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MODELING AND CORRELATION OF PLAQUE SIZE WITH HISTOLOGICAL AND BLOOD ANALYSIS DATA FOR ANIMAL RABBIT EXPERIMENTS

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Abstract. *Atherosclerosis is becoming the number one cause of death worldwide. Animal experiments are very important to better understand physiological conditions for atherosclerosis development. We here examined influence of wall shear stress (WSS), histological and blood analysis data on the atherosclerosis lesion development for animal model. The histological cross-sections and blood analysis (cholesterol, HDL, LDL and triglycerides) data are provided from study of 19 rabbits fed by atherogenic diet at Cambridge University, within the ARTreat project research (www.artreat.kg.ac.rs). The Navier-Stokes and continuity equations were the governing equations for modeling fluid dynamics in the lumen. Convection diffusion equations were used for modeling LDL transport. For coupling fluid dynamics and solute dynamics Kedem-Katchalsky equations were used. Four regression models: multiple regression, polynomial regression, factorial regression and response surface regression are used for fitting experimental data for the plaque size. These models showed strong correlation between plaque size and input experimental data. The results represent a progress in the assessment of stroke risk for a given patient's geometry and blood analysis data.*

1 INTRODUCTION

Atherosclerosis is a disease of the large arteries characterized by the blood vessel endothelial dysfunction and lipid, cholesterol, calcium and cell elements accumulations inside blood vessel wall. It is commonly referred as plaque formation, vascular remodeling, acute and chronic obstruction of blood vessel lumen, blood flow disorder and lower oxygenation of relevant tissues. Many studies confirmed different risk factor which contributes development and spreading of the atherosclerosis, the most common are hyperlipidemia, higher blood pressure and sugar values, cigarette consumption, age and sex. Great contribution to atherosclerosis development gives mechanical quantities such as low shear stress areas which causes endothelium dysfunctions and atherogenesis [1]-[3].

In order to simulate stenosis, collars have been placed around the carotid arteries for each of 19 rabbits. After that, rabbits have been fed by atherogenic diet at Cambridge University. In order to measure plaque size proximal to collar, these rabbits were sacrificed after 8, 12 and 16 weeks of atherogenic diet. In this way, we obtained data about plaque progression in three different time steps. We also did 3D reconstruction of these arteries and calculated WSS distribution by using CFD simulations. We modeled relationship between WSS and blood analysis data (cholesterol, HDL, LDL and triglycerides) on one hand and plaque size, determined from histology, on the other hand. Four different regression models have been tested for modeling this relationship: multiple regression, factorial regression, second order polynomial regression and response surface regression [4,5]. The goal of this paper is to optimize regression models according to experimental data and wall shear stress distribution, calculated from CFD simulations.

2 MATHEMATICAL MODEL

In order to simulate blood flow through rabbit's carotids we generated 3D finite element models by using IVUS medical images [6]. Wall free model were used for simulating blood flow in the lumen. This model treats wall as rigid. All nodes that represent the wall and inlet of the artery are totally constrained. Also initial velocities are prescribed at inlet nodes. Fluid is assumed to be steady, incompressible and laminar. For modeling fluid dynamics in the lumen Navier-Stokes equations were used (1), (2):

$$-\mu\nabla^2 u_l+\rho\left(u_l\cdot\nabla\right)u_l+\nabla p_l=0 \tag{1}$$

$$\nabla u_l=0 \tag{2}$$

where u_l is blood velocity, p_l is pressure, μ is blood dynamic viscosity and ρ is blood density.

By using 3D simulations we calculated wall shear stress distribution for all 19 rabbits. Figure 1 shows wall shear stress distribution for rabbits 5, 6, 7 and 8. It can be observed that all rabbit geometries have at the collar position narrow zone where shear stress is high. Also the zone between start and end collar points is more narrow than zones before and after collar position. That directly has influence on the shear stress distribution where mostly low shear stress zones are before and after the collar. These zones are highly risk for plaque formation and development. We have chosen to observe the zone proximal to collar, and tried to find correlation between plaque size (in this zone) on one hand and wall shear stress and blood analysis data on the other hand. In order to find this correlation we used different general regression models: multiple regression, factorial regression, polynomial regression and response surface regression.

