On the optimal choice of a hyperelastic model of ruptured and unruptured cerebral aneurysm

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In the last decade, preoperative modelling of the treatment of cerebral aneurysms is being actively developed. Fluid-structure interaction problem is a key point of such modelling. Hence arises the question about the reasonable choice of the model of the vessel and aneurysm wall material to build the adequate model from the physical point of view. This study covers experimental investigation of 8 tissue samples of cerebral aneurysms and 1 tissue sample of a healthy cerebral artery. Results on statistical significance in ultimate stress for the classification of 2 cohorts of aneurysms: ruptured and unruptured described earlier in the literature were confirmed \((p \leq 0.01)\). We used the four most common models of hyperelastic material: Yeoh, Neo-Hookean and Mooney-Rivlin (3 and 5 parameter) models to describe the experimental data. In this study for the first time, we obtained a classification of hyperelastic models of cerebral aneurysm tissue, which allows to choose the most appropriate model for the simulation problems requirements depending on the physical interpretation of the considered problem: aneurysm status and range of deformation.

An intracranial aneurysm (IA) is a cerebrovascular disease, which approximately occurs in 1 out of 50 people1,2. Usually unruptured aneurysms are discovered accidentally, and the techniques of surgery are controversial since the risks of postoperative complications and the risk of aneurysm rupture are comparable1,3. One of the main concerns of the modern neurosurgery is how to assess the risk of rupture of certain aneurysm and the urgent task of preoperative monitoring is determining the tactics for treatment of aneurysm depending on the dynamics of the development of such pathology. Modern methods of pre-operational computer modelling4–6 can be used for this task. For that kind of simulation, both 3D models with rigid walls and fluid structure interaction (FSI) models are used. The latter allow the most accurate consideration of the characteristics of the material of the wall of the cerebral aneurysm in solving FSI problem, but their complexity lies in determining the characteristics of the material of the wall of the cerebral aneurysm. In this study, we analysed 8 samples of cerebral aneurysms walls, belonging to 6 women and 2 men mostly of similar age. In addition to experimental data on cerebral aneurysm, we present a similar study protocol for the patient's healthy superficial temporal artery that was turned off from the circulation for microsurgical treatment of cerebral aneurysm. Data on the patients are given in Table 1.

The purpose of our work was to study the changes in the mechanics of the material of the wall of the cerebral aneurysm in the experiment and in mathematical modelling during the increase in engineering strain of the sample in uniaxial tensile test. Since in the majority of papers authors do not justify the choice of certain hyperelastic material model for modelling mechanics of IA, we intended to answer the question: which hyperelastic model should be used for a particular FSI numerical simulation problem? Our work provides the answer to this question in the context of ruptured and unruptured aneurysms, as well as depending on the level of deformation of the aneurysm tissue.

Materials and Methods

Clinical protocol. All cerebral aneurysm tissue specimens were harvested during the microsurgical clipping. This part of research was carried out in cooperation with Federal Neurosurgical Centre of Novosibirsk. The obtained tissue was preserved with saline 0.9% at +2 C–+5 C during transportaton(12–48 h). According to refrigerated vessel walls, being loaded, show slightly different results from freshly obtained tissue with relation to...
influence of friction on the measurement result. In the work16 zone of local deformations is observed visually, by each stage of the loading, the machine’s clamps returned to the original, program defined position. After every of the experiment for certain aneurysm specimen, its initial elongation was the same: i.e. after the completion of Considering the relaxation of the matrix during the experiments ensures that the true stresses in the sample are quickly degenerating under loading and becoming unfit for the further study, it was possible to carry out only one series of experiments for each sample. Speed of pulling was equal 1 mm per minute and was the same for all

Advantages of the technique described in8 as8,10,11 and others. This technique allows to locate the area of deformation of the biomaterial rather well. However, there are approaches with multiaxial loading12,13. The main difficulty in such approaches is the definition of the in the tissues, which essentially depends on the fixing of the material correctly, and not on its own properties15. The need to take into account this phenomenon was due to the complex fibrous microstructure of the aneurysm wall8,19. Significant role in the mechanics of such tissues is played by the matrix of a similar fibrous sample.

