and it is an expected consequence of the flow conditions.

However, one can distinguish three situations (in 12 investigated cases), for which the conformity of the both runs under discussion is quite high. These are the tests GW (by the way, variant G is applied in practice at present), KW and KM (when both drains are placed "diagonally"). It is interesting that the outlet concentrations in variant K show apparent fluctuations, which do not appear in other cases. It is probably
a consequence of the opposite orientation of the inflowing streams. They "collide" in the model, which can generate the observed instability of the velocity and

concentration fields in the peritoneal cavity. This instability does not appear in other variants, even in the variant S, which is very similar to the case K. It can be due to asymmetrical configuration of internal organs. In the variant S, one of the inlet drains is placed just near the liver surface. This relatively large and coherent organ can stabilize the flow parameters.

From the functional point of view the fluctuations observed in variant K seem to be a positive factor, which provides for equalization of the tracer (or pharmaceuticals in real situations) concentration. Moreover, taking into account the quite fair conformity between two curves c_{WR} and c_{WI} in this case, one can formulate an important practical conclusion that just this variant is probably the most advantageous.

The analysis of the concentration in the auxiliary point PP also leads to some interesting conclusions. It is necessary to underline that the values c_P are not mean concentrations for the whole stream (as it was in the case of function c_{WR}), but are measured locally, in the neighbourhood of the gauge. Therefore one cannot use the balance relation (8) for this point. For the variants G, D and P the values of concentration $c_{WR}(t)$ are lower than values $c_P(t)$, and the tracer appears in the point PP before it can be observed in the outlet (although these differences are not very big). This is a logical consequence of the position of drains with respect to the point PP.

For series L and S we have just the opposite situation – the outlet concentration values are higher than the auxiliary ones and they appear earlier. This means that in these variants the point PP is placed out of the main zone of the flow. It is understandable especially for the variant L, when outlets and inlets of drains are placed at a quite short distance, so that they face each other.

The mixed situation we can observe in the case K. The tracer in the outlet conduit appears before it is measured in the point PP, but its concentration in this point is higher than the terminal one. Also this fact positively testifies to the variant K.

The influence of the discharge of circulating liquid (in the investigated range of two cases) on perfusion is rather weak. This becomes clear when we take into account the inlet velocity

$$u_D = 2\, Q/(\pi\ d_D^2)\,. \qquad\qquad\qquad (9)$$

For two drains, each of the diameter $d_D = 7.0$ mm, we have $u_{DW} = 0.41$ m/s and $u_{DM} = 0.24$ m/s. Since the distance between drains equals about 0.20 m, the differences between times of advection for different discharges are really small, and can be expressed in seconds.

The concentration of tracer for higher discharge Q_W in all the cases investigated is always lower than this variable for the smaller discharge Q_M. This is logical, as at high velocities the conditions of mixing of the tracer are much better, which

causes the faster drop of its concentration in the system. Taking into account that the intensities of advection applied at present in practice approach 1.60 dm^3/min, it seems that this parameter should not be changed. All the more because the higher velocity, the stronger the possibility that the internal organs of the patient can be damaged.

7. Conclusions

As it was underlined at the beginning of this paper, the goals of the research reported above should be formulated on two levels – general and particular.

It seems that the first level was fully attained. The course of the experiment and the results of measurements show that the laboratory simulation of the medical procedure under consideration is possible and gives the opportunity to analyse the influence of the important parameters on the effects of perfusion.

The experiments carried out in the hydraulic laboratory have also showed some limitations with regard to the sensitivity and resolution of the research method applied. And although these limitations restrain the range of possible particular conclusions, they are also an important source of information. It is a question of such factors as improving the technique of the internal organs' modelling (e.g. application of casting made of the liquid rubber), amplification of the measuring instruments (recording of discharge and concentration) and application of more effective peristaltic pump. Generally it is a question of a balance between the additional costs of the model and the improvement of the investigation accuracy.

The most concrete detailed conclusion is related to the configuration of drains. At present usually the variant G is applied in practice. Based on the discussion of the results one can say that the variant K seems better (when the inlets are placed near the stomach and in the lower right part of the peritoneum, and outlets – near the liver and below the spleen).

However, it seems that because of the variability of the active zone of flow in different positions of drains it would be interesting to consider the application of a mixed variant. The essence of this suggestion would be the change of the flow direction during the treatment. This can be done easily, using a combined system of switches that change the direction of flow in each drain, in each moment of time. However such a decision should be accepted by the specialists, who apply the method of perfusion in practice.

References

[1] CAVALIERE F., DI FILIPPO F., BOTTI C. et al., *Peritonectomy and hyperthermic antiblastic perfusion in the treatment of peritoneal carcinomatosis*, Eur. Jour. Surg. Oncol., 2000, No. 26.
[2] CZERNUSZENKO W., *Dyfuzja i dyspersja w korytach otwartych*, Arch. Hydrot., 1986, No. 3.

[3] FUJIMOTO S., TAKAHASHI M., MUTOU T. et al., *Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoperfusion combined with surgery*, Cancer, 1997, No. 79.

[4] KOBER F., HEISS A., ROKA R., *Diffuse and gross peritoneal carcinomatosis treated by intraperitoneal hyperthermic chemoperfusion*, Cancer Treat Res., 1996, No. 82.

[5] NICOLETTO M.O., PADRINI R., GALEOTTI F. et al., *Pharmacokinetics of intraperitoneal hyperthermic perfusion with mitoxandrone in ovarian cancer*, Cancer Chemiother. Pharmacol., 2000, No. 45.

[6] ORZECHOWSKI Z., PRYWER J., ZARZYCKI R., *Mechanika płynów w inżynierii środowiska*, Wydawnictwo Naukowo-Techniczne, Warszawa, 1997.

[7] PIEKARSKI M., PONIEWSKI M., *Dynamika i sterowanie procesami wymiany ciepła i masy*, Wydawnictwo Naukowo-Techniczne, Warszawa, 1994.

[8] SAWICKI J.M., *Przenoszenie masy i energii*, Wydawnictwo Politechniki Gdańskiej, Gdańsk, 1993.

[9] SPRATT J., ADCOCK R., MUSCOVIN M. et al., *Clinical delivery system for intraperitoneal hyperthermic chemioterapy*, Cancer Res., 1980, No. 40.