Hierarchical Bayesian inference for a RBC model

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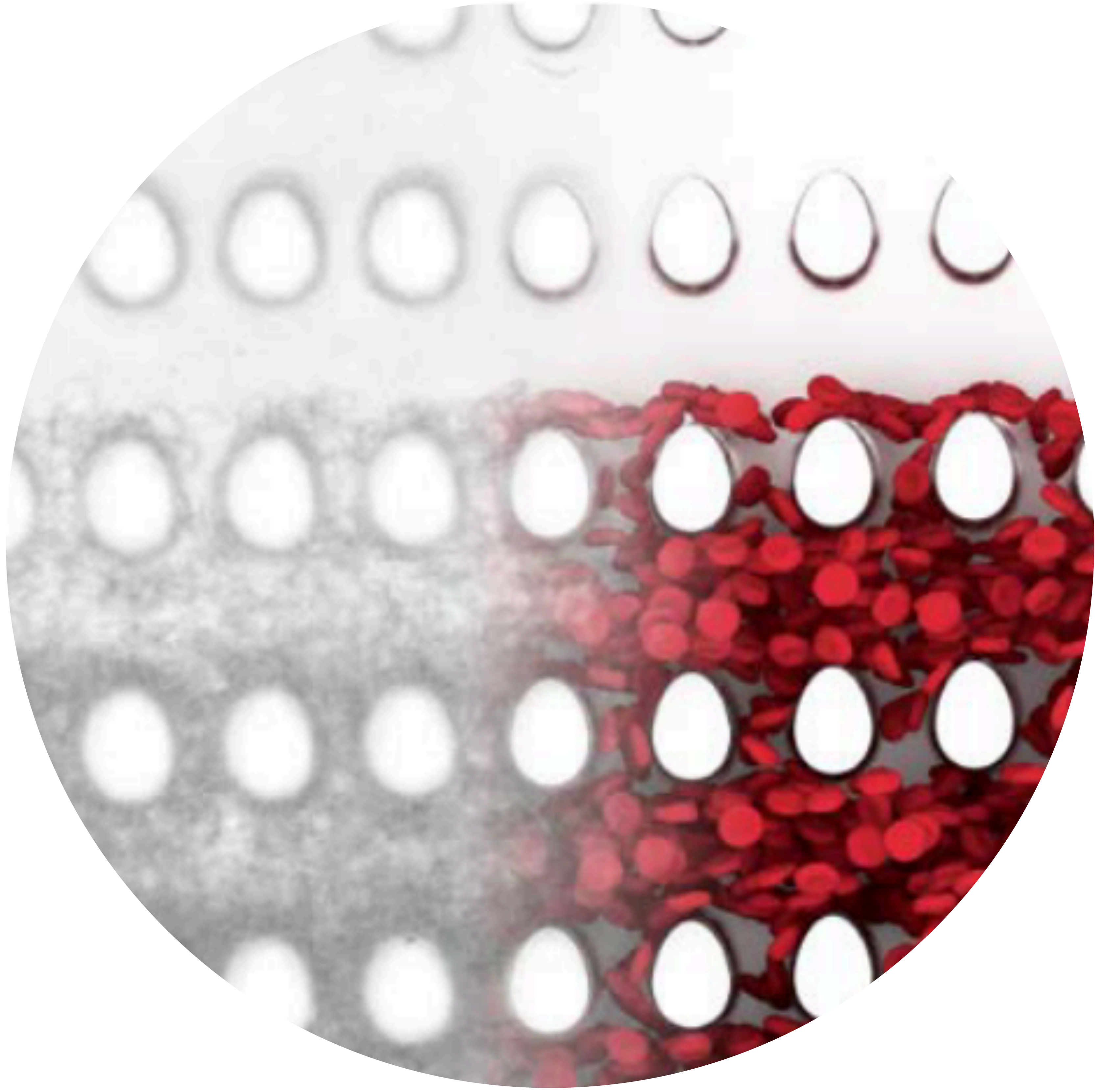
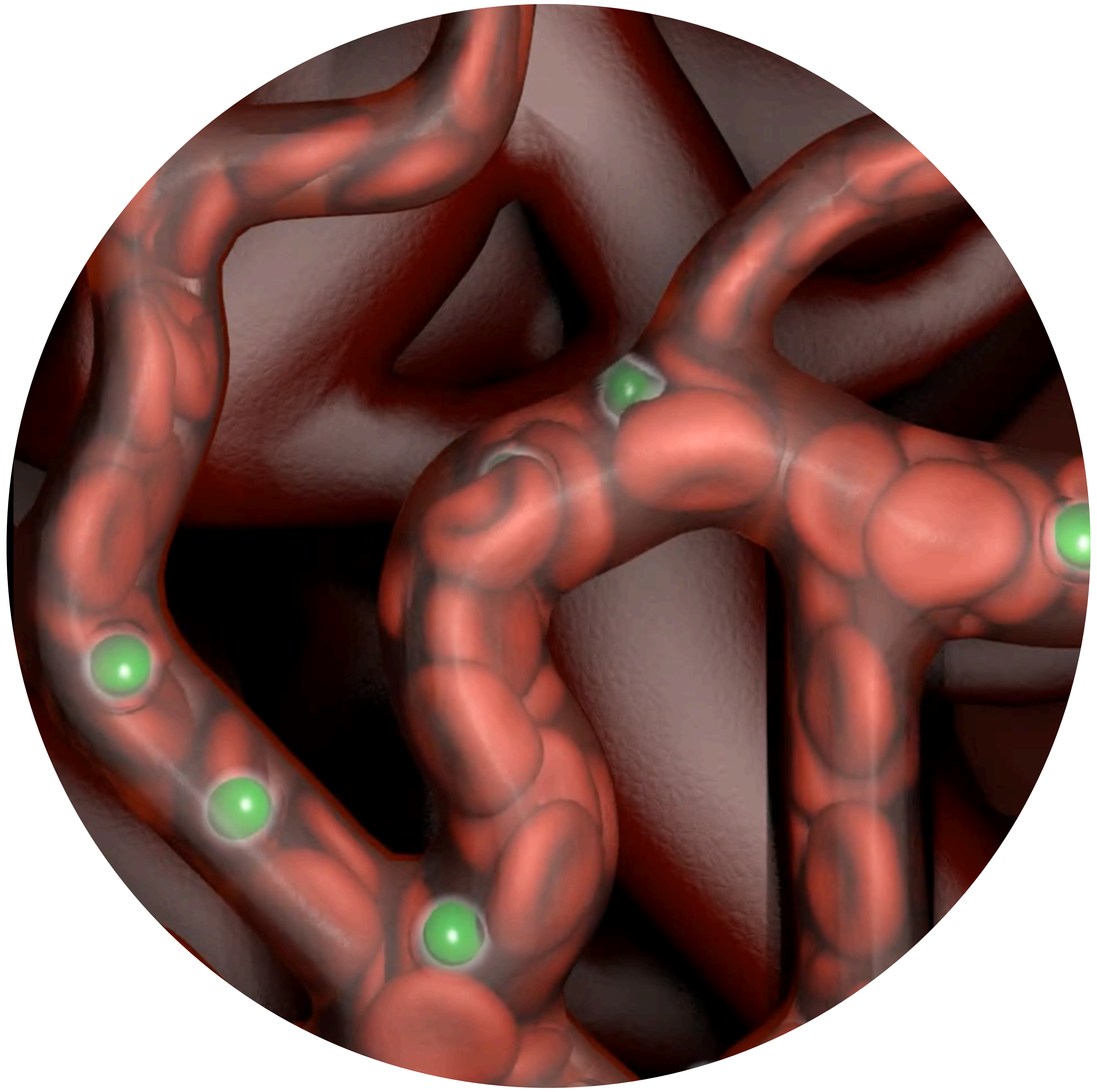
The need of predictions for biomedical applications

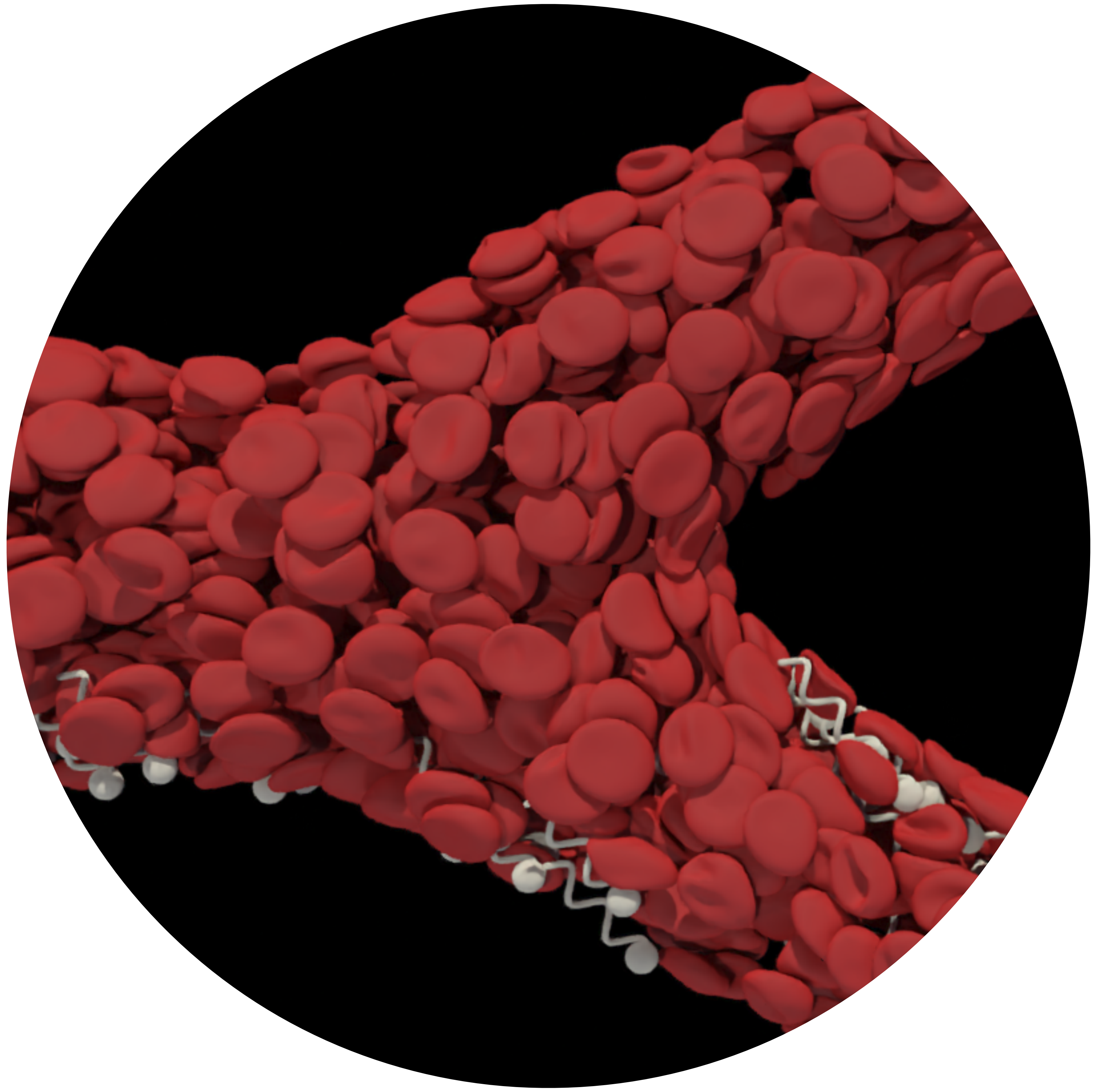
Micro-device optimization



Targeted drug delivery



Control of microswimmers



State of the art models reproduce experiments

Stretching

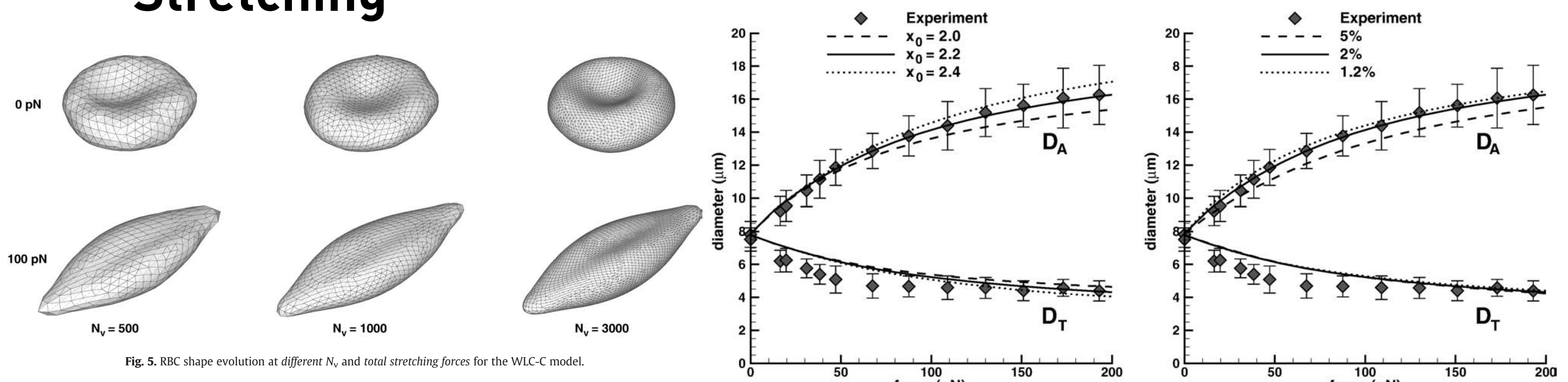


Fig. 5. RBC shape evolution at different N_v and total stretching forces for the WLC-C model.

Fedosov et al., "Systematic coarse-graining of spectrin-level red blood cell models", ***CMAME*****, 2010.**

Twisting torque cytometry

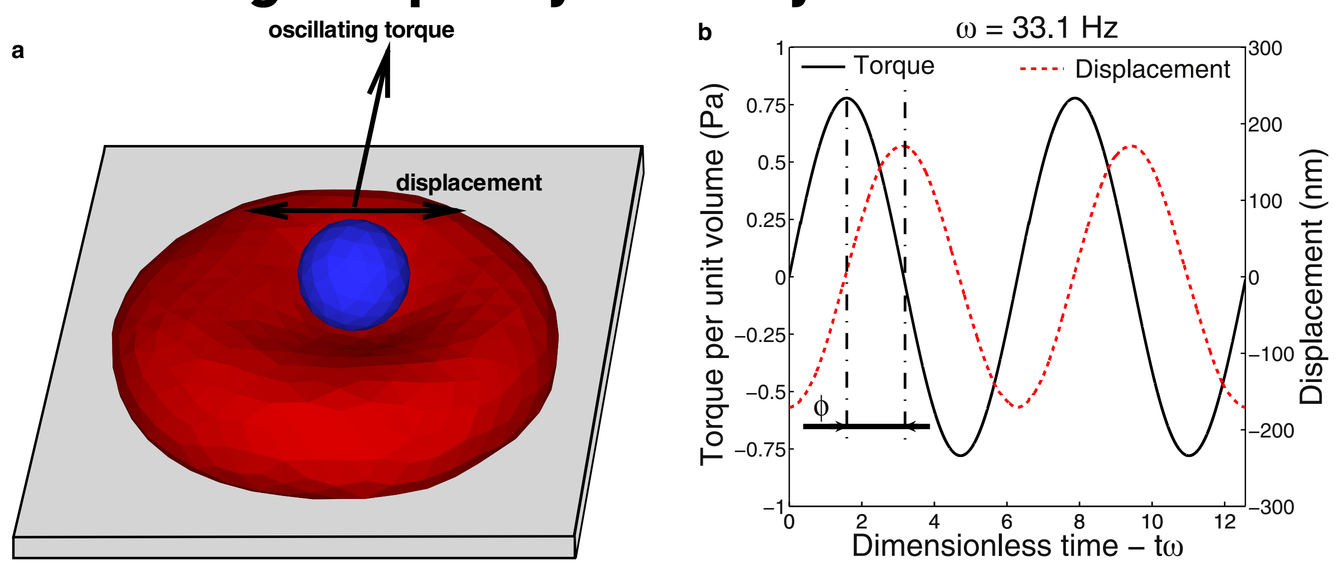
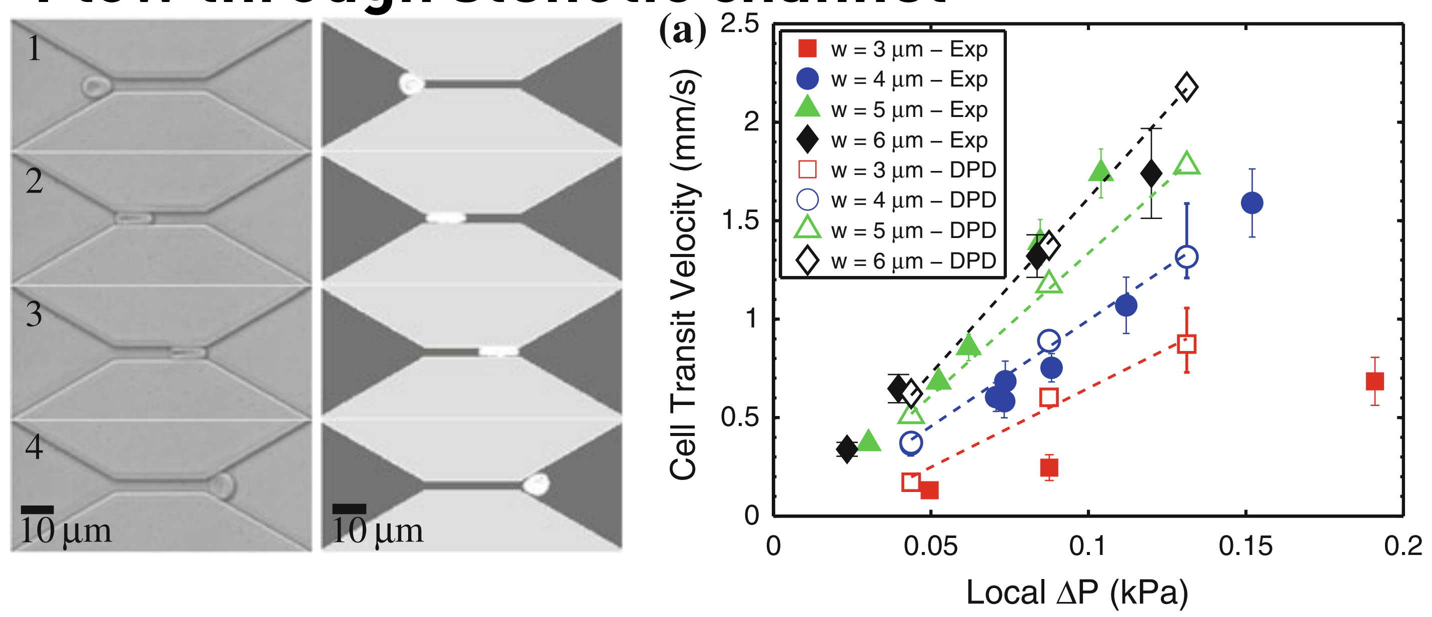


FIGURE 2 A setup of the TTC (*a*) and the characteristic response of a microbead subjected to an oscillating torque (*b*).

