Hierarchical Bayesian Uncertainty Quantification for a Red Blood Cell Model

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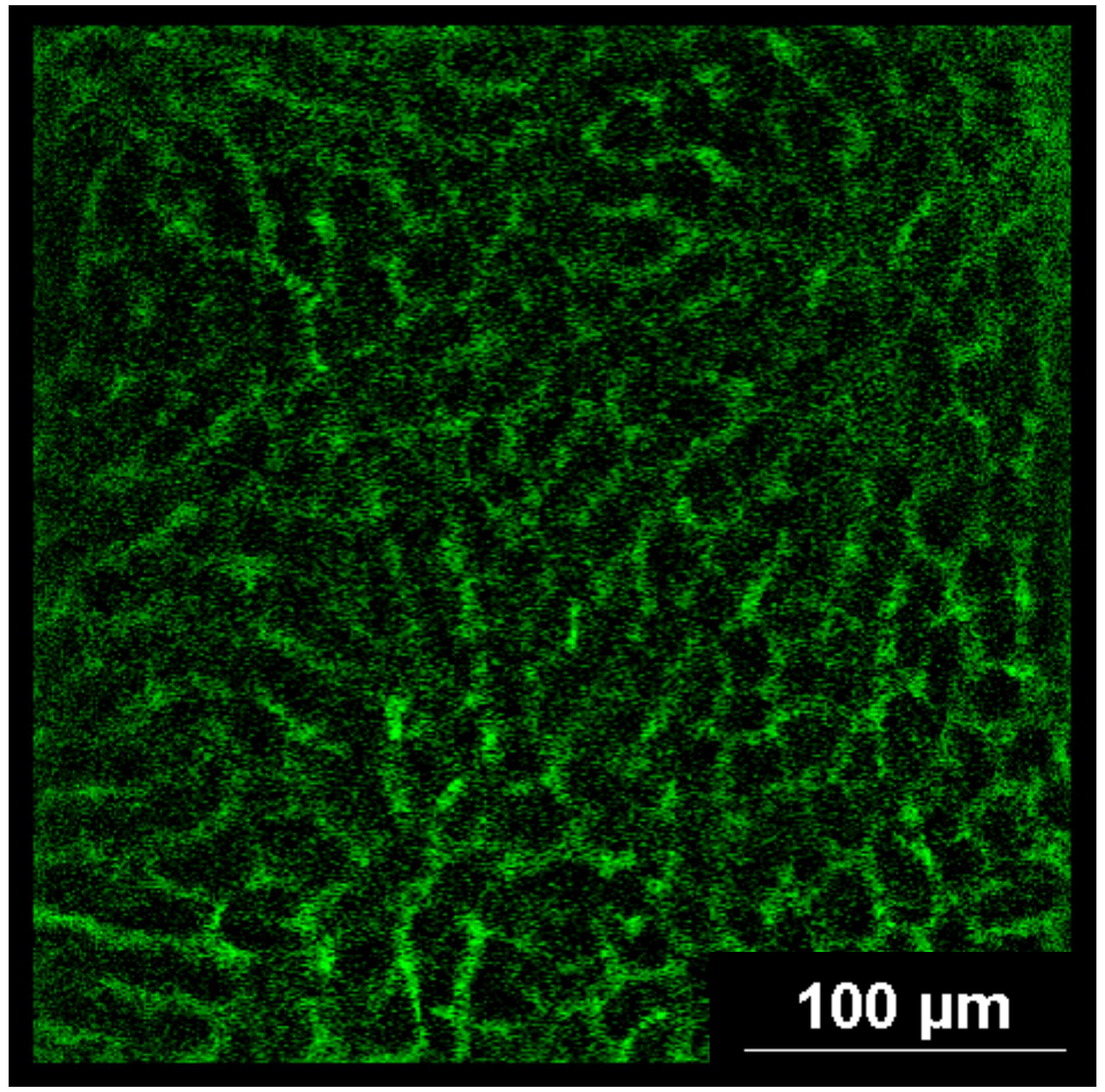
Costas Papadimitriou - University of Thessaly

Blood flow & NP in realistic vasculatures

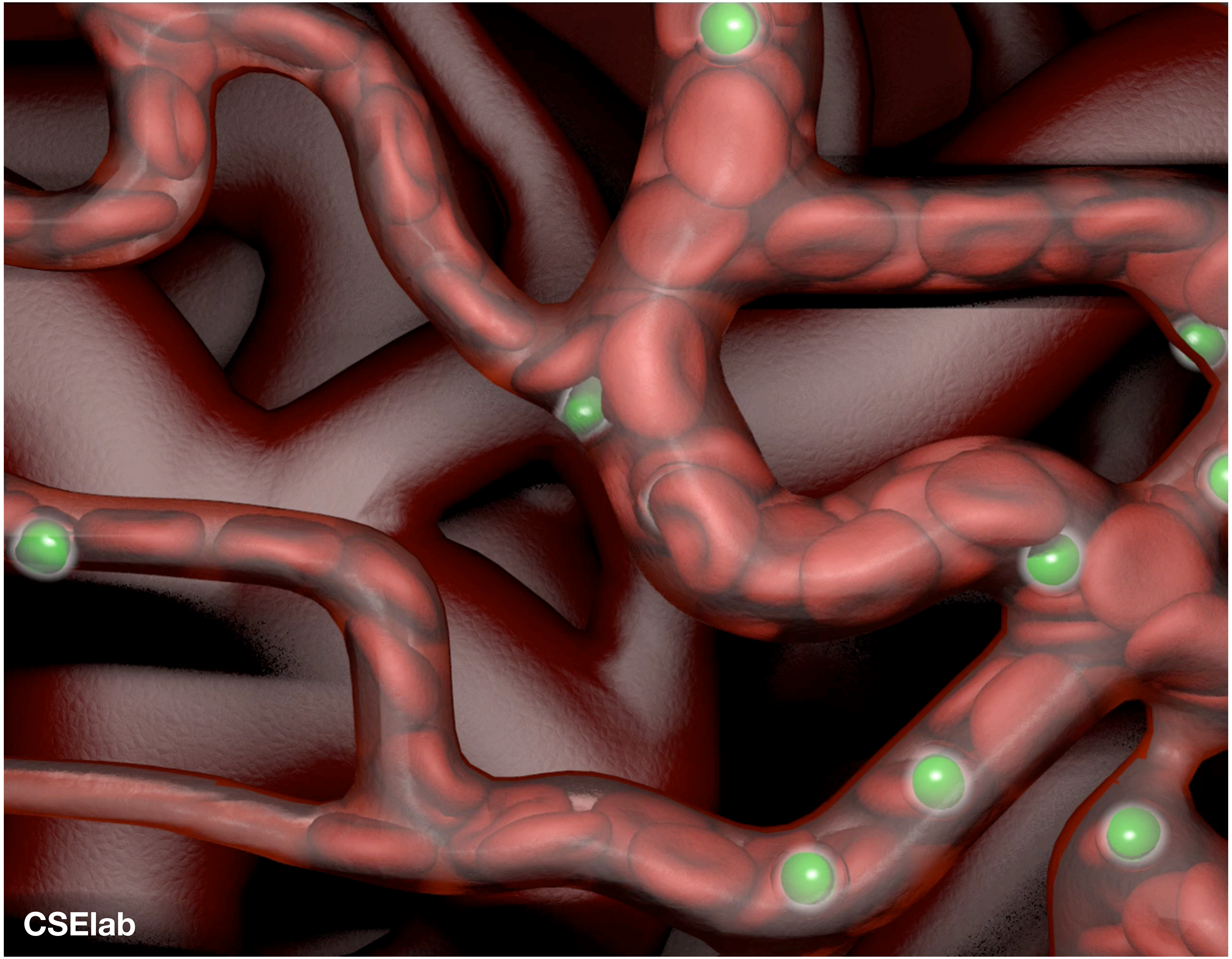
(with Ferrari Group, Houston)

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

Experimental data for vasculature.

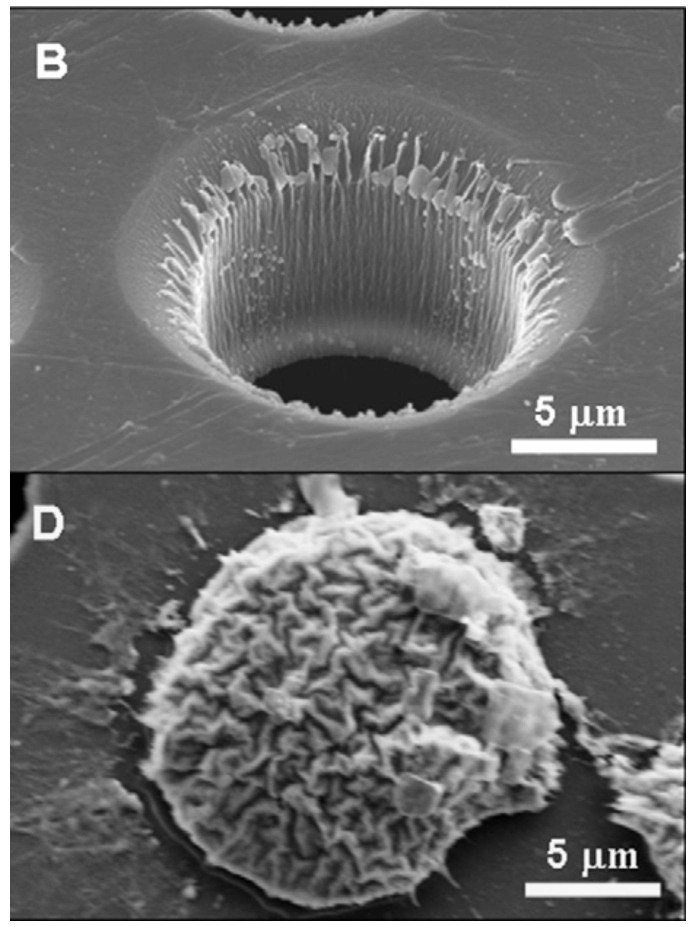


Vasculature reconstruction & Simulation.



Microfluidic isolation of CTC
(with Toner Group, Harvard)

Zheng et al., "Membrane microfilter device for selective capture, electrolysis and genomic analysis of human circulating tumor cells", Journal of Chromatography A, 2007.



Circulating tumor cells: approaches to isolation and characterization

Min Yu,[1,2] Shannon Stott,[3] Mehmet Toner,[3] Shyamala Maheswaran,[2] and Daniel A. Haber[1,2]

[1]Howard Hughes Medical Institute, [2]Massachusetts General Hospital Cancer Center, and [3]Center for Engineering in Medicine, Harvard Medical School, Charlestown, MA 02129

...

ble metastatic precursors capable of initiating a clonal metastatic lesion. However, CTCs are extraordinarily rare (estimated at one CTC per billion normal blood cells in the circulation of patients with advanced cancer); our understanding of their biological

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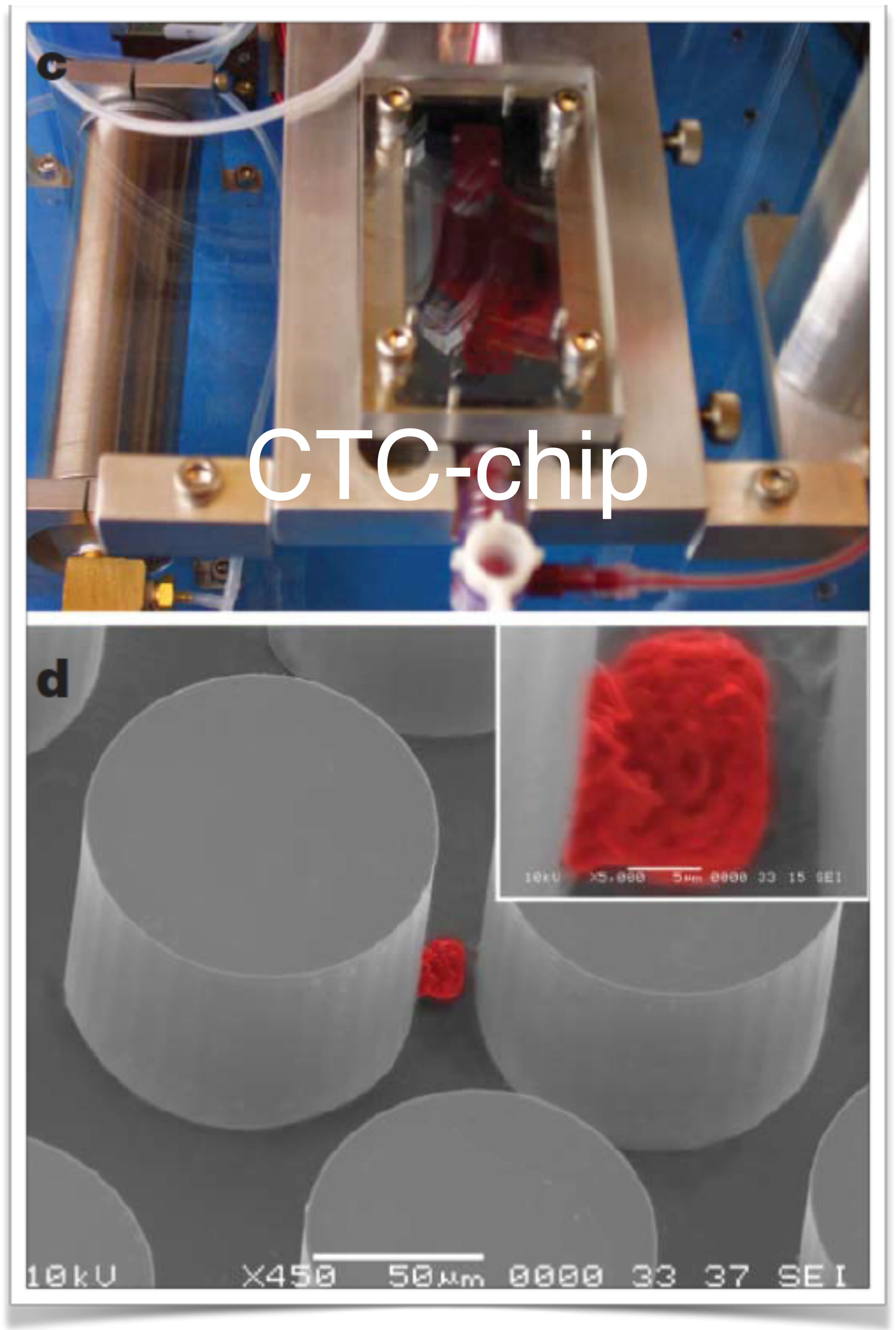
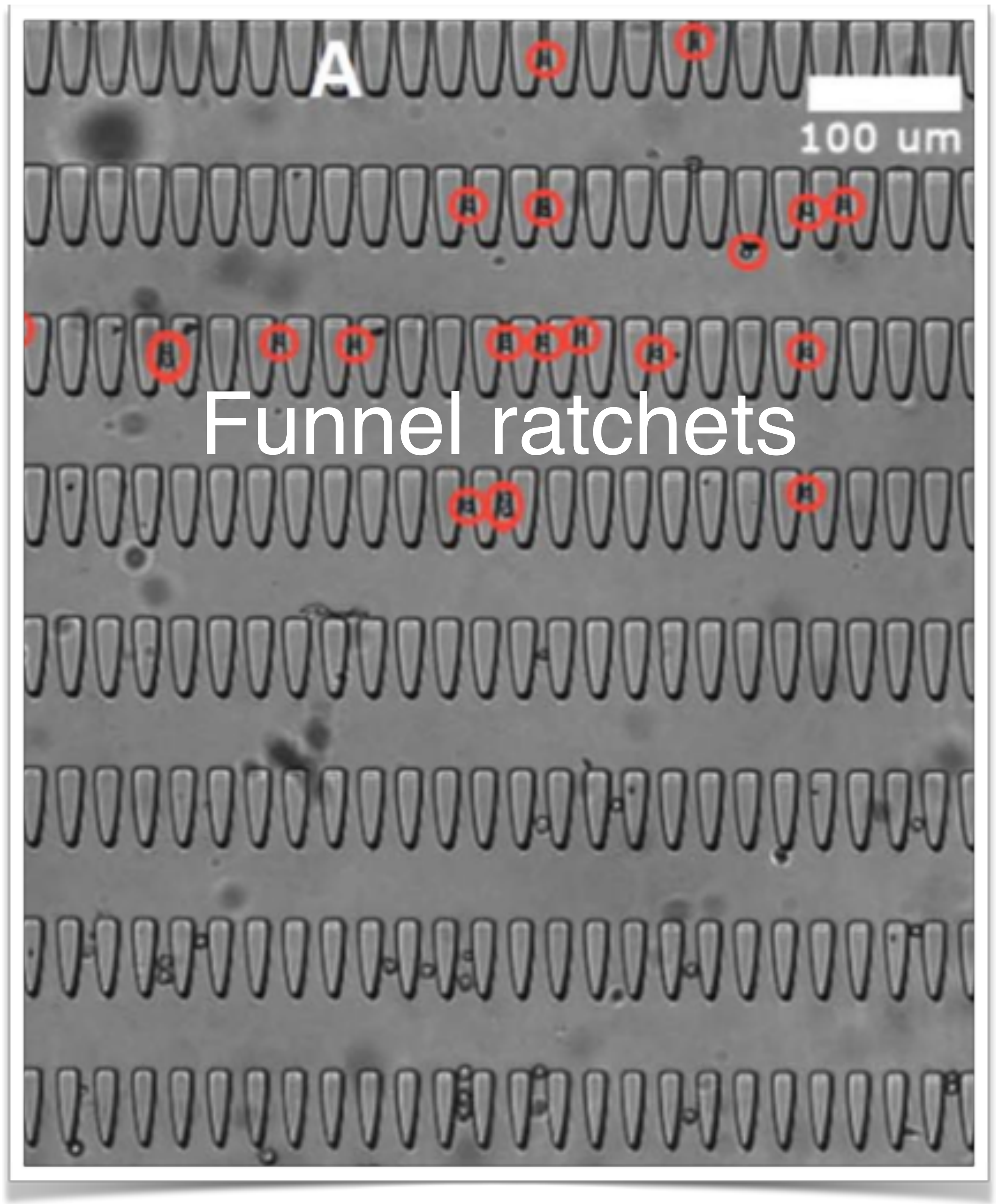
CTC detection → High throughput - mL Samples

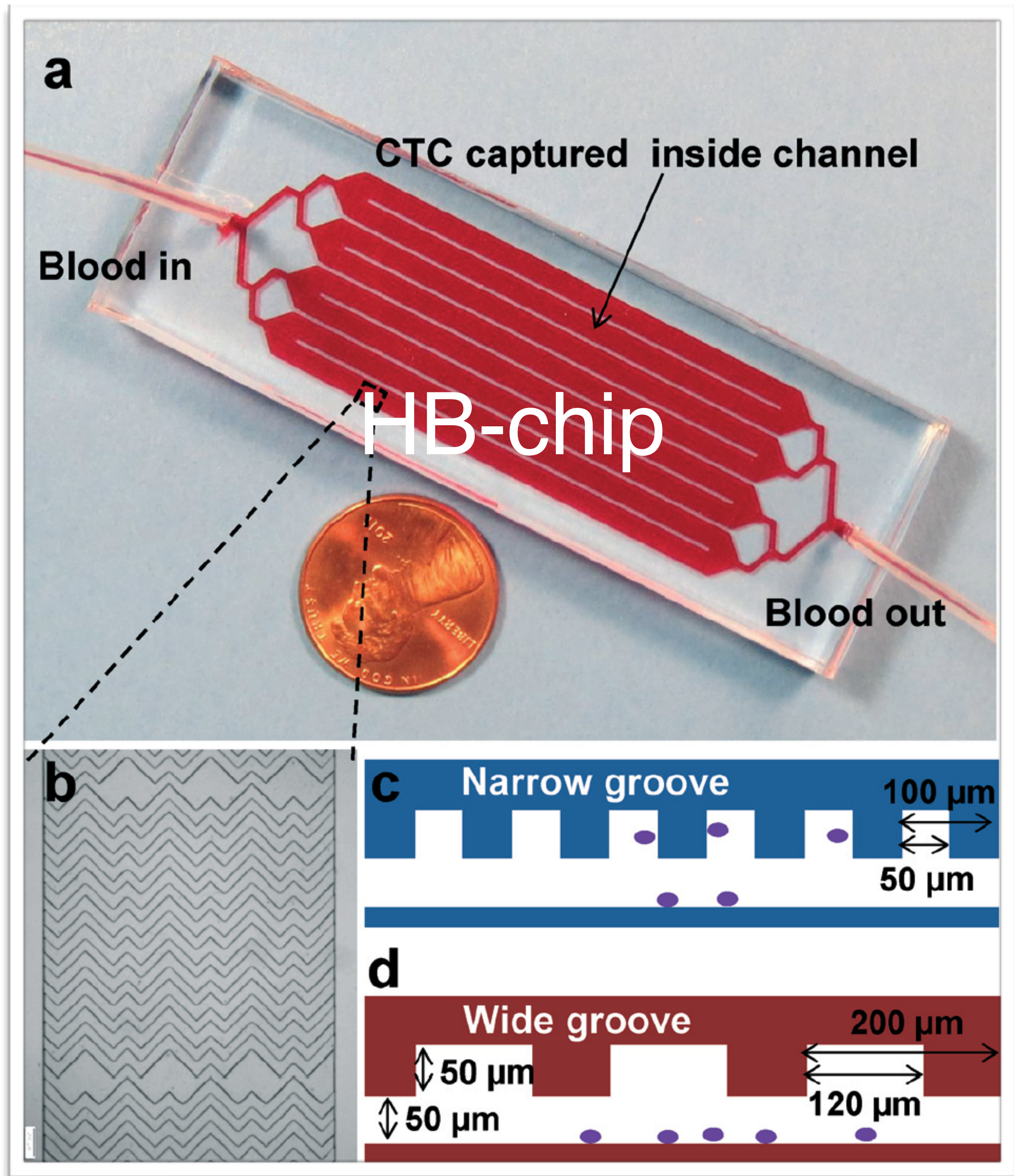
Nagrath et al., "Isolation of rare circulating tumour cells in cancer patients by microchip technology", Nature, 2007.



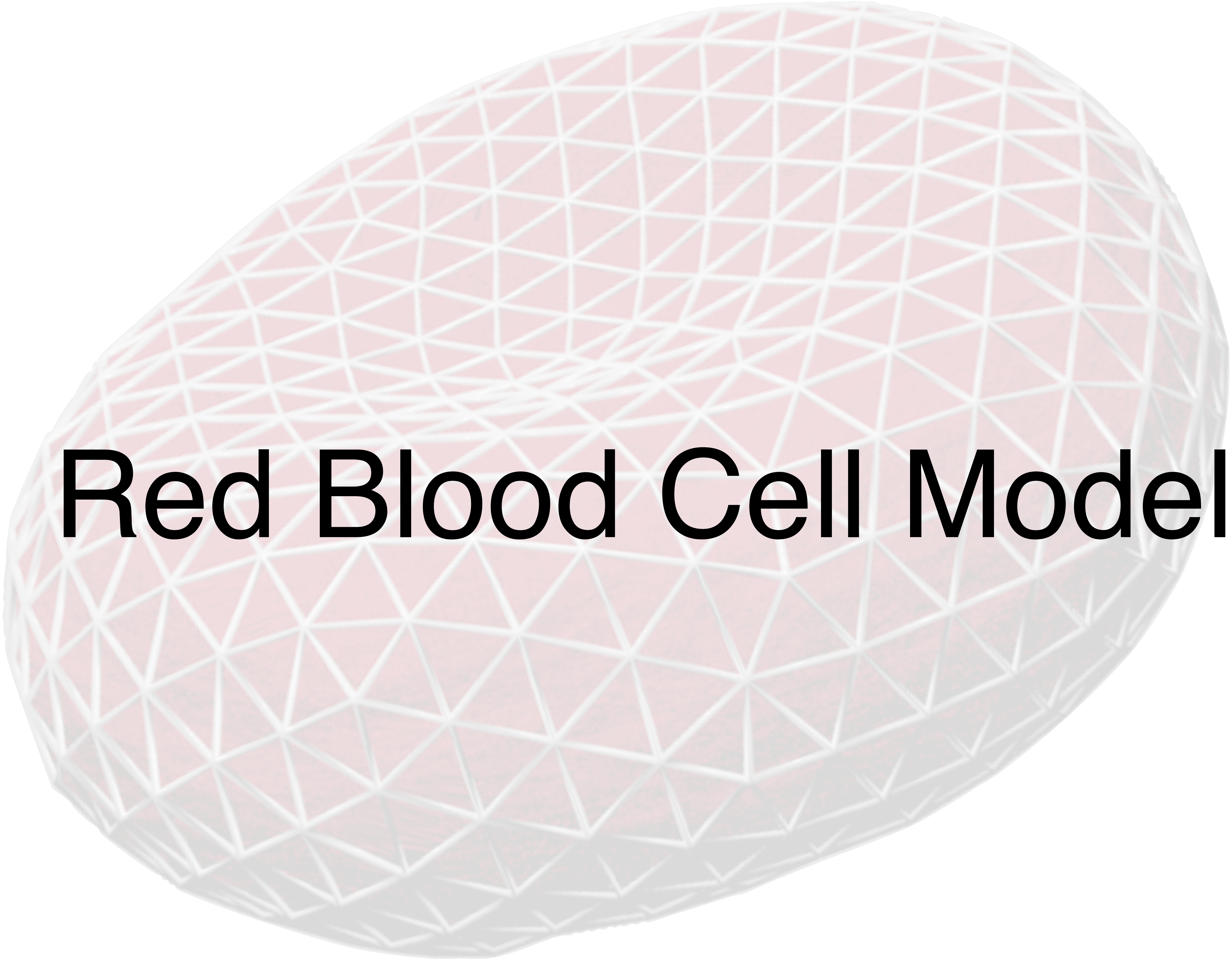
McFaul et al., "Cell separation based on size and deformability using microfluidic funnel ratchets", Lab on a Chip, 2012.