Table 1. Patient and specimen characteristics. Only circulation or systemic diseases are under consideration, such as: H – hypertension, Hep – hepatitis, D – diabetes, S – smoking, C – cholelithiasis, IS - ischemic stroke, HS – hemorrhage type stroke, Tbc – tuberculosis, A – bronchial asthma, UD – urolithiasis disease, O – obesity, Tbp – thrombophlebitis, PaF – paroxysmal atrial fibrillation.

| ID | Gender (Age) | Aneurysm location | Average thickness (MM) | Average width (MM) | Cross-sectional area (MM²) | Status | Strain limit (MPa) | Stress limit (MPa) | Risk factors |
|----|--------------|--------------------|------------------------|--------------------|-------------------------|--------|------------------|------------------|-------------|
| R. | M (60)       | TempA              | 0.4                    | 3                  | 1.2                     | Not applicable | 1.41559         | 2.4794          | IS          |
| K2.| F (55)       | MCA                | 0.05                   | 1.5                |                         | Unruptured     | 1.27639         | 1.09936         | H+Tbp+PaF    |
| V. | F (63)       | AComA              | 0.15                   | 3.75               | 0.56                    | Ruptured       | 1.06323         | 1.05493         | HS+UD       |
| Z. | F (48)       | MCA                | 0.2                    | 3.3                | 0.66                    | Ruptured       | 0.744889        | 1.00979         | HS+H       |
| U. | F (43)       | PIC(A)             | 0.25                   | 3.56               | 0.91                    | Ruptured       | 2.85794         | 1.00356         | HS+H+A      |
| K1.| F (63)       | MCA                | 0.3                    | 5                  | 1.5                     | Unruptured     | 4.6129          | 1.75217         | HS+H+D+D_{O_{equ}} |
| M. | M (38)       | AComA              | 0.7                    | 4                  | 2.8                     | Ruptured       | 1.30277         | 0.382825        | HS+H+S+Tbc  |
| U2.| M (44)       | AComA              | 0.6                    | 3.85               | 2.31                    | Ruptured       | 3.96535         | 0.33317         | HS+H+Hep+D+S+C |
| A1.| M (60)       | TempA              | 0.4                    | 3                  | 1.2                     | Not applicable | 1.41559         | 2.4794          | IS          |
| A2.| M (60)       | TempA              | 0.2                    | 1                  | 0.2                     | Not applicable | 1.37917         | 0.141357        | IS          |

Experimental setup protocol. Experiments aimed to determine the mechanical properties of the walls of cerebral aneurysms were first initiated in9. At present, there are several experimental approaches. The most common experimental approach is uniaxial loading on a tensile machine. A similar approach was used in such works as4,5,10,11 and others. This technique allows to locate the area of deformation of the biomaterial rather well. However, there are approaches with multiaxial loading2,13. The main difficulty in such approaches is the definition of the zone of two-dimensional deformation and a significant dependence on fixing the sample in the machine4,11. Even in the case when the technique of hooks is chosen, there are specific features of the propagation of a discontinuity in the tissues, which essentially depends on the fixing of the material correctly, and not on its own properties12. We selected the technique described in4 with applying the sandpaper to the clamps. An uniaxial tensile machine Zwick&Roell Z10 was used for mechanical testing of the samples. The special feature of this machine, unlike in the works4,5,10,11 was the vertical setup of the tensile test which minimises the influence of friction on the measurement result. In the work10 zone of local deformations is observed visually, by measuring the distance between the punctures in the tissue. In the10,17 the deformation is determined by change of the section – we used the same approach. Despite the fact that the first approach is more correct in the sense of taking into account the boundary conditions for fixation of the material, the second is also actively used in the experimental practice. This is due to the fact that set of parameters differs from work to work: storage conditions, model of a tensile machine, the environment of the experiment, the number of cycles used for pre-conditioning. Taking into account the high level of distinction between the characteristics of the tissue of aneurysms, the comparison of the strength properties of the walls of aneurysms obtained in our work is within the limits of the deviations described in11.