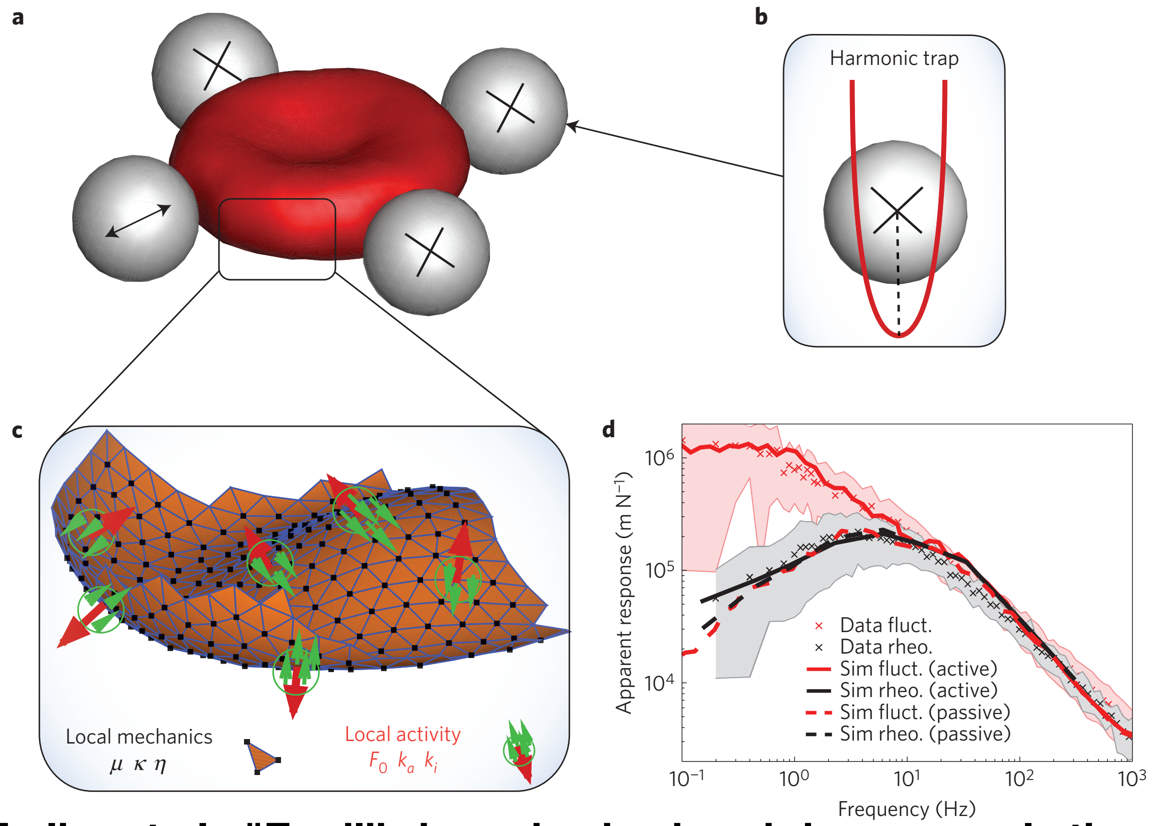
Fedosov et al., "A Multiscale Red Blood Cell Model with Accurate Mechanics, Rheology, and Dynamics", ***Biophysical Journal*****, 2010.**

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



Turlier et al., "Equilibrium physics breakdown reveals the active nature of red blood cell flickering", ***Nature Physics*****, 2016.**

Flow in cylindrical μ-channels

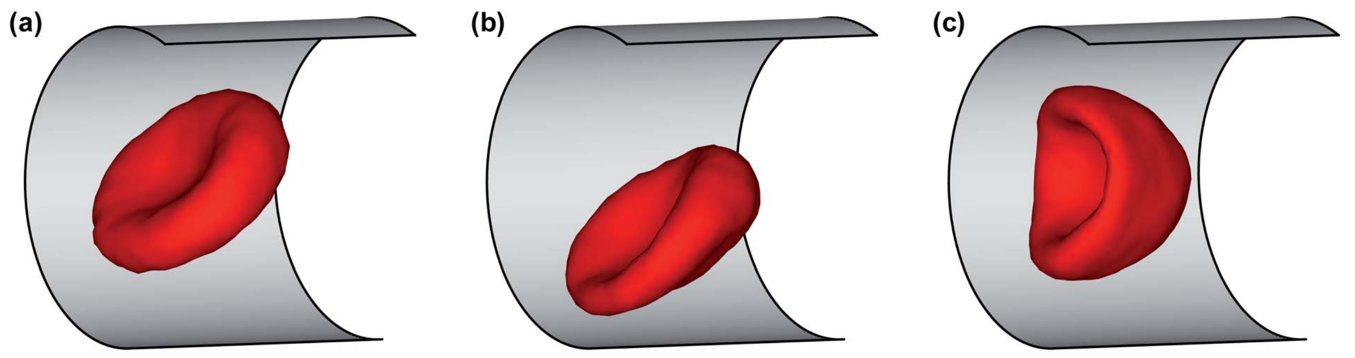
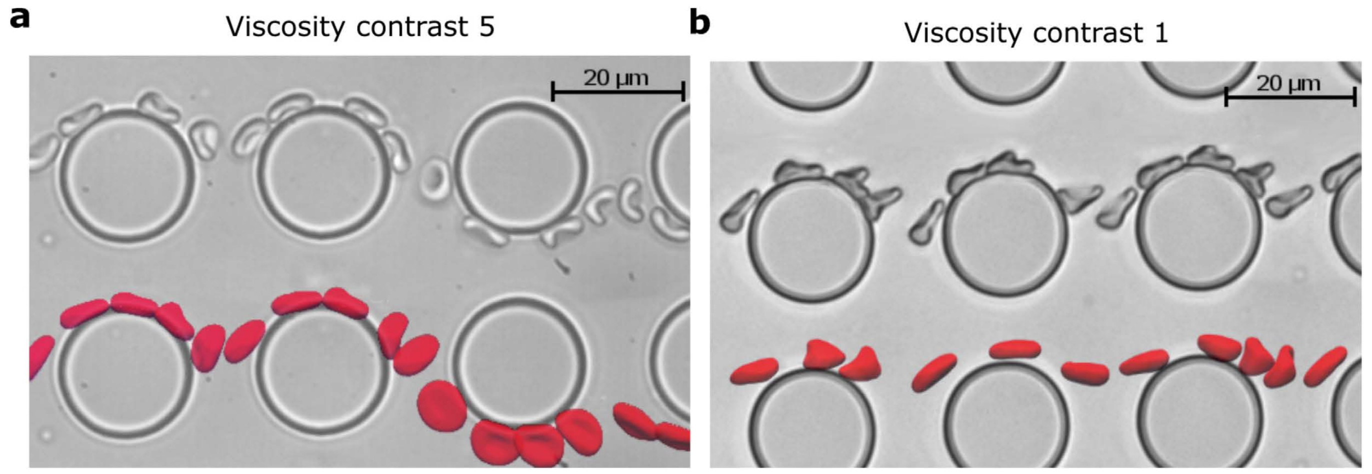


Fig. 1 Simulation snapshots of a RBC in flow (from left to right) for $\chi = 0.58$. (a) A biconcave RBC shape at $\dot{\gamma}^* = 5$; (b) an off-center slipper cell shape at $\dot{\gamma}^* = 24.8$; and (c) a parachute shape at $\dot{\gamma}^* = 59.6$. See also Movies S1–S4.†

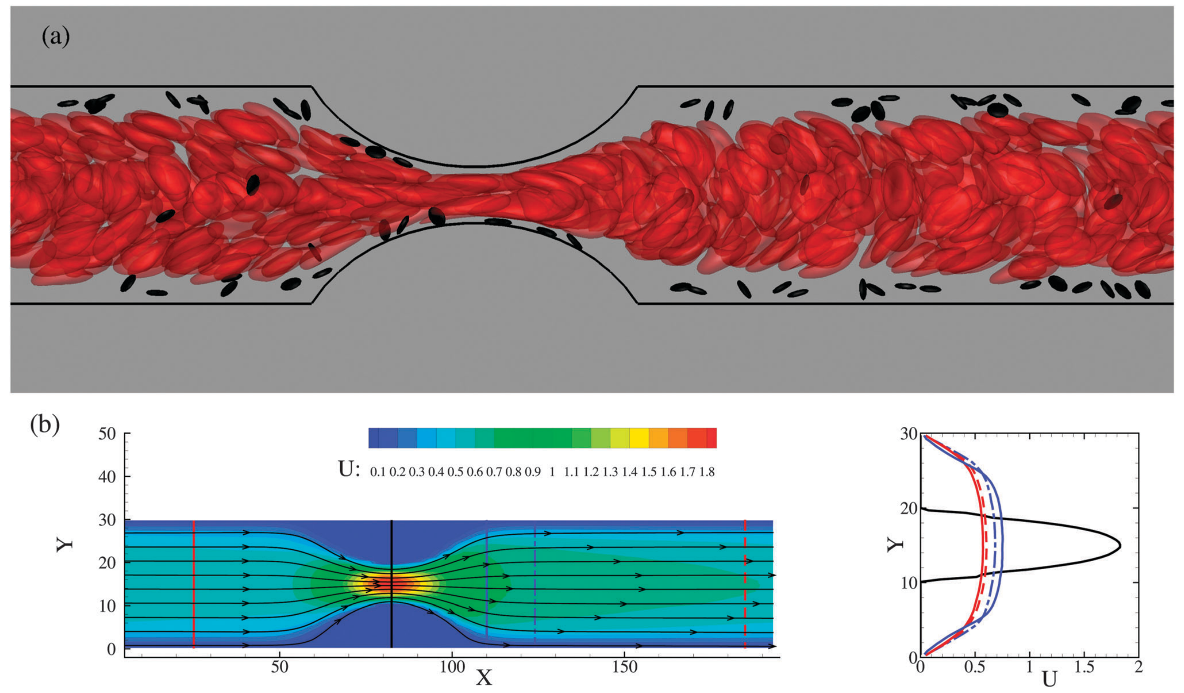
Fedosov et al., "Deformation and dynamics of red blood cells in flow through cylindrical microchannels", ***Soft Matter*****, 2014.**

Flow in microfluidics device (DLD)



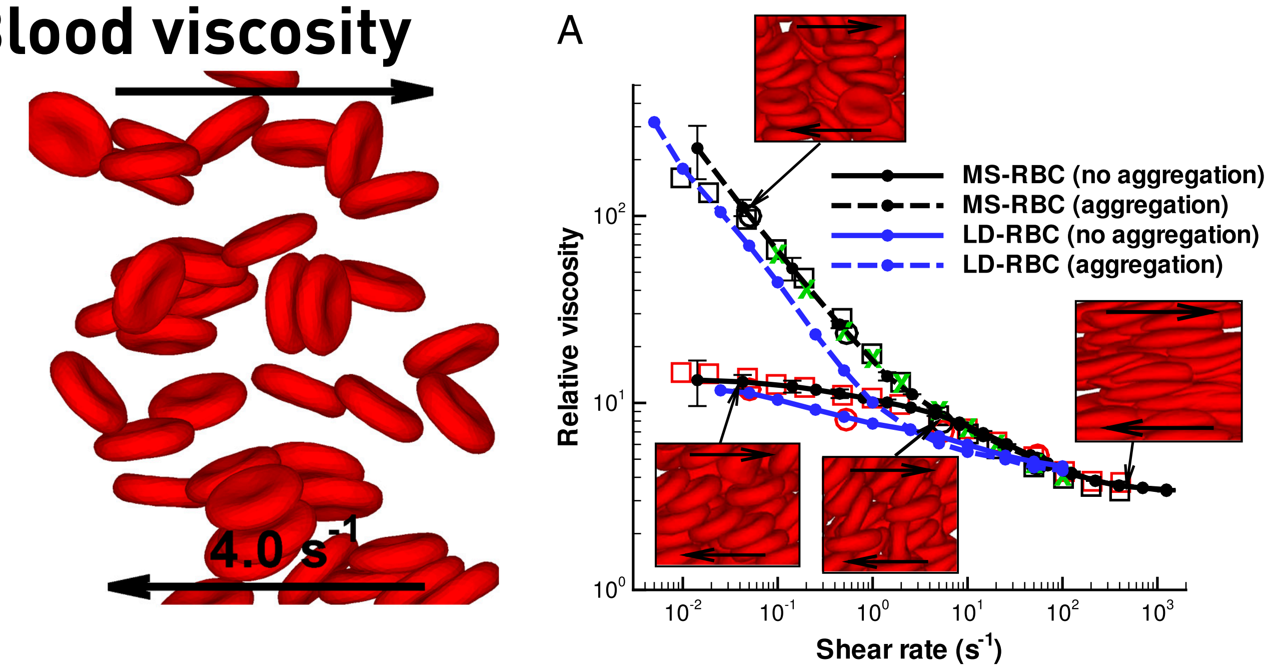
Henry et al., "Sorting cells by their dynamical properties", ***Scientific Reports*****, 2016.**

Platelet transport



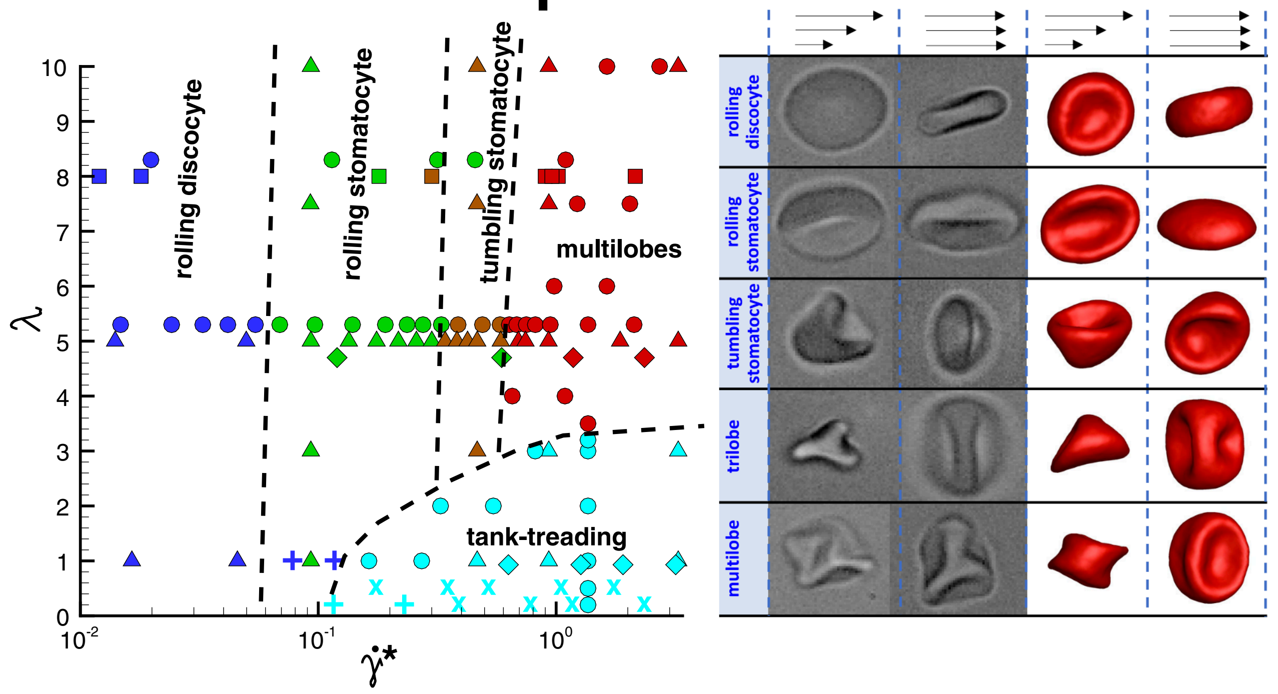
Yazdani and Karniadakis, "Sub-cellular modeling of platelet transport in blood flow through microchannels with constriction", ***Soft Matter*****, 2016.**

