e-Seminar #24

Simulating human cellular blood flow at extreme detail: a drop of blood at exascale

5 July 2022

The e-Seminar will start at 2pm CEST / 1pm BST

Presenter:
Gábor Závodszky
(University of Amsterdam, Budapest University of Technology)

Moderator:
Tim Weaving
(University College London)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823712

INSILICO WORLD

https://insilicoworld.slack.com/archives/C0151M02TA4

The e-Seminar series is run in collaboration with: VPH Institute — Building the Virtual Physiological Human

CompBioMed

A Centre of Excellence in Computational Biomedicine

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Welcome!

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Outline

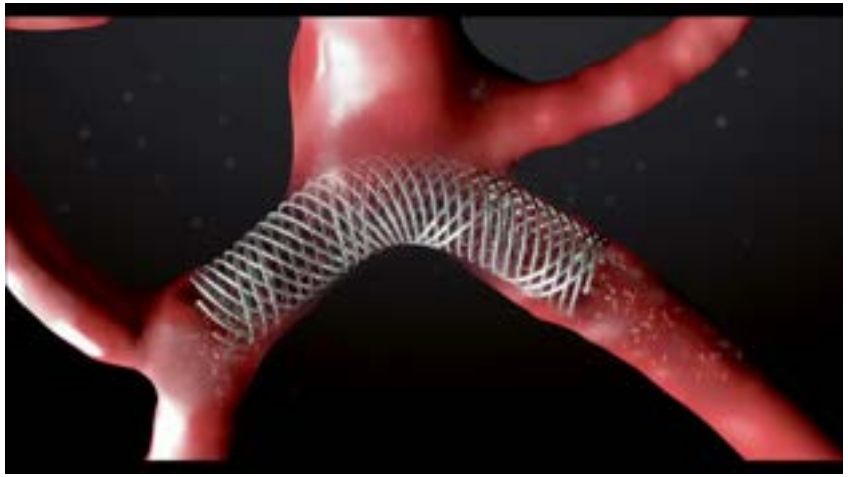
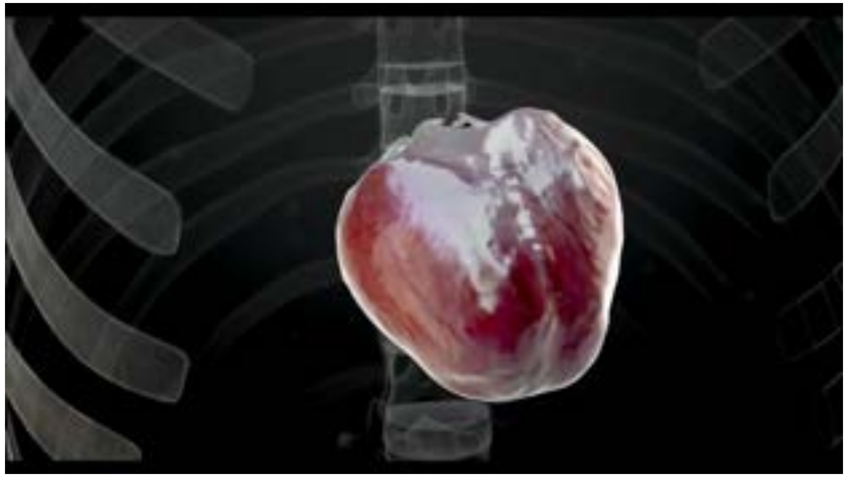
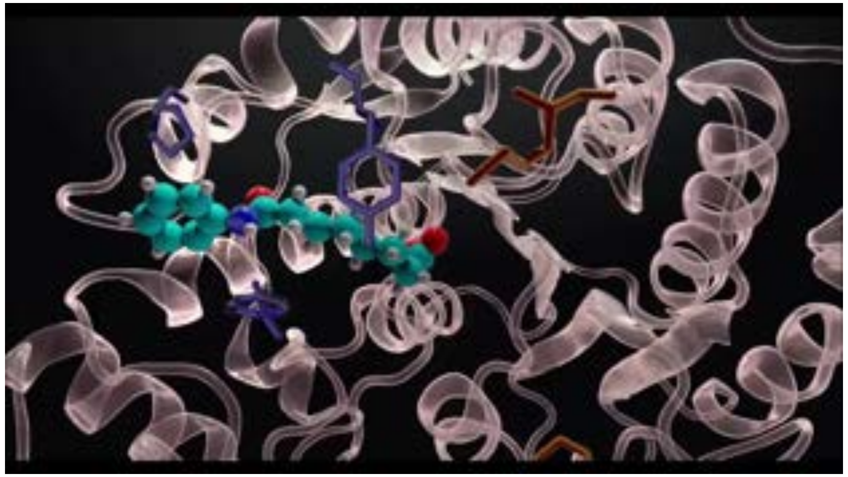
- Introduction to the numerical modelling of blood.
  Methods, validation, Uncertainty quantification