For each sample we performed a series of experiments each of those was divided into several stages. The number of steps varied from sample to sample, depending on the size of the current specimen (for very thin samples, only one step was possible, for extremely thick and strong samples – up to 10 stages). While carrying out the experiment, we took into account such a well-known phenomenon for biological tissues, as preconditioning18. The need to take into account this phenomenon was due to the complex fibrous microstructure of the aneurysm wall10,19. Significant role in the mechanics of such tissues is played by the matrix of a similar fibrous sample. Considering the relaxation of the matrix during the experiments ensures that the true stresses in the sample are correctly taken into account. We applied this technique for the initial stages (1th–5th stage for each elongation step depending on the sample), and during next stages the influence of this condition was not noticed. During our study we established that there’s no need to perform more than two preconditioning cycles. For each stage of the experiment for certain aneurysm specimen, its initial elongation was the same: i.e. after the completion of each stage of the loading, the machine’s clamps returned to the original, program defined position. After every stage of experiment the sample was moistened with physiological saline (Fig. 1). Since the aneurysm tissue was quickly degenerating under loading and becoming unfit for the further study, it was possible to carry out only one series of experiments for each sample. Speed of pulling was equal 1 mm per minute and was the same for all
experiments. In each experiment, the sample lost its elasticity. For each sample, its loading was performed until it was separated into two disconnected segments (or a visible discontinuity of the sample appeared).

Mathematical models of hyperelastic material of intracranial aneurysm. As many other live tissues, aneurysm samples were considered an hyperelastic material 10,17,20. The data obtained during the tensile

Table 2. Values of coefficients for all models used in this work in the moment of ultimate stress.
tests were used to construct mathematical models of the material of the cerebral aneurysm wall. We considered two Mooney-Rivlin models (3 and 5 parameter), Yeoh model and Neo-Hookean model. Computing the parameters for the models was performed with Wolfram Mathematica 11.3, Licence of LIH SB RAS. Using built-in Fit program function based on least squares method, the initial approximation was obtained, that served the base for approximation with a model. To construct the approximation we used the part of the curve up to the plateau zone, after which the zone of plasticity starts, and using the hyperelastic model for its modelling is inappropriate.

Gathered experimental data were analysed and processed, followed by plotting graphs for every specimen. Different stages were colour-marked, with colours corresponding to number of the stage (Fig. 2).

The Mooney-Rivlin model is a special case of the generalised Rivlin model:

$$W = \sum_{p=q=0}^{N} C_{pq}(I_1 - 3)^p(I_2 - 3)^q + \sum_{m=1}^{M} D_m(J - 1)^m$$

(1)

Where \( W \) – strain energy density function, \( C_{pq} \) – material constants related to the distortional response, \( D_m \) – material constants related to the volumetric response. As the conducted tension of aneurysm tissue in mechanic tests was uniaxial the mathematical models will be considered under that condition. Assuming the studied hyperelastic material is incompressible, this representation of Cauchy stress follows:

$$\sigma_{ij} = \frac{F}{S_0} = 2C_1\left(\frac{\lambda - \frac{1}{\lambda^2}}{\lambda}\right) + 2C_2\left(1 - \frac{1}{\lambda^2}\right) + 6C_3\left(\frac{1}{\lambda^2} - \lambda - 1 + \frac{1}{\lambda^2} + \frac{1}{\lambda^2} - \frac{1}{\lambda^2}\right).$$

(2)

$$\sigma_{ij} = \frac{F}{S_0} = 2C_1\left(\frac{\lambda - \frac{1}{\lambda^2}}{\lambda}\right) + 2C_2\left(1 - \frac{1}{\lambda^2}\right) + 6C_3\left(\frac{1}{\lambda^2} - \lambda - 1 + \frac{1}{\lambda^2} + \frac{1}{\lambda^2} - \frac{1}{\lambda^2}\right) +$$

$$+ 4C_4\left(1 - \frac{1}{\lambda^2}\right)\left(\frac{1}{\lambda^2} - 2 - \lambda\right) + 4C_3\left(\frac{1}{\lambda^2} - 2\right)\left(1 - \frac{1}{\lambda^2}\right).$$

(3)

where \( \sigma_{ij} \) and \( \sigma_{ij} \) are Cauchy stresses values and \( \lambda = \frac{F}{S_0} = \varepsilon + 1 \) – stretch ratio (while \( \varepsilon \) is engineering strain).