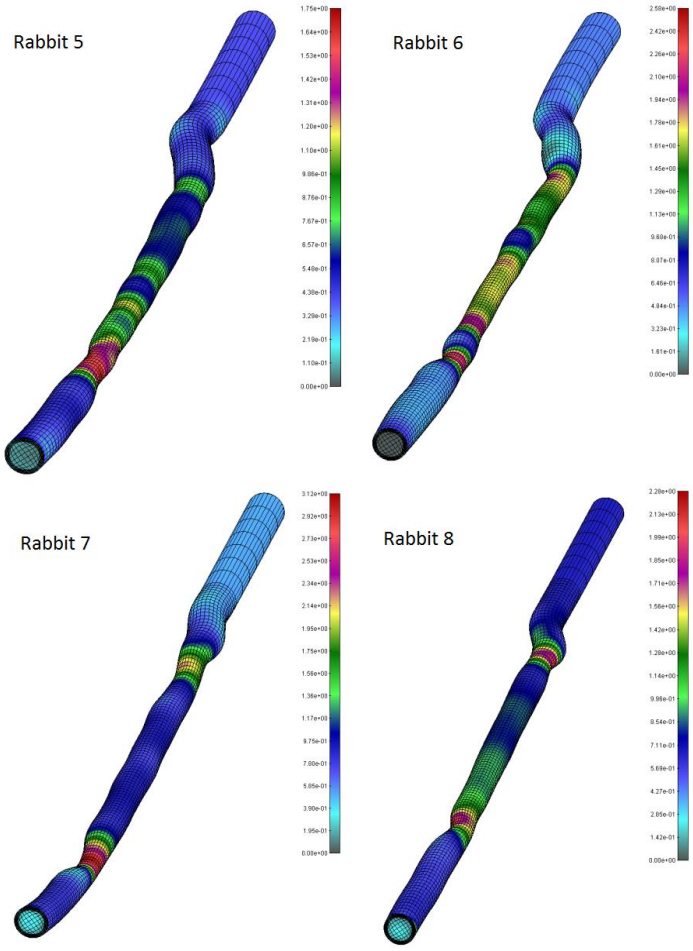

Figure 1: Wall shear stress distribution for rabbits 5, 6, 7 and 8.

3 FITTING DATA

In this section we try to model relationship between blood analysis data (cholesterol, HDL, LDL and triglycerides) and WSS on one hand and plaque progression on the other hand. In order to model this relationship we used multiple regression, factorial regression, polynomial regression and response surface regression. Table 1 contains data we used to model this relationship.

Rabbit ID	INPUTS						OUTPUT
	Time [weeks]	WSS [Pa]	Cholesterol [mmol/L]	HDL [mmol/L]	LDL [mmol/L]	Triglycerides [mmol/L]	$\frac{A_{endothelial}}{A_{intima}+A_{media}}$ [%]
Rabbit 3	16	1.39	8.1	0.98	6.6	1.1	8.635
.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.
Rabbit 16	12	5	34.6	0.7	32.4	3.2	14.195
.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.
Rabbit 19	8	2.47	7.5	0.87	6.4	0.5	7.62

Table 1: Data Used to Fit Regression Models.

As can be seen from table 1, as a measures of plaque size we used $\frac{A_{\text{endothelial}}}{A_{\text{intima}}+A_{\text{media}}}$, where $A_{\text{endothelial}}$ is plaque area inside endothelium, A_{intima} is intima area and A_{media} is media area.

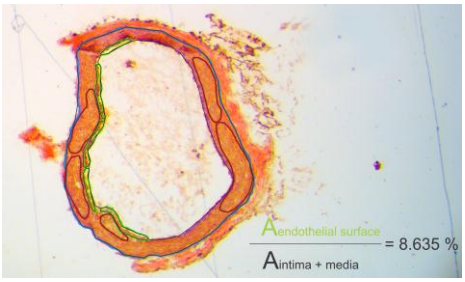

Figure 2: Carotid artery cross section for rabbit 3.