- Computational challenges and solutions at scale.
  Typical bottlenecks, adaptive time-step, dynamic load-balancing

- Use-case demonstrations.
  Production cases, experimental setups, usage strategy

Virtual Physiological Human Movie

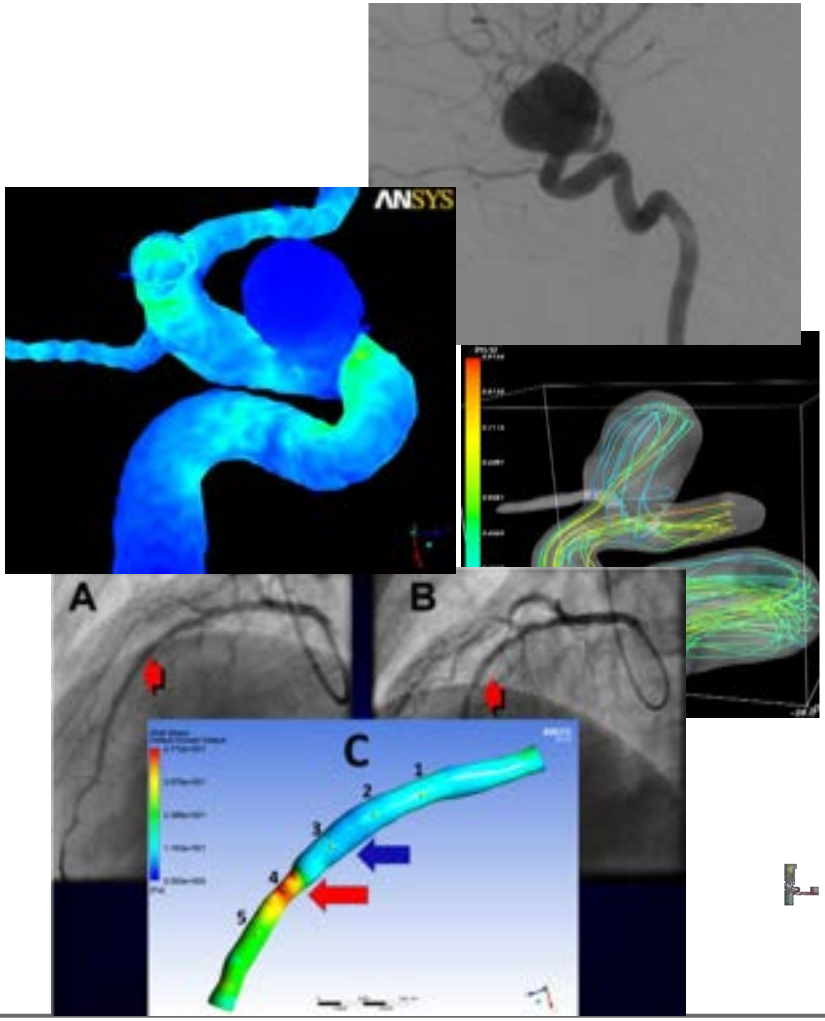


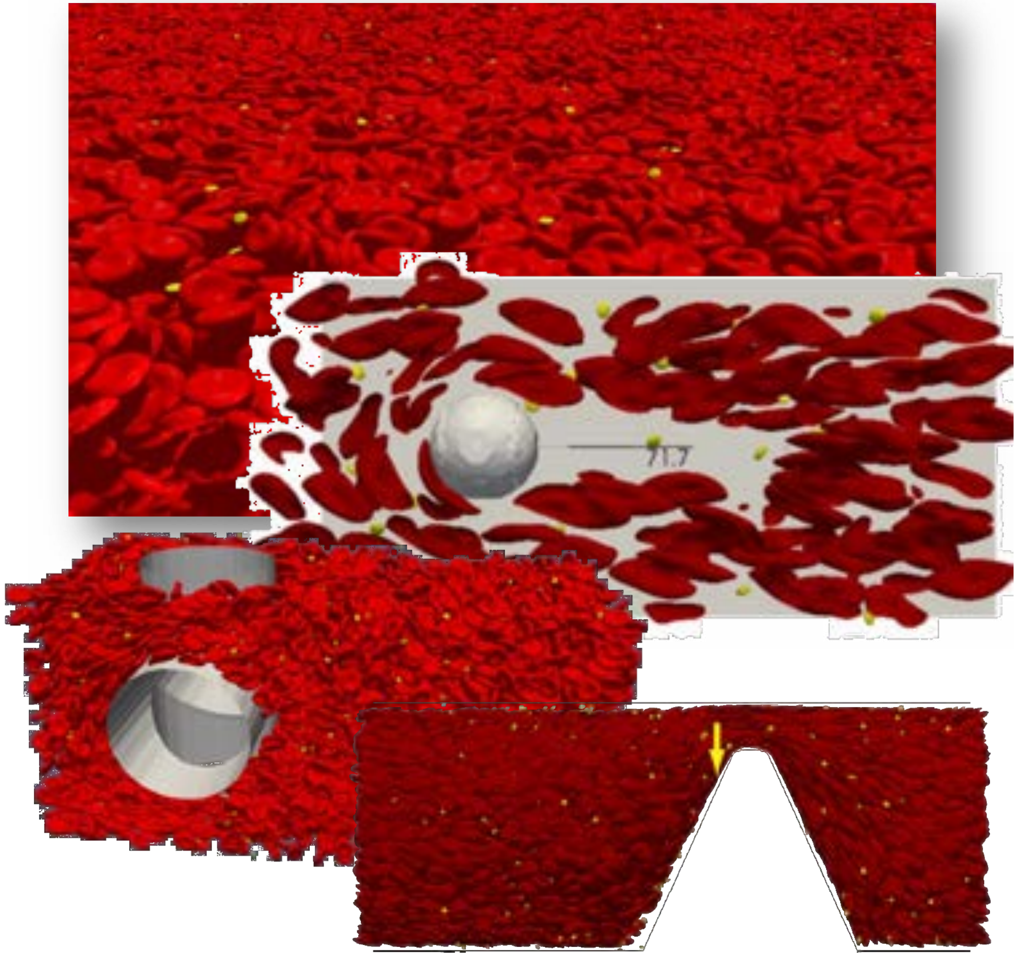

Scales of blood

Full-body scale
Reduced order models

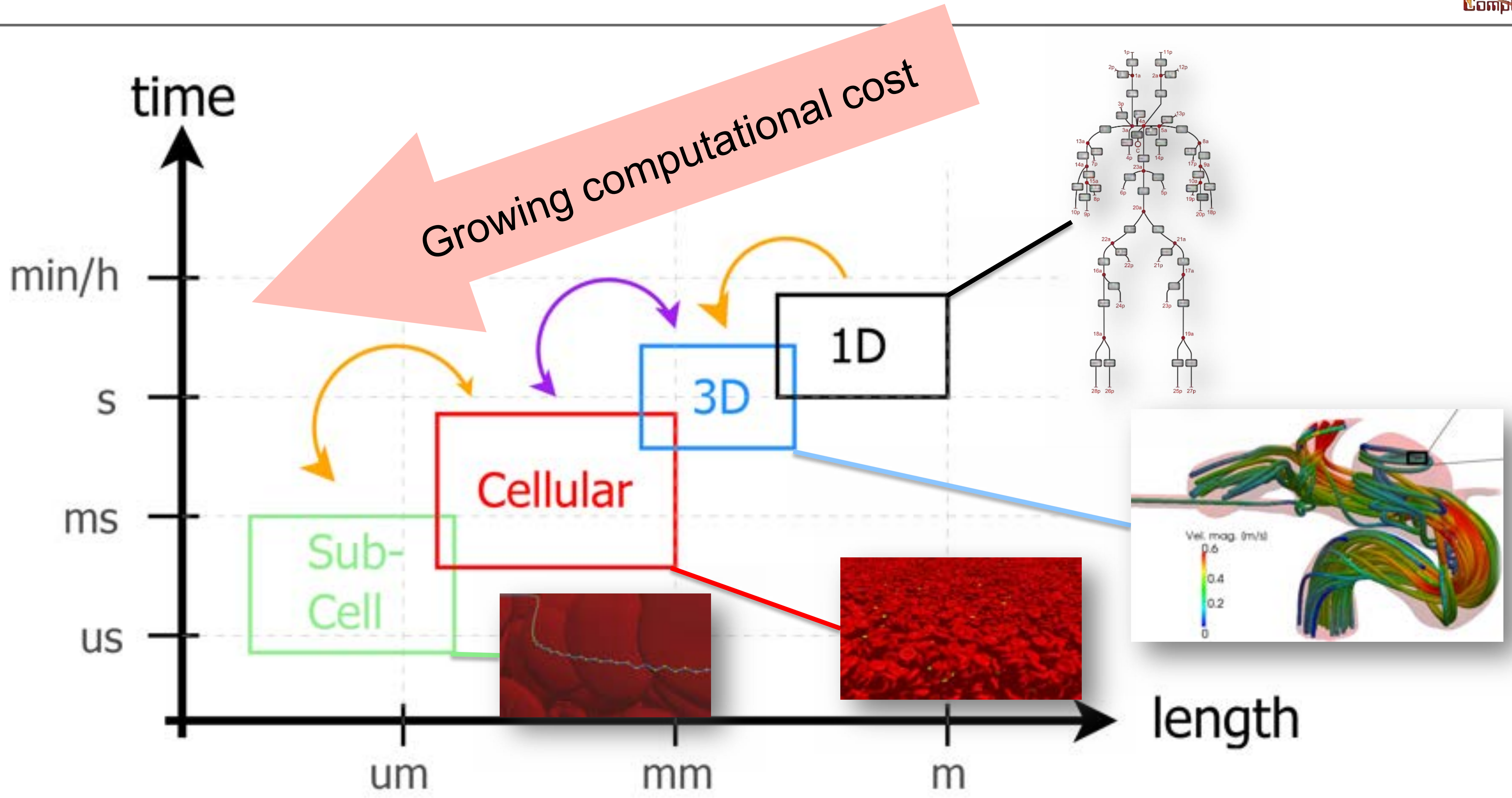
Organ scale
3D continuum models



Cellular scale
3D cellular models



Computational cost

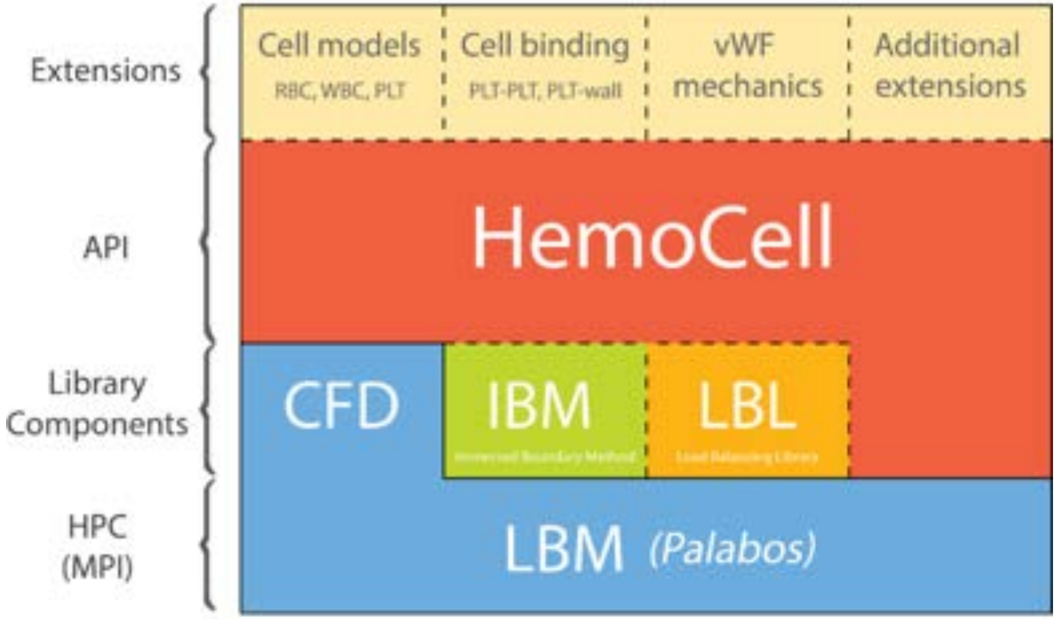