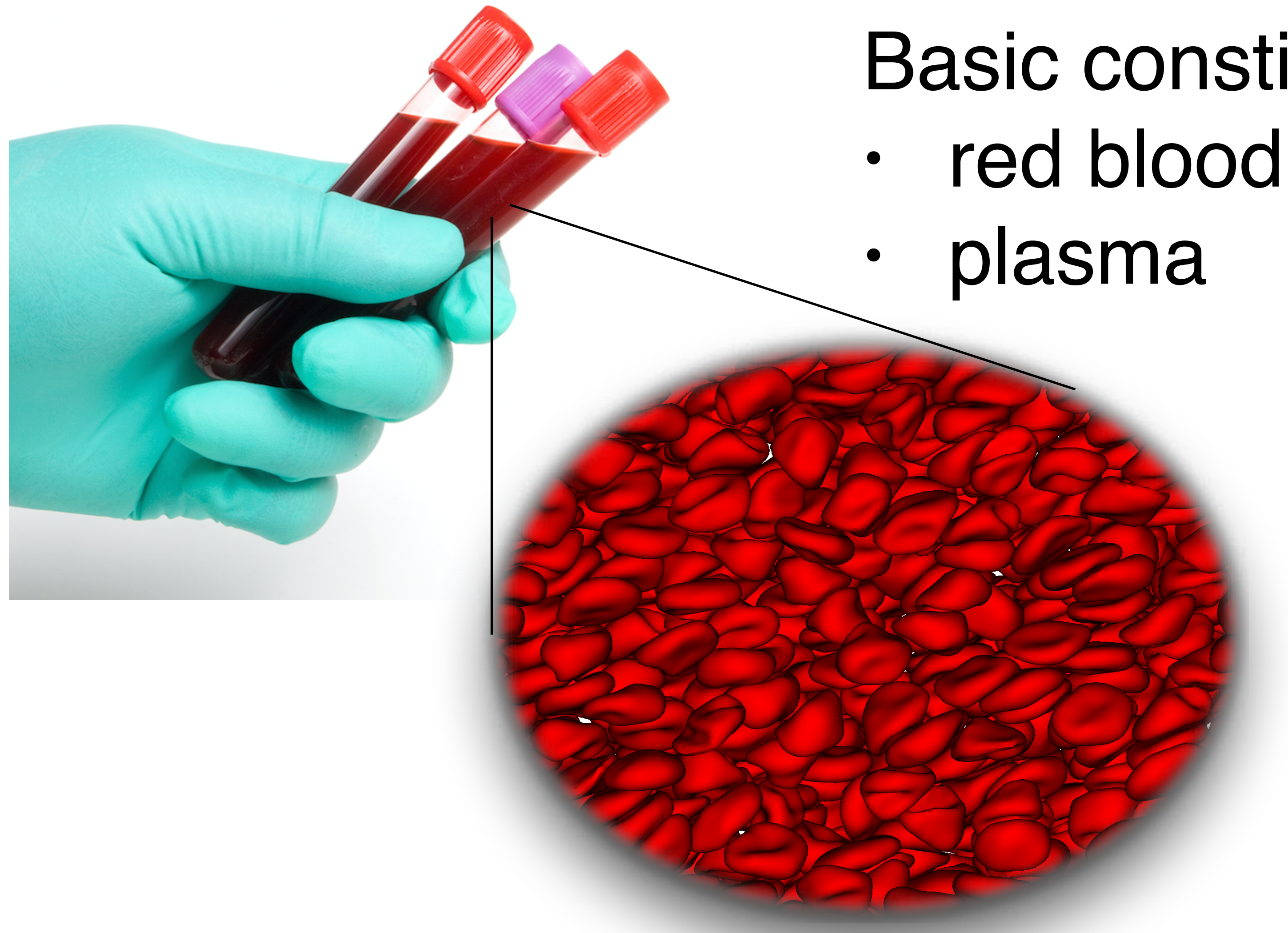
Scott et al., "Isolation of circulating tumor cells using a microvortex-generating herringbone-chip", PNAS, 2014.



Red Blood Cell Model



Blood modeling



Basic constituents of blood:

- red blood cells
- plasma

Plasma

- 95% water

modeling requirements:

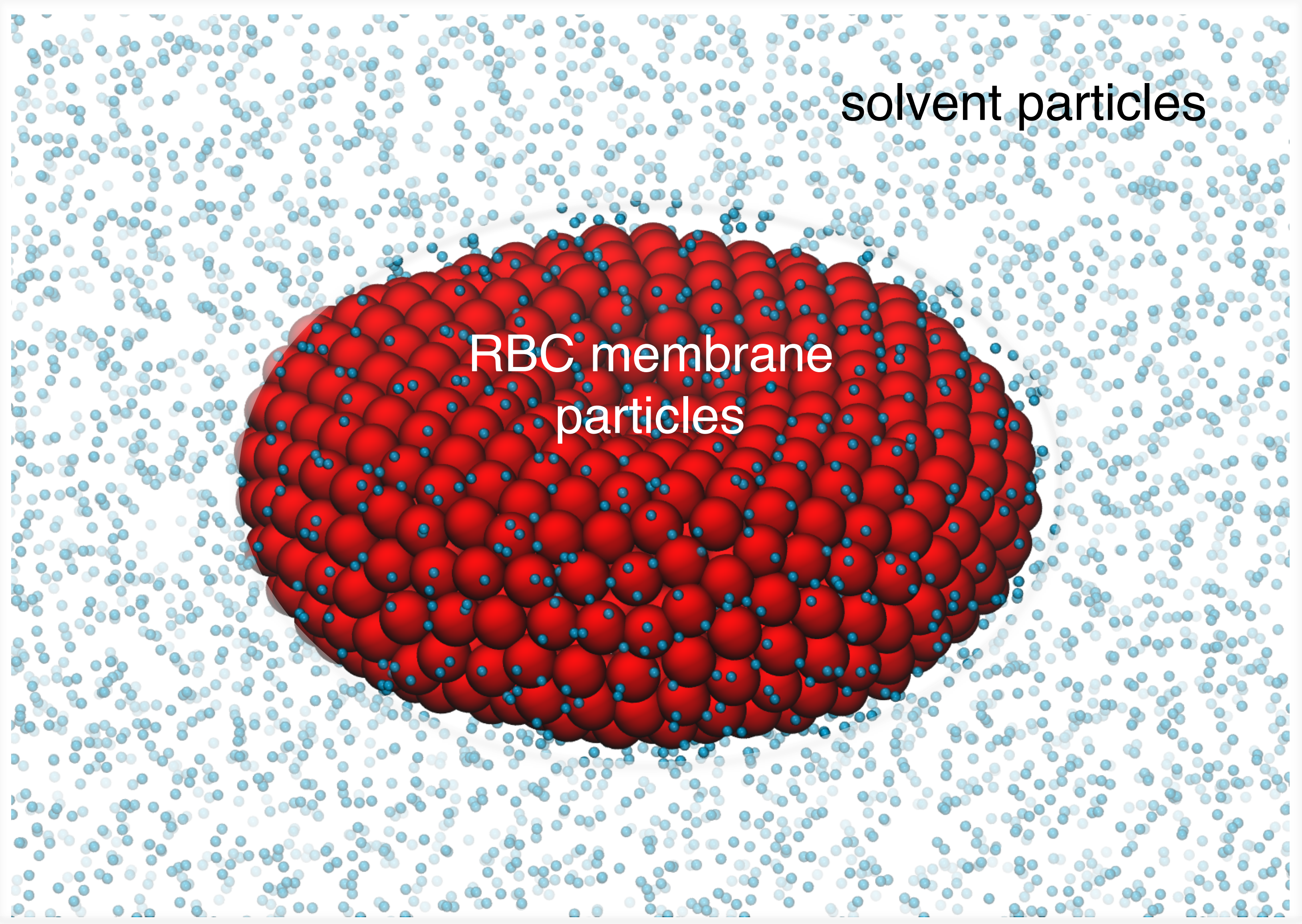
- incompressible fluid
- hydrodynamic behavior (mass & momentum conservation)

Red Blood Cells

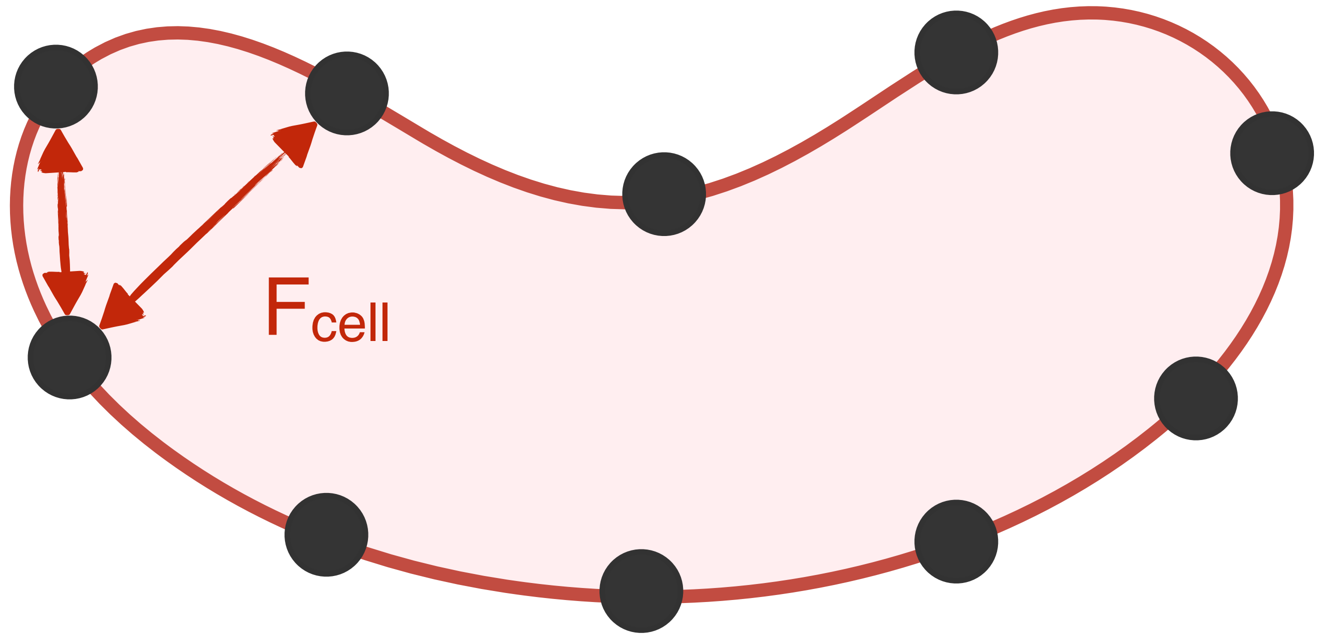
- biconcave shape
- viscoelastic membrane
- constant area & volume

Particle-based methods:

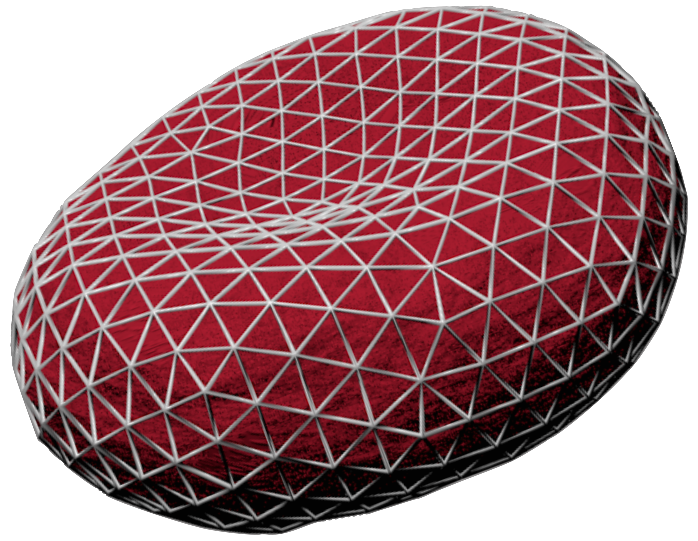
- Coarse-grained model for RBC membrane
- Dissipative Particle Dynamics for solvent



- Prescribe forces between RBC particles.
- Calibration of parameters to best fit experiments.



Most widely used RBC model



Membrane elasticity | Area+Volume incompressibility

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

(grey circle) Area and Volume coefficients fixed such that deviation is < 1%.

(yellow circle) Unknown parameters.

$$U_{\text{in-plane}} = \sum_{j=1}^{N_s}\left[\frac{k_s l_{0_j}\left(3x_j^2 - 2x_j^3\right)}{4(1-x_j)x_0} + \frac{k_{p_j}}{l_j}\right]$$

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

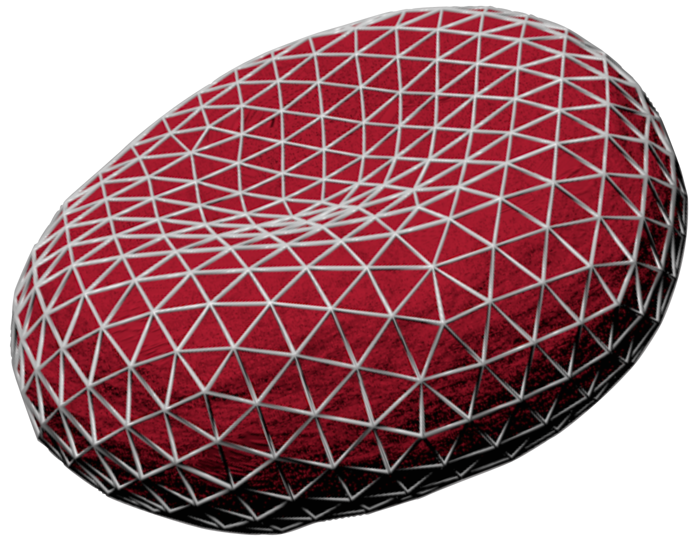
global, local

$$U_{\text{area}} = \frac{k_a (A - A_0)^2}{2A_0} + \sum_{j=1}^{N_t} \frac{k_d (A_j - A_{0_j})^2}{2A_{0_j}}$$

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

Addition of viscous diffusion: $\boldsymbol{F}^D_{m,ij} = -\gamma^C (\boldsymbol{v}_{ij} \cdot \boldsymbol{e}_{ij})\, \boldsymbol{e}_{ij}$

Most widely used RBC model



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

Membrane elasticity: $U_{\text{in-plane}} + U_{\text{bending}}$

Area+Volume incompressibility: $U_{\text{area}} + U_{\text{volume}}$

Area and Volume coefficients fixed such that deviation is < 1%.

Unknown parameters.

$$U_{\text{in-plane}} = \sum_{j=1}^{N_s} \left[\frac{k_s l_{0_j} \left(3x_j^2 - 2x_j^3\right)}{4(1-x_j)x_0} + \frac{k_{p_j}}{l_j} \right]$$

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

global, local

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

Addition of viscous diffusion: $\boldsymbol{F}^D_{m,ij} = -\gamma^C (\boldsymbol{v}_{ij} \cdot \boldsymbol{e}_{ij})\, \boldsymbol{e}_{ij}$

Potentials between pairs of particles (springs): Local potentials

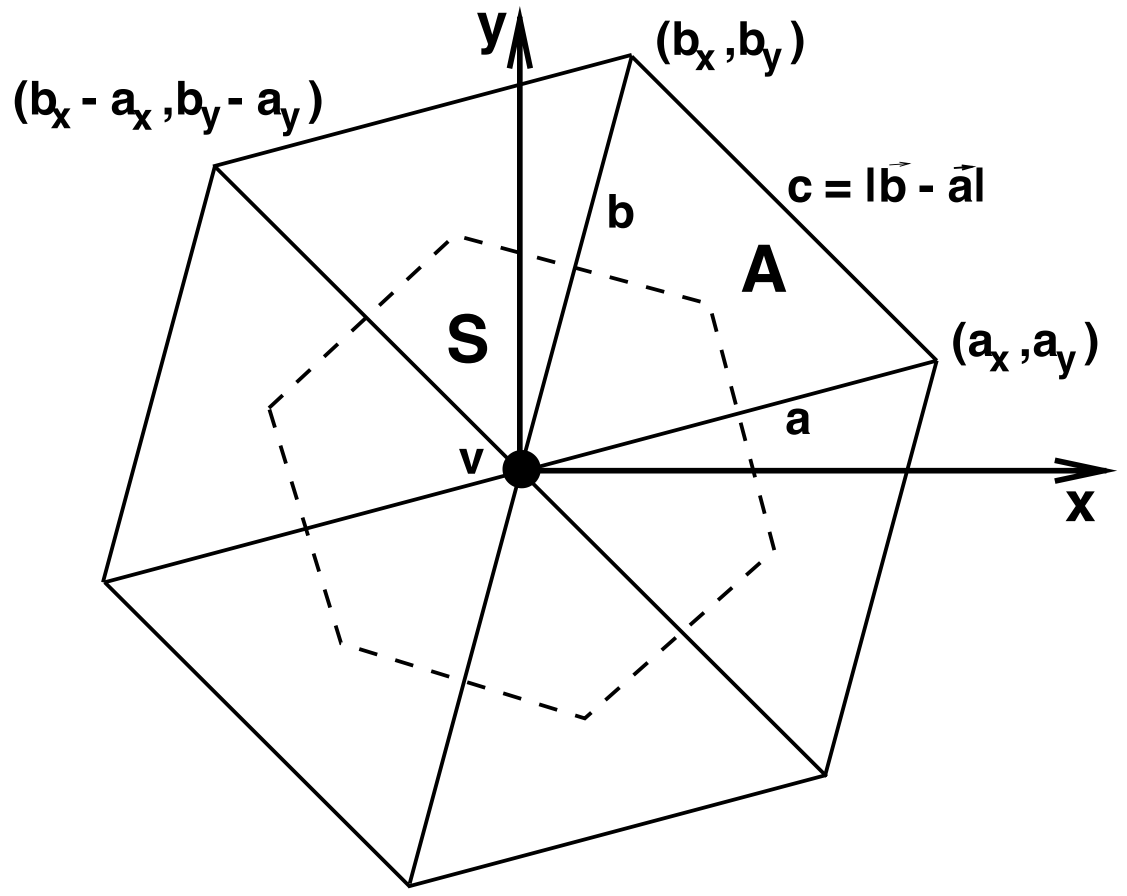
Theoretical analysis for hexagonal network:

- Approximations to macroscopic material properties.
- Comparison with existing literature / other models.

Linear shear modulus: $$\mu_0 = \frac{\partial \tau_{xy}}{\partial \gamma}\bigg|_{\gamma=0} \approx \frac{k_s\sqrt{3}}{4 l_m x_0} \left(\frac{x_0}{2(1-x_0)^3} - \frac{1}{4(1-x_0)^2} + \frac{1}{4} \right)$$

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

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

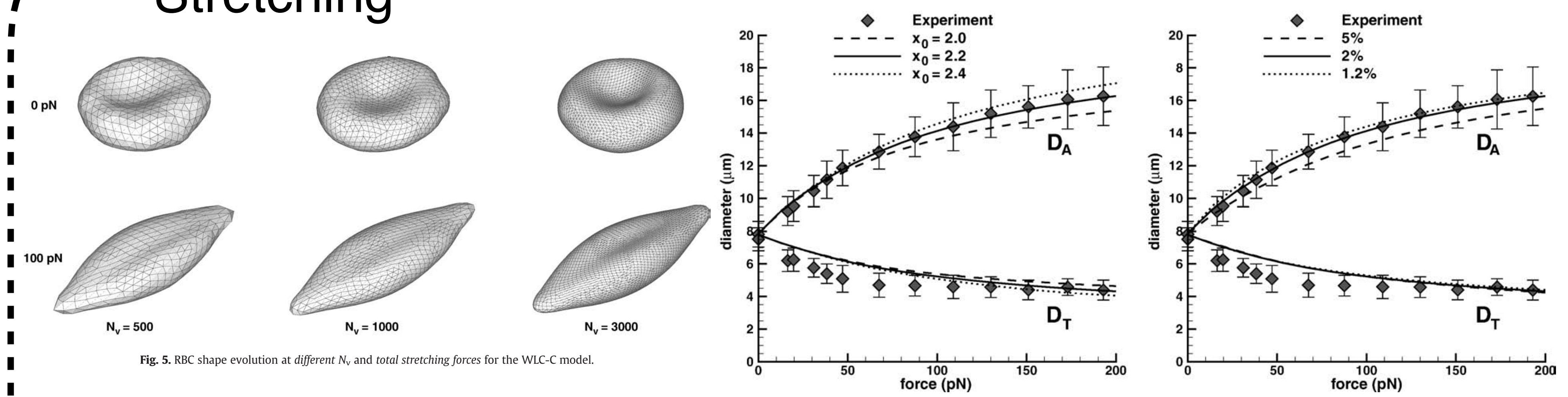


Fedosov, D., "Multiscale Modeling of Blood Flow and Soft Matter", PhD thesis, 2010.

