Hierarchical Bayesian Uncertainty Quantification for a Red Blood Cell Model

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Blood flow & NP in realistic vasculatures
(with Ferrari Group, Houston)

- Understanding of transport oncophysics.
- Optimization of drug delivery.

Experimental data for vasculature.

Vasculature reconstruction & Simulation.
Microfluidic isolation of CTC (with Toner Group, Harvard)

Circulating tumor cells: approaches to isolation and characterization

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CTC detection → High throughput - mL Samples
Blood modeling

Basic constituents of blood:
- red blood cells
- plasma

Plasma
- 95% water

 modeling requirements:
- incompressible fluid
- hydrodynamic behavior (mass & momentum conservation)

Red Blood Cells
- biconcave shape
- viscoelastic membrane
- constant area & volume

Particle-based methods:
- Coarse-grained model for RBC membrane
- Dissipative Particle Dynamics for solvent

- Prescribe forces between RBC particles.
- Calibration of parameters to best fit experiments.
Most widely used RBC model

\[ U = U_{\text{in-plane}} + U_{\text{bending}} + U_{\text{area}} + U_{\text{volume}} \]

\[ U_{\text{in-plane}} = \sum_{j=1}^{N_s} \left[ \frac{k_{p_j} \left( 3x_j^2 - 2x_j \right)}{4(1 - x_j(x_0))} + \frac{k_{b_j}}{l_j} \right] \]

\[ U_{\text{bending}} = k_b \sum_{j=1}^{N_s} \left[ 1 - \cos \theta_j \right] \]

\[ U_{\text{area}} = \frac{k_a (A - A_0)^2}{2A_0} + \sum_{j=1}^{N_s} \frac{k_d (A_j - A_0)^2}{2A_0} \]

\[ U_{\text{volume}} = \frac{k_v (V - V_0)^2}{2V_0} \]

Addition of viscous diffusion:

\[ F_{m,ij}^D = -\nabla \cdot (v_{ij} \cdot e_{ij}) e_{ij} \]
Most widely used RBC model

\[ U = U_{\text{in-plane}} + U_{\text{bending}} + U_{\text{area}} + U_{\text{volume}} \]

where:
- \( U_{\text{in-plane}} \) is the in-plane membrane potential.
- \( U_{\text{bending}} \) is the bending potential.
- \( U_{\text{area}} \) is the area potential.
- \( U_{\text{volume}} \) is the volume potential.

Addition of viscous diffusion:
\[ F_{m,ij}^D = -\gamma^C (v_{ij} \cdot e_{ij}) e_{ij} \]

Theoretical analysis for hexagonal network:
- Approximations to macroscopic material properties.
- Comparison with existing literature / other models.

Linear shear modulus:
\[ \mu_0 = \left. \frac{\partial \tau_{xy}}{\partial \gamma} \right|_{\gamma=0} \approx \frac{k_0 \sqrt{3}}{4} \left( \frac{x_0}{2(1-x_0)^3} - \frac{1}{4(1-x_0)^2} + \frac{1}{4} \right) \]

Membrane viscosity:
\[ \eta_m = \frac{\tau_{xy}}{\dot{\gamma}} \approx \gamma^C \frac{\sqrt{3}}{4} \]

validate that our DPD model for RBC translation across a 4/C15 microfluidic channel is robust against variations in channel geometry introduced during their fabrication.

FIGURE 2. Shape characteristics of RBC traversal across microfluidic channels: (a) experimental (left) and simulated (right) for a 4/C15 microfluidic channel. (b) Comparison of DPD simulation results with experimental data of Puig de Morales et al., "Microfluidics for cell sorting based on their dynamical properties", Biophysical Journal, 2010.

Equilibrium fluctuations


Flow in cylindrical μ-channels


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.

Flow induced shape transitions


Blood viscosity

## Model Parameters

We consider the coarse-grained RBC model described in Section 2.1. This model has seven parameters, of which four are directly related to the equilibrium shape of the RBC: the equilibrium-to-maximum spring length ($l_0$), modulus ($\mu_0$), bending rigidity ($\kappa_b$), and ratio of membrane-to-hemoglobin viscosities ($\eta_m/\eta_{Hb}$). The remaining four quantities are the equilibrium-to-maximum spring length, modulus, bending rigidity, and ratio of membrane-to-hemoglobin viscosities.