Blood viscosity



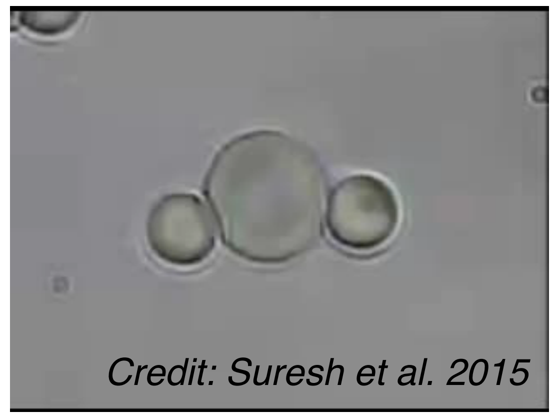
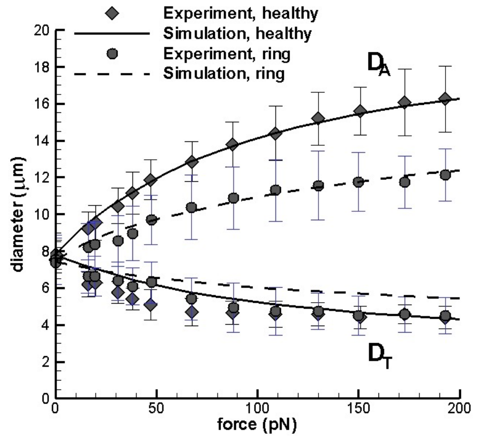
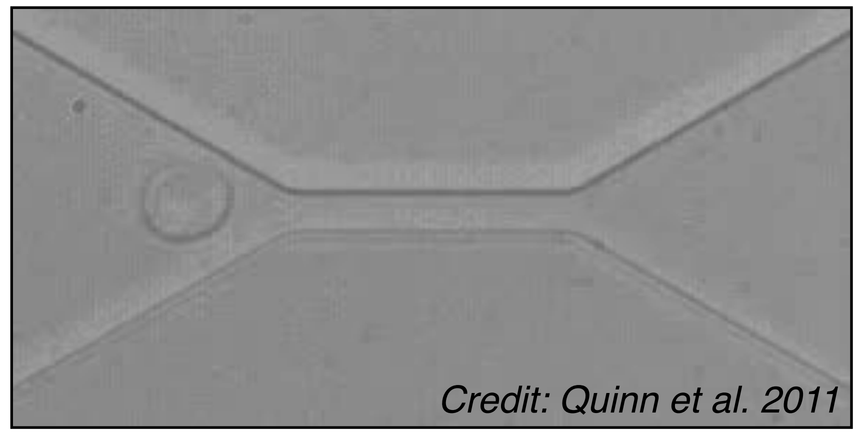
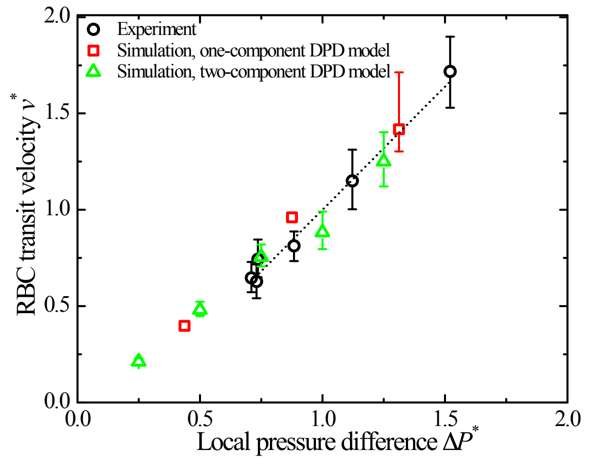
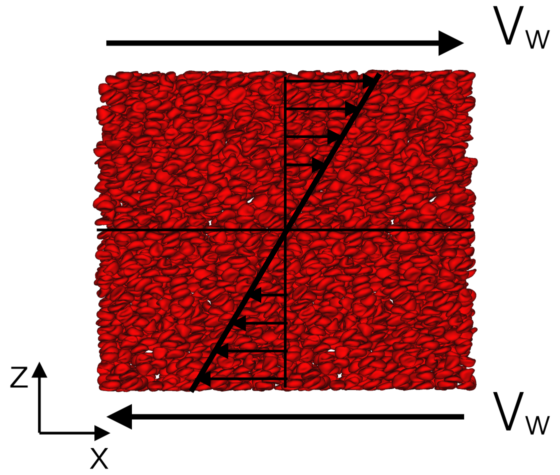
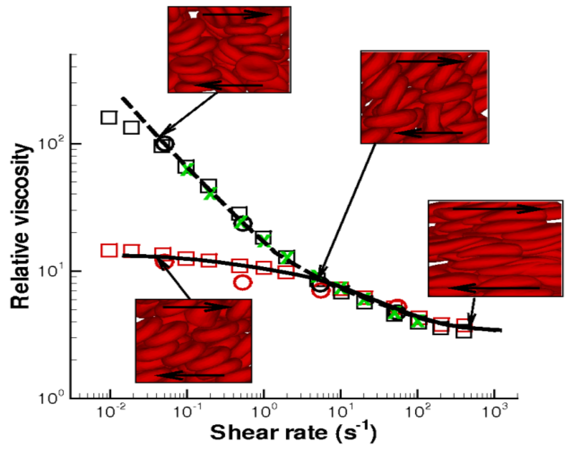
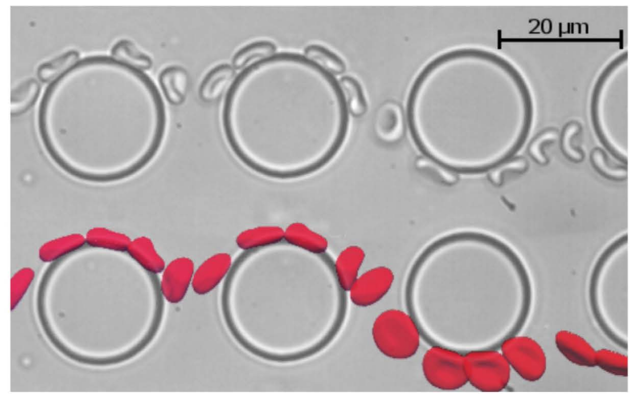
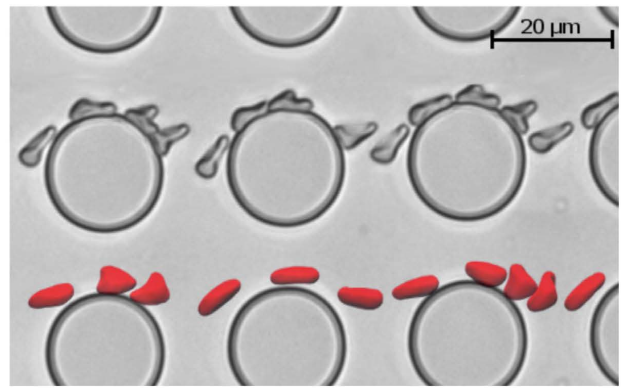
Fedosov et al., "Predicting human blood viscosity in silico", ***PNAS*****, 2011.**

Flow induced shape transitions



Mauer et al., "Flow-Induced Transitions of Red Blood Cell Shapes under Shear", ***PRL*****, 2018.**

Different parameters for different experiments

TEST CASE	Solvent Model / RBCmodel	Membrane rigidity	Membrane viscosity	Shear modulus	viscosity-contrast
stretching (Fedosov et al., 2010)  	DPD / stress-free	4.8E-19 [J]	0.022 [Pa.s]	6.3 e-6 [N/m]	1
squeeze in micro-channel (Bow et al., 2011)  	DPD / constant spring eq. length	7.5 E-19 [J]	varied to study its effect	6.3 e-6 [N/m]	1
shear of whole blood (Fedosov et al., 2011)  	DPD / stress-free	3.0 E-19 [J]	0.0144 [Pa.s]	6.3 e-6 [N/m]	1
DLD device (Henry et al., 2016)  	SDPD+a / stress-free	4.8 E-19 [J]	0.022 [Pa.s]	2.4 e-6 [N/m]	5

Different parameters for different experiments

Application	T (°C)	μ_0 (µN/m)	κ_b (10^{-19} J)	η_m/η_{Hb}
		single RBC		
Stretching[20]	23	6.30	2.40	–
TTC and shear flow[19]	23	6.30	4.80	4.4
Cylindrical μ-channel flow[24]	37	4.83	3.00	*n.a.*
Equilibrium[70]	23	2.42	1.43	22.2
DLD device[34]	37	4.83	3.00	*n.a.*
Dynamic morphologies in shear[44]	37	4.83	3.00	*n.a.*
Flow-induced shape transitions[49]	37	4.80	3.00	0
		multiple RBCs		
Cell-free layer[21]	23	4.59	2.40	18.3
Pf-malaria biophysics[22]	37	6.30	2.40	*n.a.*
Blood viscosity prediction[23]	37	4.82	3.00	12.0
Platelet transport[76]	27	4.50	2.98	*n.a.*

Outline

1. Blood model
2. Hierarchical Bayesian inference
3. Transferability of the calibrated model

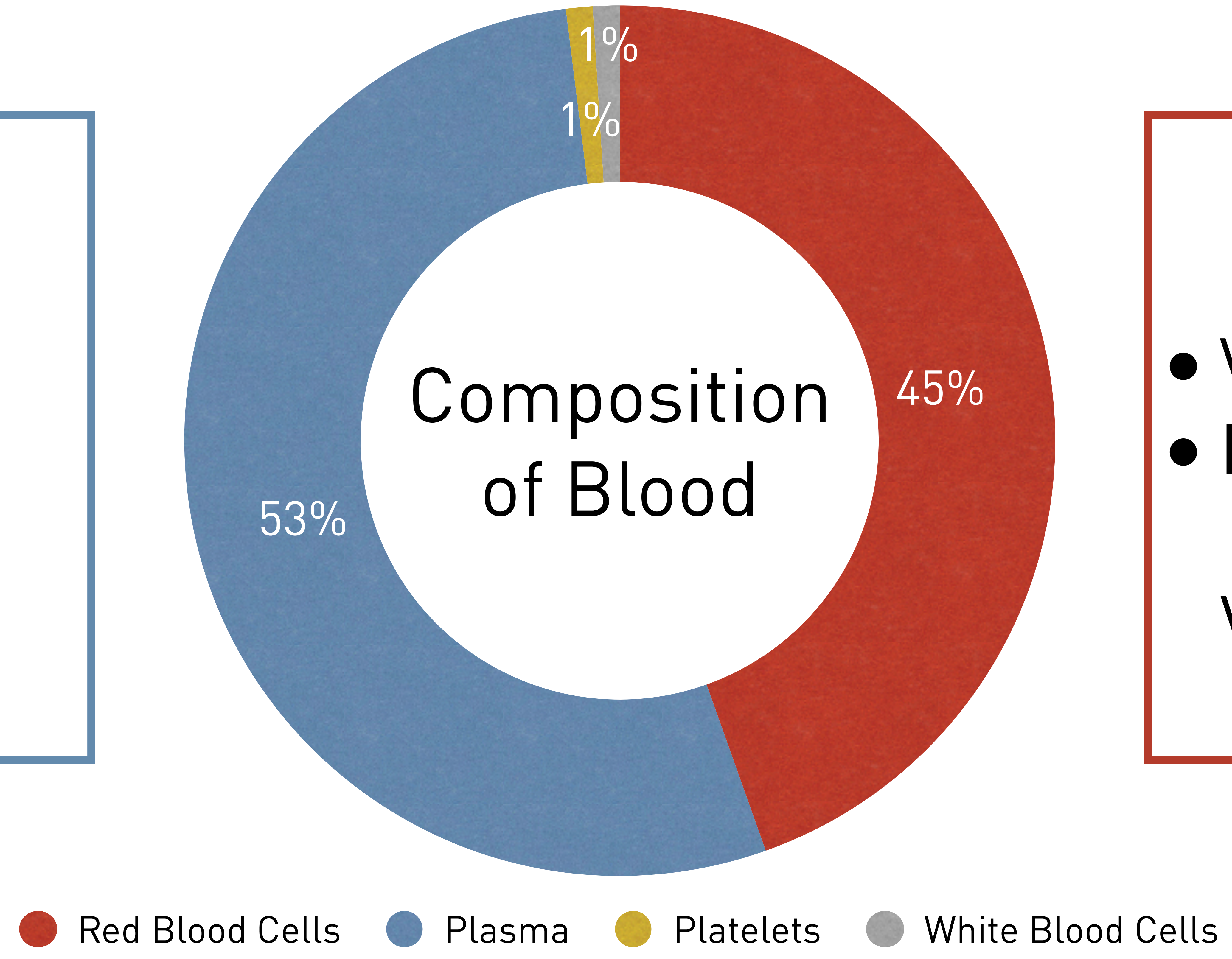
Blood Model

Blood model

Blood Plasma

- Newtonian fluid
- Incompressible

Dissipative particle dynamics (DPD)



Red Blood Cells

- Visco elastic membranes
- No nucleus

Viscoelastic forces on a triangle mesh

Dissipative Particle Dynamics (DPD)

