Method of calibration of red blood cell model by stretching experiments

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Abstract: This article describes method for calibration of red blood cell model. We have several elastic coefficients in our model and we need to make sure, that our model of red blood cell has the same behavior as real red blood cell. We prepared simulations according to experiments and compared the results. We found out that elastic coefficients depend on number of triangulation nodes. We have calibrated two meshes with our method and predicted the correct values for a third mesh from these two.

1 Introduction

These days modeling of elastic object in fluid flow is very popular in many science region in many applications.

Our model of elastic object is based on a triangular spring mesh on object surface. We can change number of nodes in the mesh. Less nodes mean less accuracy, but faster computing. Elastic behavior is due to five elastic moduli: stretching, bending, local and global area conservation and volume conservation. Each modulus has its own parameter - elastic coefficient. In the following, we use k_s for stretching coefficient, k_b for bending, k_{al} for local area, k_{ag} for global area and k_v for volume. For complete description of the model we refer reader to [1]. The model is implemented in Object-in-fluid framework [2] as part of open-source software Espresso [3].

In this work, we take a model of red blood cell (RBC) and calibrate it. It means finding values for parameters of five elastic moduli in the model. In earlier work [4], we have shown there is no a general formula for recalculating parameters for different mesh (different number of nodes on surface) from one reference mesh.

2 Calibration set up

One way to determine elastic coefficients of RBC is to compare the results of stretching experiments of RBC in-vitro with simulation of stretching RBC. [5, 6] describe data from experiments with biological RBC. They measured the change of shape, in particular the values of transversal and axial diameter, see Figure 1. If we apply external force, RBC stretches and its diameters change. The experiments provide data on stretching by several discrete forces. If we use interpolation, we obtain continuous information. Of course, each RBC is one of a kind, so the experimental data show mean value with variance.

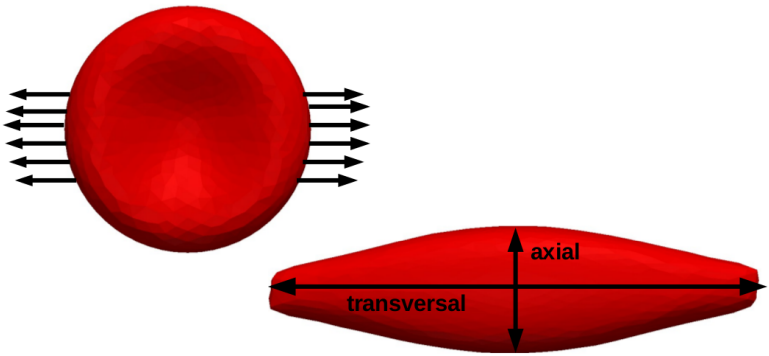

Figure 1: Stretching of RBC. On the left, we see the beginning of simulation: we stretched cell by applying force at several nodes on surface, illustrated by black arrows. On the right: final stage of simulation - relaxed state, we measured transversal and axial diameter.

We had prepared a set of simulations. We took one mesh (a particular triangulation of cell surface) and determined the stretch points. These points were on a ring with diameter about $2\mu m$, the same as in experiments, in which RBC was stretched by attached silica beads. For different meshes we have different number of stretched points and diameter of stretched rings. In the next step, we chose value ranges for elastic coefficients. Then we took one combination of coefficients, stretched cell by several forces and measured diameters in relaxed state for each applied force. Next, we evaluated how well we fitted experimental data. For this purpose, we have defined Σ_{dev} as sum of squares of diameter's deviations for each applied force: $\Sigma_{dev} = \sum_i [(a_s^i - a_e^i)^2 + (t_s^i - t_e^i)^2]$, where a_s^i and t_s^i are i$^{\text{th}}$ axial and transverse diameters measured in simulations for i$^{\text{th}}$ force, a_e^i and t_e^i have same meaning, but they were measured in experiment with biological RBC. Each number, Σ_{dev}, belongs to one set of values of five elastic coefficients k_s, k_b, k_{al}, k_{ag}, k_v. The example of simulation outputs with different Σ_{dev} is in Figure 2.

2.1 Value range for coefficient

We had several possibilities, how to look for the range of coefficients. From purely mathematical point of view, we should take coarse range of values of elastic coefficients, same for each coefficient, divide to e.q. ten intervals and then run simulations for each combination. But that would mean huge number of simulations. From physical point of view, many of these combinations do not make sense and we may choose a specific range for coefficients. We can start from a coarse range, coarse division and continue with fine division in subranges with better fit. The calibration process will not be purely automatic, but iterations will be faster.

2.2 Finding good fit

For each combination of coefficients, we had one value for Σ_{dev}. The easiest way to identify the most appropriate coefficients is to find the global minimum from these values. However, we are looking for stable coefficients, because we need to have stable cell for further simulations. So for our purposes, we are looking for relatively wide local minimum region, not for the single smallest value of Σ_{dev}. Several combinations of coefficients have caused completely unphysical behavior of cell. Therefore, another selection criterion is relative large distance from these "bad" regions.

We have several options to find "good" regions. The first one is calculation of the range of deviations as $range_{dev} = \Sigma_{dev}^{max} - \Sigma_{dev}^{min}$ and looking at the simulations, which have $\Sigma_{dev} < (\Sigma_{dev}^{min} + 0.05 \times range_{dev})$. This approach is not sufficiently general, if the value $range_{dev}$ is too large. The second one is selection of the best 5% of simulations. It means we sort simulations, i.e. combination of coefficients, by Σ_{dev} and then we look at top 5% of combinations. Probably the most general approach is taking all combinations, which have Σ_{dev} less than some value.