### Table 1

<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>single RBC</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>multiple RBCs</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>
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<tr>
<td>Platelet transport$^{76}$</td>
<td>27</td>
<td>4.50</td>
<td>2.98</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

### Inferred Quantities

**Scale:** $\mu_0$

Relative strength between RBC energy potentials:

\[
Q_1 = \frac{l_0}{l_{max}} \quad Q_2 = \frac{\mu_0R_0^2}{k_b} \quad Q_3 = \frac{\eta_m}{\eta_{Hb}} \quad Q_4 = \frac{\eta_{Hb}^2}{\mu_0R_0^2\rho}
\]
Bayesian Inference
Bayesian Inference

Data, \( d \) \( \oplus \) Computational Model with Parameters, \( \vartheta \)
\[ f(x \mid \vartheta) \]
\( \oplus \) Statistical Assumption connecting \( \vartheta \) and \( d \)
\[ p(d \mid \vartheta) \]

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

Bayes’ Theorem
Bayesian Inference

Experimental Data

Computational Model

\[ d = f(x | \theta) + \epsilon \]

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

\[ p(\theta_1 | d_1, \mathcal{M}_1) \]
Hierarchical Bayesian Inference

\[ p(\theta_1 | d_1, d_2) \]

\[ p(\theta_2 | d_2, d_N) \]

\[ p(\theta_N | d_1, d_2) \]
Hierarchical Bayesian Inference

\[ \psi \]

\[ \vartheta \]

\[ y_1, y_2, \ldots, y_N \]

\[ y_{\text{new}} \]

hyper-parameters, e.g.,

\[ \vartheta \sim U(\psi_1, \psi_2) \]
Hierarchical Bayesian Inference

- lost of individual information
- one parameter explains all data
- large uncertainty

- no exchange of information between data
- some data sets may be more informative

- information flows through the hyper-parameters
- uncertainty of individual parameters may be reduced
- the hyper-parameters serve as a data driven prior for future inferences
Hierarchical Bayesian Inference

\[ p(\psi | d) \propto p(d | \psi)p(\psi) \]

\[ p(d | \psi) = \int p(d, \vartheta | \psi) \, d\vartheta \]

\[ = \prod_{i=1}^{N} \int p(d_i | \vartheta_i) p(\vartheta_i | \psi) \, d\vartheta_i \]

\[ d = \{d_1, d_2, \ldots, d_N\} \]

prior on hyperparameters \[ \cdots \cdots \, p(\psi) \]

prior on model parameters \[ \cdots \cdots \, p(\vartheta_i | \psi) \]

likelihood of the data \[ \cdots \cdots \, p(y_i | \vartheta_i) \]

\[ y_1 \quad \cdots \quad y_i \quad \cdots \quad y_N \]

\[ y_i^{\text{new}} \quad \cdots \quad y_N^{\text{new}} \]

\[ \vartheta_1 \quad \cdots \quad \vartheta_i \quad \cdots \quad \vartheta_N \]

\[ \vartheta_{\text{new}} \]
Surrogate Model
Gaussian Processes

Discretize the parameter space $\vartheta(i), i = 1, \ldots, M$

Run the computational model on $\vartheta(i)$ with input $x(i)$ and get the output $t_M = (t_1, \ldots, t_M)$

Set $D_M = \{t_1, \ldots, t_M, \zeta_1, \ldots, \zeta_M\}$ where $\zeta_i = (x(i), \vartheta(i))$

The prediction $t_{M+1}$ of the GP model for a new $\zeta_{M+1}$ given the data $D_M$ is a random variable

$$p(t_{M+1}, D_M) = \mathcal{N}(t_{M+1} | m(D_M), \sigma^2(D_M))$$

$$m(D_M) = k_{M+1}^{\top} C^{-1}_M t_m$$

$$\sigma^2(D_M) = c_{M+1} - k_{M+1}^{\top} C^{-1}_M k_{M+1}$$

$$[k_{M+1}^{\top}]_i = \kappa(\zeta_i, \zeta_{M+1}), \quad i = 1, \ldots, M$$

$$[C]_{i,j} = \kappa(\zeta_i, \zeta_j), \quad i, j = 1, \ldots, M$$

$$c_{M+1} = \kappa(\zeta_{M+1}, \zeta_{M=1})$$
Gaussian Processes: Validation
Results
Design Principles

• **Modularity.** Korali is designed as a completely modular software.
• **Scalability.** We have designed Korali’s problem definition interface to remain agnostic about its execution platform.
• **High-Throughput.** Complete utilisation of the given computational resources.
• **High-Performance.** Supports the execution of parallel (MPI, UPC++) and GPU-based (CUDA) computational models.

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coming soon in https://github.com/cselab/
Stretching experiment

Experimental Setup


Stretching data sets considered in UQ

Single-level UQ for stretching

\[ \sigma_i = (Q_1, Q_2, \mu_0, \sigma_{ax}, \sigma_{tr}), \quad i = 1, 2 \]
Shear flow experiment

Experimental Setup


Shear flow data sets considered in UQ

Shear rate=500/s. $\eta=12$ mPa.s
Shear rate=600/s. $\eta=170$ mPa.s

Tank treading of the membrane is shown by the motion of a Latex marker. The motion is visualized by drawing a connecting line between markers in subsequent pictures. Shear rate=140/s. $\eta=18$ mPa.s


