Quantification of material properties and stress-free state of a RBC model, through hierarchical Bayesian inference

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The need of predictions for biomedical applications

- Micro-device optimization
- Targeted drug delivery
- Control of microswimmers
State of the art models reproduce experiments


Twisting torque cytometry


Flow through stenotic channel

Quinn et al., "Combined simulation and experimental study of large deformation of red blood cells in microfluidic systems", Annals of Biomedical Engineering, 2011.

Equilibrium fluctuations


Flow in cylindrical μ-channels


Flow in microfluidics device (DLD)


Platelet transport


Blood viscosity


Flow induced shape transitions

In this study, we integrate RBC models and DPD flow simulations with experimental data under a Bayesian UQ framework. We infer the posterior distributions for the RBC model parameters given multiple experimental data sets for cells under stretching and in shear flow. We construct single-level and hierarchical Bayesian models, and compare their posterior distributions to assess the transferability of the model parameters between different types of experiments. Following the Bayesian framework, we propagate the parameter uncertainty in the model output and compare the single-level and hierarchical Bayesian model predictions. Finally, we test the predictive capabilities of the Bayesian models on unseen data, for the prediction of the equilibrium shape thickness and the inclination angle of RBCs in shear flow. The paper is structured as follows: Section 2 introduces the computational methods related to the RBC and fluid modeling, the UQ framework, the Surrogate models used to alleviate the computational cost, and the computational setups. Sections 3 and 4 present the results of the single-level and hierarchical Bayesian inference respectively. Section 4.2 discusses the transferability of the model between experiments, and Section 5 gives a summary and concluding remarks.

### Table 1. Summary of RBC mechanical properties used in the literature.

<table>
<thead>
<tr>
<th>Application</th>
<th>T (°C)</th>
<th>$\mu_0$ (μN/m)</th>
<th>$\kappa_b$ ($10^{-19}$ J)</th>
<th>$\eta_m/\eta_{Hb}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>single RBC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stretching(^{20})</td>
<td>23</td>
<td>6.30</td>
<td>2.40</td>
<td>–</td>
</tr>
<tr>
<td>TTC and shear flow(^{19})</td>
<td>23</td>
<td>6.30</td>
<td>4.80</td>
<td>4.4</td>
</tr>
<tr>
<td>Cylindrical $\mu$-channel flow(^{24})</td>
<td>37</td>
<td>4.83</td>
<td>3.00</td>
<td>n.a.</td>
</tr>
<tr>
<td>Equilibrium(^{70})</td>
<td>23</td>
<td>2.42</td>
<td>1.43</td>
<td>22.2</td>
</tr>
<tr>
<td>DLD device(^{34})</td>
<td>37</td>
<td>4.83</td>
<td>3.00</td>
<td>n.a.</td>
</tr>
<tr>
<td>Dynamic morphologies in shear(^{44})</td>
<td>37</td>
<td>4.83</td>
<td>3.00</td>
<td>n.a.</td>
</tr>
<tr>
<td>Flow-induced shape transitions(^{49})</td>
<td>37</td>
<td>4.80</td>
<td>3.00</td>
<td>0</td>
</tr>
<tr>
<td><strong>multiple RBCs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell-free layer(^{21})</td>
<td>23</td>
<td>4.59</td>
<td>2.40</td>
<td>18.3</td>
</tr>
<tr>
<td>Pf-malaria biophysics(^{22})</td>
<td>37</td>
<td>6.30</td>
<td>2.40</td>
<td>n.a.</td>
</tr>
<tr>
<td>Blood viscosity prediction(^{23})</td>
<td>37</td>
<td>4.82</td>
<td>3.00</td>
<td>12.0</td>
</tr>
<tr>
<td>Platelet transport(^{76})</td>
<td>27</td>
<td>4.50</td>
<td>2.98</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

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Outline

1. Blood model
2. Hierarchical Bayesian inference
3. Transferability of the calibrated model
Blood Model
Basic constituents of blood:
- red blood cells
- plasma

Plasma
- 95% water
modeling requirements:
- incompressible fluid
- Newtonian fluid

Red Blood Cells
- viscoelastic membrane
- no nucleus
- constant area & volume

Dissipative Particle Dynamics (DPD)

Particle-particle interactions:
- cell-cell (internal)
- cell-cell (external)
- wall-solvent
- wall-cell

Interaction types:
- solvent-solvent
- solvent-cell

Blood model
Fluid model: Dissipative Particle Dynamics

**Fluid represented by particles**
- Positions $\mathbf{r}_i$
- Velocities $\mathbf{v}_i$
- Mass $m$

**Newton motion**
- $\dot{\mathbf{r}}_i = \mathbf{v}_i$
- $\dot{\mathbf{v}}_i = \frac{1}{m} \mathbf{f}_i$

**Dissipative Particle Dynamics forces**

\[ \mathbf{f}_i = \sum_{j=1}^{N} \mathbf{f}_{ij}^C + \mathbf{f}_{ij}^D + \mathbf{f}_{ij}^R \]

- $\mathbf{f}_{ij}^C = a w(r_{ij}) \mathbf{e}_{ij}$, hydrostatic pressure
- $\mathbf{f}_{ij}^D = -\gamma w_D(r_{ij}) \left( \mathbf{e}_{ij} \cdot \mathbf{v}_{ij} \right) \mathbf{e}_{ij}$, viscosity
- $\mathbf{f}_{ij}^R = \sigma \xi_{ij} w_R(r_{ij}) \mathbf{e}_{ij}$, fluctuations

Wall surface
Frozen particles
Bounce-back
RBC membrane model

**Bending Energy**

\[ E_b = 2\kappa_b \oint H^2 dA \]

Jülicher, F. 1996. Journal de Physique II, 6[12], 1797–1824.