Fluid represented by particles

Positions $\mathbf{r}_i$,

Velocities $\mathbf{v}_i$,

Mass m

Newton motion

$$\dot{\mathbf{r}}_i = \mathbf{v}_i,$$

$$\dot{\mathbf{v}}_i = \frac{1}{m}\mathbf{f}_i,$$

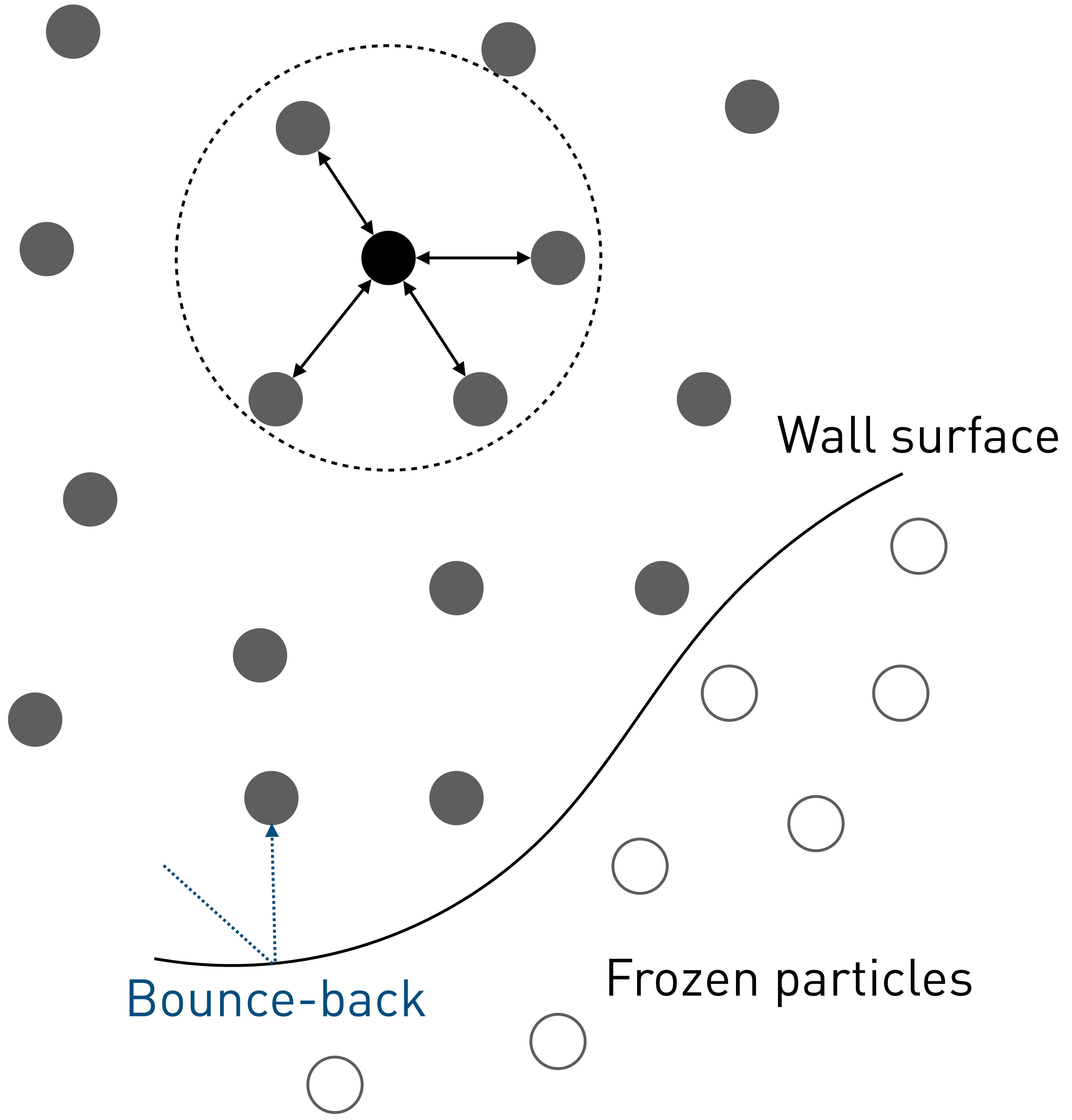
Dissipative Particle Dynamics forces

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

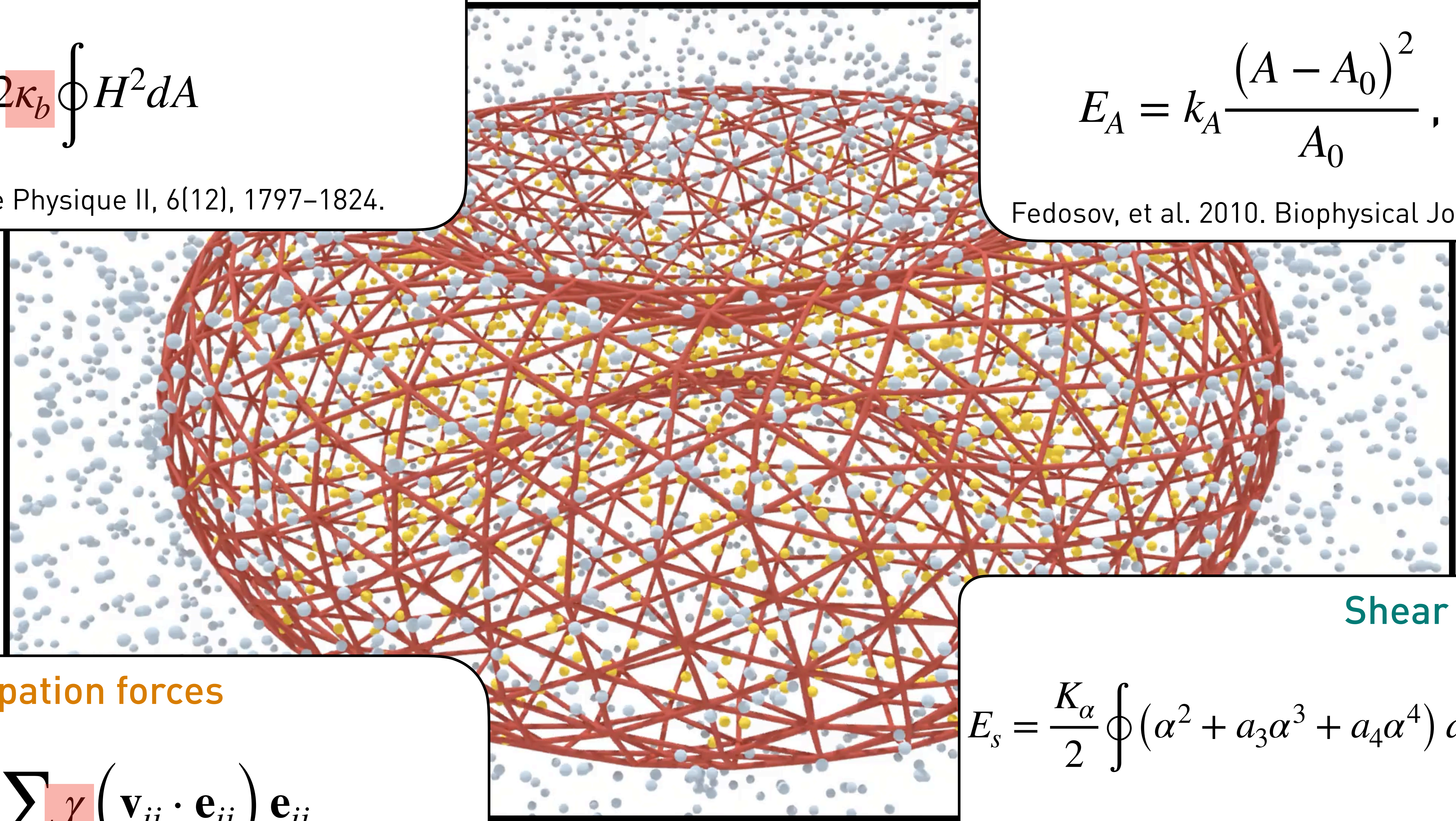
$\mathbf{f}_{ij}^C = a w(r_{ij})\mathbf{e}_{ij},$ hydrostatic pressure

$\mathbf{f}_{ij}^D = -\gamma w_D(r_{ij})\left(\mathbf{e}_{ij}\cdot\mathbf{v}_{ij}\right)\mathbf{e}_{ij},$ viscosity

$\mathbf{f}_{ij}^R = \sigma \xi_{ij} w_R(r_{ij})\mathbf{e}_{ij}$ fluctuations



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

$$E_A = k_A \frac{\left(A - A_0\right)^2}{A_0}\,, \qquad E_V = k_V \frac{\left(V - V_0\right)^2}{V_0}$$

Fedosov, et al. 2010. Biophysical Journal, 98(10), 2215–2225.

Dissipation forces

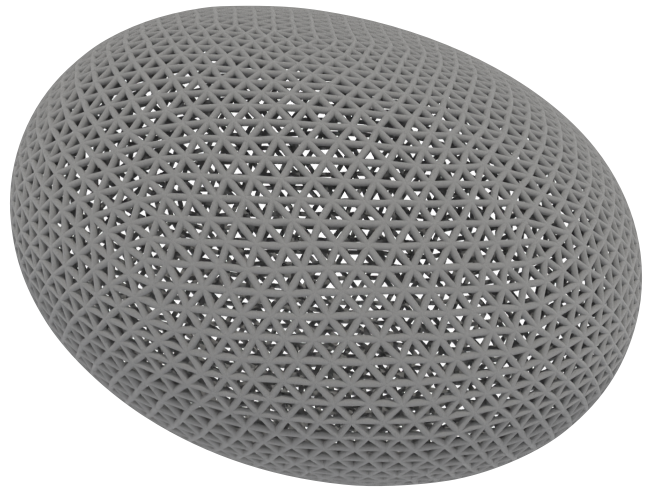
$$\mathbf{f}_i^{visc} = -\sum_j \gamma \left(\mathbf{v}_{ij} \cdot \mathbf{e}_{ij}\right) \mathbf{e}_{ij}$$

Fedosov, et al. 2010. Biophysical Journal, 98(10), 2215–2225.

Shear Energy

$$E_s = \frac{K_\alpha}{2} \oint \left(\alpha^2 + a_3\alpha^3 + a_4\alpha^4\right) dA_0 + \mu \oint \left(\beta + b_1\alpha\beta + b_2\beta^2\right) dA_0$$

with respect to stress-free shape of reduced volume v:



Lim et al. 2008. Soft Matter, 4.