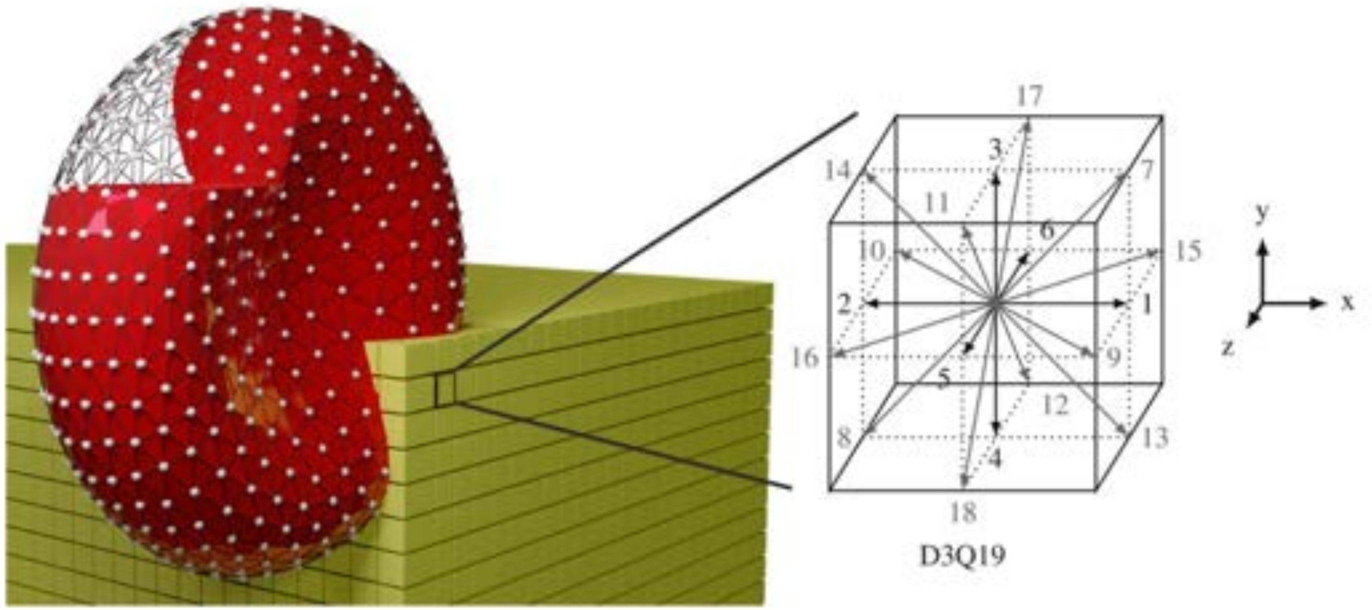
Main features of HemoCell

- **Open-source code**
  www.hemocell.eu
- **Fully validated model**
  VVUQ
- **High-performance execution**
  (>70% efficiency over 300,000+ cores)
- **Advanced boundary conditions**
  E.g., continuous cell influx.
- **Numerically stable high-shear**
  Up to 40,000 s-1 (geometry dependent)
- **Various cell types**
  E.g., Human and mouse blood, diabetic blood
- **Internal cell viscosity**
  Fast algorithms to track internal nodes.
- **More than 20 related publications**

HemoCell - Modelling blood flows on a cellular level