Validation & Applications in Literature

SINGLE CELLS

Stretching



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

Twisting torque cytometry

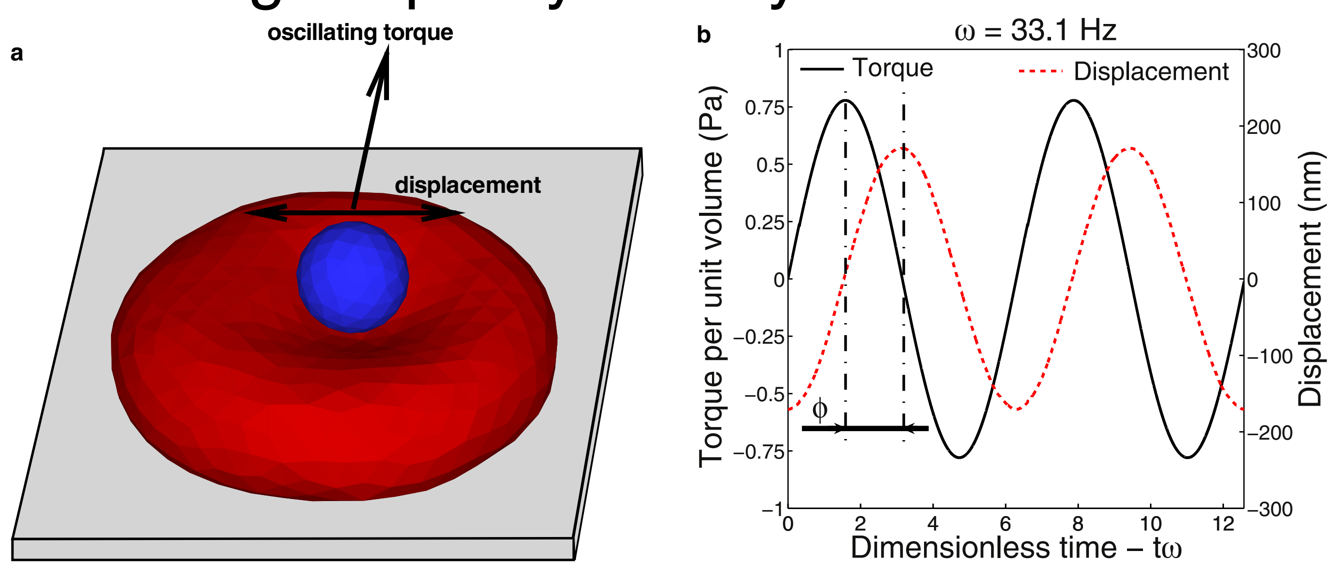
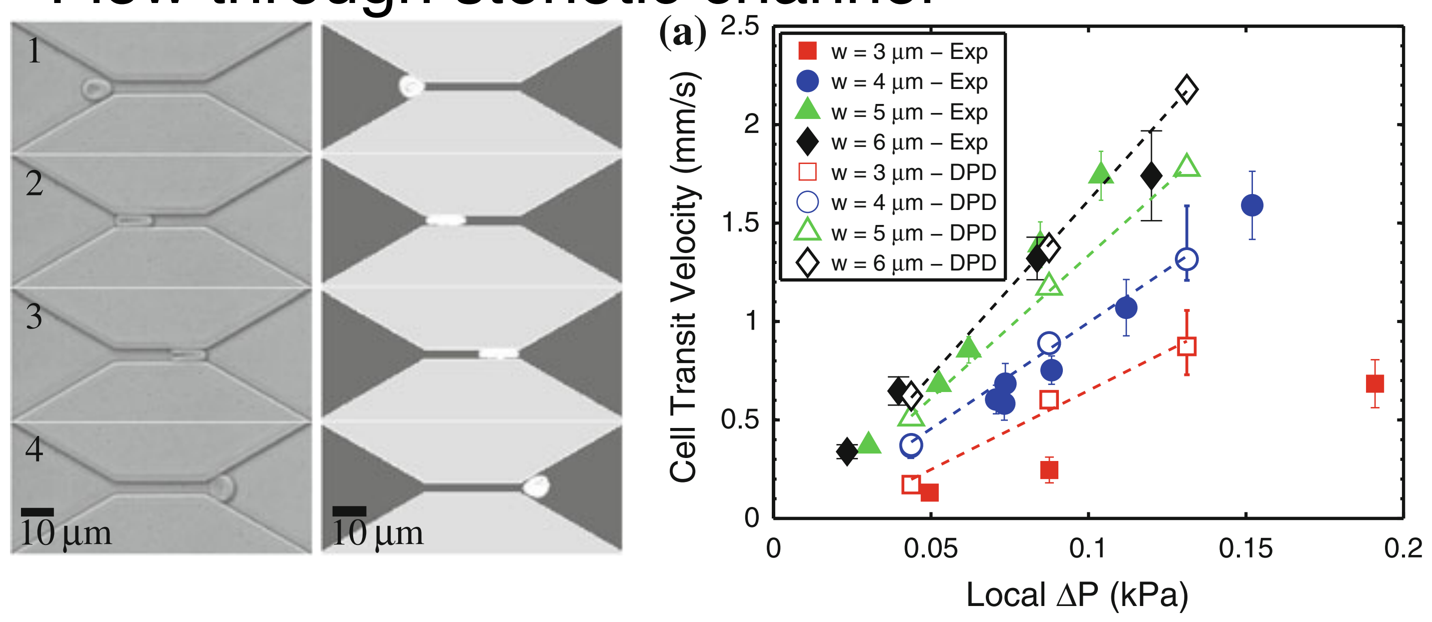


FIGURE 2 A setup of the TTC (*a*) and the characteristic response of a microbead subjected to an oscillating torque (*b*).

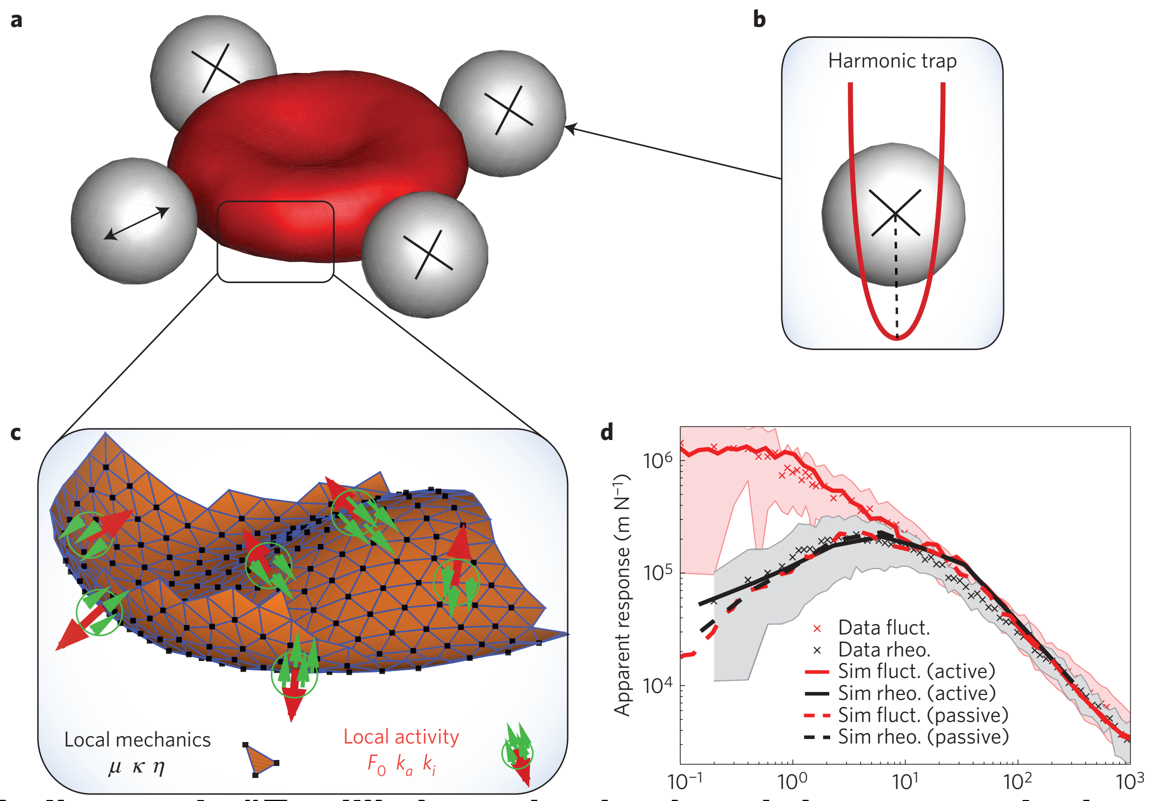
Fedosov et al., "A Multiscale Red Blood Cell Model with Accurate Mechanics, Rheology, and Dynamics", Biophysical Journal, 2010.

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

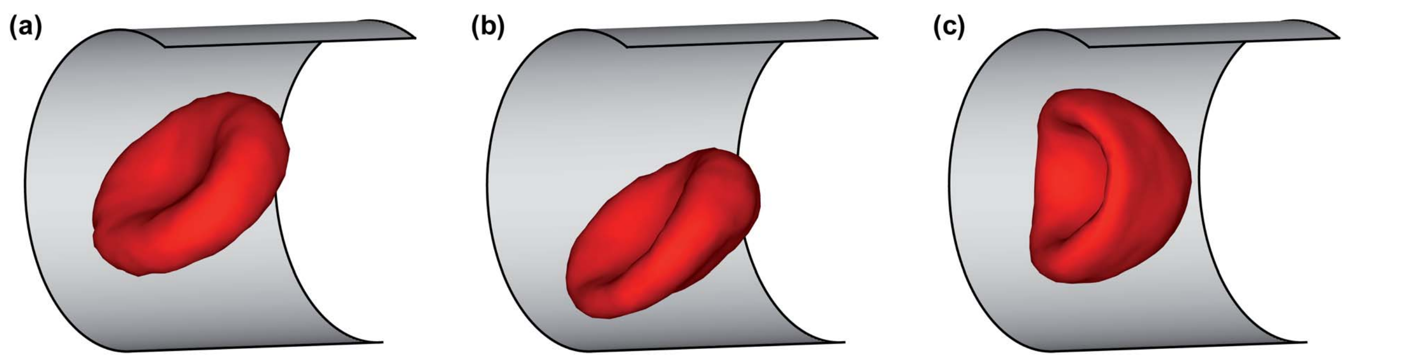
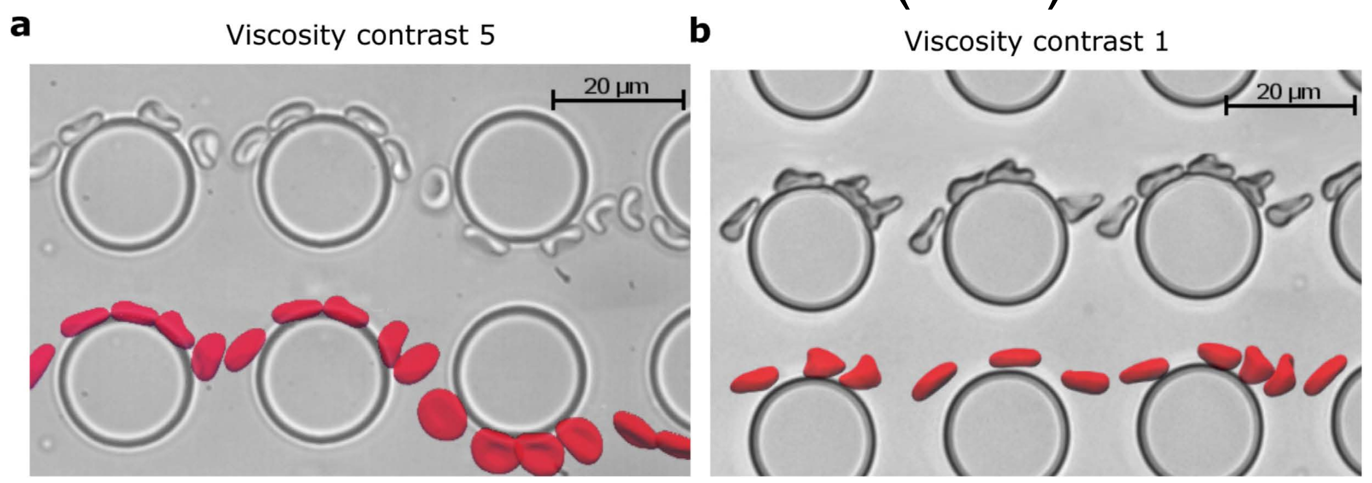


Fig. 1 Simulation snapshots of a RBC in flow (from left to right) for χ = 0.58. (a) A biconcave RBC shape at $\dot{\gamma}^* = 5$; (b) an off-center slipper cell shape at $\dot{\gamma}^* = 24.8$; and (c) a parachute shape at $\dot{\gamma}^* = 59.6$. See also Movies S1–S4.†

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

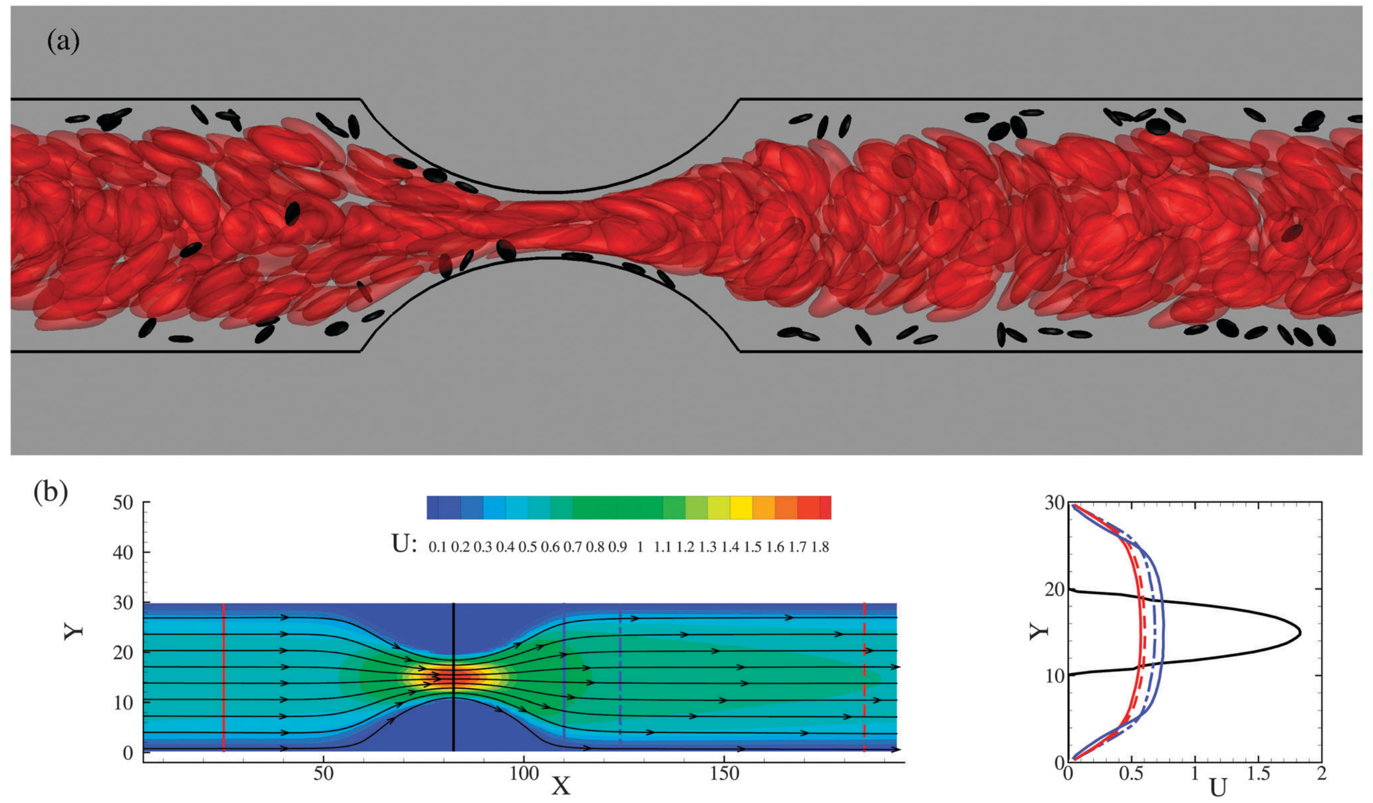
Flow in microfluidics device (DLD)



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

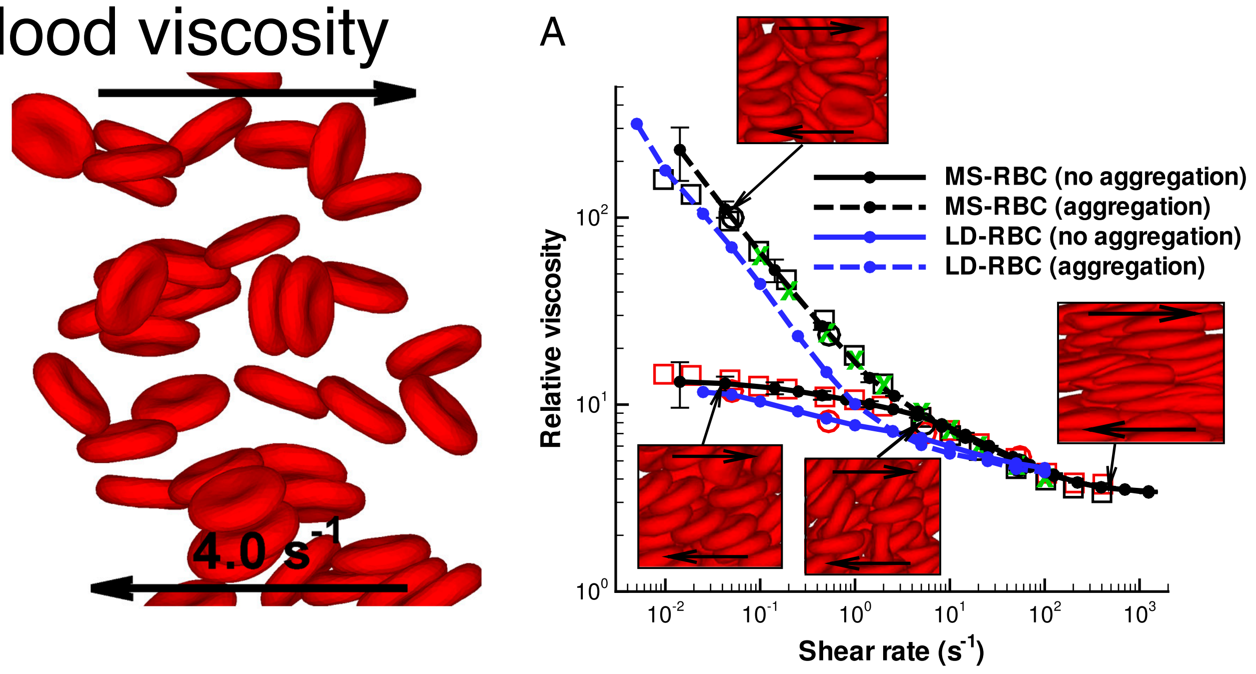
MANY CELLS

Platelet transport



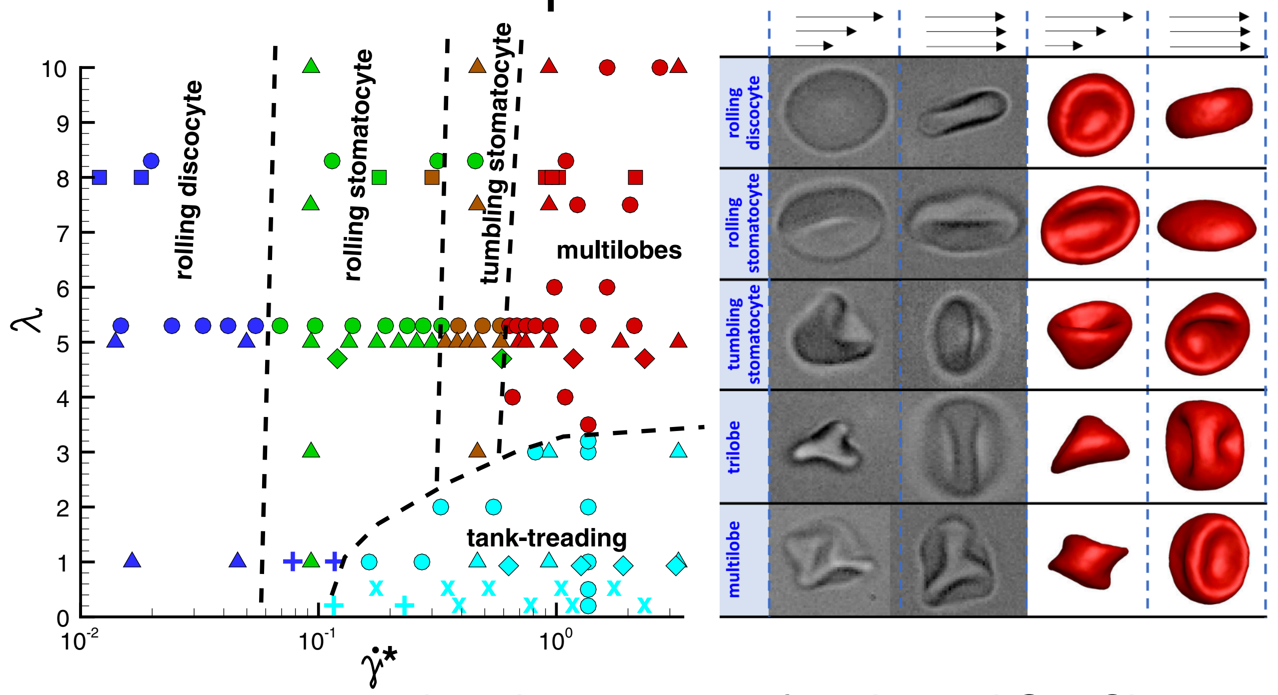
Yazdani and Karniadakis, "Sub-cellular modeling of platelet transport in blood flow through microchannels with constriction", Soft Matter, 2016.

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.

Model Parameters: Different experiments - different model

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.*

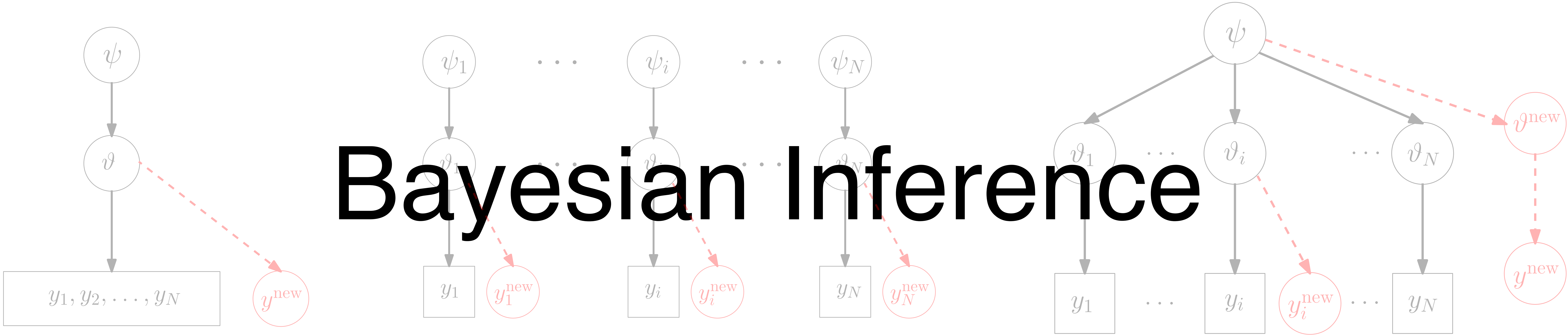
Inferred Quantities

Scale: μ_0

Relative strength between RBC energy potentials:

$$Q_1 = \frac{l_0}{l_{max}} \qquad Q_2 = \frac{\mu_0 R_0^2}{k_b} \qquad Q_3 = \frac{\eta_m}{\eta_{Hb}} \qquad Q_4 = \frac{\eta_{Hb}^2}{\mu_0 R_0 \rho}$$

Bayesian Inference



Bayesian Inference

Data,
d

$\oplus$

Computational Model
with Parameters, ϑ
$f(x \,|\, \vartheta)$

$\oplus$

Statistical Assumption
connecting ϑ and d
$p(d \,|\, \vartheta)$ ⋯→ likelihood

⇨

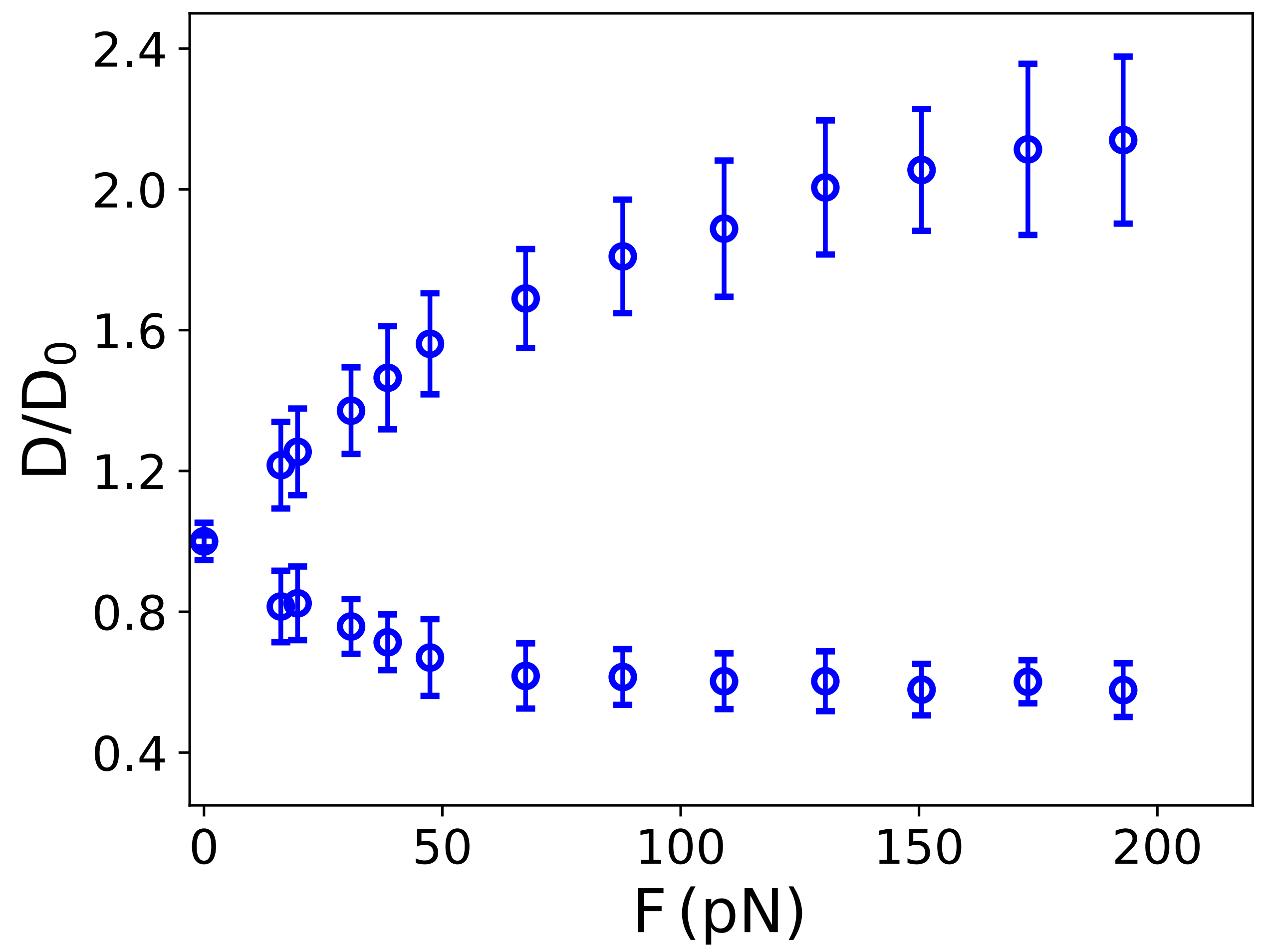
Probability Distribution
of the Parameters,
$p(\vartheta \,|\, d)$