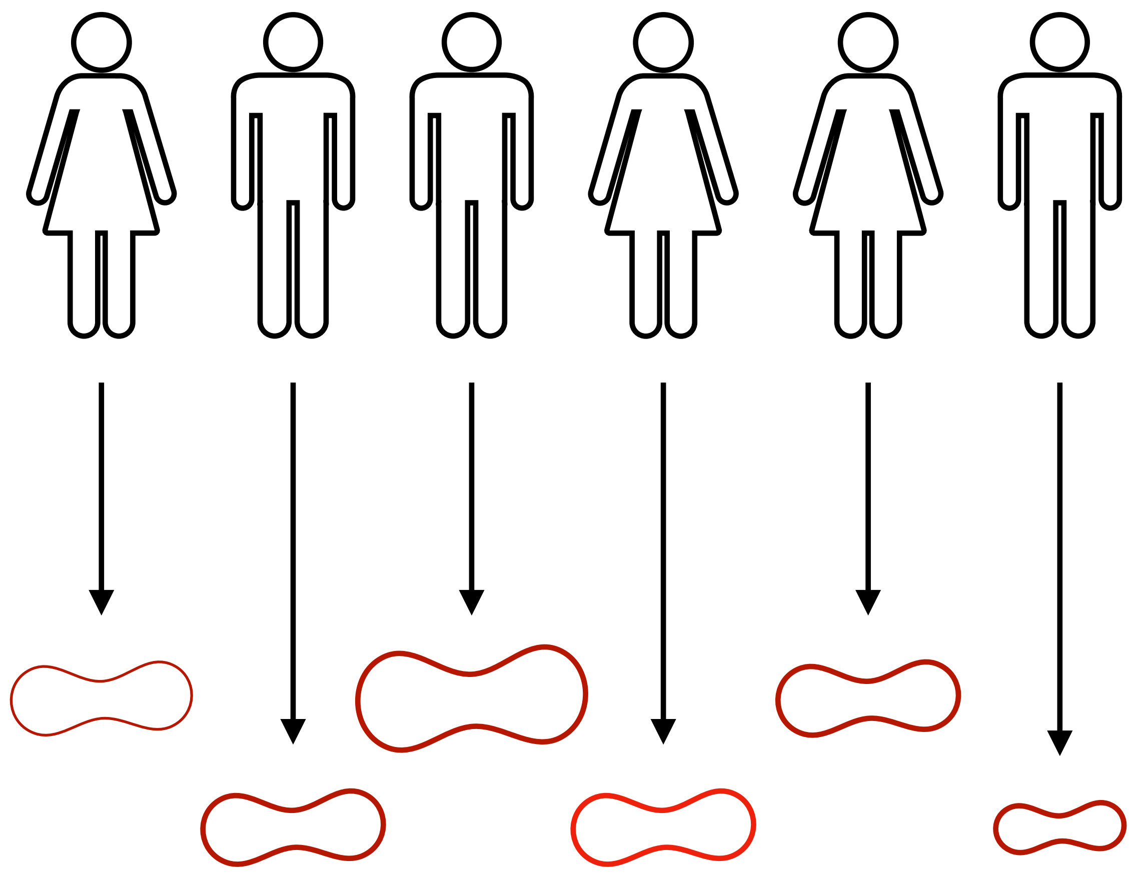
Hierarchical Bayesian model

The need to combine multiple datasets

Different individuals

=

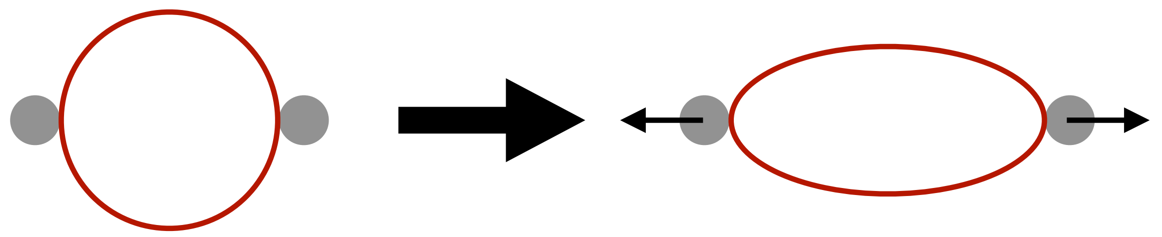
different RBCs



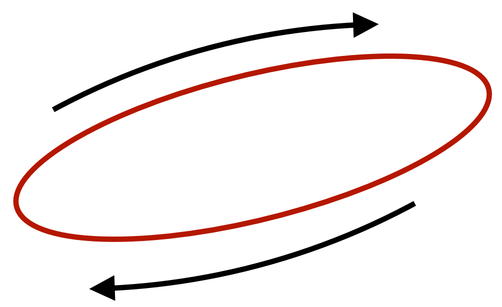
Different experiments

=

different sensitivity to parameters



Elastic parameters

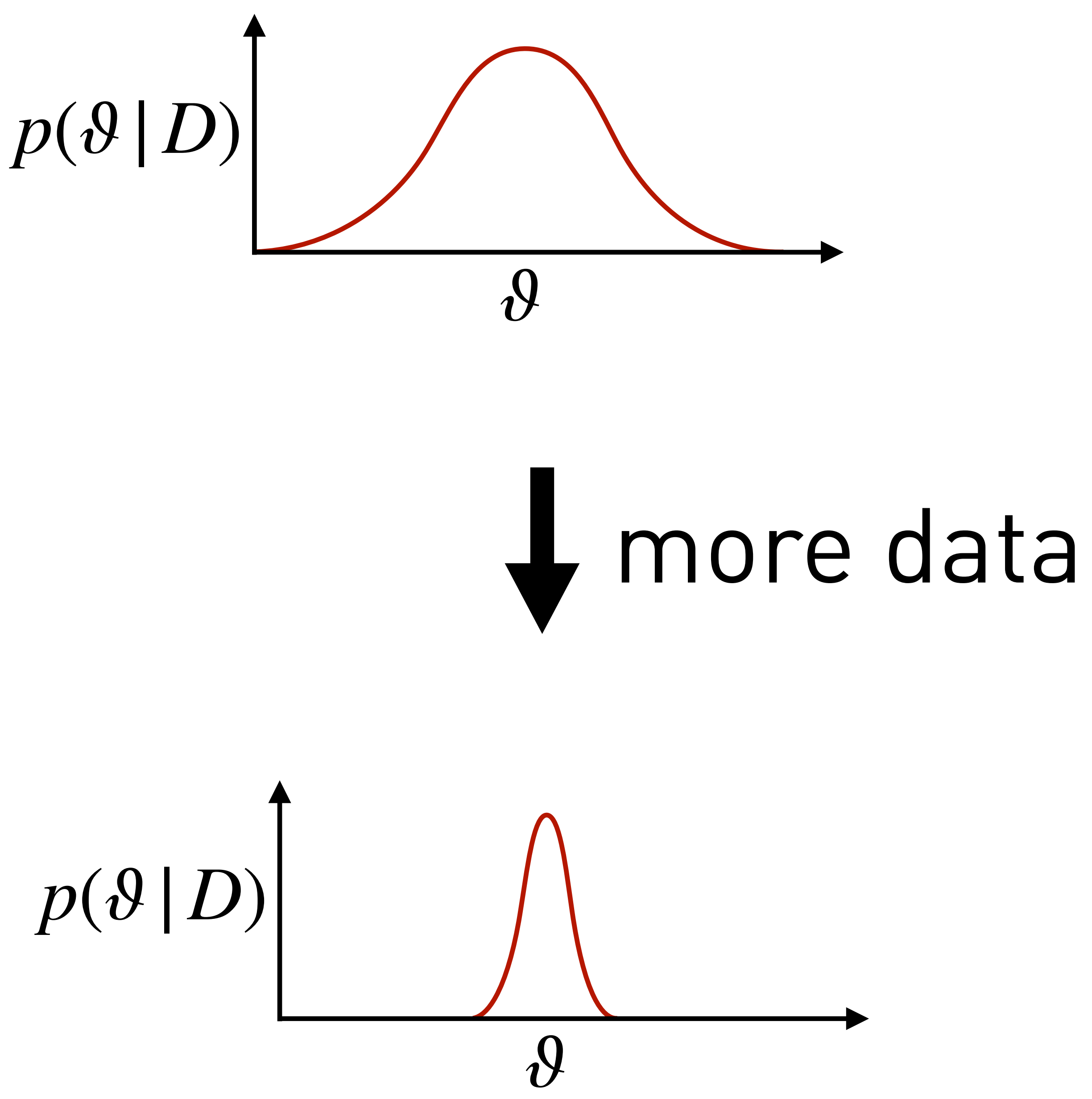


Elastic + Viscous parameters

More data

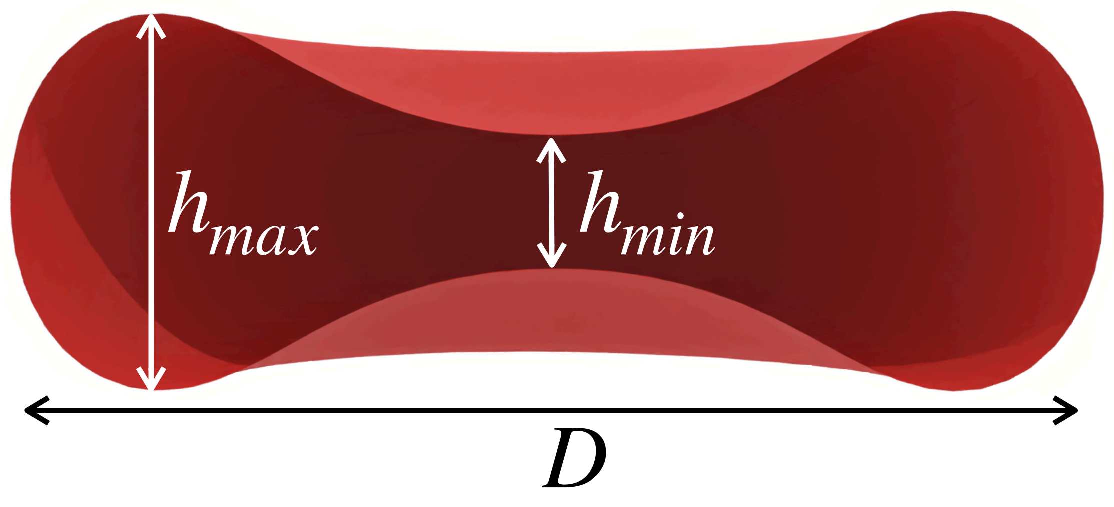
=

less uncertainty



Single-cell experimental data

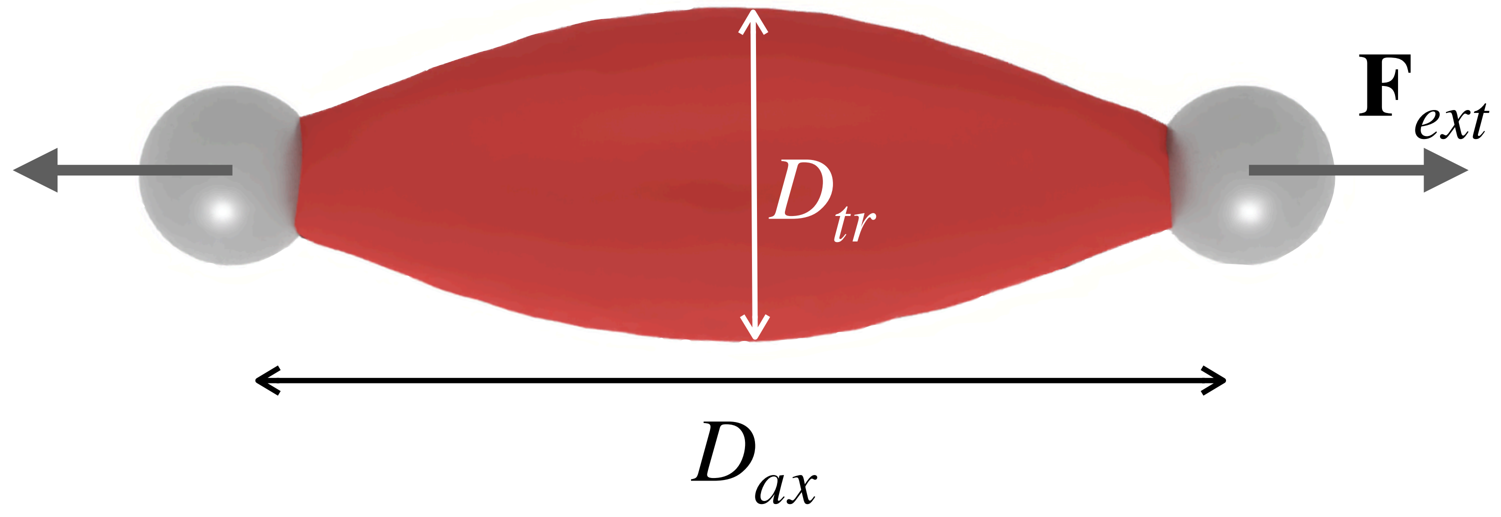
Equilibration

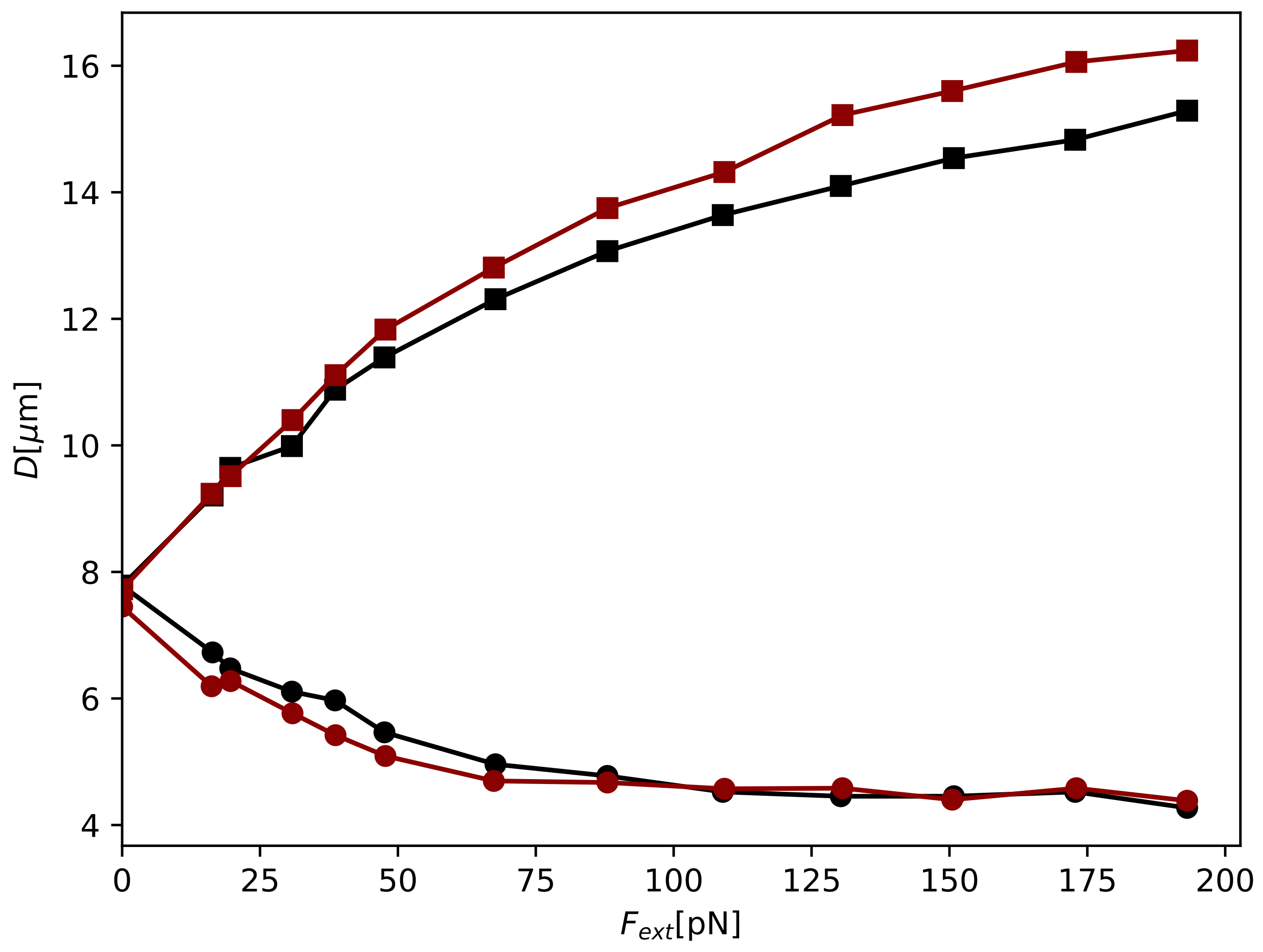


Diameter	Minimum thickness	Maximum thickness
7.82 μm	0.81 μm	2.58 μm

Evans, Evan, and Yuan-Cheng Fung. "Improved measurements of the erythrocyte geometry." *Microvascular research* 4.4 (1972): 335-347.

Stretching

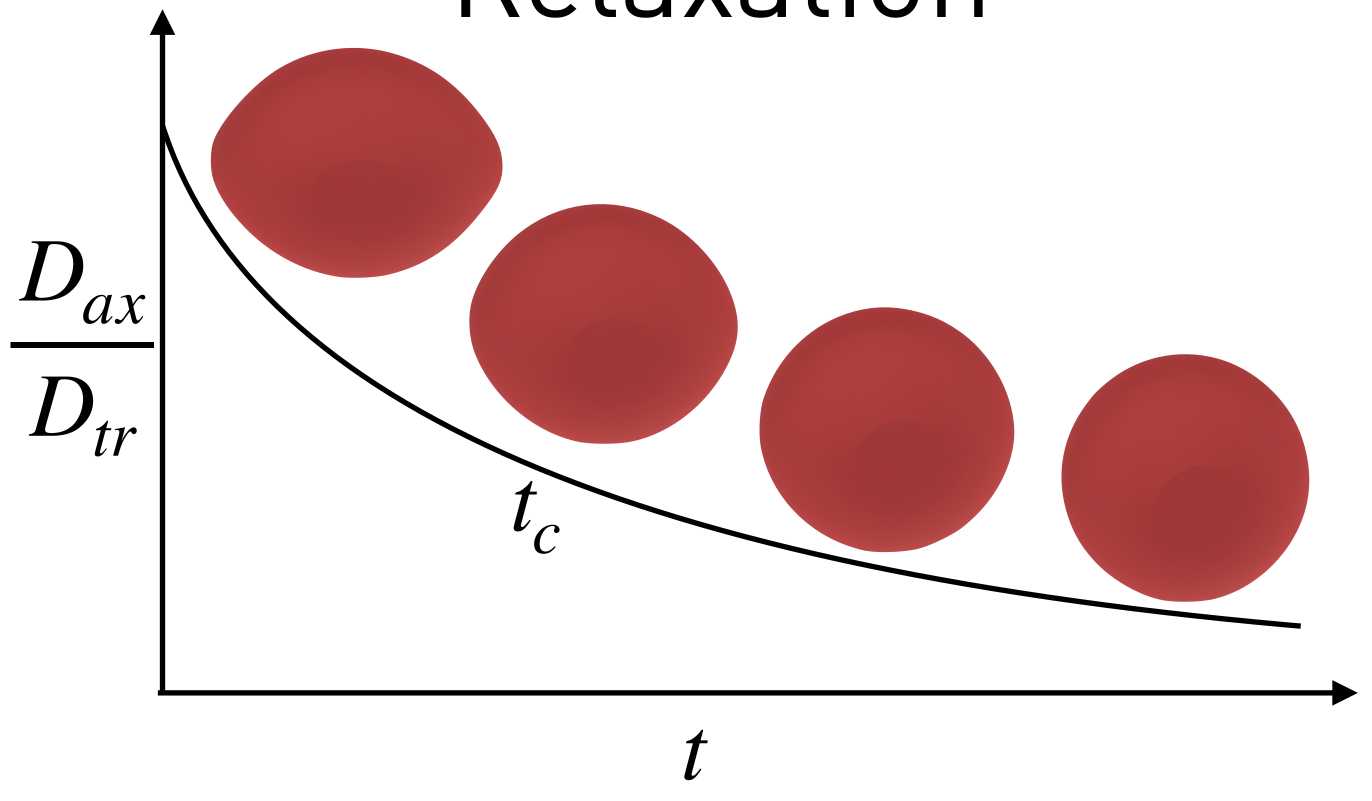


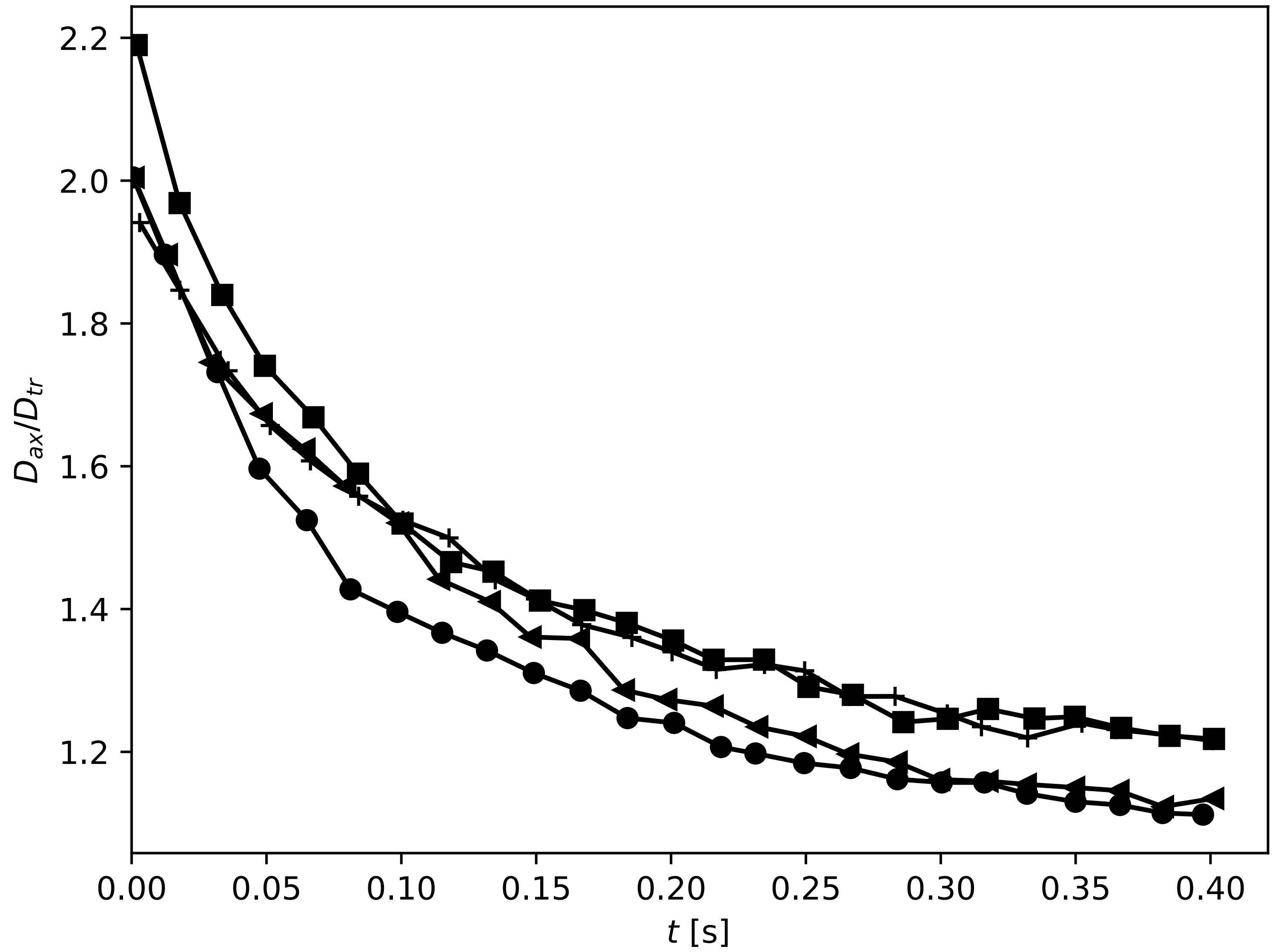


● Mills, J. P., et al. "Nonlinear elastic and viscoelastic deformation of the human red blood cell with optical tweezers." *Molecular & Cellular Biomechanics* 1.3 (2004): 169.

● Suresh, Subra, et al. "Connections between single-cell biomechanics and human disease states: gastrointestinal cancer and malaria." *Acta biomaterialia* 1.1 (2005): 15-30.

Relaxation



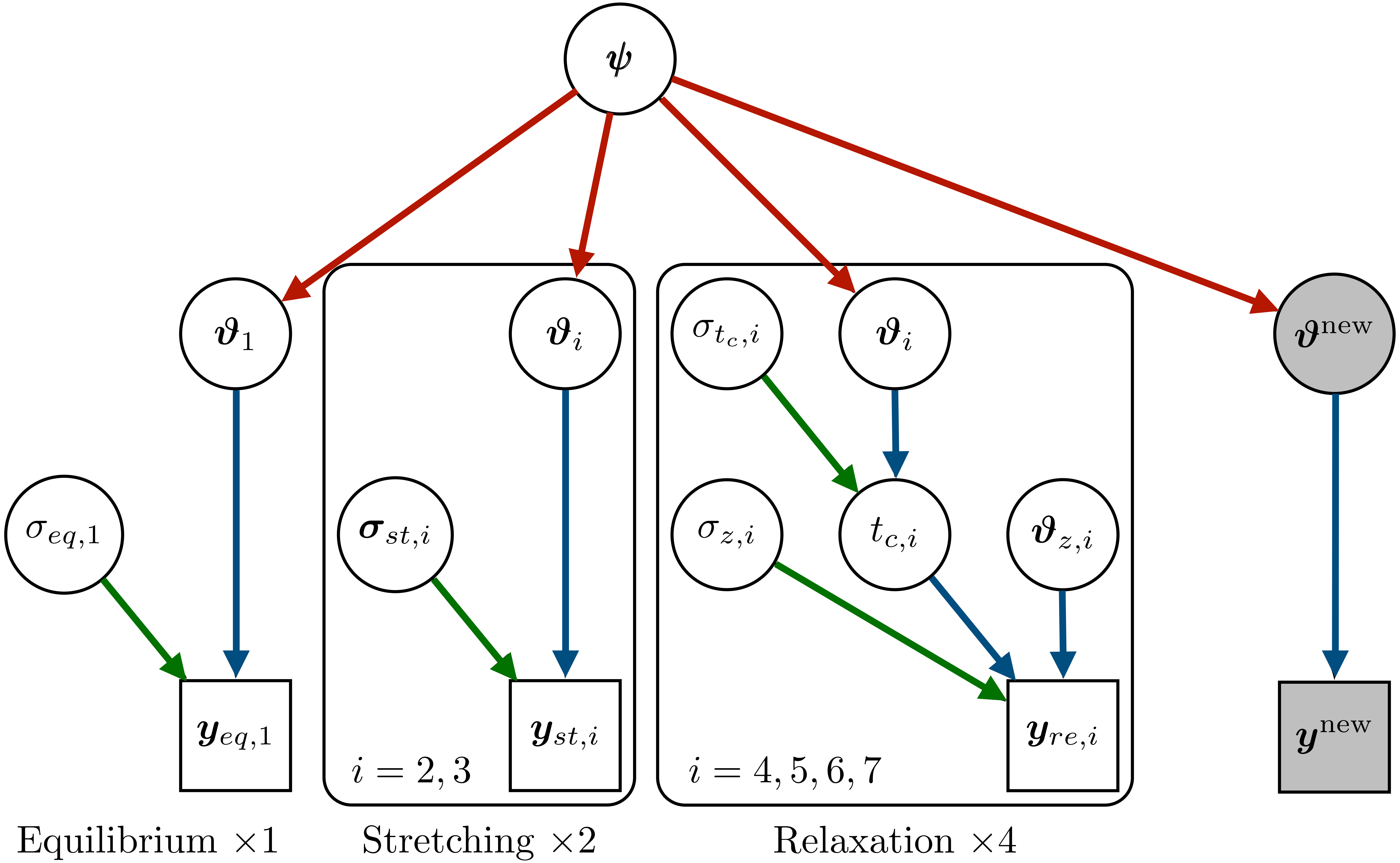


Hochmuth, Robert M., P. R. Worthy, and Evan A. Evans. "Red cell extensional recovery and the determination of membrane viscosity." *Biophysical journal* 26.1 (1979): 101-114.