www.hemocell.eu





Czaja et al. (2022). Comp. M. in Biomech. and Biomed. Eng. 1-19.
Spieker et al. (2021). Ann. of Biomed. Eng., 49(12), 3609-3620.
Závodszky, et al. (2019) Physics of Fluids, 31 (3), 031903
van Rooij, et al. (2019) J. Royal Society Interface 16 (159).
Alowayyed et al. (2018) Journal of Comp. Sci., 24, 1-7.
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de Haan et al. (2018) Applied Sciences, 8(9), 1616.
Závodszky, et al. (2017) Fontiers in Physiology, 8, 563
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Czaja, et al. (2020). PLOS Comp. Biology 16.3 (2020): e1007716.
De Vries et al., (2020) Int. J. for Uncertainty Quantification, 10 (4)
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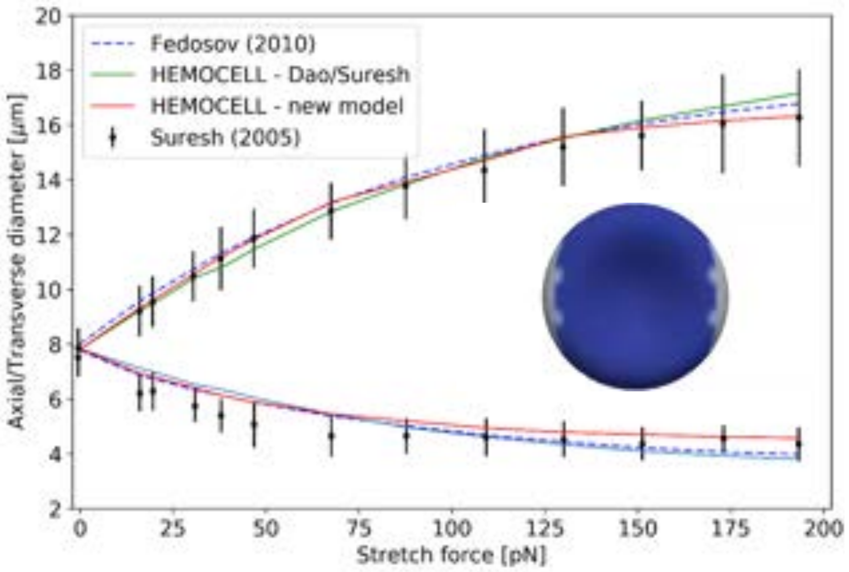
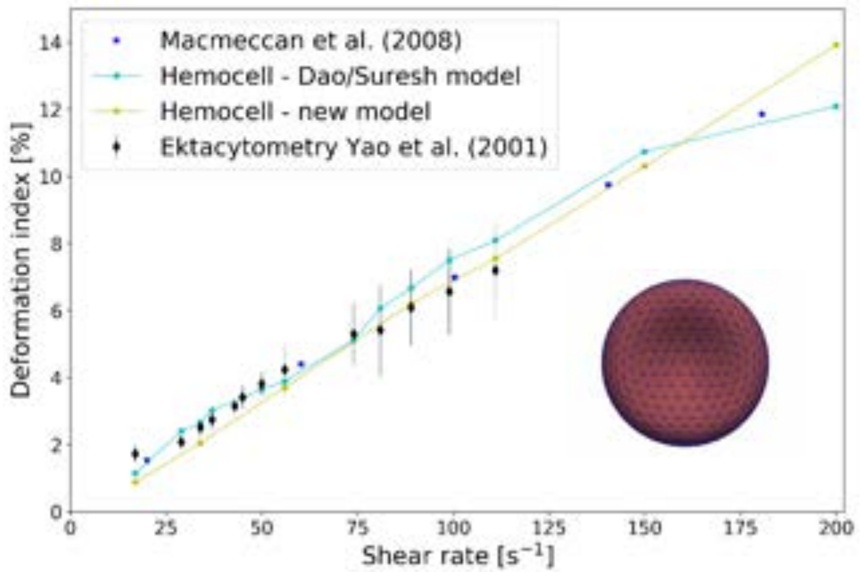
Tarksalooyeh et al. (2018) Computers & Fluids, 172, 312-317.
Mountrakis et al. (2016) EPL (Europhysics Letters) 114.1: 14002.
Hoekstra et al. (2016). Phil. Trans. R. Soc. A. 374
Mountrakis, et al. (2015) Journal of Computational Science 9 : 45.
Závodszky, et al.. (2013). Int. J. of Heat and Fluid Flow, 44, 276