The following regression models have been tested:

- Multiple regression:

$$OUTPUT = a_0 + \sum_{i=1}^{6}\left(a_i \cdot INPUT_i\right) \tag{3}$$

- Second order polynomial regression:

$$OUTPUT = a_0 + \sum_{i=1}^{6}\left(a_i \cdot INPUT_i + b_i \cdot INPUT_i^2\right) \tag{4}$$

- Factorial regression:

$$\begin{aligned} OUTPUT = a_0 + \sum_{i=1}^{6}\left(a_i \cdot INPUT_i\right) + \\ \sum_{i=1}^{6}\sum_{j=1}^{6}\left(c_{i,j} \cdot INPUT_i \cdot INPUT_j\right); \forall i \le j : c_{i,j} = 0 \end{aligned} \tag{5}$$

- Quadratic response surface regression:

$$\begin{aligned} OUTPUT = a_0 + \sum_{i=1}^{6}\left(a_i \cdot INPUT_i\right) + \sum_{i=1}^{6}\left(b_i \cdot INPUT_i^2\right) + \\ \sum_{i=1}^{6}\sum_{j=1}^{6}\left(c_{i,j} \cdot INPUT_i \cdot INPUT_j\right); \forall i \le j : c_{i,j} = 0 \end{aligned} \tag{6}$$

where

$$INPUT = \begin{bmatrix} Time \\ WSS \\ Cholesterol \\ HDL \\ LDL \\ Triglycerides \end{bmatrix},$$

and $OUTPUT$ is $\frac{A_{\text{endothelial}}}{A_{\text{intima}}+A_{\text{media}}}$.

Coefficients a, b and c from equations (3)-(6) are determined by using INPUT-OUTPUT data (table 1). We used a simplex optimization method developed by John Nelder and Roger Mead [7] to reach the best fit. This method involves only function evaluations (no derivatives).

Regression models have been tested by using leave-one-out cross validation procedure. As a measure of accuracy we calculated relative mean squared error:

$$RMSE = \frac{(p_1 - t_1)^2 + \cdots + (p_n - t_n)^2}{(t_1 - \bar{t})^2 + \cdots + (t_n - \bar{t})^2} \tag{7}$$

where p_i is i-th predicted value of the output, t_i is i-th target value of the output and $\bar{t}$ is average value of the output

$$\bar{t} = \frac{1}{n}\sum_{i=1}^{n} t_i$$

The RMSE represents the ratio between total squared error of our model and total squared error of default predictor (i.e. a model which always predicts an average output value). The value of RMSE less than 1.0 indicates that the model is useful [8]. The lower the RMSE, the more accurate is the model. Table 2 shows relative squared error and correlation coefficient values for all four tested regression models. We can conclude that all four regression models are useful (RMSE<1). Also, we can conclude that polynomial regression model gave the best result among tested (RMSE=0.408).

Regression model	RMSE	Correlation coefficient
Multiple regression	0.801	0.573
Polynomial regression	0.408	0.792
Factorial regression	0.480	0.772
Response surface regression	0.562	0.711

Table 2: Relative Squared Errors for Tested Regression Models.

Results of polynomial regression model compared with experimental results are depicted on figure 3.

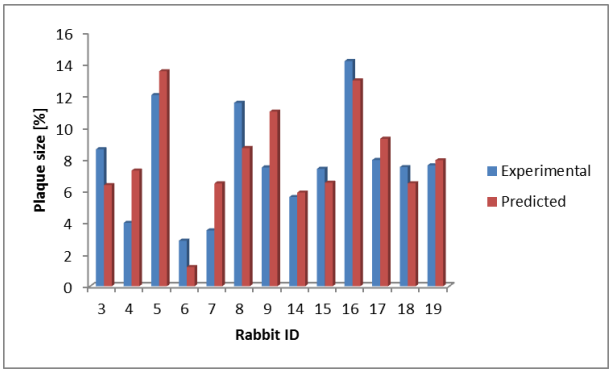

Figure 3: Comparison of experimental and predicted values (polynomial regression model).

4 CONCLUSION

In this paper we tried to model relationship between WSS, blood analysis data (cholesterol, HDL, LDL and triglycerides) on one hand and plaque size (determined from histology) on the

other hand. Among four tested regression models, second order polynomial regression gave the best result. Obtained results show that there is a strong connection between plaque size and input data. The achieved results represent progress in the assessment of stroke risk for a given patient's geometry and blood analysis data.

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