Hierarchical statistical model

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

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



○ unobserved variables

□ observed variables

Inferring the parameters

$$p(\psi | D) = \frac{p(D | \psi) p(\psi)}{p(D)}$$

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

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

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

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

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

Sampling with TMCMC, 50’000 samples

https://github.com/cselab/korali

Wu et al. *ASCE-ASME J Risk and Uncert in Engrg Sys*, 2019

From parameters to observables

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

Stress-free state generation → Equilibration → Stretching → Relaxation

Equilibration → D, h_{min}, h_{max}

Stretching → D_{ax}, D_{tr}

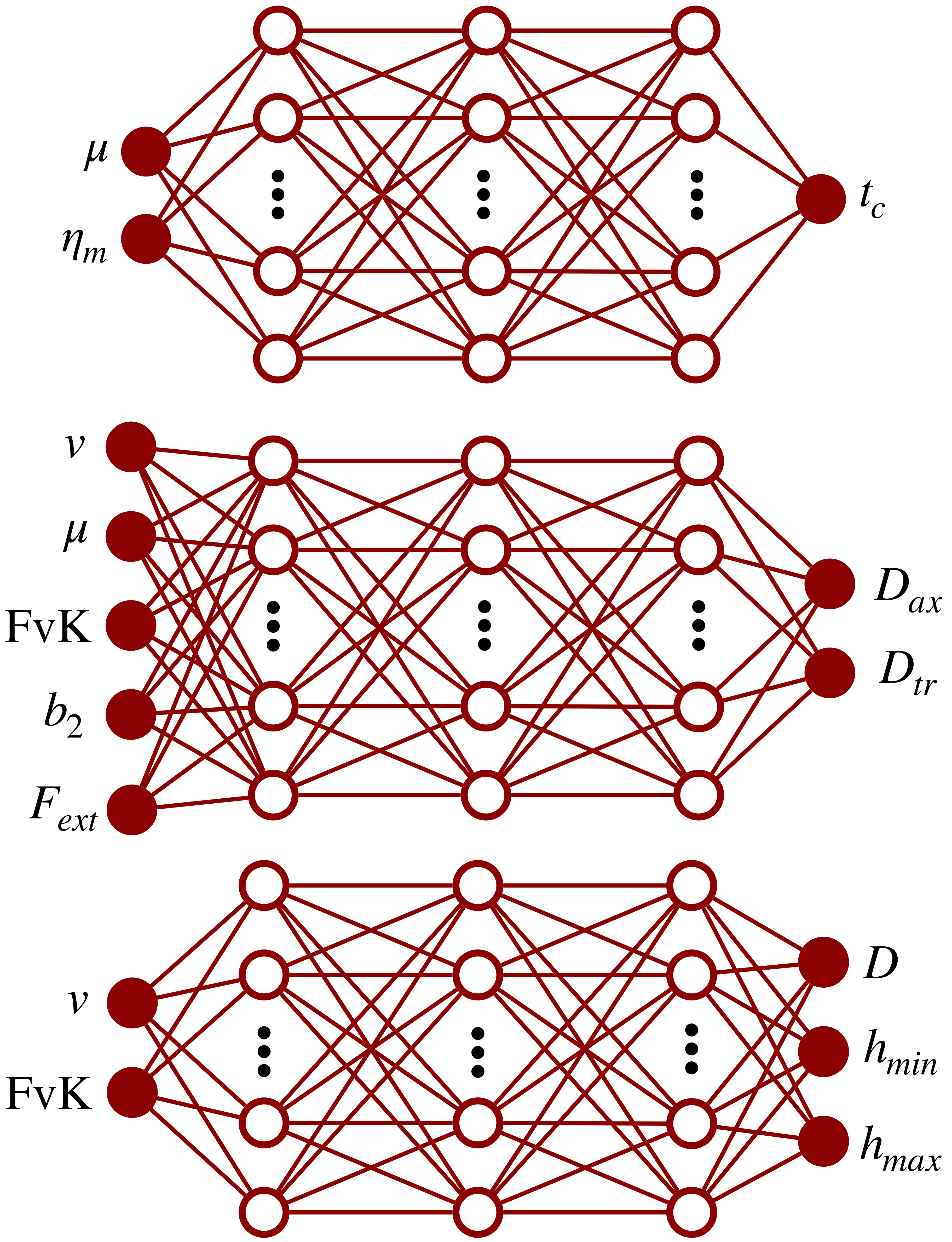
Relaxation → t_c

Offline surrogate to accelerate inference

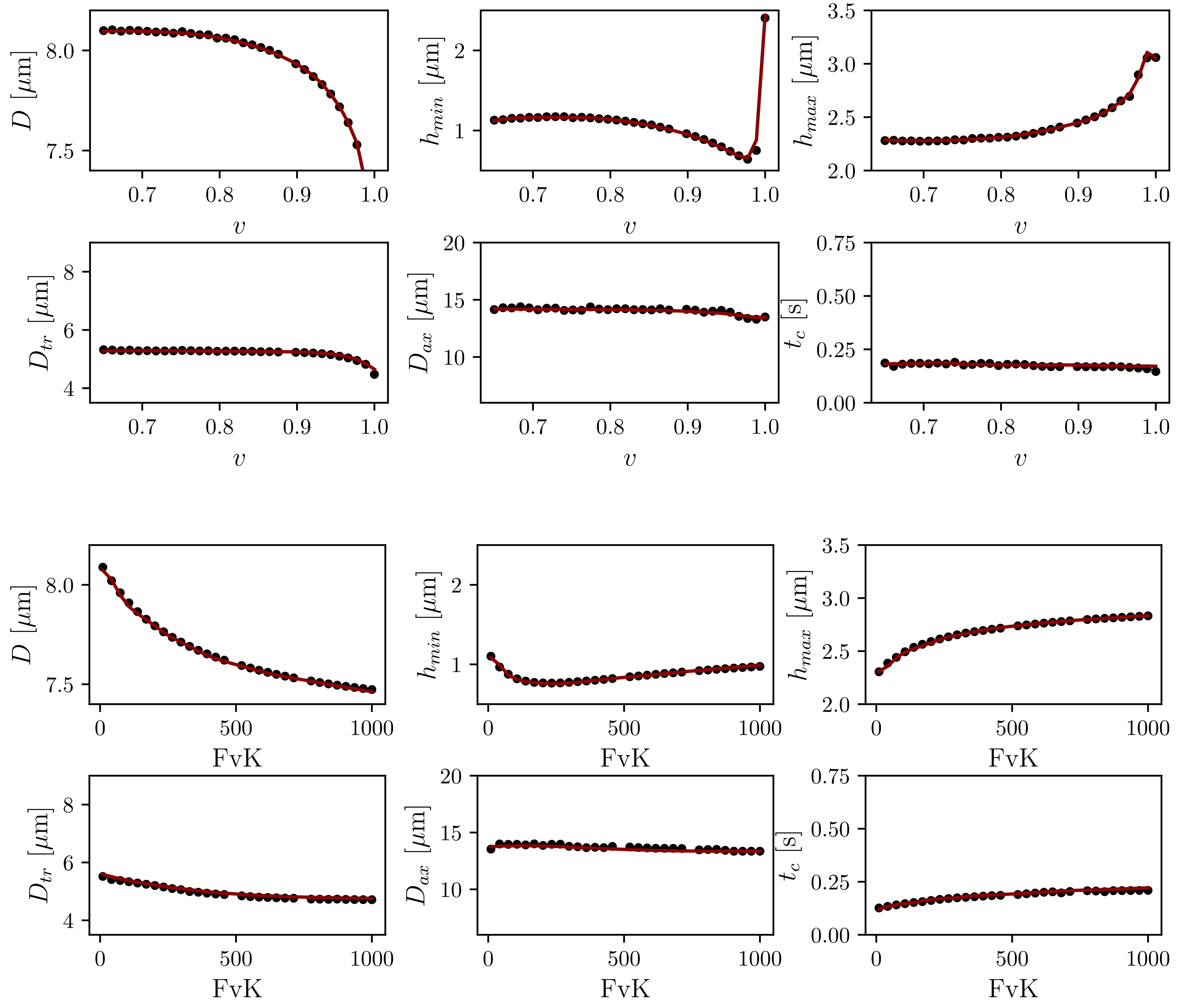
Relaxation

Stretching

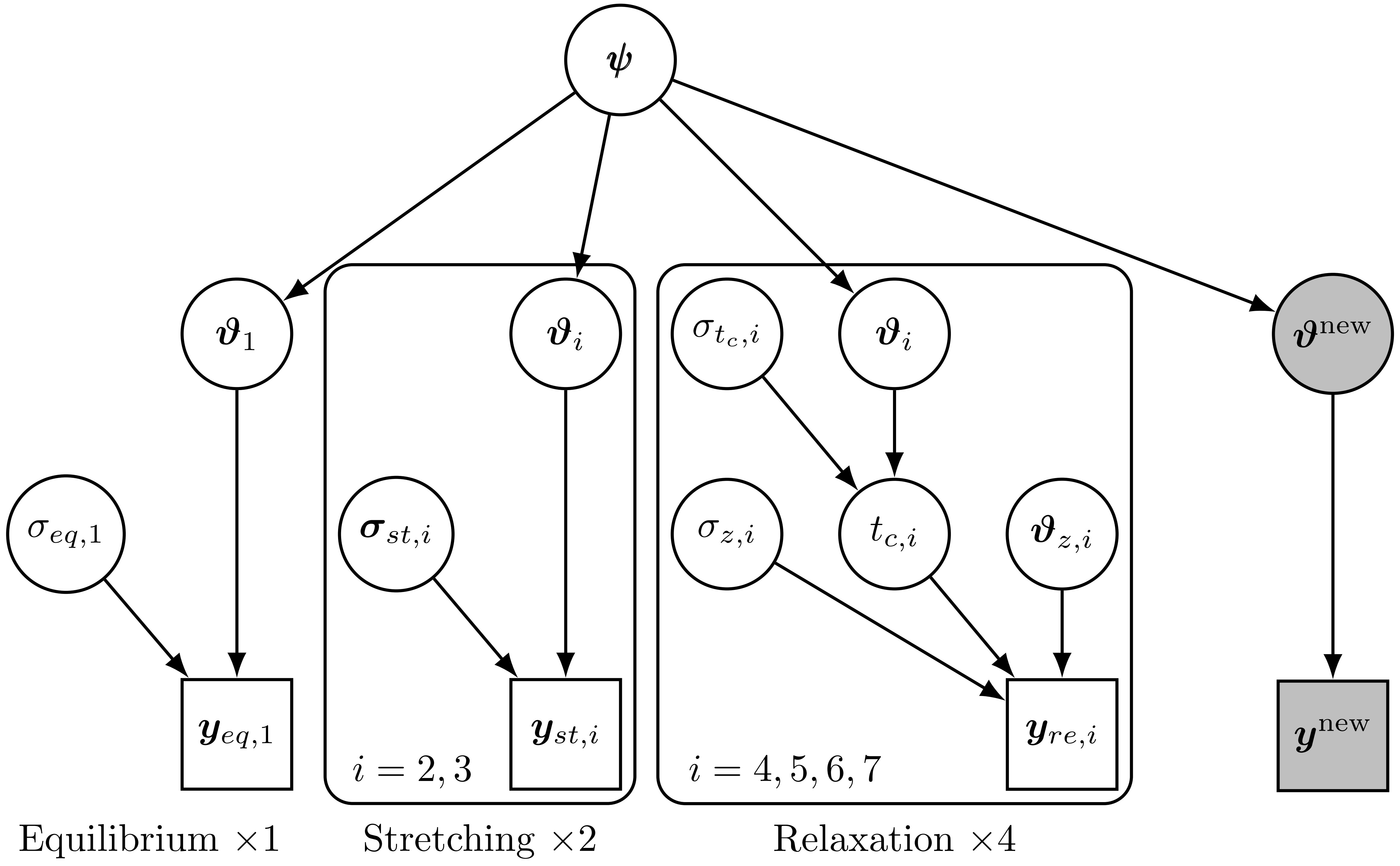
Equilibration

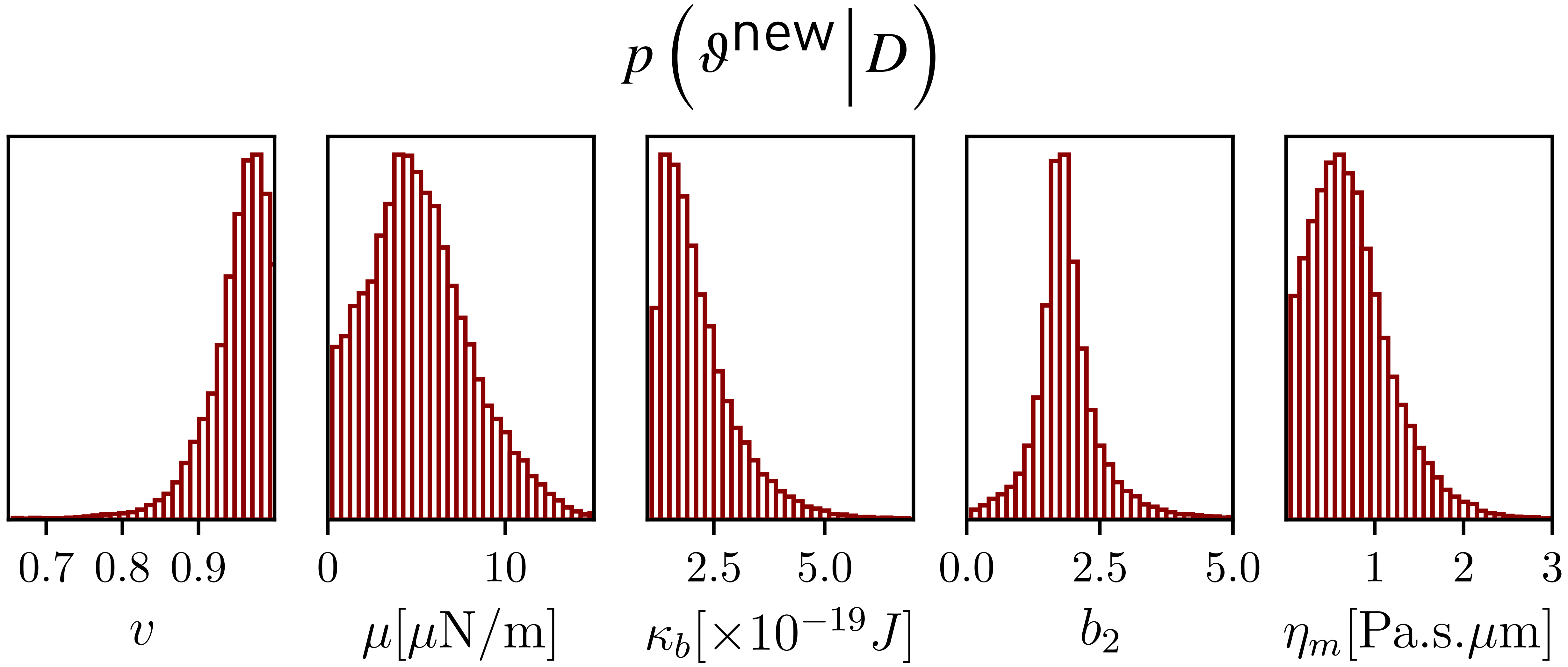


Feed-forward Neural Networks,
3 hidden layers of 32 neurons

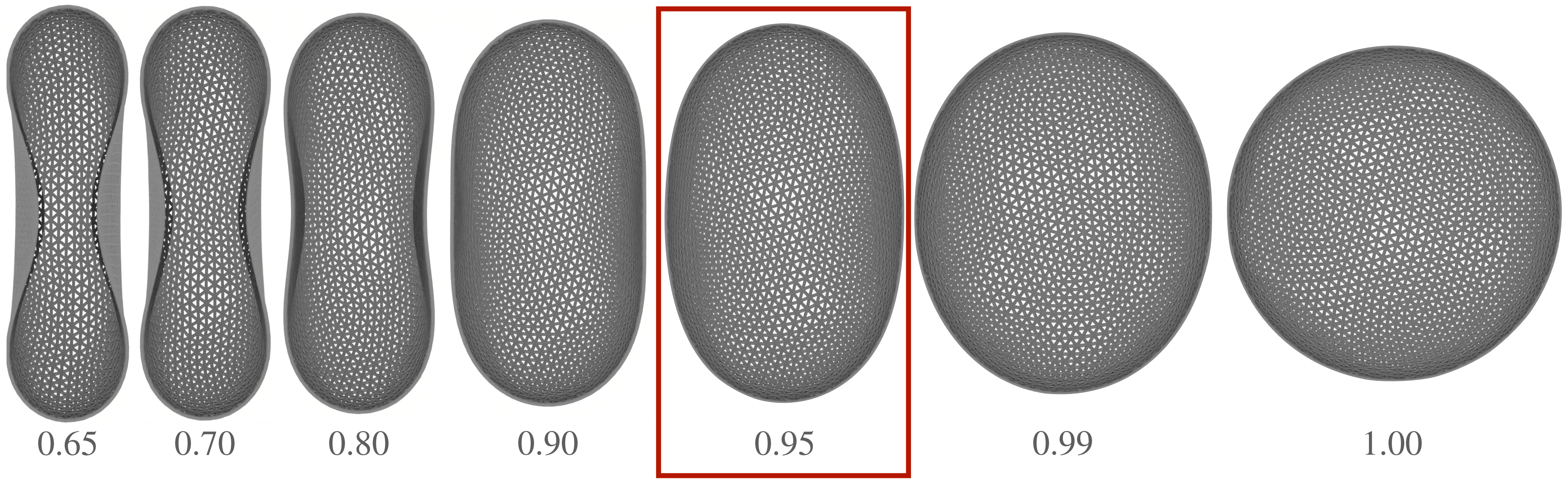


Posterior distribution

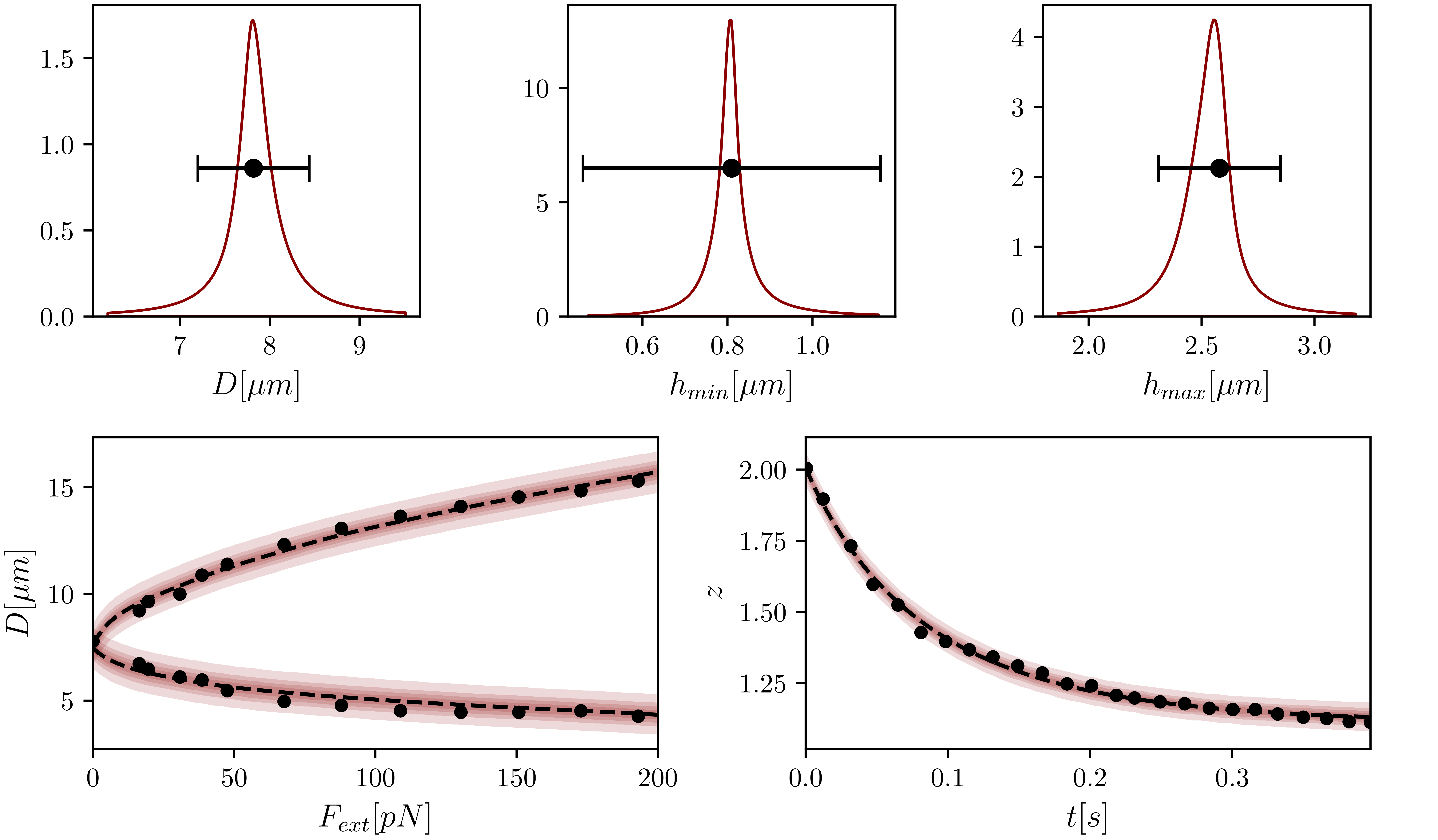




Most likely
Stress-free state



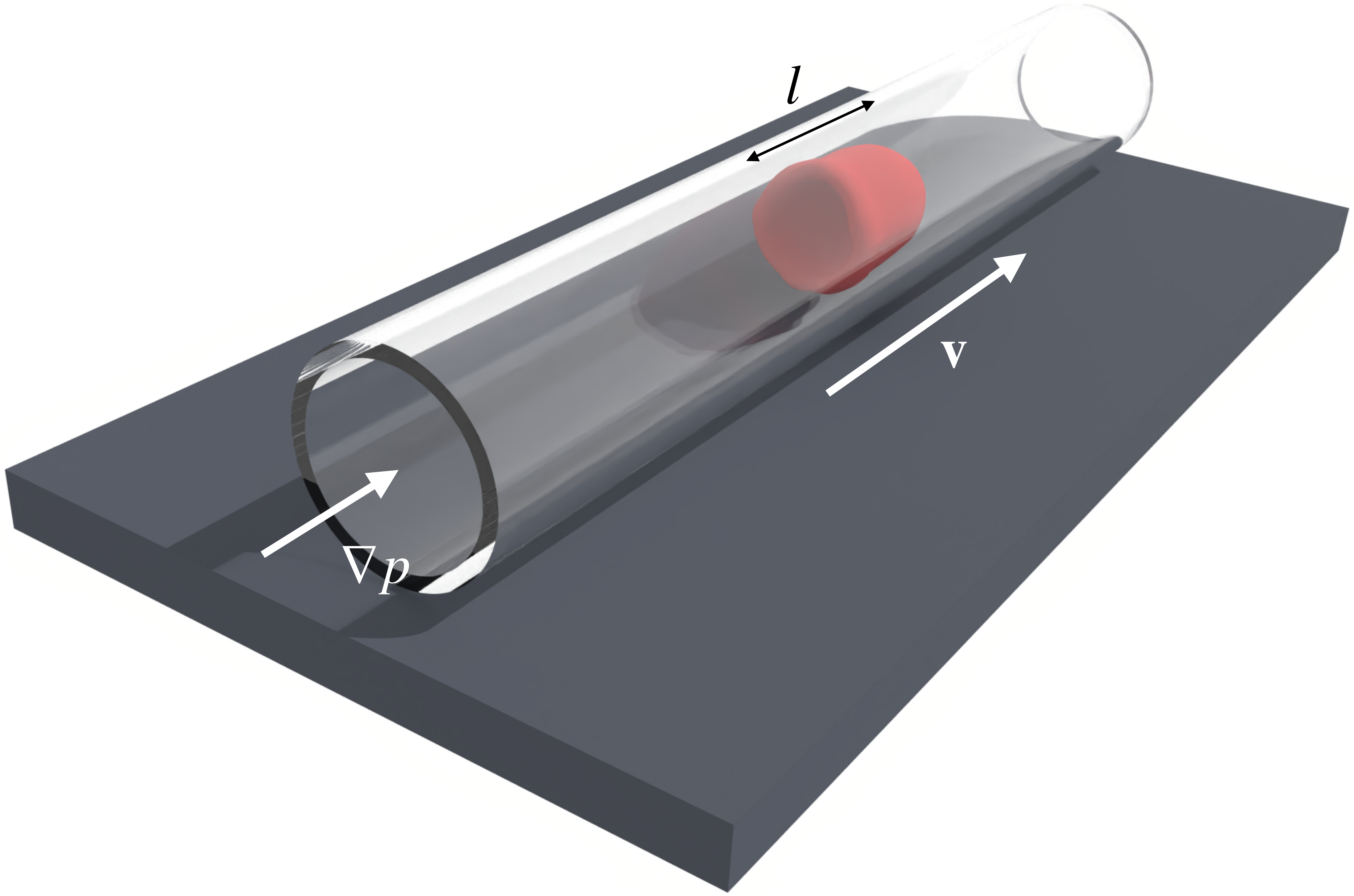
Model predictions on the calibration data sets