Certain conditions on Mooney-Rivlin parameters are necessary\(^{21}\) to satisfy the stability criterion:

$$\frac{\partial \sigma_{ij}}{\partial \varepsilon_{ij}} \geq 0, \quad \frac{\partial \sigma_{ij}}{\partial \varepsilon_{ij}} \geq 0,$$

(4)

where \( \partial \sigma_{ij} \) is the stress increment tensor associated with the strain increment tensor \( \partial \varepsilon_{ij} \) through the constitutive relation. The conditions caused by this limitation are as follows: \( C_1 + C_2 \geq 0 \) and \( C_3 \geq 0 \) for 3-parameter Mooney-Rivlin model, \( C_1 + C_2 \geq 0, C_3 \geq 0, C_4 < 0 \) and \( C_4 + C_5 + C_6 \geq 0 \) for 5-parameter Mooney-Rivlin model. We analyzed the applicability of various hyperelastic models both ways: with and without this criterion.

For Yeoh model corresponding formulas are:

$$W = \sum_{i=0}^{N} C_i(I_i - 3)^i,$$

(5)

and under the same assumptions, the Cauchy stress is represented by the formula:

$$\sigma = \frac{F}{S_0} = 2(\lambda - \lambda^{-3})(C_1 + 2C_2(\lambda^2 + 2\lambda^{-3} - 3)).$$

(6)

The last considered model was Neo-Hookean, for which in the same notation strain energy density function is:

$$W = C_1(I_1 - 3),$$

(7)

and the uniaxial stress is:

$$\sigma = 2C_1\left(\frac{\lambda - \frac{1}{\lambda^2}}{\lambda}\right).$$

(8)

where \( C_1 \) - linear part of elastic energy (Young modulus). We considered this most elementary hyperelastic model due to numerous papers\(^{22} \), where Neo-Hookean model is used for modelling the mechanics of cerebral aneurysm wall and solving the FSI problem.

At all cases the approximation of experimental data was carried out considering the non-negativity of linear coefficient in energy density formula. For Yeoh model coefficient \( C_1 \) defines the linear component of energy, while both \( C_1 \) and \( C_2 \) in summation define the non-linear component. Mooney-Rivlin models are significantly more complicated: even linear energy component is defined by several coefficients. As for 3-parameter model it is \( C_1 - 3C_2 \) and for 5-parameter least it is \( C_1 - 3C_2 - 6C_3 + 4C_4 \). That means Mooney-Rivlin models consider how the non-linear component affects linear component. When fitting the model curves to the experimental ones, we controlled the value of the coefficient in front of the linear term (we imposed the condition on the linear part that it cannot be negative), preserving the adequate physical nature of the hyperelastic model.

During the calculation the coefficients for various hyperelastic models describing a series of experimental data, we faced the problem of choosing an interval of strain ratio for describing the mechanical characteristics of
a material using different hyperelastic models. For all patients, this interval was different in terms of separate case and in terms of the loading stage (small deformations, average deformations, large deformations). We used the semi-robust technique to calculate the limiting value of the relative elongation (see Wolfram Mathematica module in the supplementary materials) for which the hyperelastic model approximates the experimental data with a given accuracy. To analyse the quality of fit we used value of normalised root mean square error (NRMSE), which is commonly used for such tasks

\[
NRMSE = \sqrt{\frac{1}{n} \sum_{i=1}^{n} \left( \frac{y_{ei} - y_{mi}}{\sigma(i)} \right)^2},
\]

where \( n \) is the number of experiment data points, \( y_{ei} \) is experiment value and \( y_{mi} \) the value of the model. The essence of the error calculation method is the standard normal deviation.

**Results**

As a result of experimental data processing Table 2 was created where coefficients of Yeoh, Neo-Hookean, and 3 and 5-parameter Mooney-Rivlin models are shown at the moment of maximum relative elongation, as it was done in \(^{10,17} \), while the approximation was still accurate enough.

After analysis it turned out that Mooney-Rivlin models do not have any significant advantages over Yeoh model for small strain values. However as strain value increases, Yeoh model stops to approximate experimental data sufficiently. As it is shown on Fig. 3 even 3-parameter Mooney-Rivlin model does not approximate with satisfying accuracy, with little relation to usage of stability criterion. Only 5-parameter Mooney-Rivlin model adequately approximates experimental data for both small as well large strain values.

Complex models, such as ones described in \(^{23} \), have much wider range of usage, however they start to approximate the experimental data well enough only starting with quite big values of relative elongation (\( \lambda > 1.76 \)) \(^{24} \), while the approximation was still accurate enough.