Validation of cellular mechanics

Single-cell

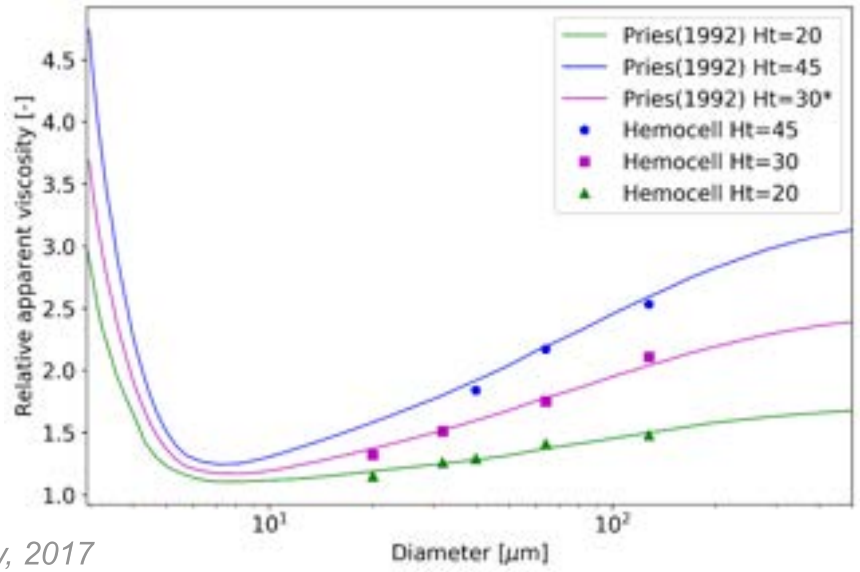
Cell stretching, cell shearing

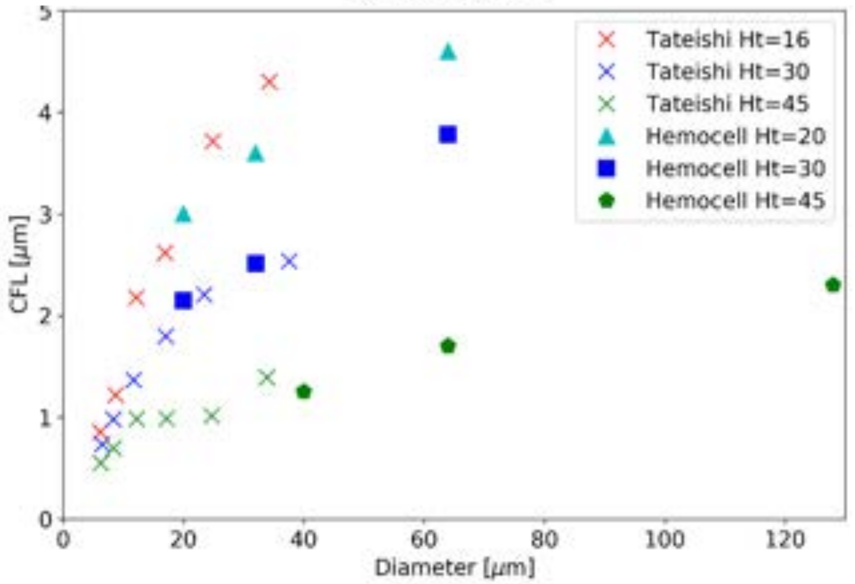




Many-cell flows