Bayes' Theorem

$$p(\vartheta \,|\, d) = \frac{p(d \,|\, \vartheta) \, p(\vartheta)}{p(d)}$$

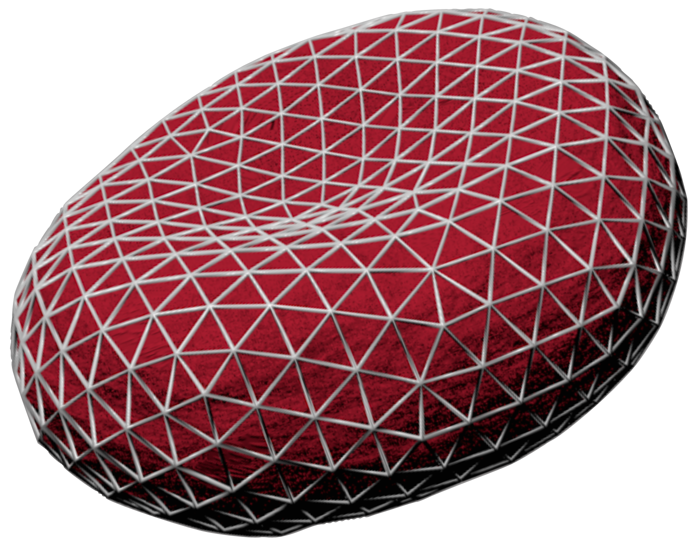
Bayesian Inference

Experimental Data



$\oplus$

Computational Model

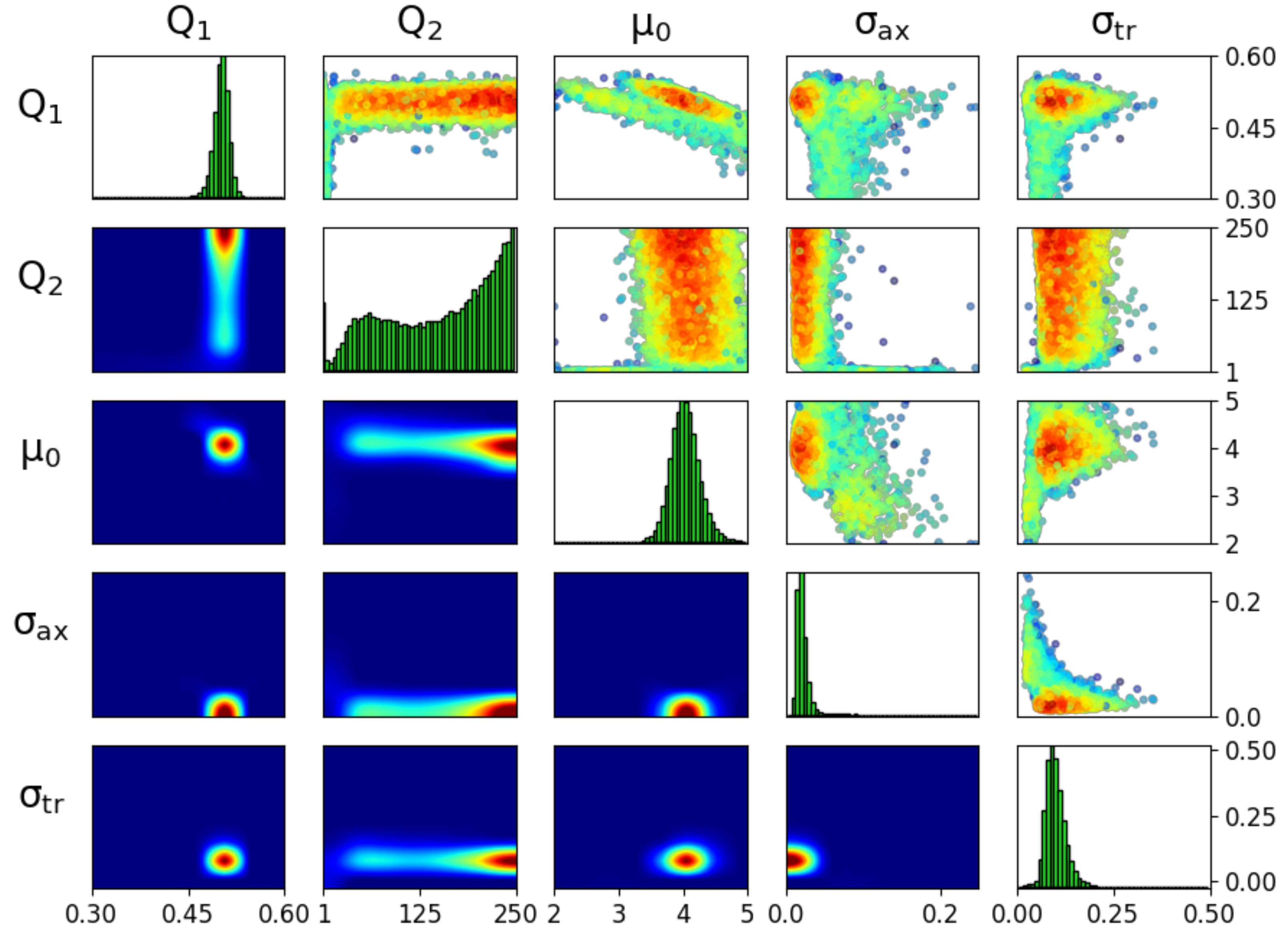


$\oplus$

$$d = f(x \mid \vartheta) + \epsilon$$

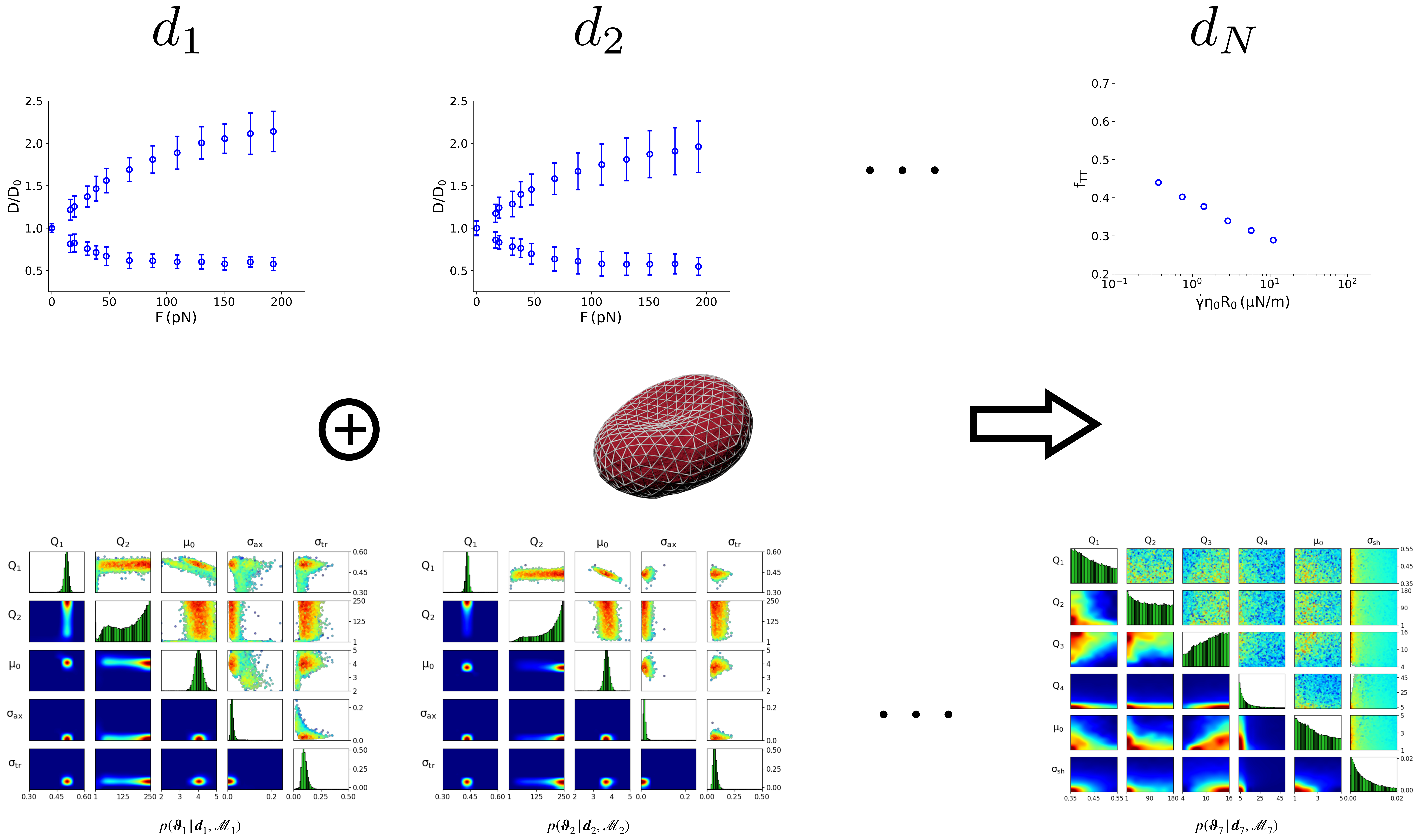
$$\epsilon \sim \mathcal{N}(0, \sigma_n)$$

$\Rightarrow$



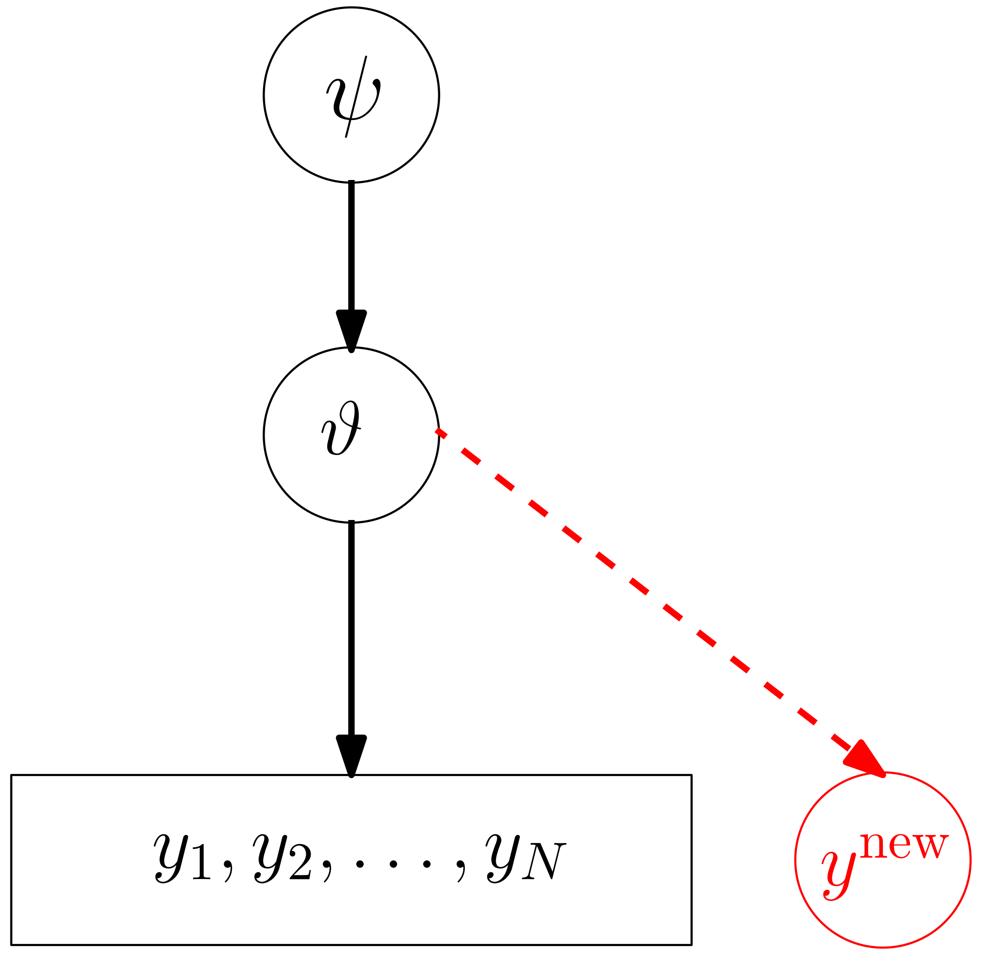
$p(\boldsymbol{\vartheta}_1 \mid \boldsymbol{d}_1, \mathscr{M}_1)$

Hierarchical Bayesian Inference

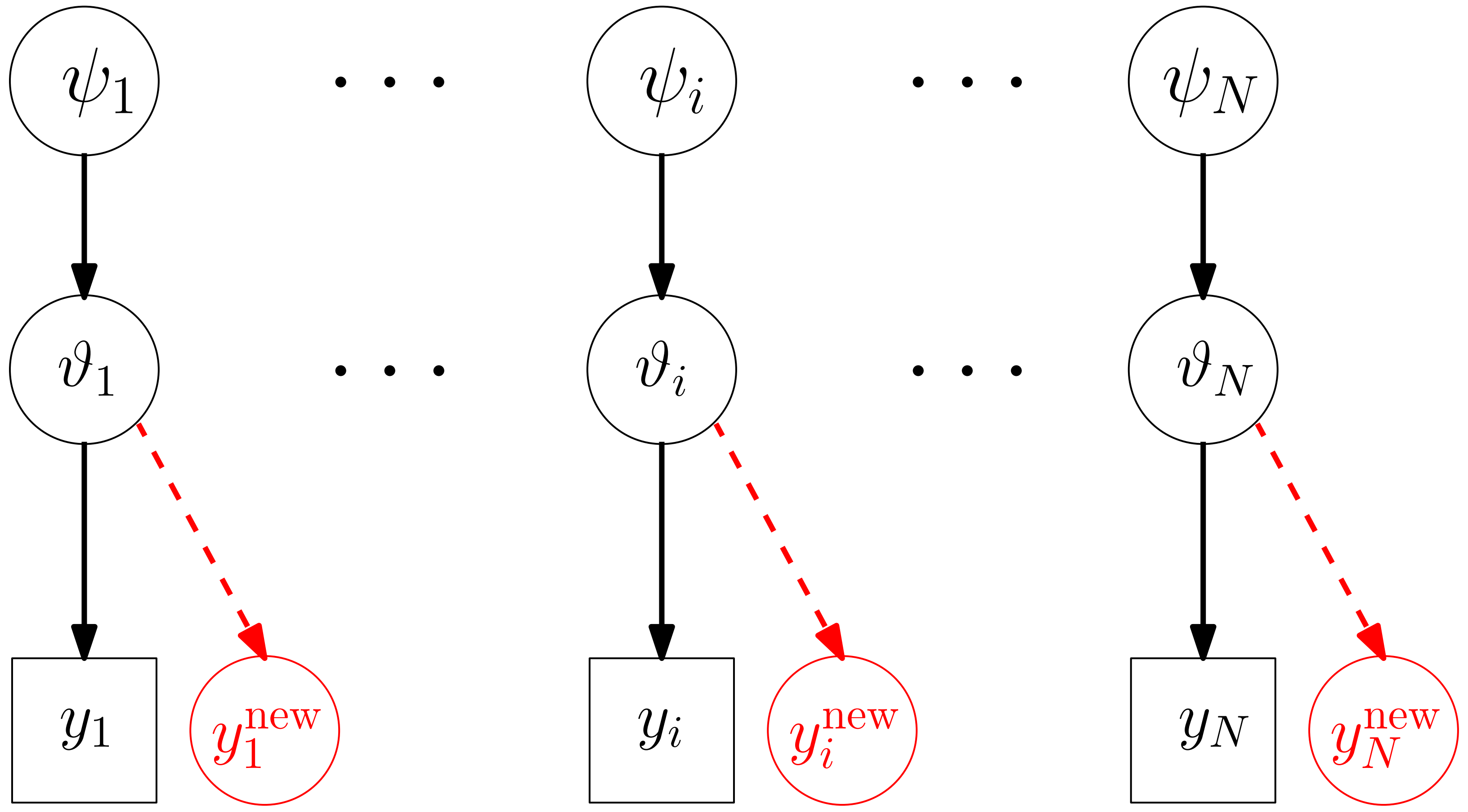


Hierarchical Bayesian Inference

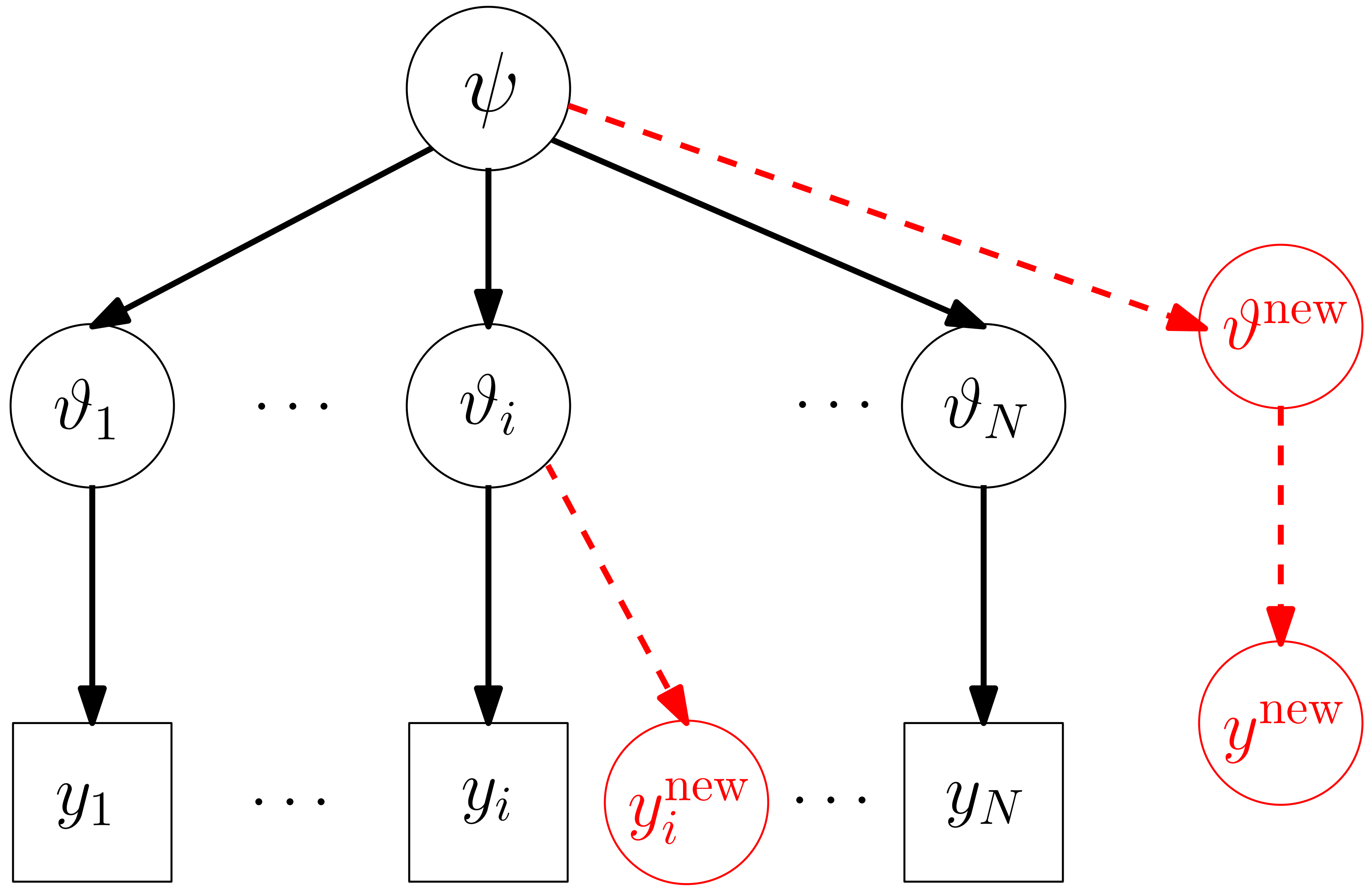
Hierarchical Bayesian Inference



- lost of individual information
- one parameters 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

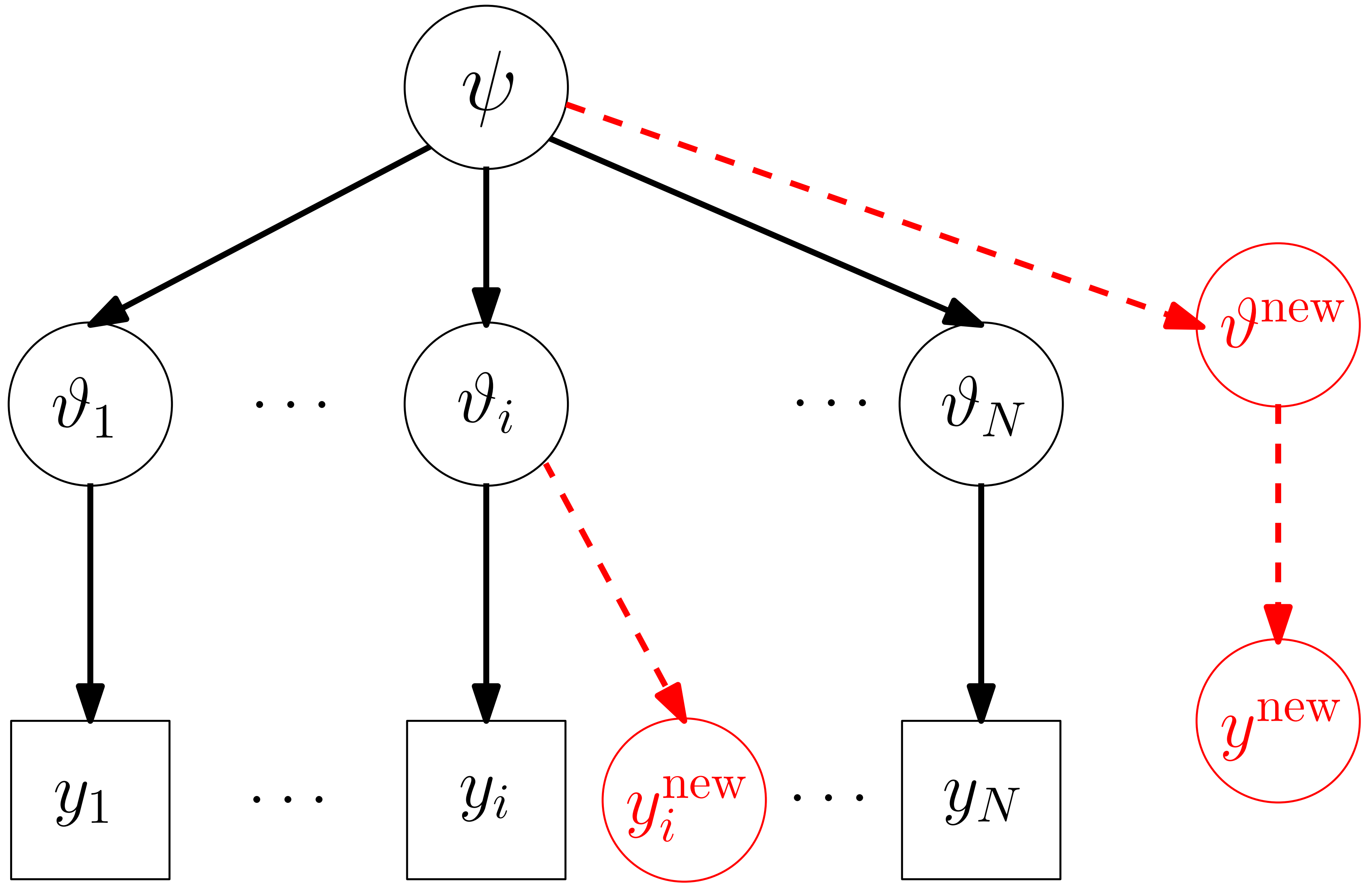
$$p(\psi|d) \propto p(d|\psi)p(\psi)$$

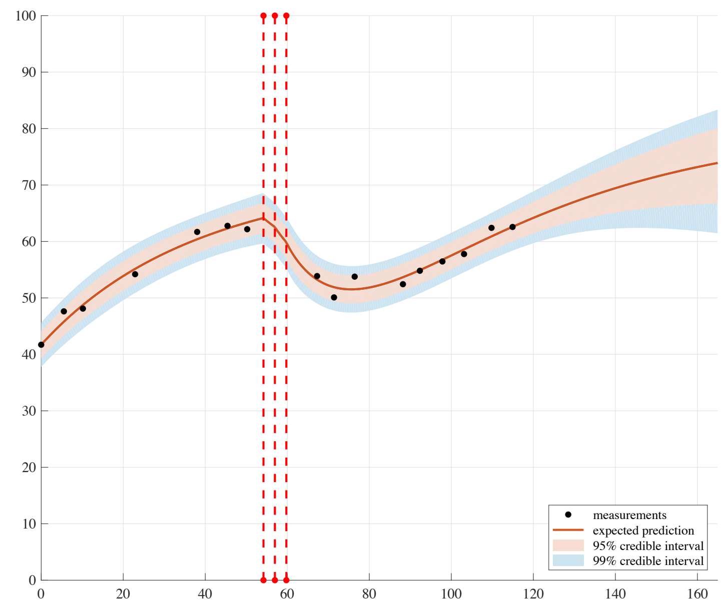
$$d = \{d_1, d_2, \ldots, d_N\}$$

prior on hyperparameters ← $p(\psi)$

prior on model parameters ← $p(\vartheta_i|\psi)$

likelihood of the data ← $p(y_i|\vartheta_i)$





prediction for the i-th individual

$$p(d|\psi) = \int p(d, \vartheta|\psi) \, \mathrm{d}\vartheta$$

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

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 $\mathbf{t}_M = (t_1, \ldots, t_M)$