The analysis of the results on the limits of hyperelastic models applicability summarised on the Figs 3 and 3 show a good applicability of hyperelastic models both at the stages when the elastin matrix carries the main tension load, and at the beginning of that zone when only collagen fibers bear the loading.

Figure 4a shows that the zone of large deformations (\( \lambda > \lambda_a \)) when in the fibrous structure of the sample is mainly involved in the loading) captures only the MR5 model, whereas at small deformations (\( \lambda < \lambda_a \)) the Neo-Hookean model shows good applicability to both ruptured and unruptured aneurysms. In the interval (\( \lambda_a < \lambda < \lambda_b \)) we observe different mean values, which are shown by the Neo-Hookean and Yeoh models for ruptured and unruptured aneurysms, respectively. The result is especially interesting because the struggle of choosing the best model happens around the interval (\( \lambda_a < \lambda < \lambda_b \)), which characterizes the involvement in the mechanical work of the elastic matrix, fiber or both, as shown in \(^{25} \).

We have also carried out the comparison for ultimate stress and strain (see Table 3) for two cohorts of experimental samples (ruptured and unruptured), as it was done in \(^{17} \). The Mann-Whitney test for small samples was chosen and showed no statistically significant difference for ultimate strain was discovered for specimens from our research even for \( p \leq 0.05 \), while there was shown statistical significance for differences in values of ultimate stress for \( p \leq 0.01 \).

It turned out that various hyperelastic models describe experimental data for ruptured and unruptured aneurysms at completely different \( \lambda \) intervals. Ruptured aneurysms are characterized by good approximation of the considered models in the zone of small and medium deformations (see Fig. 4b), at the same time for unruptured aneurysms the considered models work for small, medium, and large deformations. Basing on the obtained histograms on Fig. 4b we created the Table 4 of recommendations on choosing the hyperelastic model depending on the particular task.

**Discussion**

It is worth noting a few limitations that were present during this work. First limitation was performing the test in air, rather than in a thermostatic bath, as such tests were conducted in \(^{10,16,17} \). However, we are convinced that such study is relevant for a number of reasons. First, in modern neurosurgical practices there are many methods in which a blood vessel remains "dry" (not filled with blood, and in the absence of perivascular space substance).
for a long period of time (up to several hours) while being periodically moistened with saline, and fully restores its physiological properties after the resumption of blood flow and perivascular environment. Second, paper 20 presents the results of comparing the experimental data of mechanical tests with specimens in the air and the saline, which do not show a significant difference. Therefore, conducting an experiment in such setup plays an important role. Restoration of mechanical properties was not described in the literature, and in the course of performing the experiments described in our work, we resorted to wetting the sample located in the clamps with saline (0.9%) using a spray bottle. Besides, as the practice of such studies shows16,17, the mechanical properties of samples of intracranial aneurysms have a very high diversity depending on the conditions of the experiment, and it only makes sense to compare different sets of mechanical properties of intracranial aneurysms, ruptured and unruptured, measured under the same conditions, as it was done in this work.

Another aspect limiting this study is the uniaxial approach to the mechanical experiment, as the walls of the vessels are essentially anisotropic material even in the case of healthy vessels, not to mention a cerebral aneurysm which wall has more complex structure19. We considered hyperelastic models in the work on the assumption that the material of the wall of the cerebral aneurysm is homogeneous, which is more natural for constructing the most common grids in the literature for modelling material, since assuming the structure of the material
is fibrous, it would be more correct in this case to consider the hierarchy of models of GOH type (generalized Ogden-Holzapfel models), which is partly done in25. An obvious solution to this problem is a biaxial mechanical experiment. However, as many studies show, there are many problems when performing an experiment in this case: from choosing the shape of the test sample to choosing the method of fixing the material and analysing the deformation zone. In particular, it was shown that the zone of two-dimensional deformations with a biaxial test is extremely small, which, together with the extremely small size of tissue samples of the wall of cerebral aneurysms, makes conducting such an experiment difficult. The semi-biaxial test is known15, however, a significant limitation with respect to this type of research is the required size of the sample (the sample must be wide enough), which is almost impossible to achieve with intracranial aneurysms.