**Area and Volume penalization**

\[ E_A = k_A \frac{(A - A_0)^2}{A_0}, \quad E_V = k_V \frac{(V - V_0)^2}{V_0} \]


**Dissipation forces**

\[ f_i^{\text{visc}} = - \sum_j \gamma (v_{ij} \cdot e_{ij}) e_{ij} \]


**Shear Energy**

\[ E_s = \frac{K_s}{2} \oint (a^2 + a_3 a^3 + a_4 a^4) dA_0 + \mu \oint (\beta + b_1 a \beta + b_2 \beta^2) dA_0 \]

with respect to stress-free shape of reduced volume \( V \):

Bayesian Inference

Computational Model with Parameters, $\vartheta$

\[ f(x \mid \vartheta) \]

prediction error equation

\[ d = f(x \mid \vartheta) + \epsilon \]

\[ \epsilon \sim \mathcal{N}(0, \sigma_n) \]

Which parameter values can best explain the data?

\[ p(d \mid \vartheta) \]

Bayes’ Theorem

\[ p(\vartheta \mid d) = \frac{p(d \mid \vartheta) p(\vartheta)}{p(d)} \]

\[ p(\vartheta) \]

Result: a distribution over the parameters of the model
Hierarchical Bayesian model
The need to combine multiple datasets

Different individuals = different RBCs

Different experiments = different sensitivity to parameters

More data = less uncertainty

Elastic parameters

Elastic + Viscous parameters

$p(\theta|D)$

↓ more data
Single-cell experimental data: 7 data sets

- **Equilibration**
  - Diameter: 7.82 μm
  - Minimum thickness: 0.81 μm
  - Maximum thickness: 2.58 μm

- **Stretching**
  - $h_{\text{max}}$
  - $h_{\text{min}}$
  - $D_{\text{tr}}$
  - $D_{\text{ax}}$

- **Relaxation**
  - $D_{\text{ax}}/D_{\text{tr}}$
  - $t_c$


Hierarchical statistical model

Computational parameters $\vartheta = (\nu, \mu, \kappa_b, b_2, \eta_m)$

1. Select a RBC
2. Propagate through computational model
3. Random noise

Equilibrium $\times 1$  Stretching $\times 2$  Relaxation $\times 4$
Inferring the parameters

\[
p(\psi | D) = \frac{p(D | \psi) p(\psi)}{p(D)}
\]

\[
p(D | \psi) = \prod_{i=1}^{N} \int p(D_i | \theta_i) p(\theta_i | \psi) d\theta_i,
\]

\[
= \prod_{i=1}^{N} \int \frac{p(D_i | \theta_i) p(\theta_i | \psi)}{p(\theta_i | D_i)} p(\theta_i | D_i) d\theta_i,
\]

\[
= \prod_{i=1}^{N} p(D_i | \mathcal{M}_i) \int \frac{p(\theta_i | \psi)}{p(\theta_i)} p(\theta_i | D_i) d\theta_i,
\]

\[
\approx \prod_{i=1}^{N} p(D_i | \mathcal{M}_i) \frac{1}{N_S} \sum_{k=1}^{N_S} \frac{p(\theta_i^{(k)} | \psi)}{p(\theta_i^{(k)})}, \quad \theta_i^{(k)} \sim p(\theta_i | D_i)
\]

1. Compute posterior for each dataset separately
2. Use the samples to estimate the likelihood

Sampling with TMCMC, 50'000 samples


https://github.com/cselab/korali
From samples to observables

Stress-free state generation

Equilibration

Stretching

Relaxation

\((v, \mu, FvK, b_2, \eta_m, F_{ext})\)

\(D, h_{\text{min}}, h_{\text{max}}\)

\(D_{ax}, D_{tr}\)

\(t_c\)
Offline surrogate to accelerate inference

Feed-forward Neural Networks,
3 hidden layers of 32 neurons
Posterior distribution

\[ p(\theta_{\text{new}}|D) \]

- \( \sigma_{eq,1} \)
- \( y_{eq,1} \)
- \( \sigma_{st,i} \)
- \( y_{st,i} \)
- \( \sigma_{z,i} \)
- \( y_{z,i} \)
- \( t_{c,i} \)
- \( y_{re,i} \)
- \( \vartheta_{c,i} \)
- \( \vartheta_{1} \)
- \( \vartheta_{2} \)
- \( \vartheta_{3} \)
- \( \vartheta_{4} \)
- \( \vartheta_{5} \)
- \( \vartheta_{6} \)
- \( \vartheta_{7} \)
- \( \vartheta_{8} \)
- \( \vartheta_{9} \)

Equilibrium \( \times 1 \)
Stretching \( \times 2 \)
Relaxation \( \times 4 \)

Most likely
Stress-free state
Model predictions on the calibration data sets

- $D$ refers to the diameter.
- $h_{\text{min}}$ and $h_{\text{max}}$ represent minimum and maximum heights.
- $D_{\text{wp}}$ and $p_{\text{wp}}$ are likely parameters or variables.
- $F_{\text{ext}}$ represents external force.
- $t$ represents time.

Graphs show distributions and trends for different parameters.
Transferability of the model
Prediction on previously unseen data
Single cell in straight micro-tube


Single cell in linear shear flow


Summary

• **Transferable** model: prediction of previously unseen flow conditions

• Inferred **stress-free state** of cytoskeleton

SOFTWARE:

- [https://github.com/cselab/Mirheo](https://github.com/cselab/Mirheo)
- [https://github.com/cselab/korali](https://github.com/cselab/korali)


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THANK YOU!

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