Set $\mathbf{D}_M = \{t_1, \ldots, t_M, \zeta_1, \ldots, \zeta_M\}$ where $\zeta_i = (x^{(i)}, \vartheta^{(i)})$

The prediction t_{M+1} of the GP model for a new ζ_{M+1} given the data $\mathbf{D}_M$ is a random variable

$$p(t_{M+1}, \mathbf{D}_M) = \mathcal{N}\left(t_{M+1} \,|\, m(\mathbf{D}_M), \sigma^2(\mathbf{D}_M) \right)$$

$$m(\mathbf{D}_M) = k_{M+1}^{\top} C_M^{-1} t_m$$

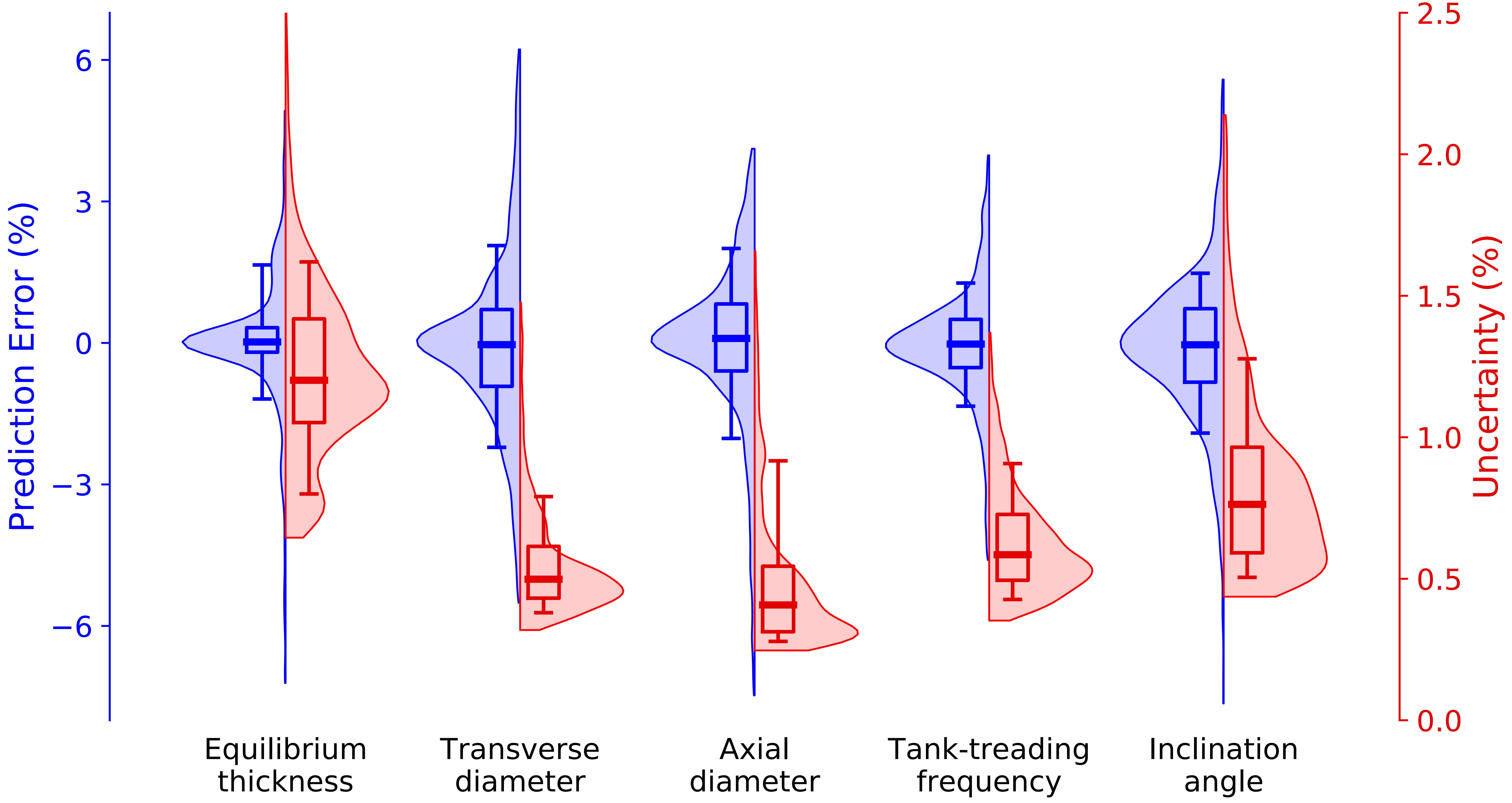
$$\sigma^2(\mathbf{D}_M) = c_{M+1} - k_{M+1}^{\top} C_M^{-1} k_{M+1}$$

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

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

$$c_{M+1} = \kappa(\zeta_{M+1}, \zeta_{M=1})$$

Gaussian Processes: Validation



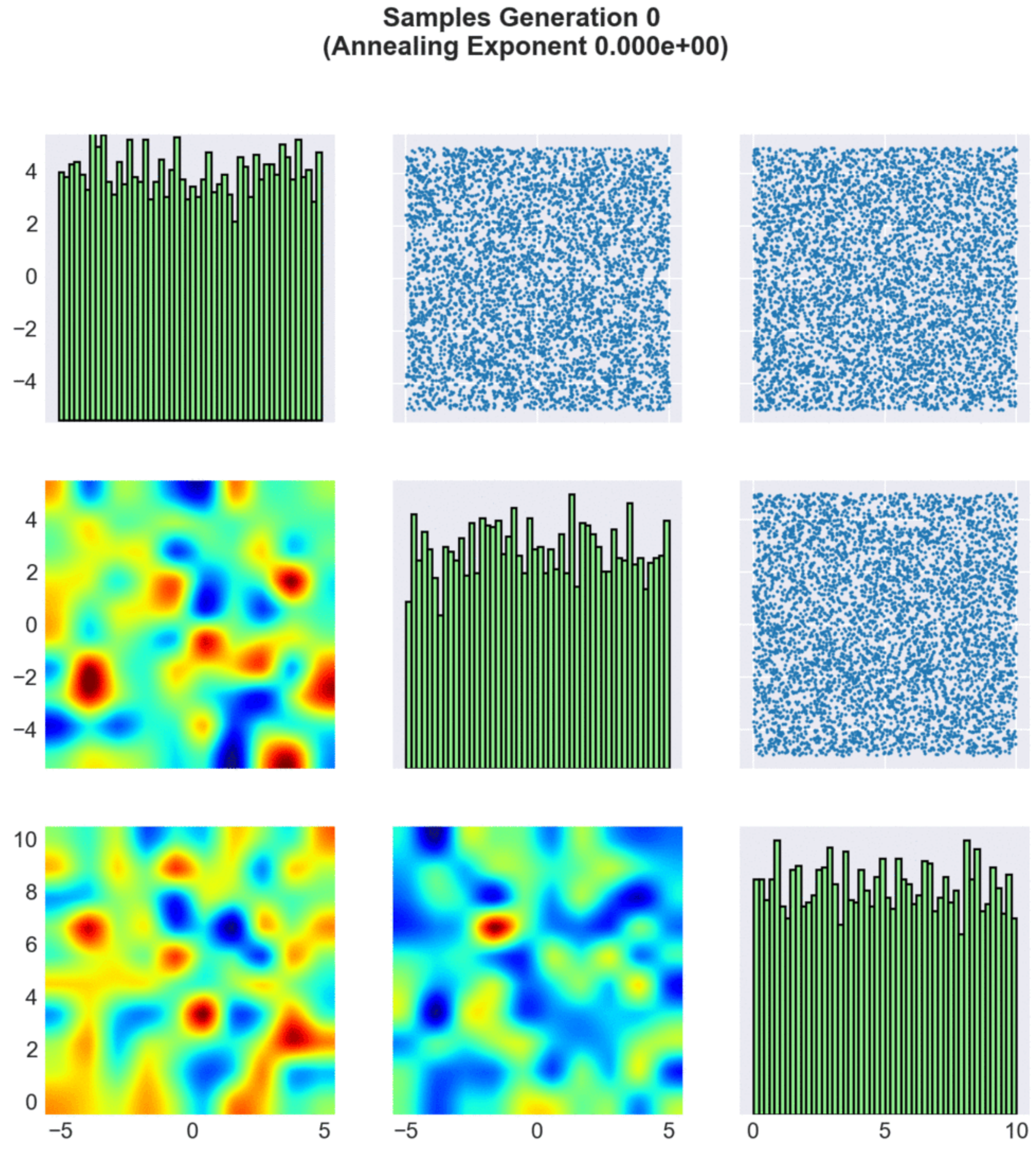
Results

korali

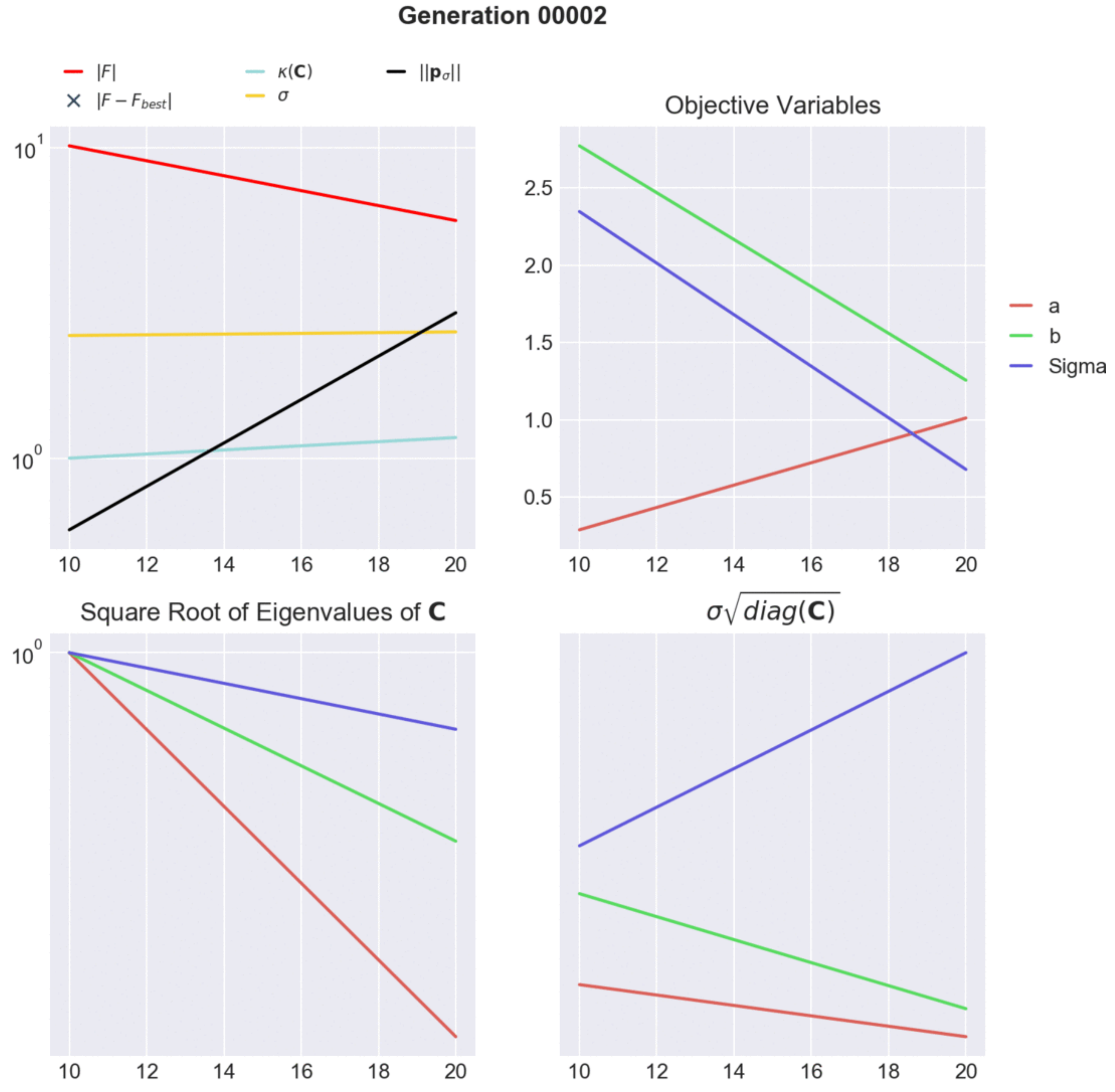
an HPC framework for optimization, sampling and Bayesian UQ of large-scale computational models

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.



Sampling (TMCMC)



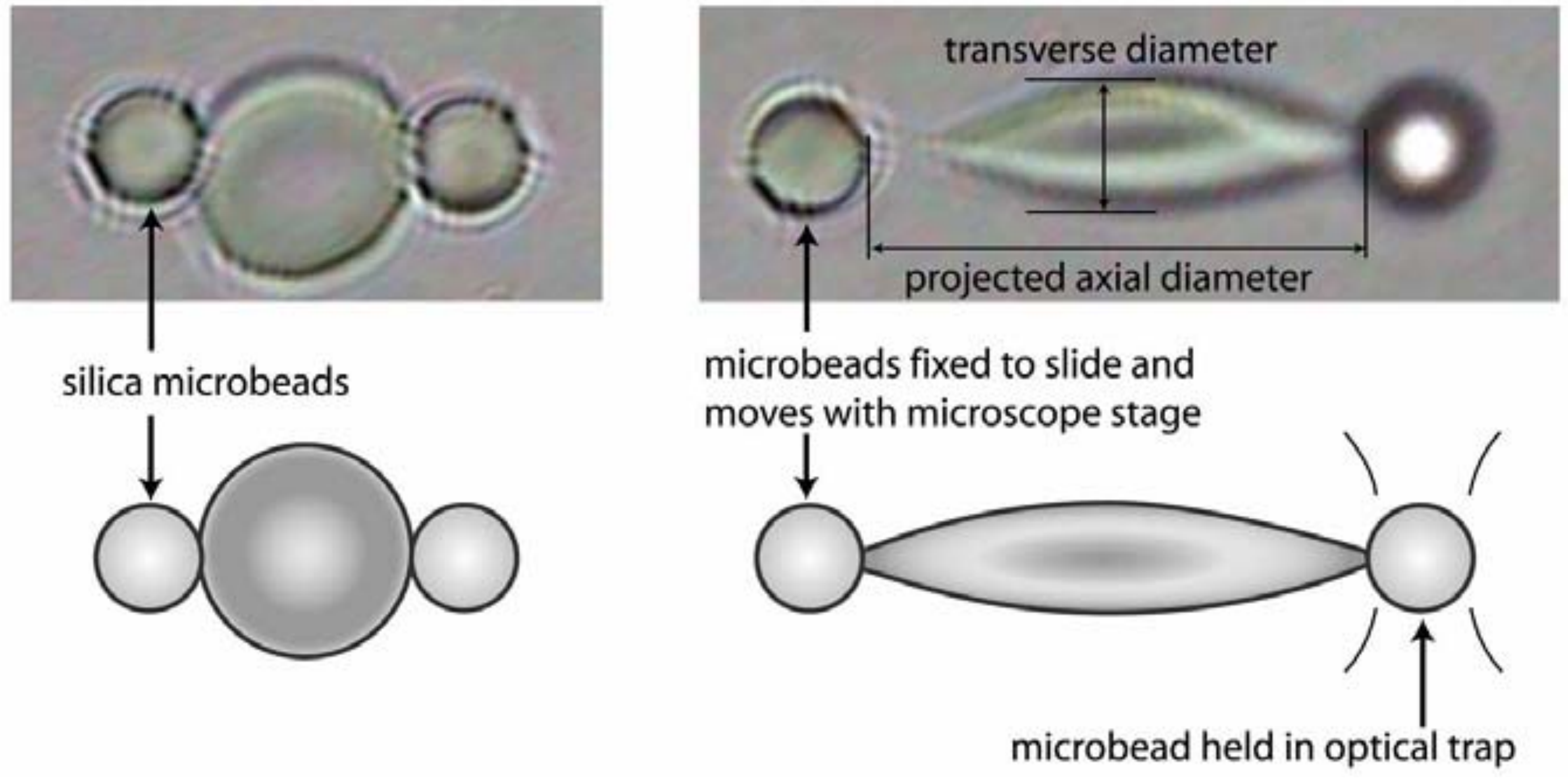
Optimization (CMA-ES)

G. Arampatzis, S. Martin, D. Wälchli

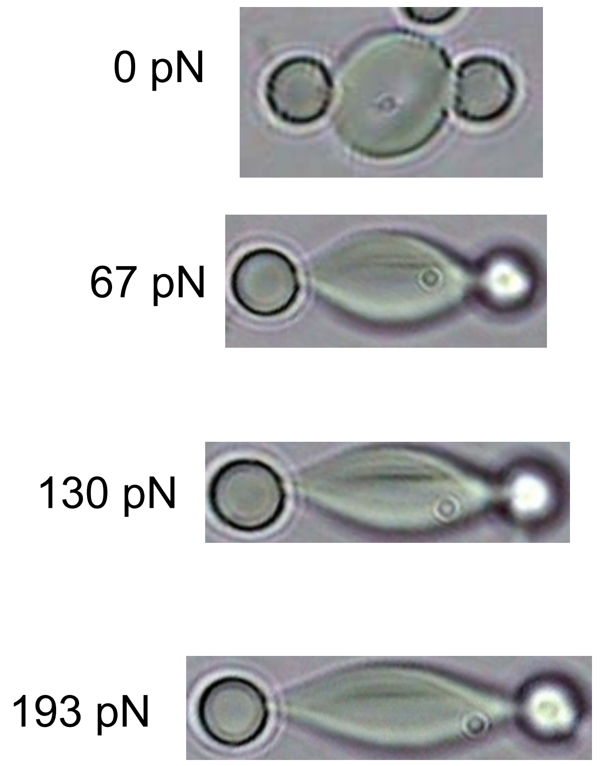
coming soon in https://github.com/cselab/

Stretching experiment

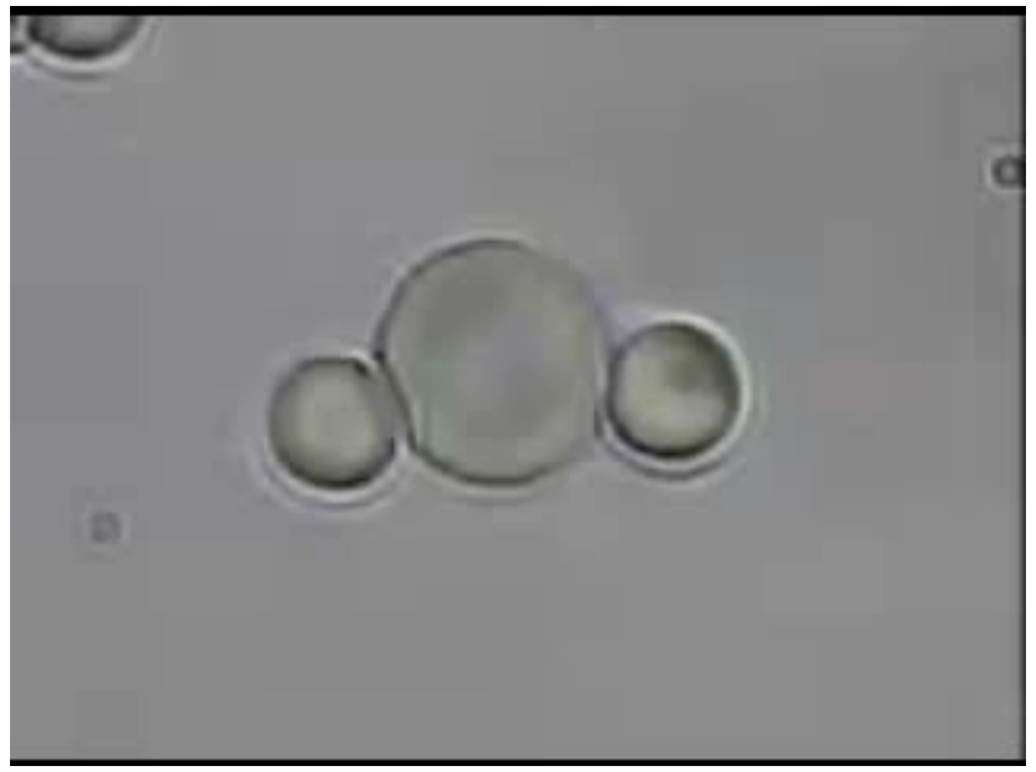
Experimental Setup



Mills et al., "Nonlinear Elastic and Viscoelastic Deformation of the Human Red Blood Cell with Optical Tweezers", MCB Tech Science Press, 2004.