3 Outcomes

In the following, we give two examples for cell with triangulation mesh with 141 and 958 nodes on surface. We have used the set up, which is described in the previous section. For both meshes we ran same first iteration with coarse ranges of coefficients. The range for each parameter was split into three values. With 5 parameters, this gives $3^5 = 243$ combinations of 5 parameters. Second iterations had different fine ranges and included again 243 combinations of coefficients. We selected those combinations of elastic coefficients, for which Σ_{dev} was less then 1, this means very good fit with experimental values. This suitable coefficients are in Table 1.

$nodes$	k_s	k_b	k_{al}	k_{ag}	k_v
141	0.0055	0.055	0.005	$0.275; 0.5$	$1; 3; 5$
958	0.0055	0.01	$0.01; 0.02$	0.05	$2; 6; 10$

Table 1: The suitable coefficients for 141 and 958 from calibration process, more than one value means that the fit was equally well for each of them.

3.1 Sensitivity of coefficients

We looked at the sensitivity of the model with respect to change of elastic coefficients. Greater sensitivity means greater change in outcomes (value of transverse and axial diameter in relaxed state), if we change the value of coefficients. Our hypothesis was that k_s and k_b (stretching and bending) are much more sensitive than k_{al}, k_{ag} and k_v (local and global area and global volume). To confirm our hypothesis about sensitivity, we have changed sequentially each one coefficient, while we were keeping others fixed. The coefficients were changed to quadruple, double, half and quarter of the original value. Then we run calibration process again and evaluated how many times change Σ_{dev} relative to original value. The outputs are in Table 2. We see much more greater change for k_s and k_b than for k_{al}, k_{ag} and k_v. In the same time, there are some limits for each coefficient (denoted by "-" in the table), beyond which has the cell model completely unphysical behavior, as we wrote above.

$141 nodes$					
$change$	k_s	k_b	k_{al}	k_{ag}	k_v
$4 \cdot k_i$	106.4	–	2.8	1.6	1.0
$2 \cdot k_i$	23.1	–	1.6	1.2	1.0
$0.5 \cdot k_i$	8.6	30.7	1.0	2.5	1.0
$0.25 \cdot k_i$	23.2	7.9	1.2	10.0	1.0
$958 nodes$					
$change$	k_s	k_b	k_{al}	k_{ag}	k_v
$4 \cdot k_i$	95.4	–	2.2	4.2	2.8
$2 \cdot k_i$	21.9	–	1.5	2.9	1.2
$0.5 \cdot k_i$	4.4	13.9	1.7	1.2	2.0
$0.25 \cdot k_i$	11.9	31.5	3.5	6.4	1.7

Table 2: The values of Σ_{dev} due to changed coefficients. In the first column, there are written the changes of coefficients. Inside the table, there is value, how many times was change Σ_{dev} due to the change of particular coefficient. The " $-$ " means, that there was unphysical behavior for this value of coefficient.

3.2 Prediction for uncalibrated mesh

We predicted values of coefficients for mesh with 510 nodes. Its density is roughly between 141 and 958, so we took arithmetic mean of the coefficients, which had $\Sigma_{dev} < 1$, they are in Table 1. We ran the simulation with predicted coefficients and the Σ_{dev} was less then 1, too. It means, we can make prediction for a new mesh and find good enough coefficients faster.

3.3 Graphical representation

In Figure 2 we see results of experimental stretching of biological RBC - black solid lines with error bars that denote variance and results from our simulations for cell with 958 nodes on surface - colored lines for three different Σ_{dev}. There are results for the best fit (the coefficients are in Table 1) and for worse fits, when we changed k_s to double and half of original value, see Table 2.

Each biological RBC is unique, so each has different measurements in the stretching experiment. One can say that simulation line inside the error bars is good enough. However, we were aiming for fit of the mean values.

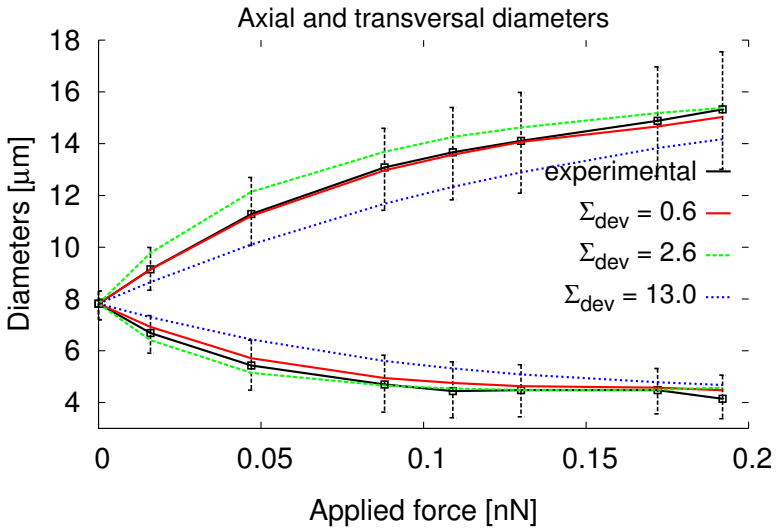

Figure 2: There are three lines from three simulations and one black experimental line in the graph. We compare values at 7 points (black squares) to calculate Σ_{dev}. The error bars show the variance of experimental data.

4 Conclusion

We showed that we have sufficiently precise and relatively quick method for calibration of our cell model. We showed, that model exhibits different sensitivity to different elastic coefficients. From results of coefficient calibrations of two different mesh cell, we were able to predict elastic coefficients of a third mesh. In the future, it will be necessary and interesting to compare the results with some from different experiment with RBC, e.q. cell passing thorough narrow opening in the channel.

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