<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>symbol (Fig. 2)</th>
<th>Viscosity ratio, $\lambda$</th>
<th>data set ID in UQ</th>
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</thead>
<tbody>
<tr>
<td>Fischer et al.</td>
<td>1978</td>
<td>○</td>
<td>0.56</td>
<td>$d_3$</td>
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<tr>
<td>Fischer</td>
<td>1980</td>
<td>△</td>
<td>0.43</td>
<td>$d_4$</td>
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<tr>
<td>Tran-Son-Tay</td>
<td>1983</td>
<td>+</td>
<td>0.50</td>
<td>$d_5$</td>
</tr>
<tr>
<td>Fischer</td>
<td>2007</td>
<td>◇</td>
<td>0.35</td>
<td>$d_6$</td>
</tr>
<tr>
<td>Fischer and Korzeniewski</td>
<td>2015</td>
<td>○</td>
<td>0.35</td>
<td>$d_7$</td>
</tr>
</tbody>
</table>
Single-level UQ for shear flow

\[ m_{i,i} = 1, 2 \]

\[ \vartheta_i = (Q_{1,i}, Q_{2,i}, \mu_{0,i}, Q_{3,i}, Q_{4,i}, \sigma_{sh,i}) \text{, } i = 3, \ldots, \]

\[ p(\vartheta_3 | d_3, M_3) \]

\[ p(\vartheta_4 | d_4, M_4) \]

\[ p(\vartheta_5 | d_5, M_5) \]

\[ p(\vartheta_6 | d_6, M_6) \]

\[ p(\vartheta_7 | d_7, M_7) \]
Hierarchical Bayesian Inference for the RBC model

\[ \vartheta_i = (Q_{1,i}, Q_{2,i}, \mu_{0,i}, \sigma_{st,i}), \quad i = 1, 2 \]

\[ \vartheta_i = (Q_{1,i}, Q_{2,i}, \mu_{0,i}, Q_{3,i}, Q_{4,i}, \sigma_{sh,i}), \quad i = 3, \ldots, 7 \]

\[ \vartheta_{\text{new}} = (Q_1, Q_2, \mu_0, Q_3, Q_4, \sigma_{sh}, \sigma_{st}) \]
Hierarchical Bayesian UQ

\[ p(\psi | \vec{d}, \mathcal{M}_{HB}) \]

\[ p(\mathfrak{g}_{\text{new}} | \hat{d}, \mathcal{M}_{HB}) \]
Model Transferability: Infer for quantity X - Propagate to quantity Y

to stretching

| to TTF |
| to inclination angle |
| to equilibrium shape |

![Graphs showing model transferability](image)

- **Fig. 2.1**: The black dotted line represents the MAP value. The colored areas denote the 99% (blue), 90% (green), 75% (yellow) and 50% (red) quantiles. Circles correspond to the experimental data.

- **Fig. 4.2.1**: The predictions of the single-level stretching models and the hierarchical model for the RBC TTF are shown in the best MAP fit, Bayesian models to stretching and (ii) from the new general parameter distribution of the HB model, (iii) from the new experimental thickness of the RBC at equilibrium, as given by Eq. (new parameter). The colored areas denote the 99% (blue), 90% (green), 75% (yellow) and 50% (red) quantiles. Circles correspond to the experimental data.

- **Fig. 13**: The predictions of the single-level stretching models and the hierarchical model for the RBC TTF are shown in the best MAP fit, Bayesian models to stretching and (ii) from the new general parameter distribution of the HB model, (iii) from the new experimental thickness of the RBC at equilibrium, as given by Eq. (new parameter). The colored areas denote the 99% (blue), 90% (green), 75% (yellow) and 50% (red) quantiles. Circles correspond to the experimental data.

- **Fig. 14**: The predictions of the single-level stretching models and the hierarchical model for the RBC TTF are shown in the best MAP fit, Bayesian models to stretching and (ii) from the new general parameter distribution of the HB model, (iii) from the new experimental thickness of the RBC at equilibrium, as given by Eq. (new parameter). The colored areas denote the 99% (blue), 90% (green), 75% (yellow) and 50% (red) quantiles. Circles correspond to the experimental data.

- **Fig. 21**: The predictions of the single-level stretching models and the hierarchical model for the RBC TTF are shown in the best MAP fit, Bayesian models to stretching and (ii) from the new general parameter distribution of the HB model, (iii) from the new experimental thickness of the RBC at equilibrium, as given by Eq. (new parameter). The colored areas denote the 99% (blue), 90% (green), 75% (yellow) and 50% (red) quantiles. Circles correspond to the experimental data.

- **Fig. 29**: The predictions of the single-level stretching models and the hierarchical model for the RBC TTF are shown in the best MAP fit, Bayesian models to stretching and (ii) from the new general parameter distribution of the HB model, (iii) from the new experimental thickness of the RBC at equilibrium, as given by Eq. (new parameter). The colored areas denote the 99% (blue), 90% (green), 75% (yellow) and 50% (red) quantiles. Circles correspond to the experimental data.
Thank you!