Relative apparent viscosity in a pipe, cell free layer in a pipe

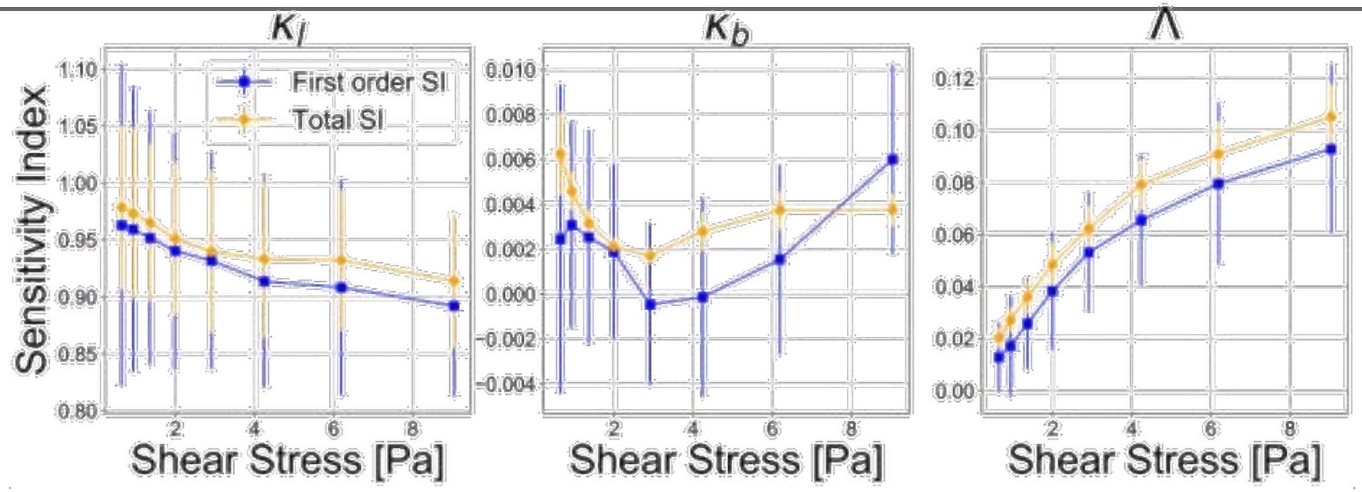




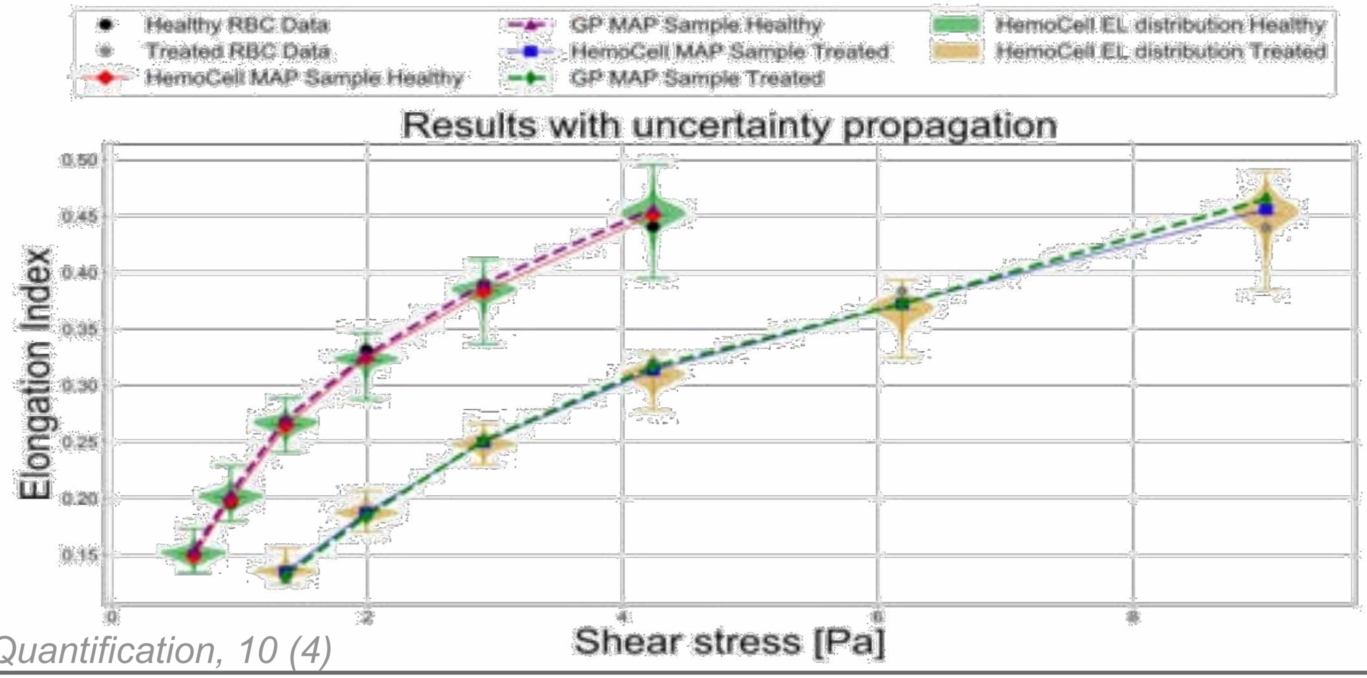
Zavodszky et al., Frontiers physiology, 2017