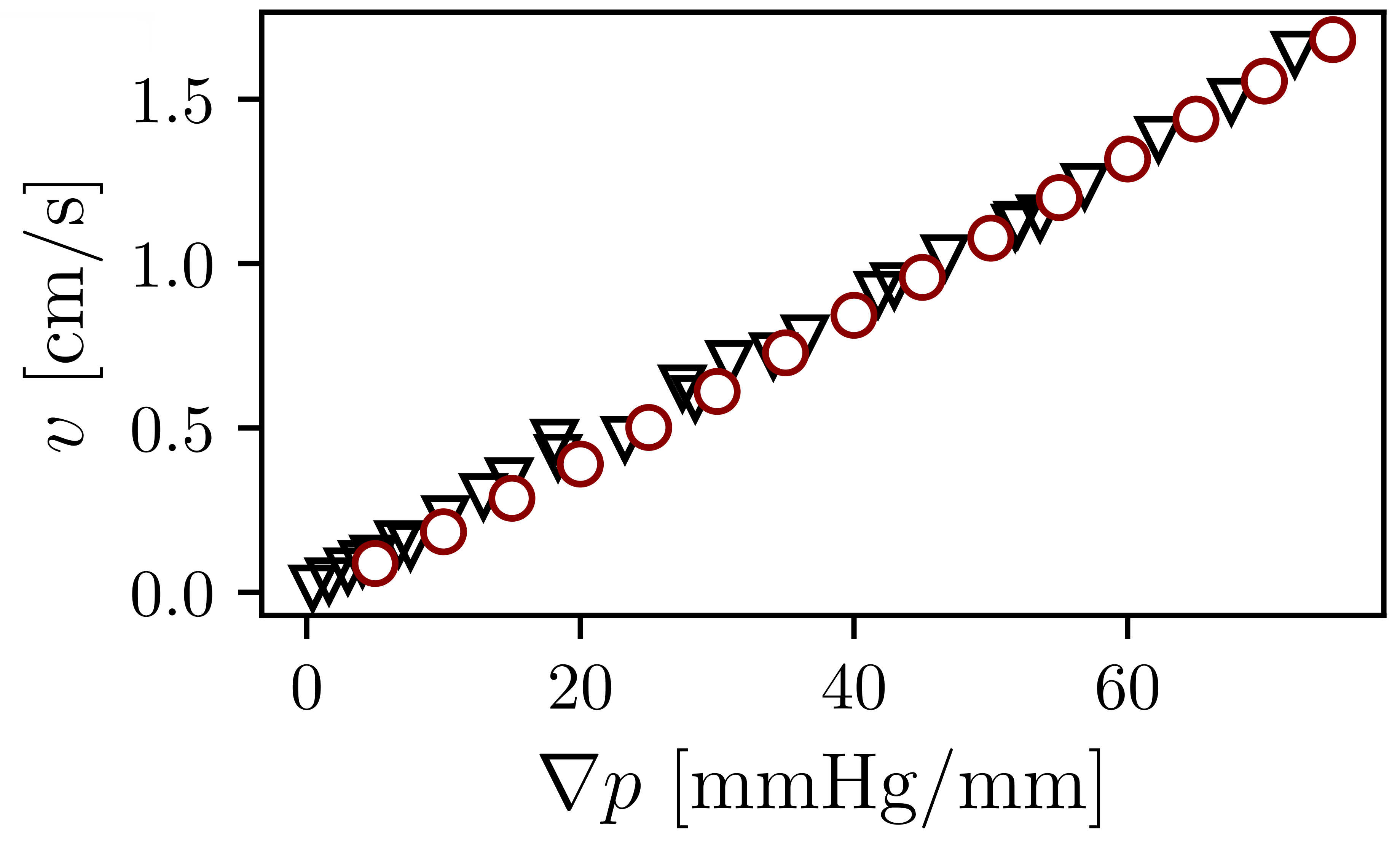


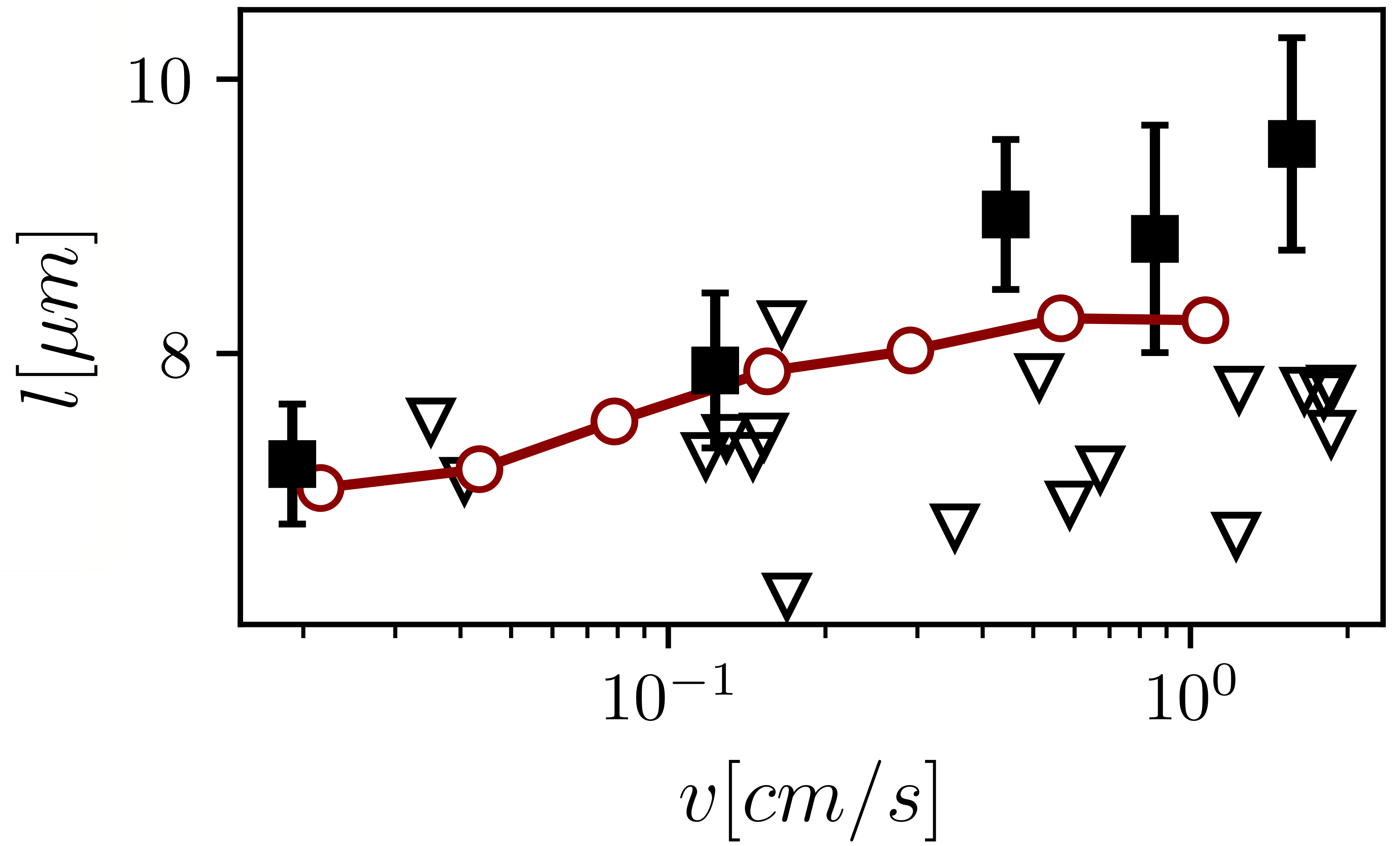
Transferability of the model

Prediction on previously unseen data

Single cell in straight micro-tube



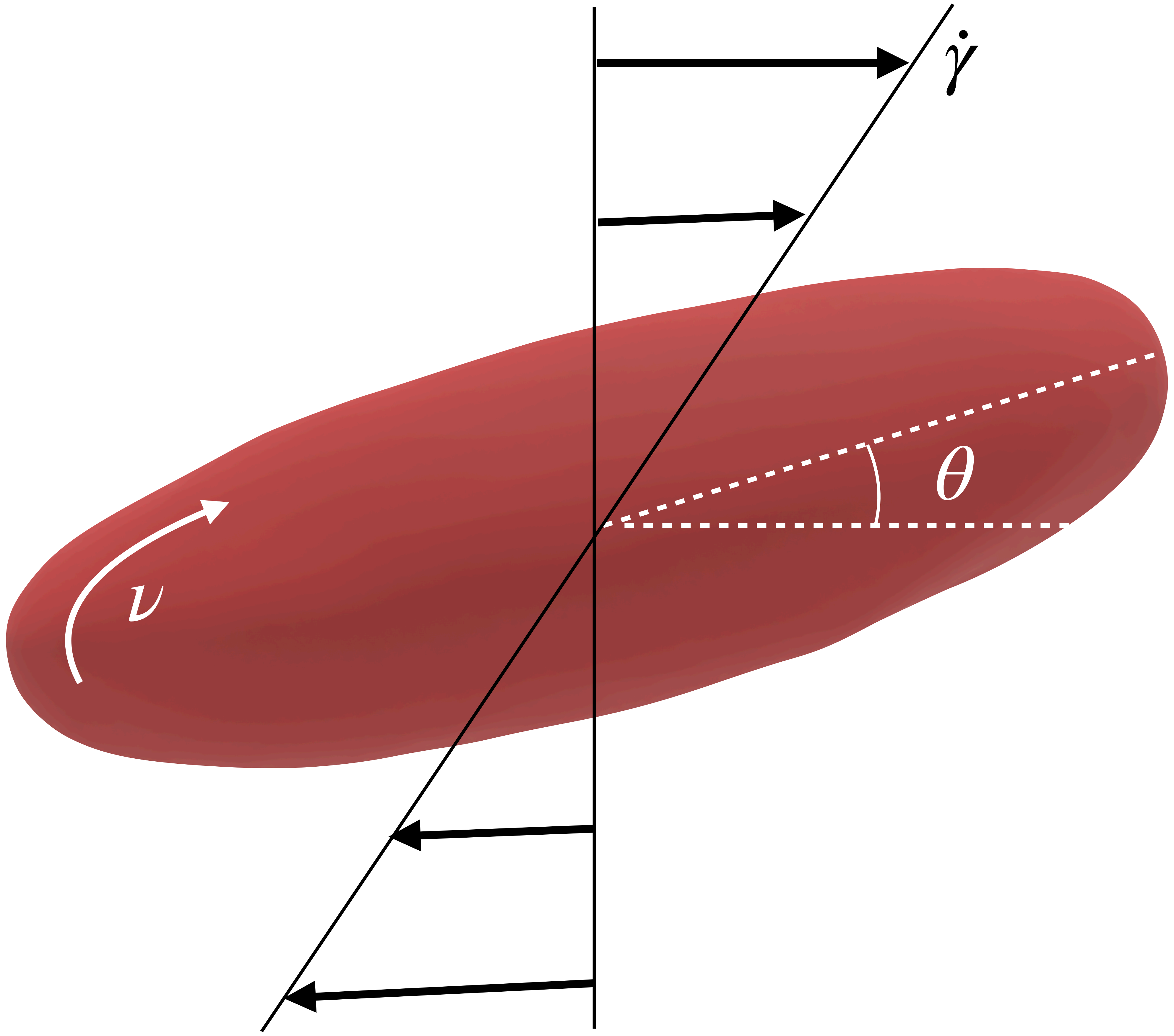




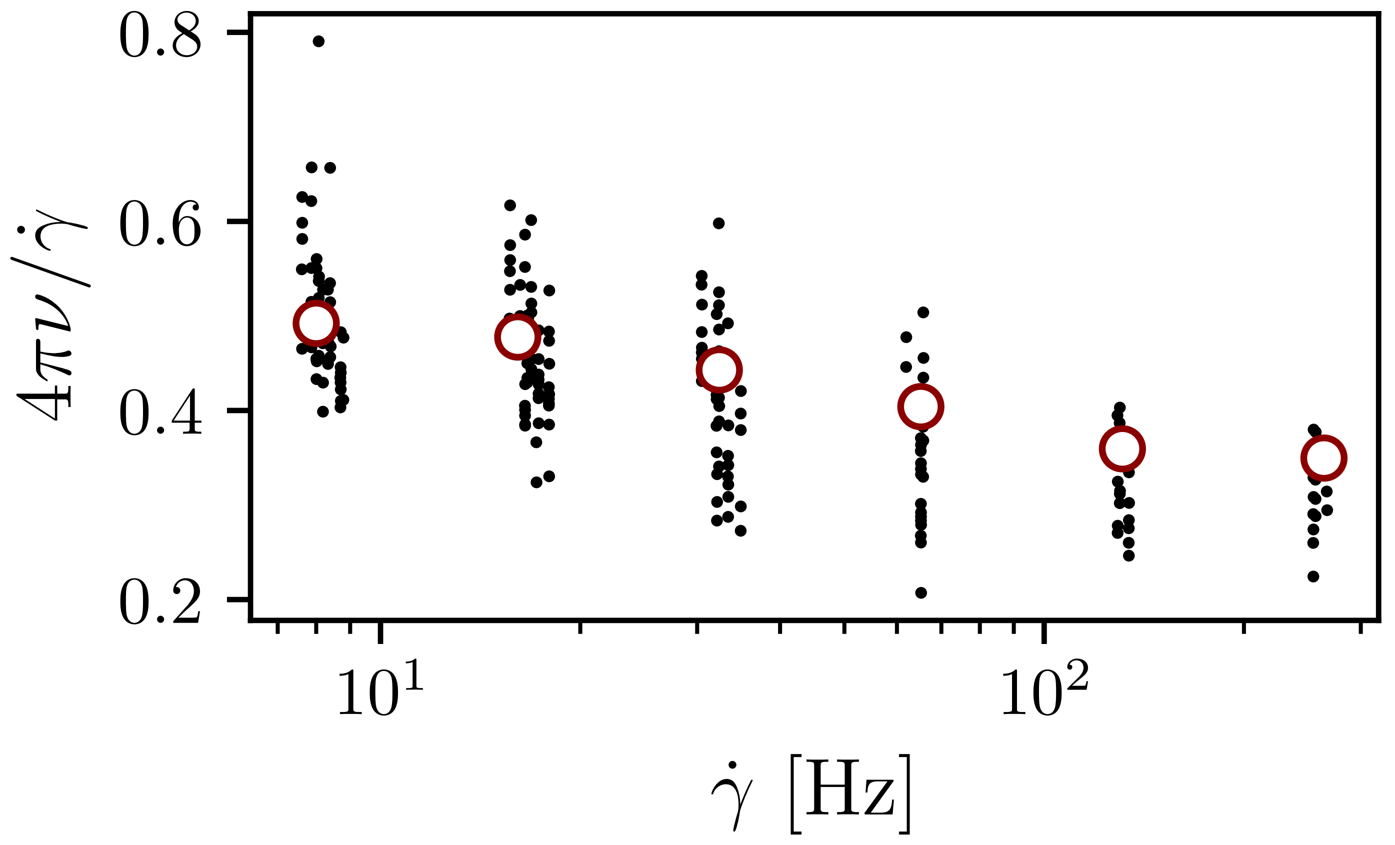
Tomaiuolo, Giovanna, et al. "Red blood cell deformation in microconfined flow." *Soft Matter* 5.19 (2009): 3736-3740.

Hochmuth, R. M., R. N. Marple, and S. P. Sutera. "Capillary blood flow: I. Erythrocyte deformation in glass capillaries." *Microvascular research* 2.4 (1970): 409-419.

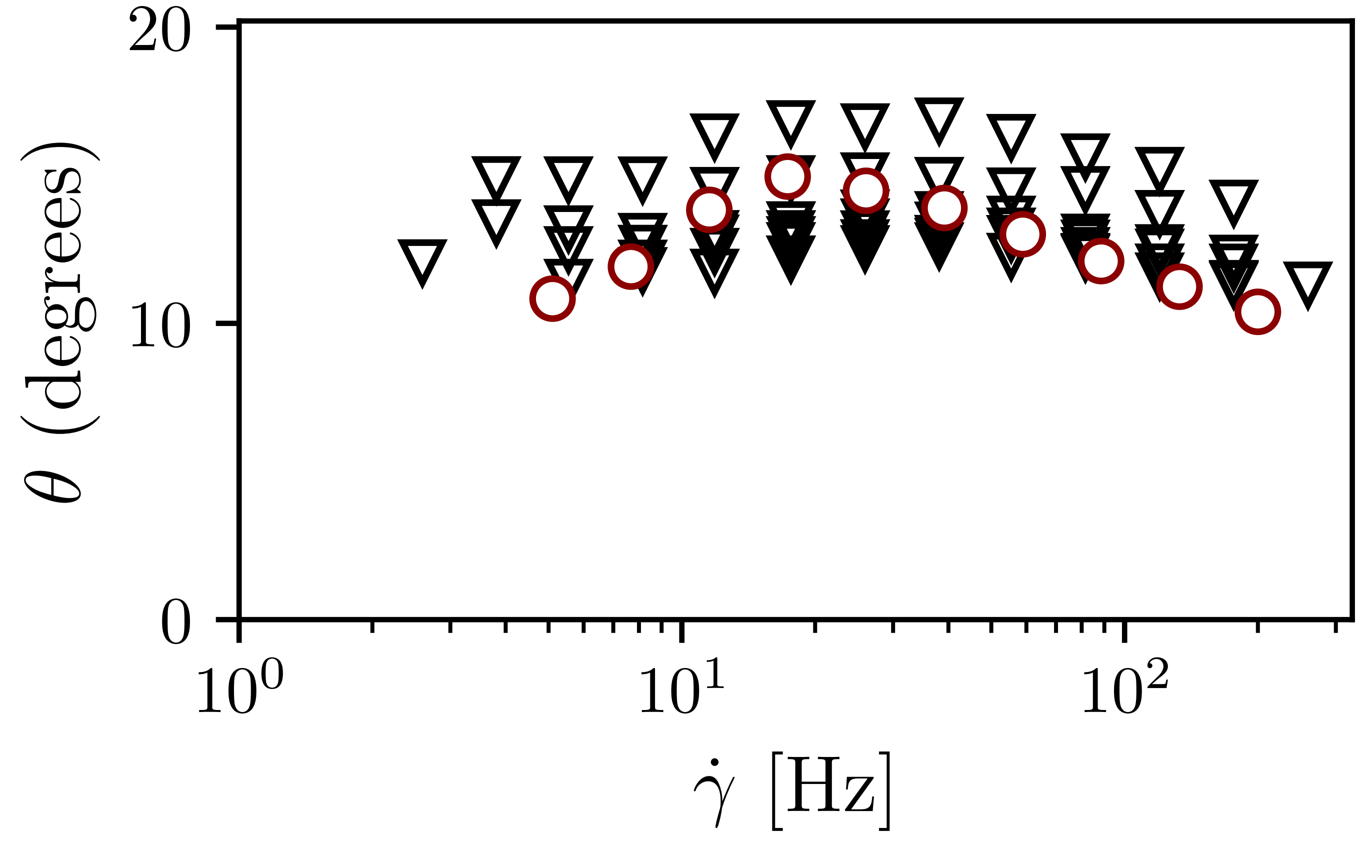
Single cell in linear shear flow



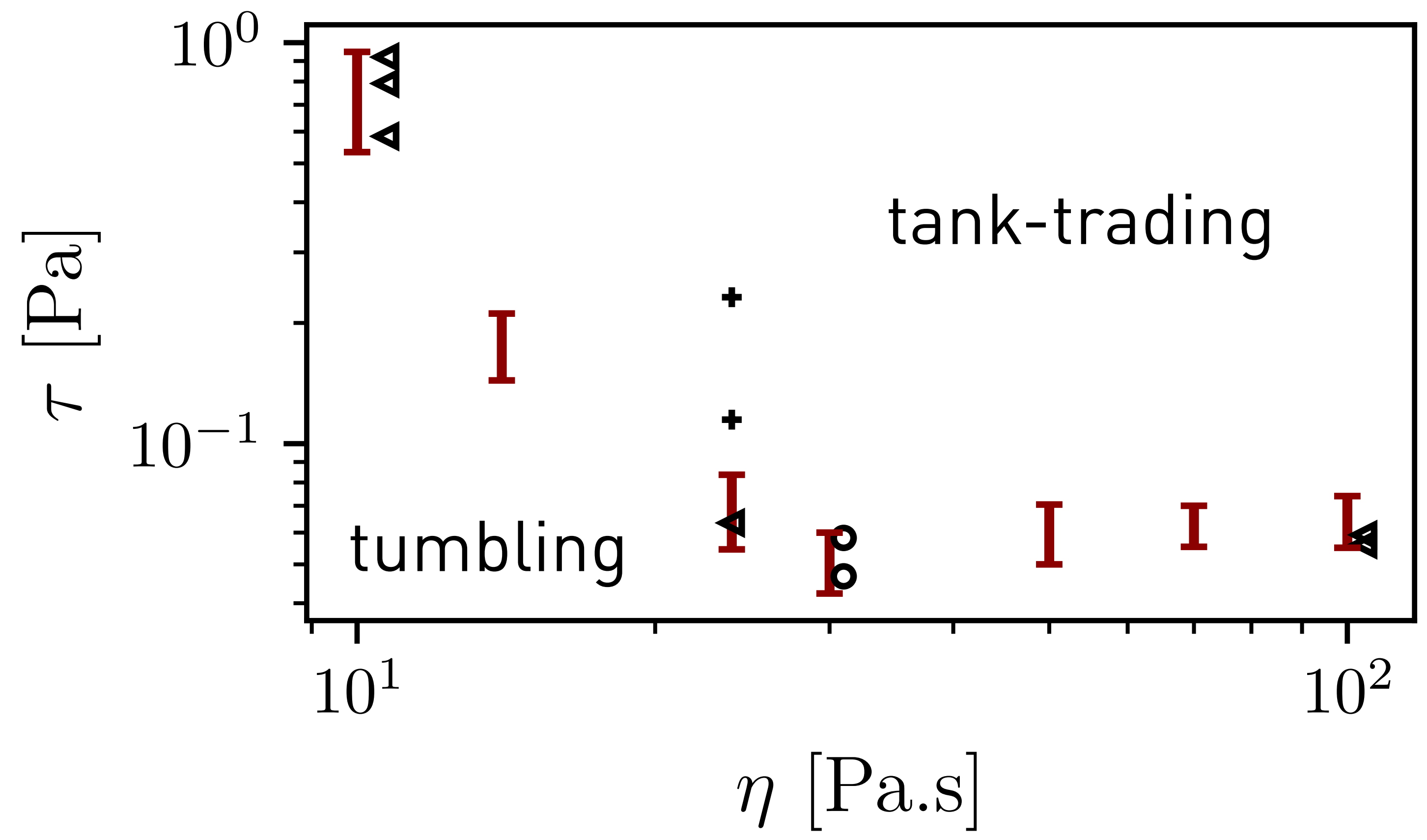
Tank-treading frequency



Inclination angle



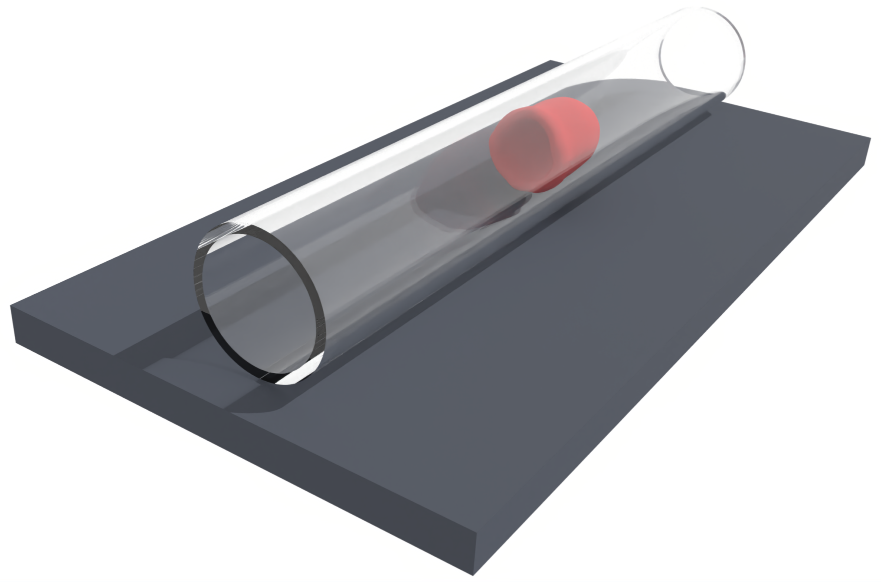
Critical shear stress