The software of the machine we used did not allow to measure the relaxation of material during its restoration to original state after each measurement. A series of experiments with consistent increase in the engineering strains of the material in the course of the experiment is, in fact, analogous to the natural growth of aneurysm and thinning of its wall. The purpose of such experiments is to assess the changes in the mechanical characteristics of an aneurysm with its growth (Fig. 2).

In the course of conducting experiments and analysing the obtained results, we were convinced that the obtained experimental results in general correspond to the results already described in the literature. Of course, the results obtained (strain-stress relationships, Neo-Hookean, Yeoh, and Mooney-Rivlin parameters) differ from those given in the literature10,17,20, however, as mentioned above, for example, in17, the significant factor in comparing the results is the conditions of experiment: used tensile testing machine, method for determining the deformation of the material, control of temperature and humidity of the material, method of conservation before experiment. In particular, in25, the advantages of choosing the dog-bone shaped type of specimen to achieve its rupture in the centre (in length) rather than near the clamps are shown. However, this form of material has several drawbacks: it is necessary to take into account that even when considering hyperelastic models of sample mechanics, in fact, the test material is fibrous and similar excision leads to an uneven distribution of fiber families (with angle to the central axis) in the sample along its length, which makes it impossible to correctly process the results of an experiment only when controlling the deformation. However, it is worth noting that this technique is good for observing the rupture front in the sample, since the point of rupture is determined by sample's shape. In our case the measured geometric characteristics of the sample which allow us to calculate stresses correctly, have more important role. The choice of the direction of deformation relative to the main direction of collagen fibers in the sample may be another important factor. Collagen fibers, as shown in the literature, have a Poisson distribution and preserve that distribution under moderate uniaxial tension26.

Figure 5. Specimen in tensile machine.
In the work\textsuperscript{16} one can observe the punctures in the sample, which are necessary to control the change in true strain value. In our protocol, since it was not possible to capture the measurements visually, we minimised the distance between clamps to lower the effects of edge disturbance.

The methods currently used, like punctures of a sample, also have their limitations, namely: the puncture point is prone to unpredictable deformation, which does not allow us to unambiguously judge the correct tracking of deformation markers. To eliminate the limitations associated with the methods used in the work, one should more accurately take into account the deformation of the sample. Namely, it is proposed to develop a technique for gluing markers and tracking their movement, as is done, for example, in\textsuperscript{27}. A similar approach will allow to obtain true uniaxial deformation of samples with minimal impact of edge effects.

The measurement of the change in the shape of the sample (cross-sectional area in various places) after the test was not carried out, since we have not seen such data anywhere in the reviewed literature. However, we believe that the assessment of such changes will allow verification with the results of maximum wall displacements and stresses on it by FSI calculations. Such a measurement could be carried out using a notched substrate for an aneurysm sample and using 2 video extensometers located on the sides of the sample during a mechanical test. Thus,
ruptured and unruptured aneurysms. The calculated constants of hyperelastic models were substantially different in comparison with the case of both importance of controlling the main direction of the distribution of fibers in the material during the experiment. strain in tension of two adjacent parts of the artery in axial and circumferential direction. This suggests the was demonstrated, this work focuses precisely on the tissues of cerebral aneurysms. References

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Additional Data. In this section, we provide additional information that may be useful.

Method of measuring geometric characteristics. As shown in Fig. 7, the sample, while measuring its geometric characteristics, is lying freely on the clamps, which in turn are located on the engineering paper and the laminated substrate. In the case when there was insufficient natural light, the measurement zone was illuminated with an LED lamp. The sample was measured mechanically using an electronic caliper, as well as visually (relatively), against a background of engineering paper, the data of both measurements were averaged. The thickness of the sample was measured using an electronic caliper with a decrease in the gap between the measuring girths until the condition for the onset of deformation of the sample was reached.

Data availability

All initial data on the force, absolute elongation of the samples, as well as the geometric characteristics of the samples are available for public download.

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Author contributions

Contribution of the authors D. Parshin - the idea of the research, analysis of the results, mechanical experiment, manuscript draft preparation; A. Lipovka - processing of experimental data, manuscript draft preparation; A. Yunoshin - a mechanical experiment, a critical review of the study; A. Dubovoy and K. Osvyannikov - extracting IA, discussing medical aspects, A. Chupakhin - critical review of the study.

Competing interests

The authors declare no competing interests.

Additional information

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