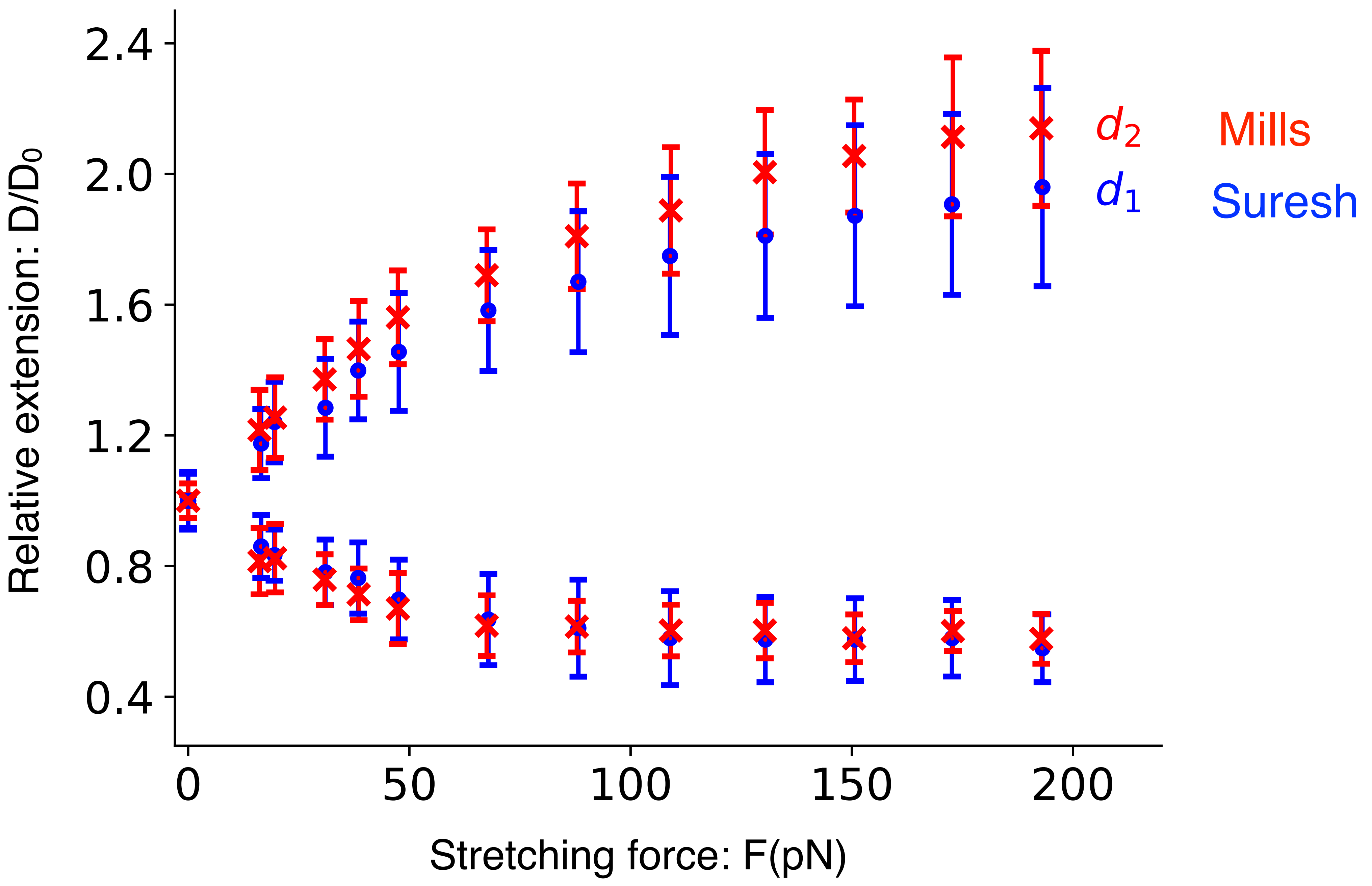


Mills et al., 2004.

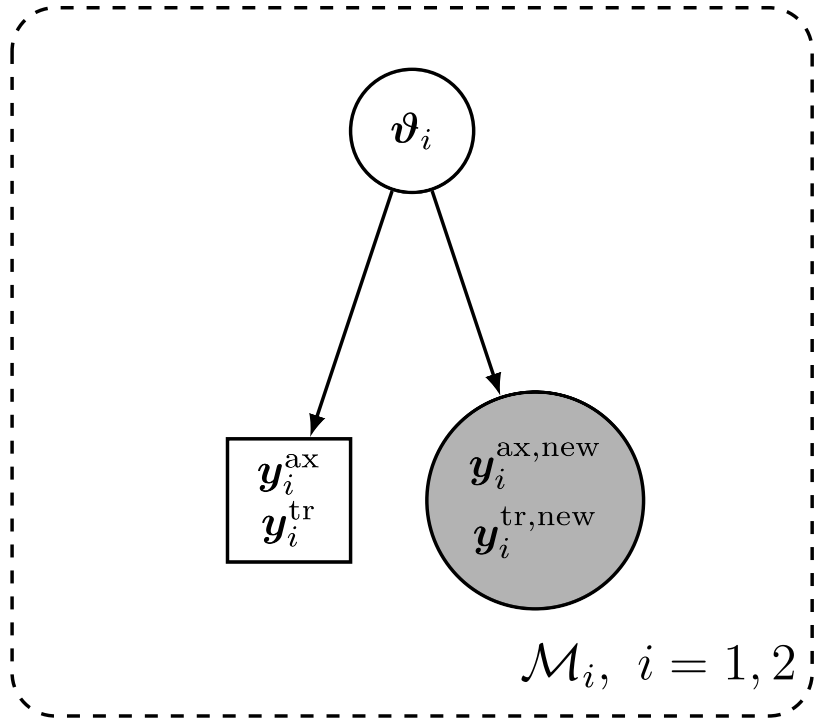


Suresh et al., "Connections between single-cell biomechanics and human disease states: gastrointestinal cancer and malaria", Acta Biomaterialia, 2005.

Stretching data sets considered in UQ

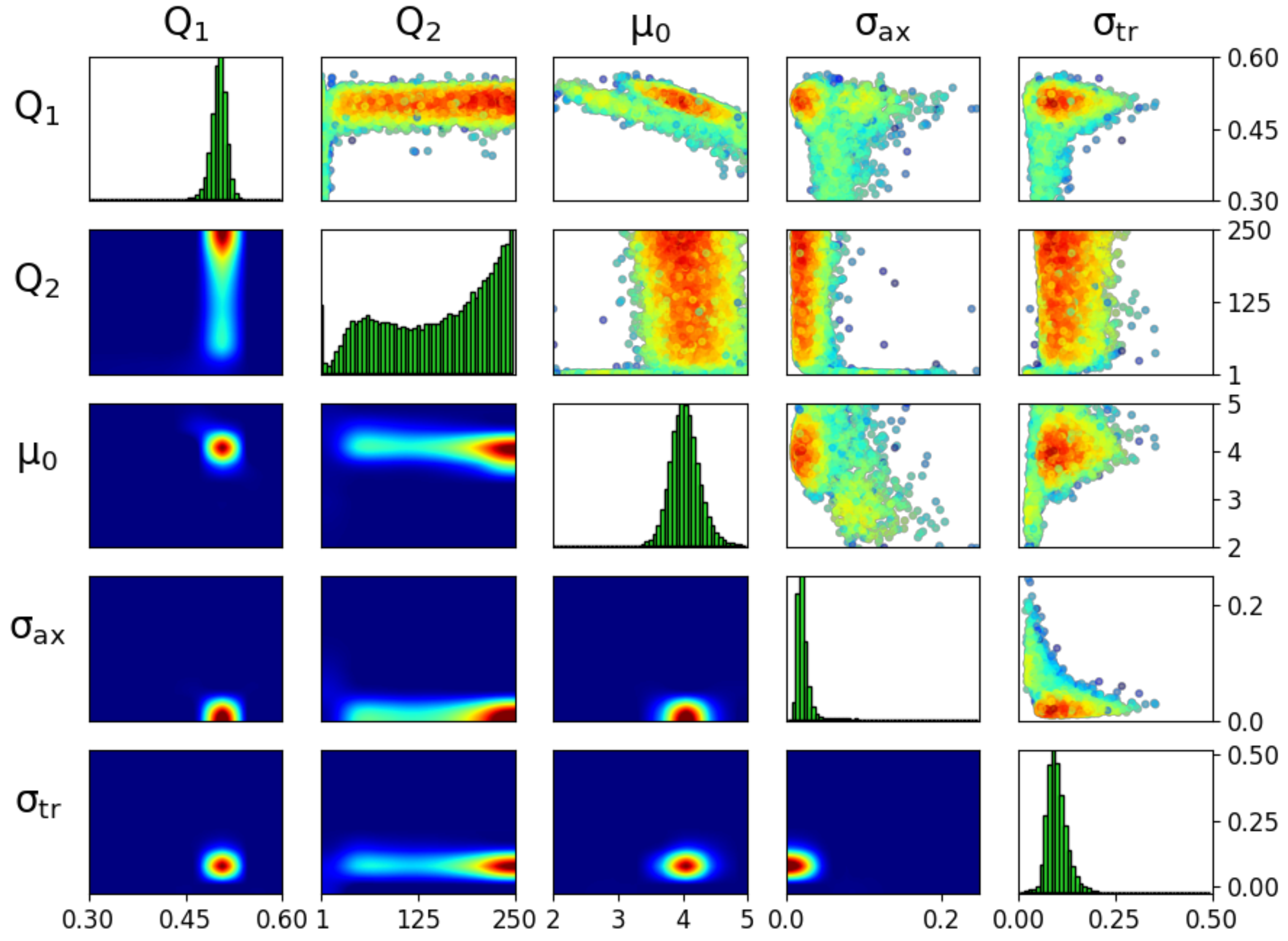


Single-level UQ for stretching

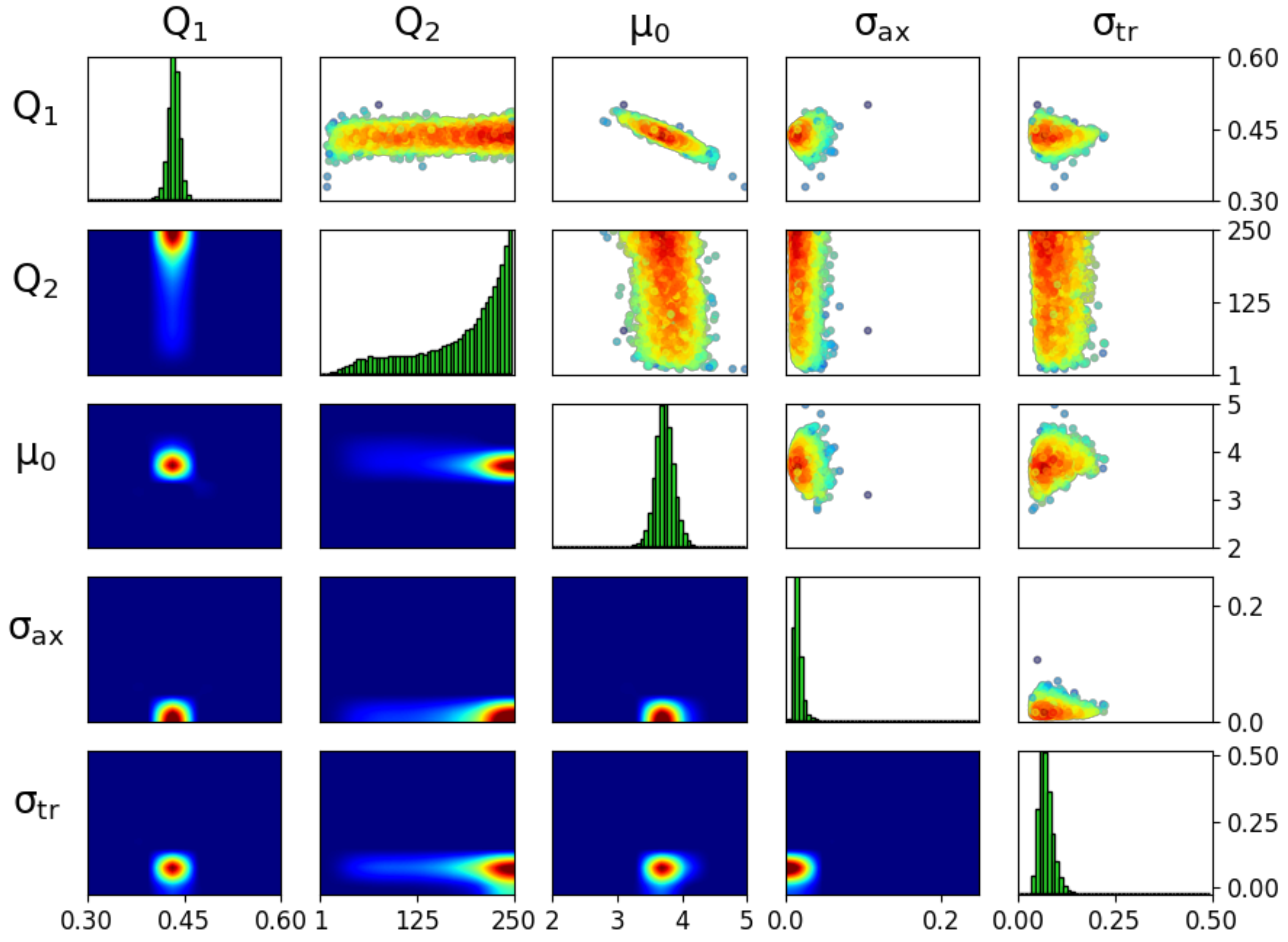


stretching

$\vartheta_i = (Q_{1,i}, Q_{2,i}, \mu_{0,i}, \sigma_{\mathrm{st},i}),\ i = 1, 2$



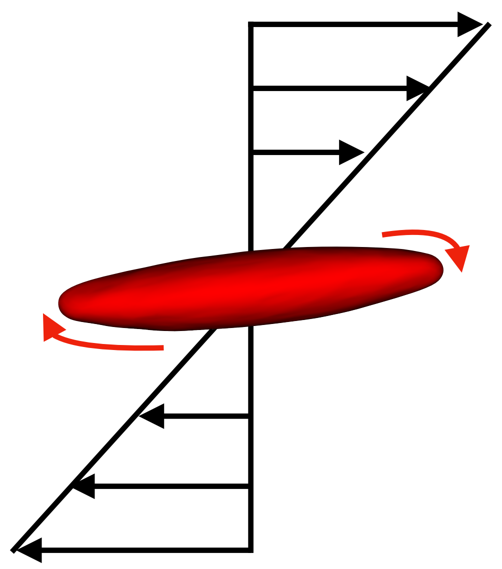
$p(\boldsymbol{\vartheta}_1 \,|\, \boldsymbol{d}_1, \mathscr{M}_1)$

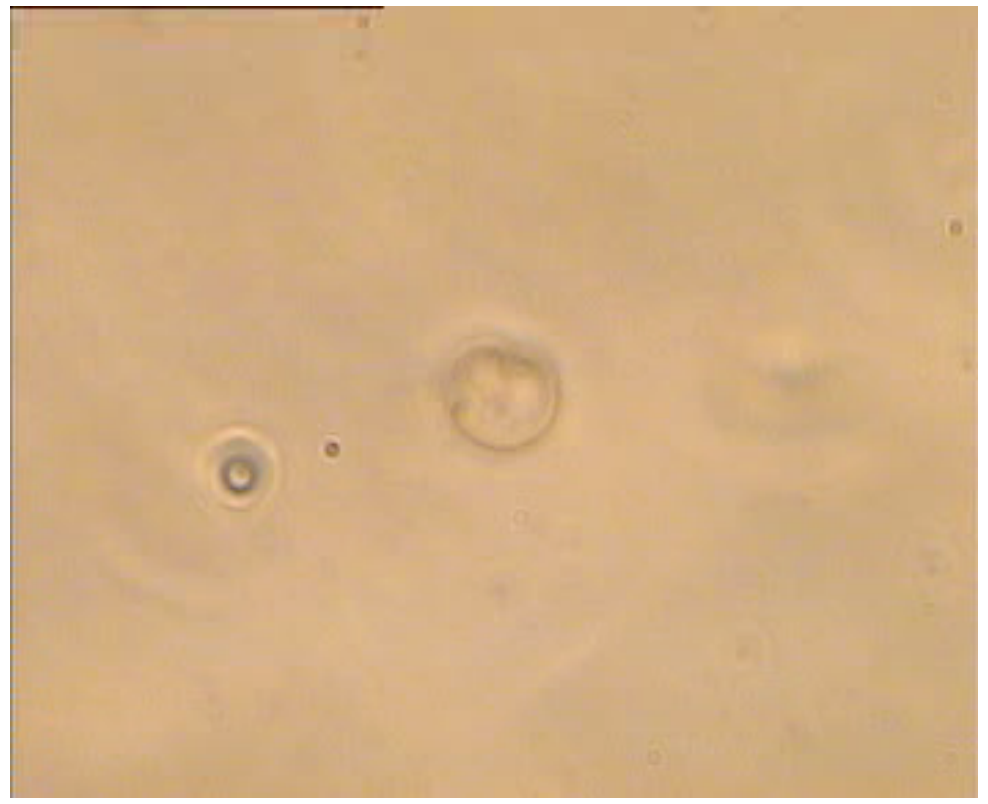


$p(\boldsymbol{\vartheta}_2 \,|\, \boldsymbol{d}_2, \mathscr{M}_2)$

Shear flow experiment

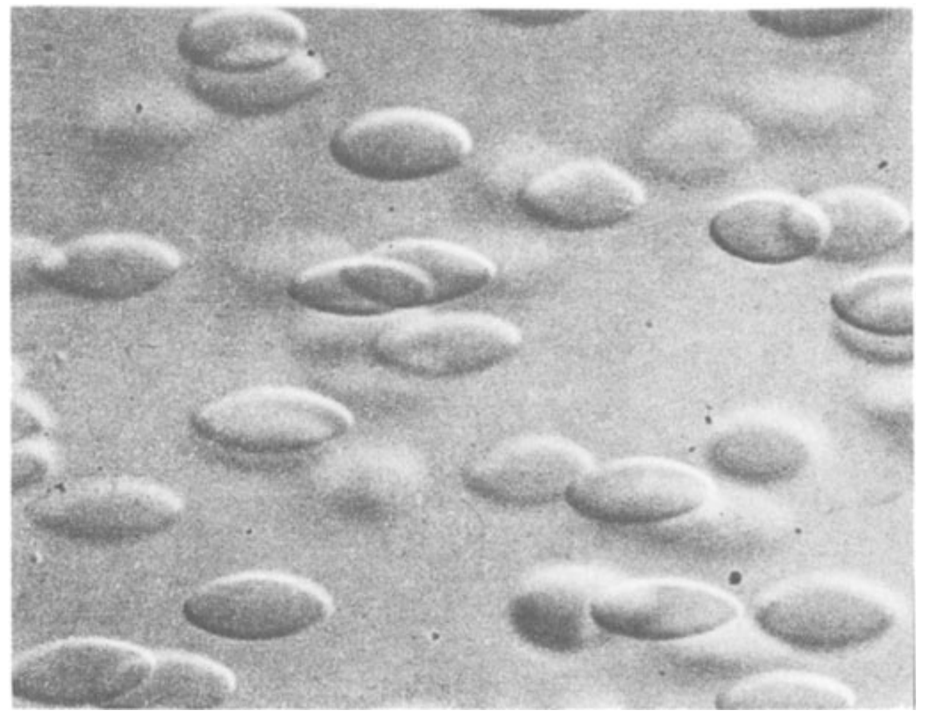
Experimental Setup



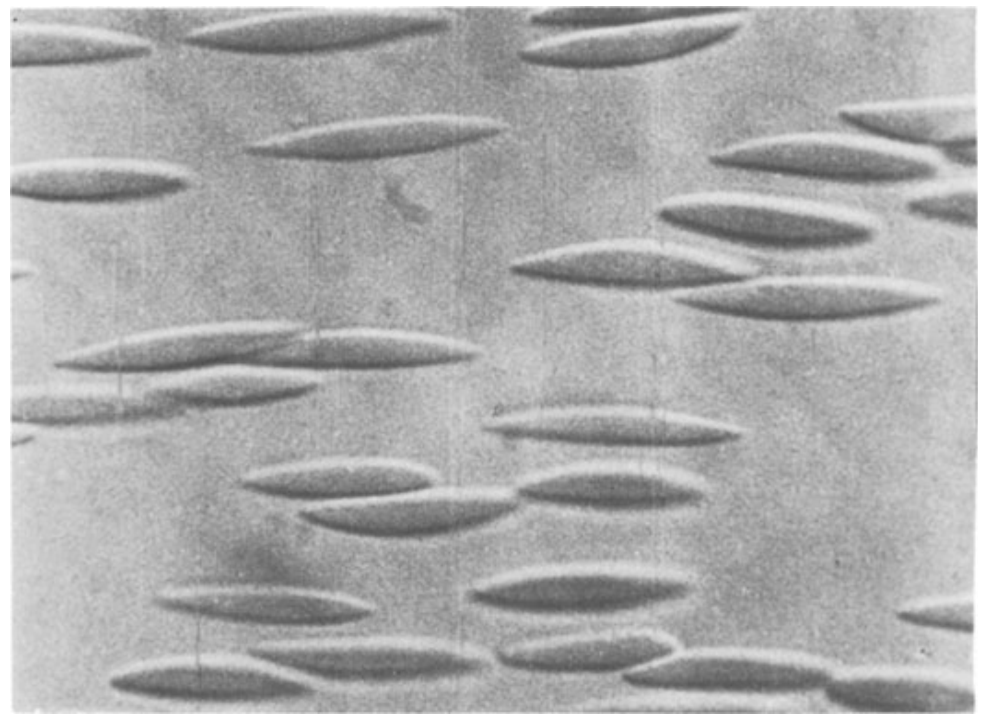


Basu et al., "Tank Treading of Optically Trapped Red Blood Cells in Shear Flow", Biophysical Journal, 2011.