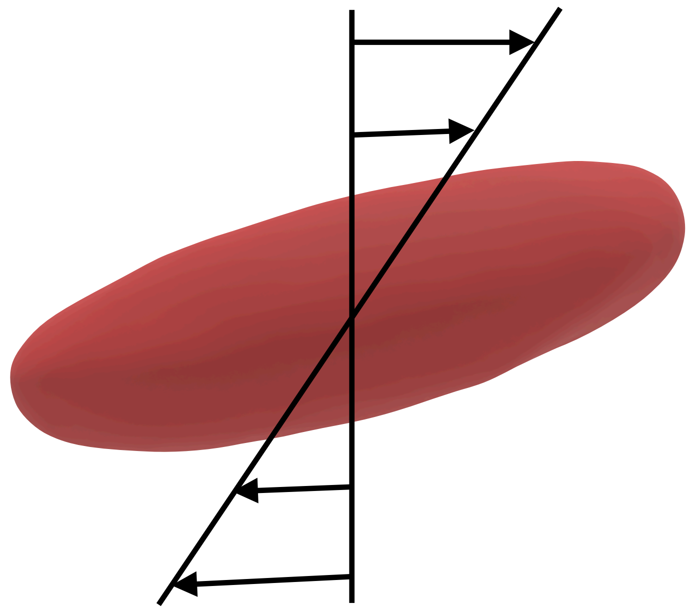


Fischer, Thomas M., and Rafal Korzeniewski. "Angle of inclination of tank-treading red cells: dependence on shear rate and suspending medium." *Biophysical journal* 108.6 (2015): 1352-1360.

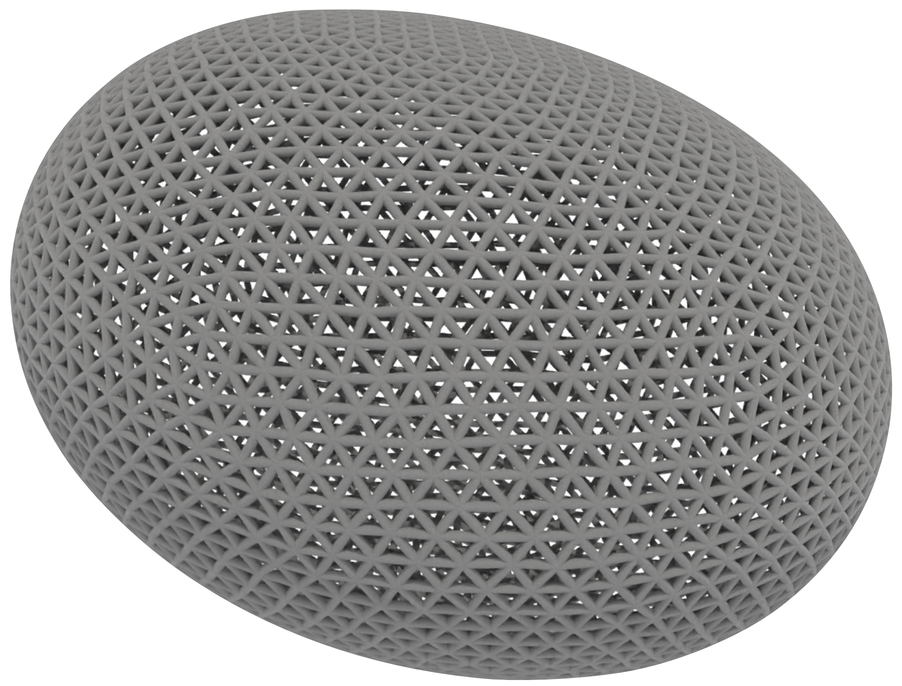
Fischer, Thomas M., and Rafal Korzeniewski. "Threshold shear stress for the transition between tumbling and tank-treading of red blood cells in shear flow: dependence on the viscosity of the suspending medium." *Journal of fluid mechanics* 736 (2013): 351-365.

Summary

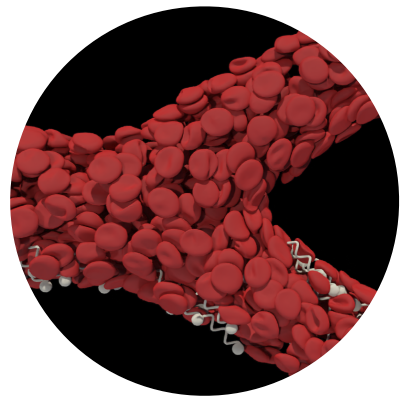




- **Transferable** model: prediction of previously unseen flow conditions



- Inferred stress-free state of cytoskeleton



https://github.com/cselab/Mirheo

https://github.com/cselab/korali