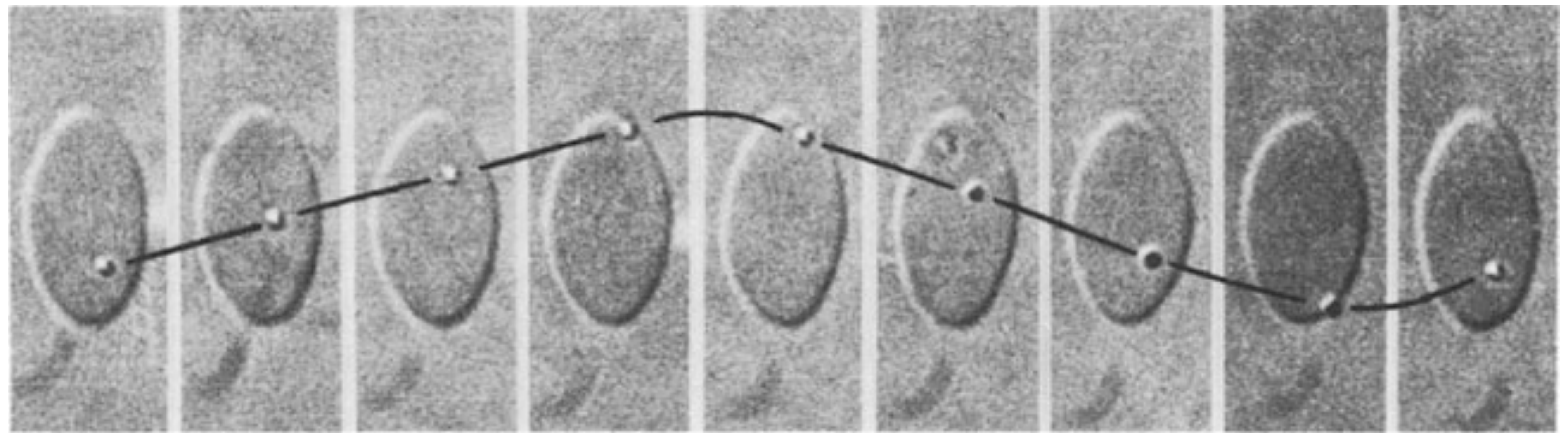
top-view



Shear rate=500/s. η_0=12 mPa.s



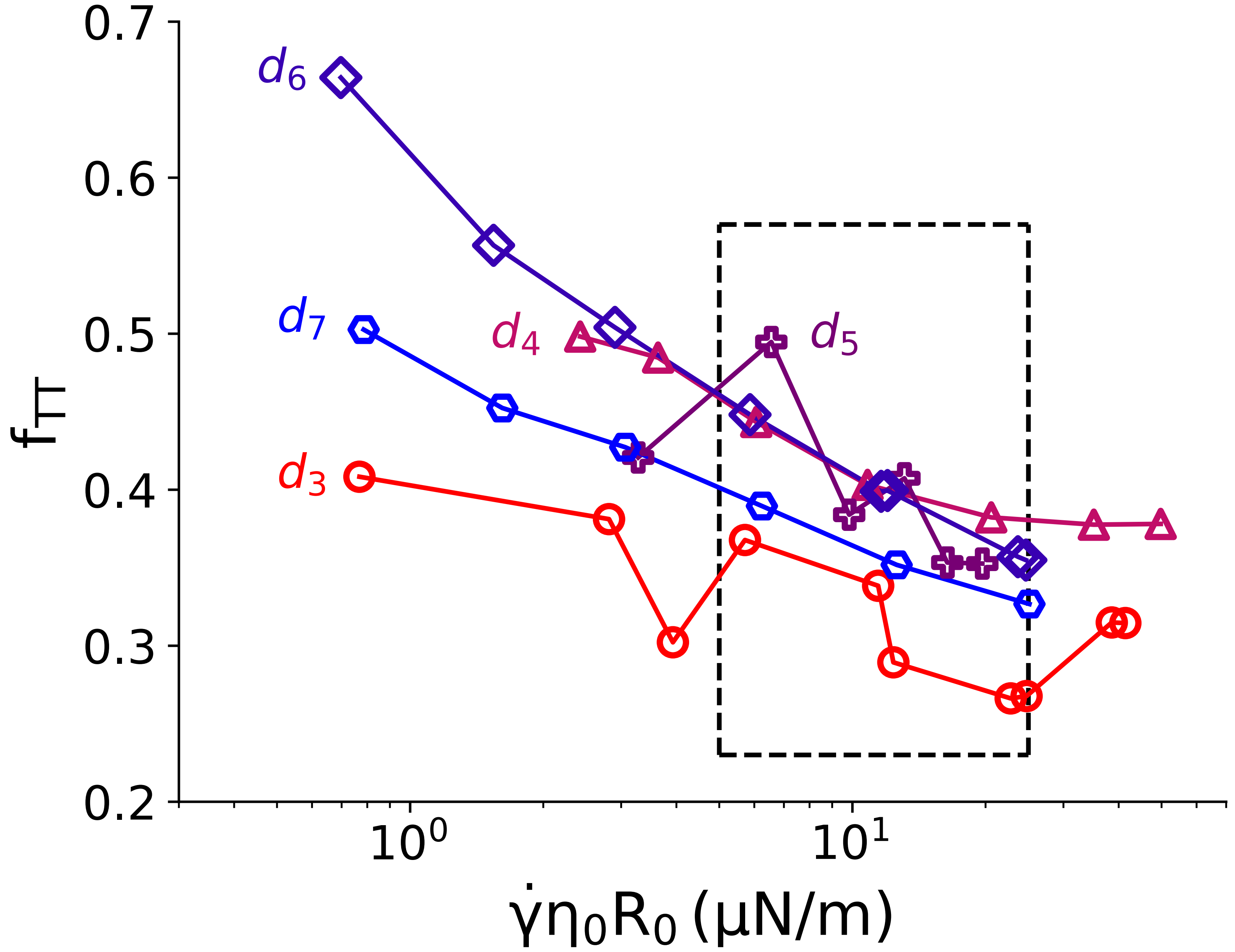
Shear rate<600/s. η_0=170 mPa.s



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. η_0=18 mPa.s

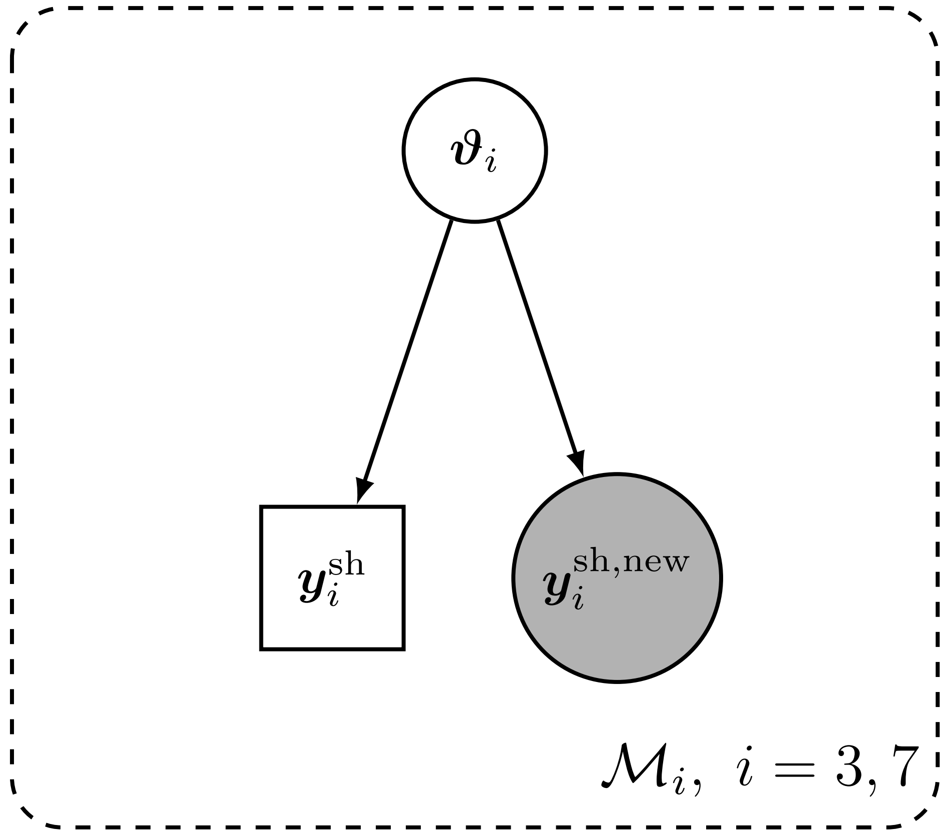
Fischer and Schmid-Schönbein. "Tank tread motion of red cell membranes in viscometric flow: behavior of intracellular and extracellular markers (with film)." Red Cell Rheology, Springer 1978.

Shear flow data sets considered in UQ



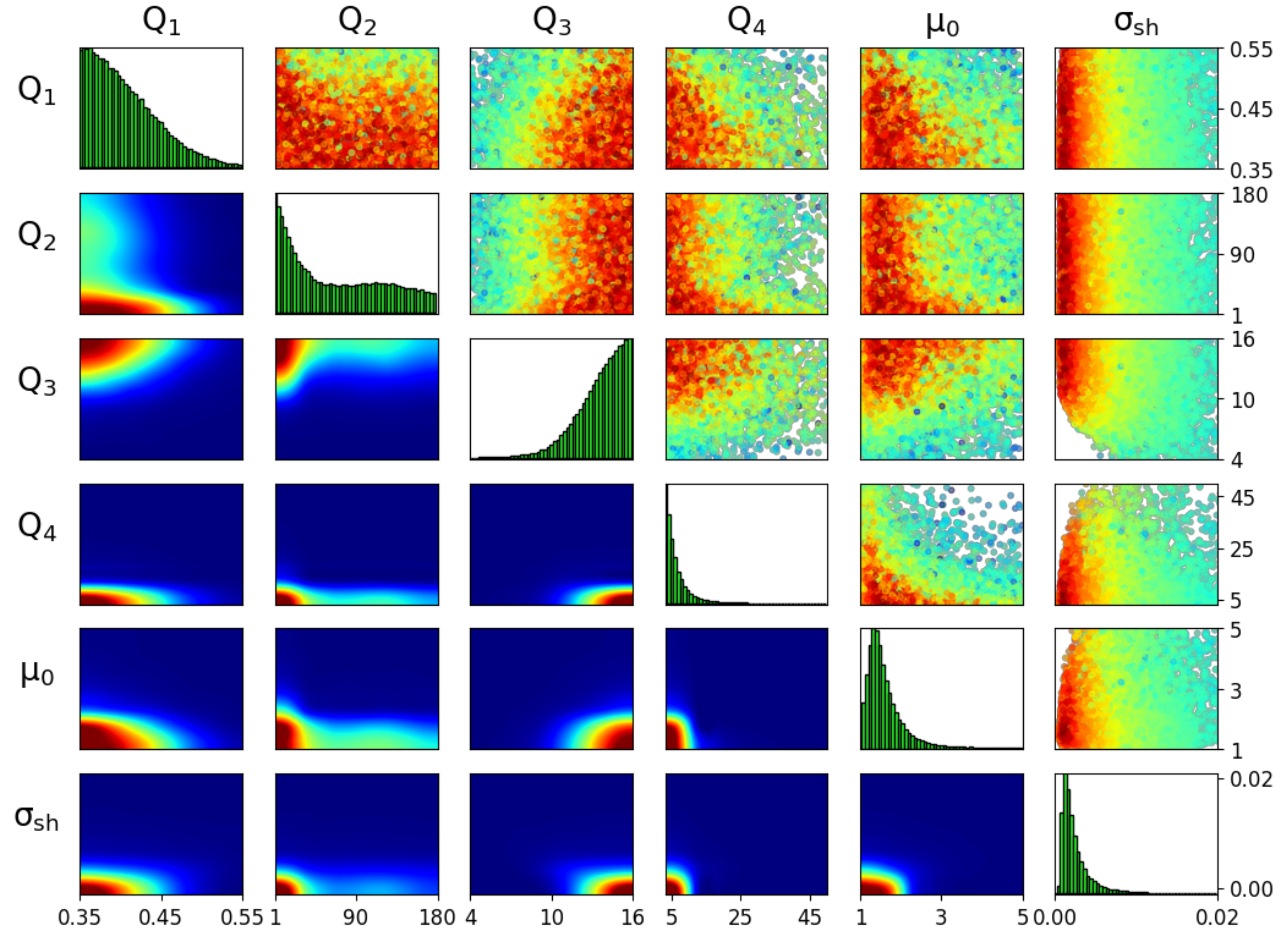
Reference	Year	symbol (Fig. 2)	Viscosity ratio, λ	data set ID in UQ
Fischer et al.	1978	◯	0.56	$\boldsymbol{d_3}$
Fischer	1980	△	0.43	$\boldsymbol{d_4}$
Tran-Son-Tay	1983	✙	0.50	$\boldsymbol{d_5}$
Fischer	2007	◇	0.35	$\boldsymbol{d_6}$
Fischer and Korzeniewski	2015	⬡	0.35	$\boldsymbol{d_7}$

Single-level UQ for shear flow

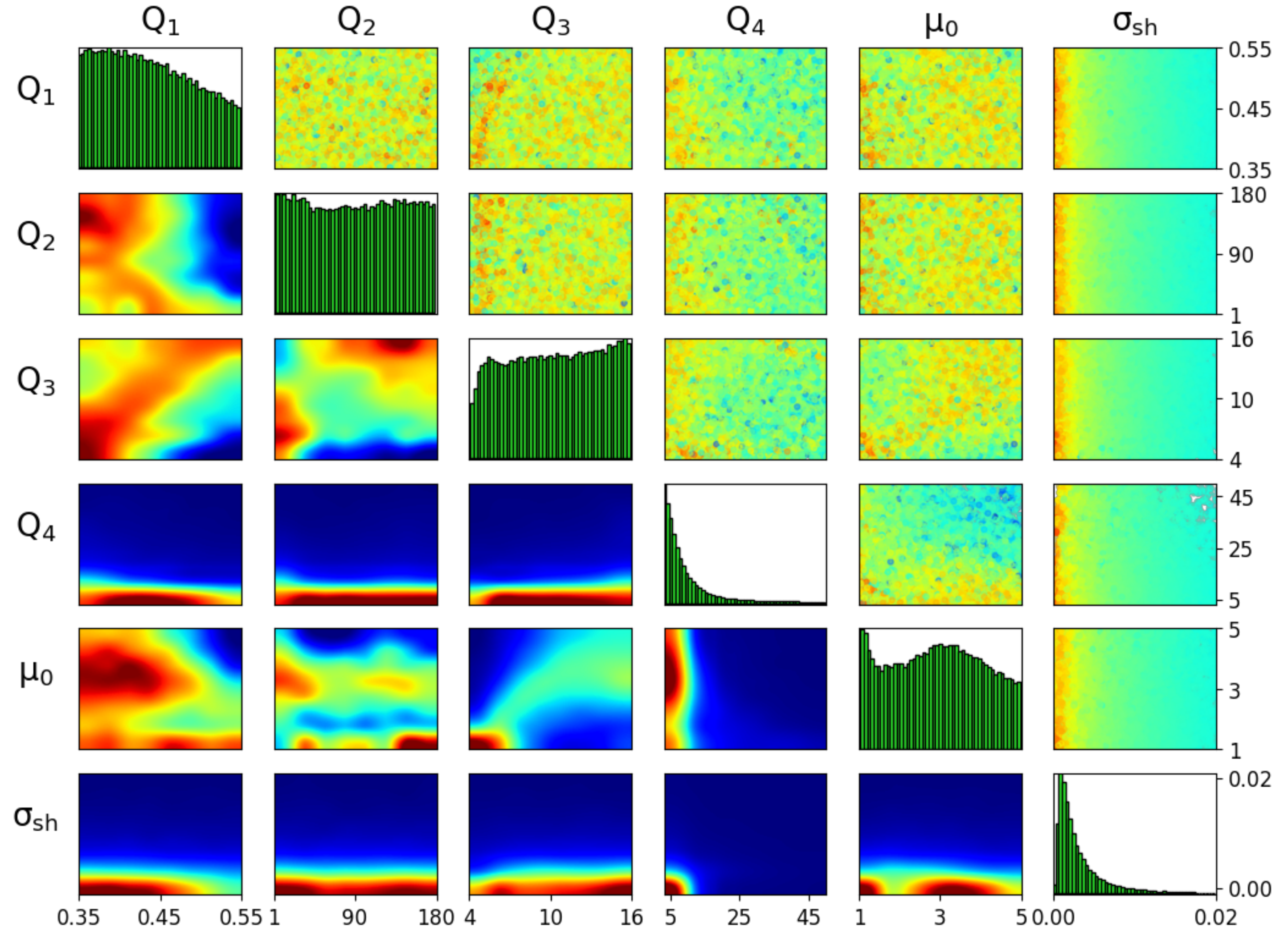


shear

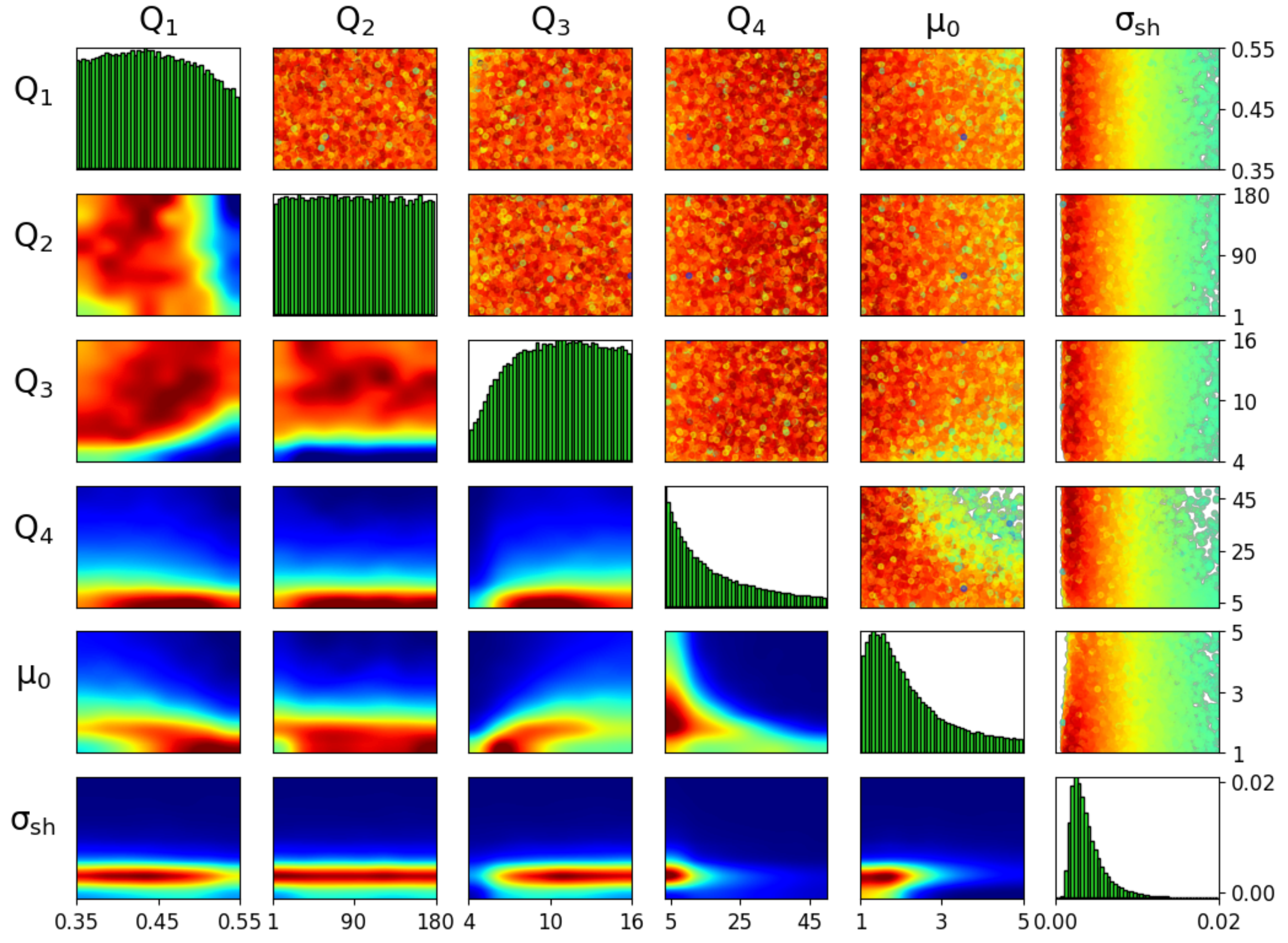
$$\vartheta_i = (Q_{1,i}, Q_{2,i}, \mu_{0,i}, \; Q_{3,i}, Q_{4,i}, , \sigma_{\mathrm{sh},i}), \; i = 3, \ldots, 7$$



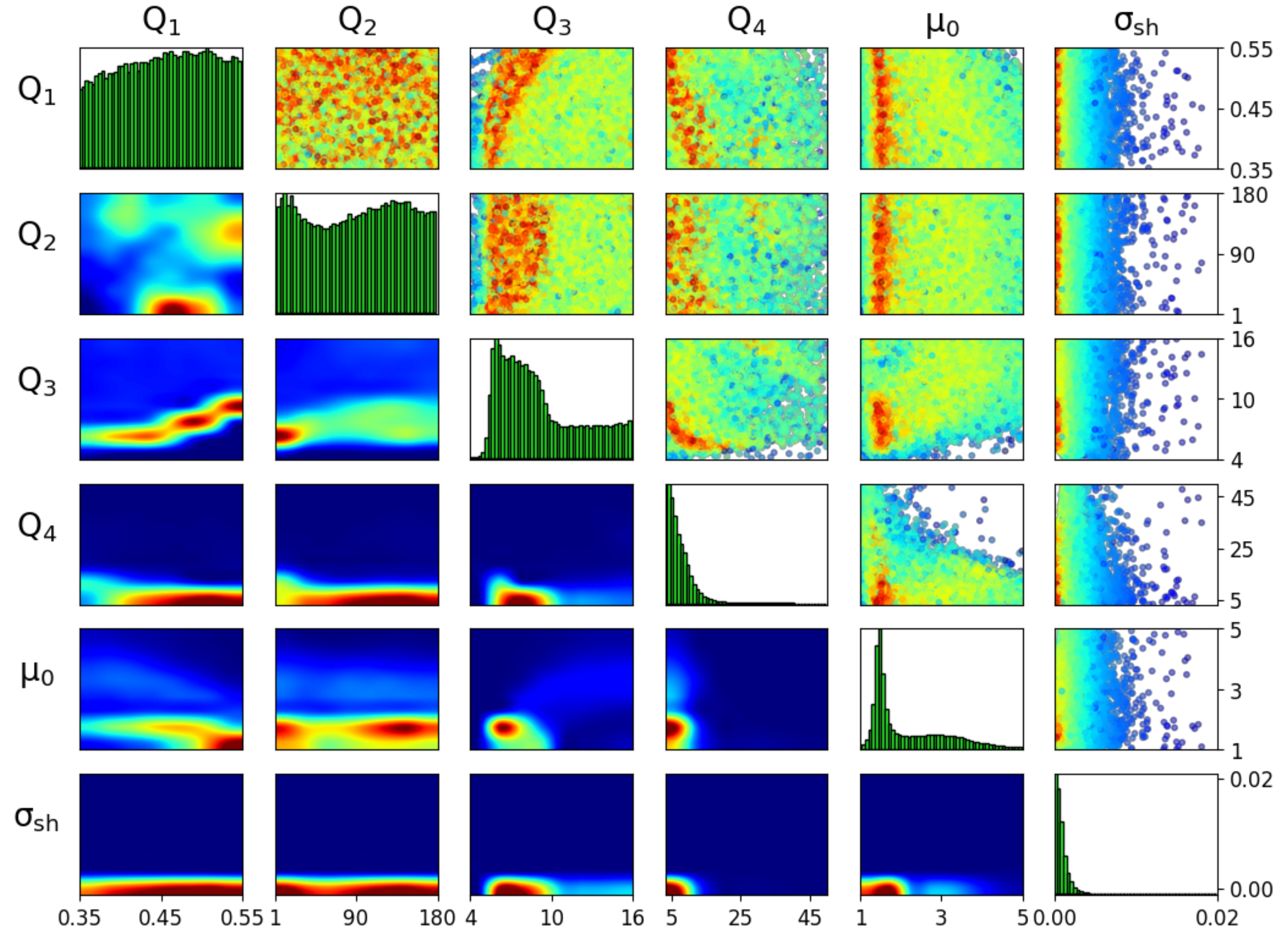
$p(\vartheta_3 \,|\, d_3, \mathcal{M}_3)$



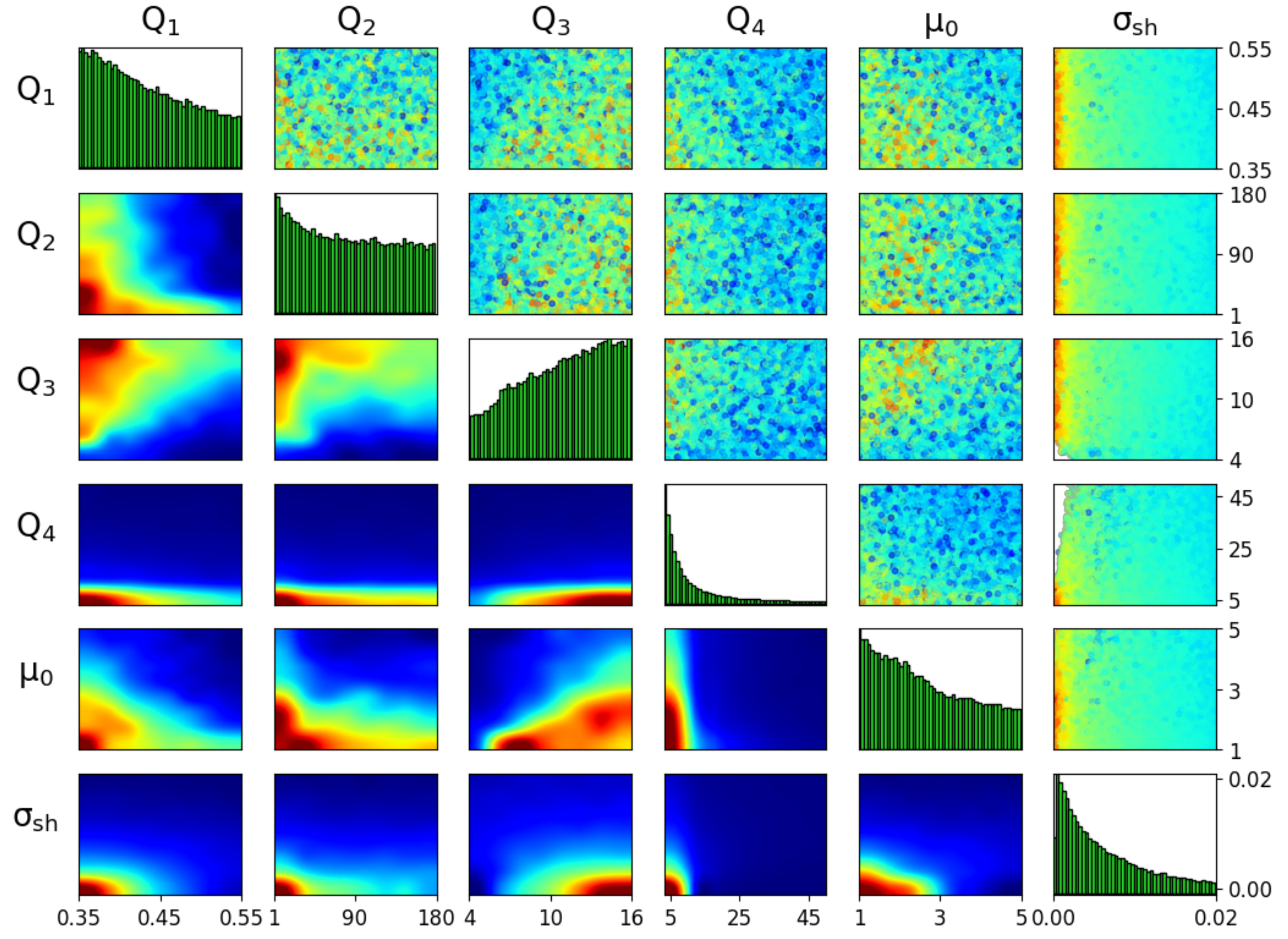
$p(\vartheta_4 \,|\, d_4, \mathcal{M}_4)$



$p(\vartheta_5 \,|\, d_5, \mathcal{M}_5)$

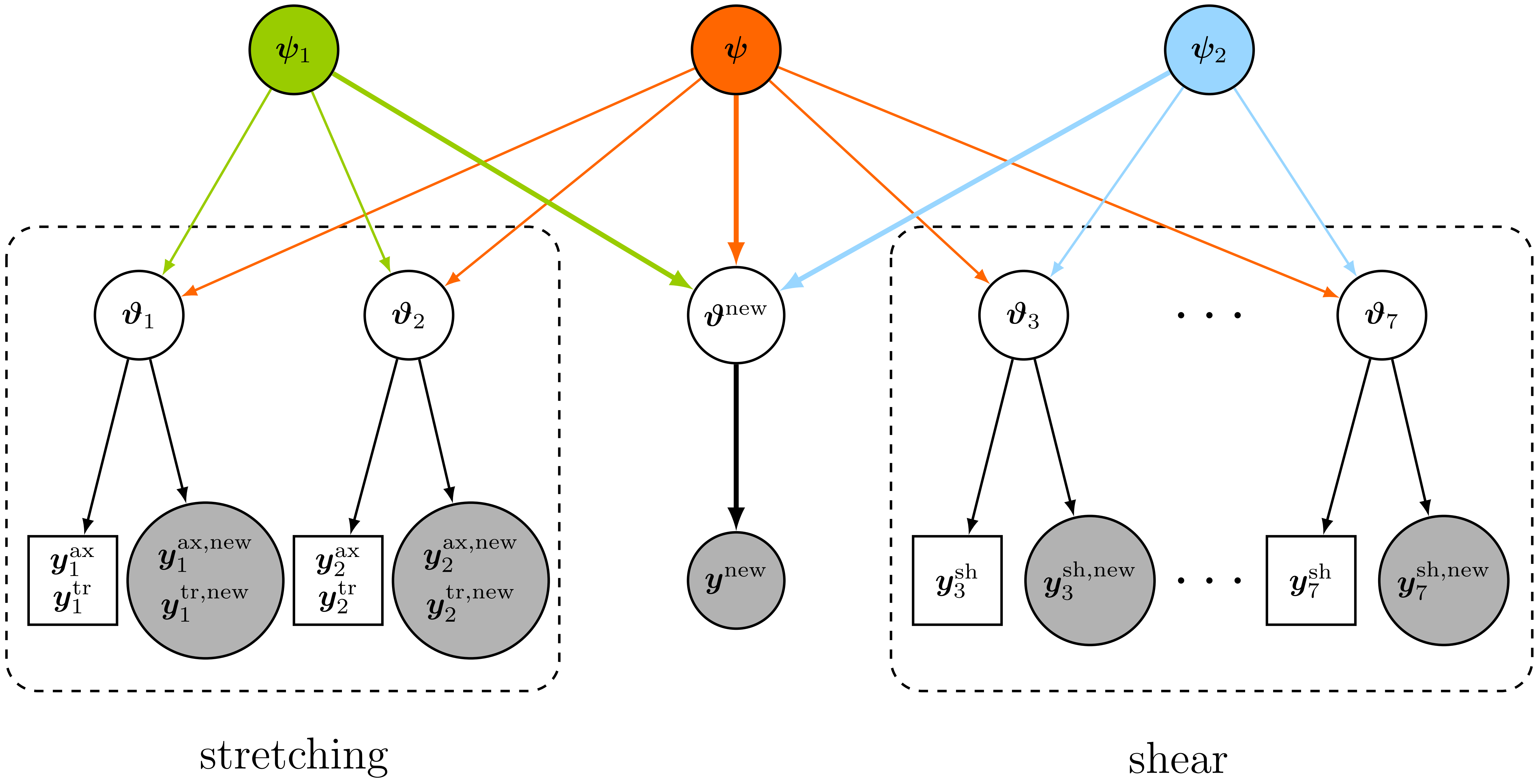


$p(\vartheta_6 \,|\, d_6, \mathcal{M}_6)$



$p(\vartheta_7 \,|\, d_7, \mathcal{M}_7)$

Hierarchical Bayesian Inference for the RBC model

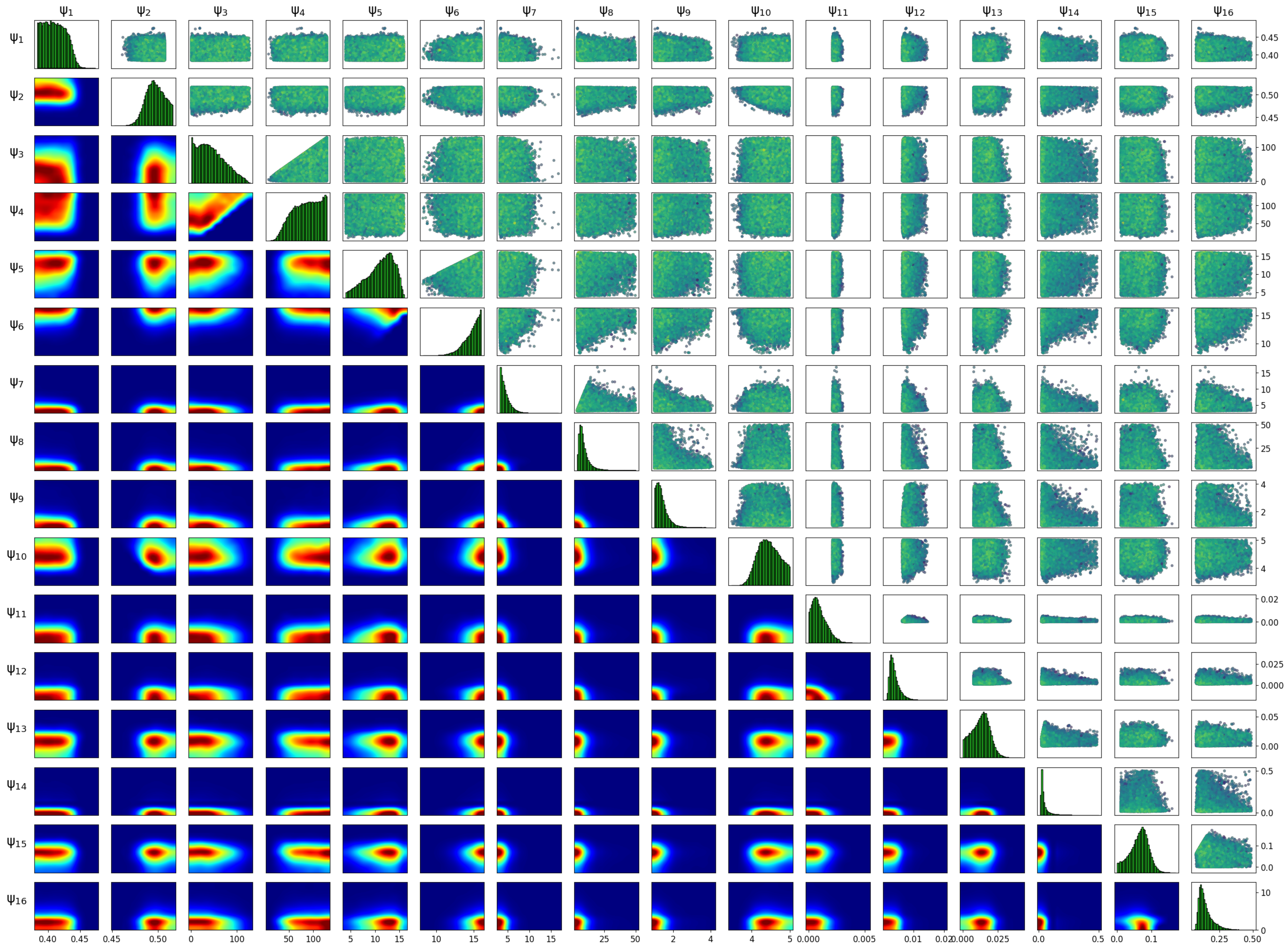


$\boldsymbol{\vartheta}_i = (Q_{1,i}, Q_{2,i}, \mu_{0,i}, \sigma_{\mathrm{st},i}),\ i = 1, 2$

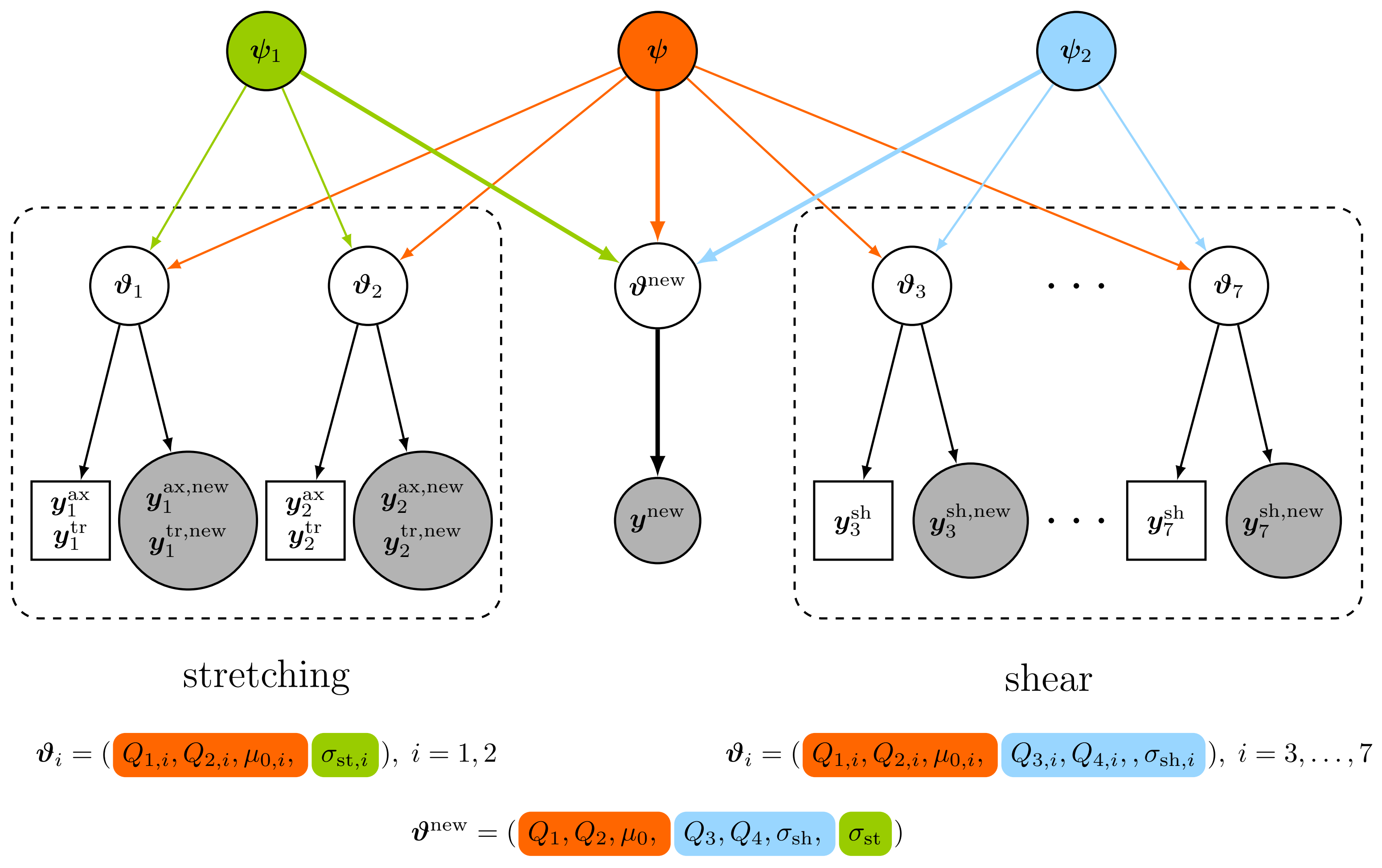
$\boldsymbol{\vartheta}_i = (Q_{1,i}, Q_{2,i}, \mu_{0,i}, Q_{3,i}, Q_{4,i}, , \sigma_{\mathrm{sh},i}),\ i = 3, \ldots, 7$

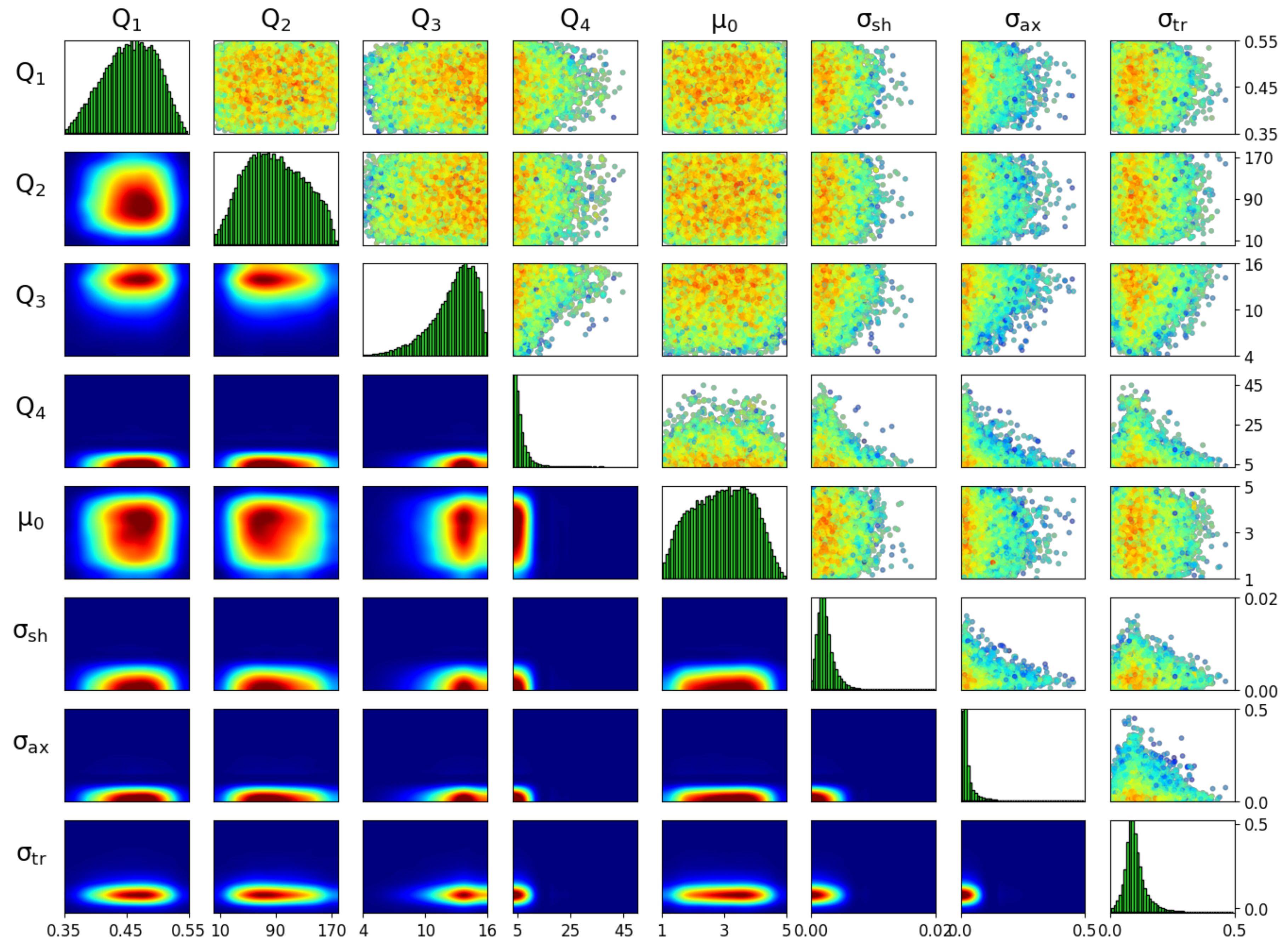
$$\boldsymbol{\vartheta}^{\mathrm{new}} = (Q_1, Q_2, \mu_0, Q_3, Q_4, \sigma_{\mathrm{sh}}, \sigma_{\mathrm{st}})$$

Hierarchical Bayesian UQ



$p(\boldsymbol{\psi} \mid \overrightarrow{\boldsymbol{d}}, \mathcal{M}_{HB})$





$p(\boldsymbol{\vartheta}^{new} \mid \overrightarrow{\boldsymbol{d}}, \mathcal{M}_{HB})$

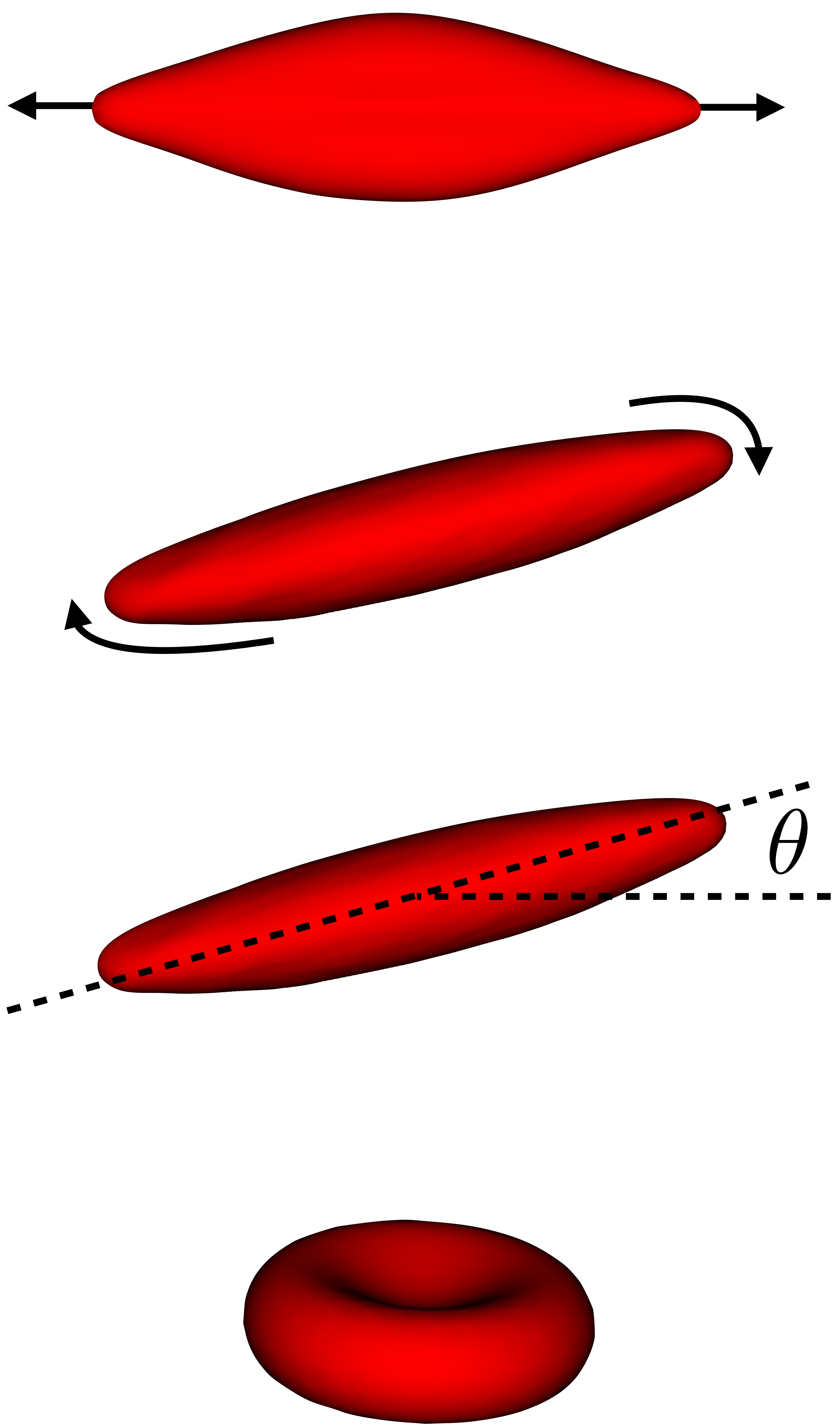
Model Transferability: Infer for quantity X - Propagate to quantity Y

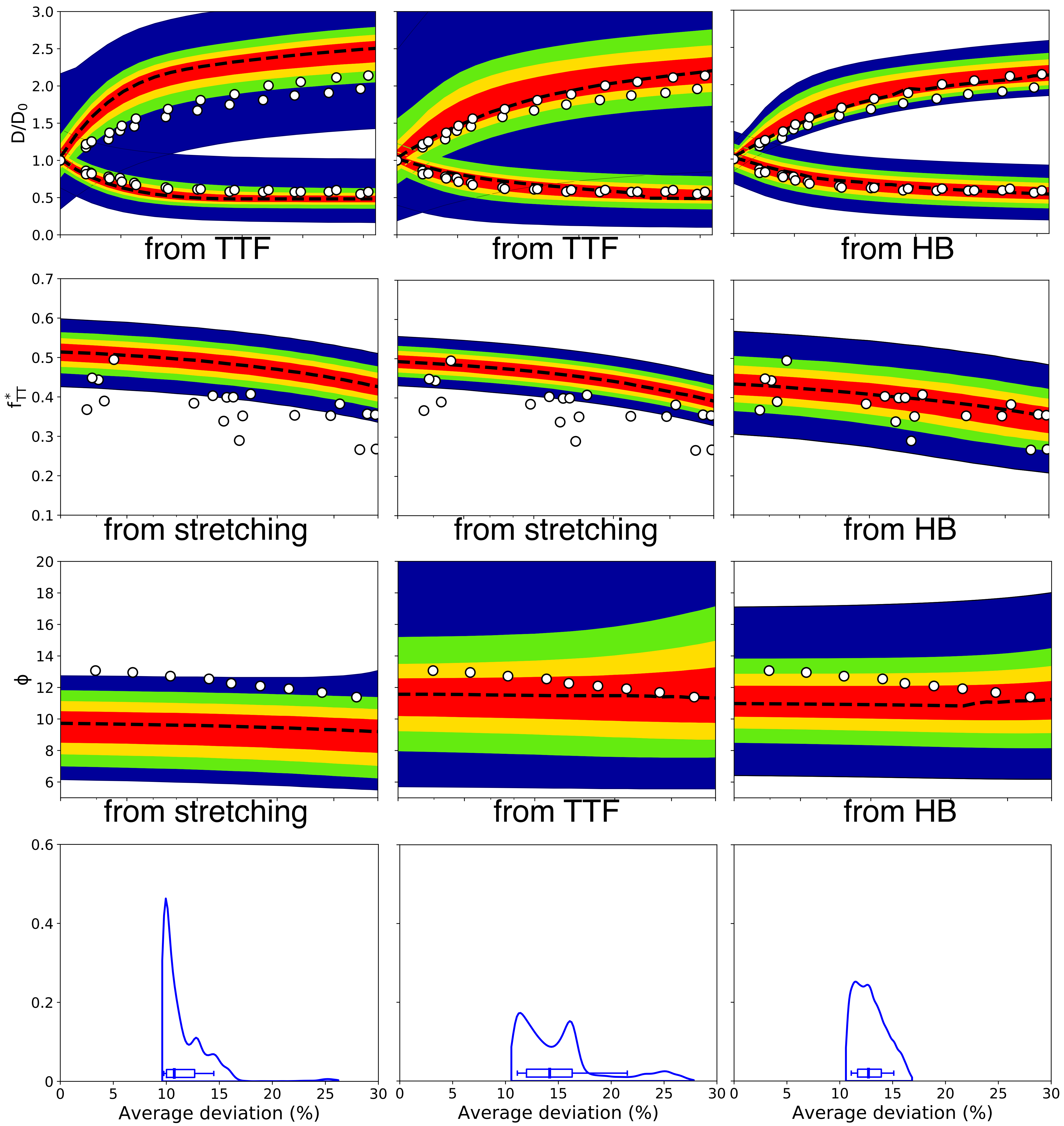
to stretching

to TTF

to inclination angle

to equilibrium shape





Thank you!