Sensitivity analysis and inverse uncertainty quantification

Sensitivity analysis
Helped reduce the complexity of the mechanical model description.

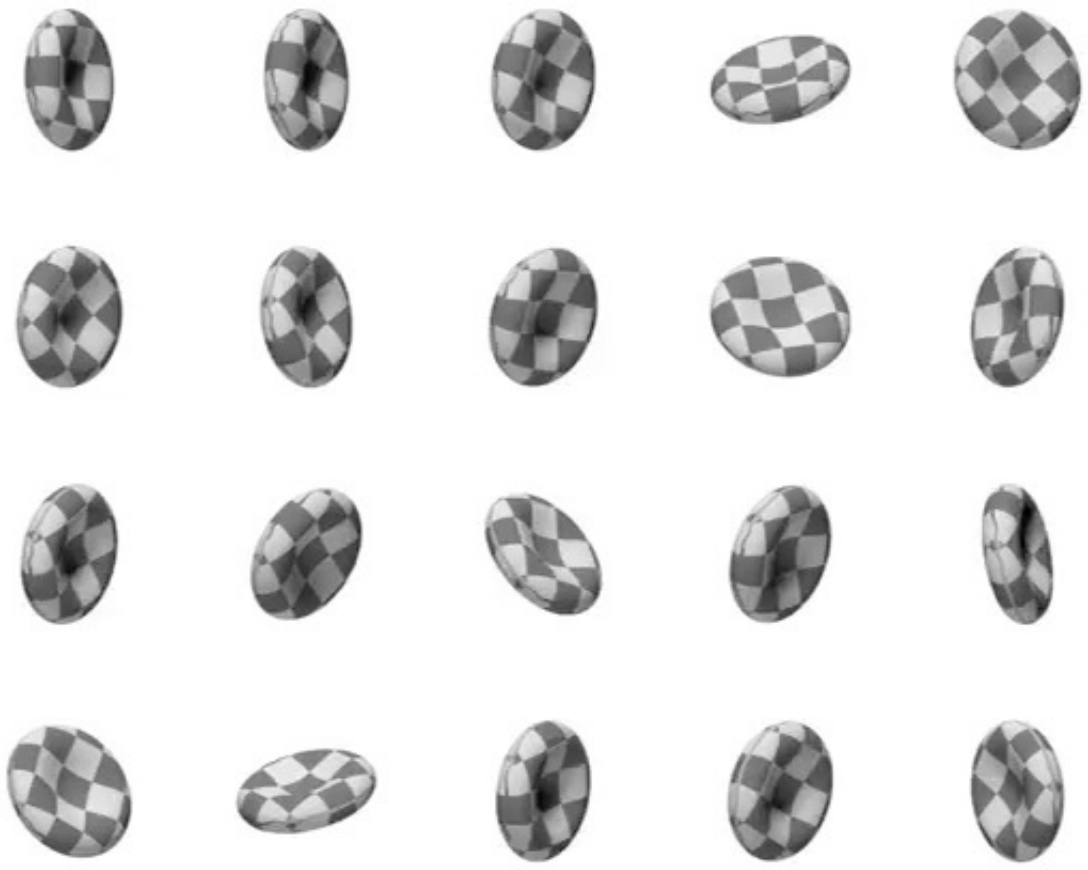


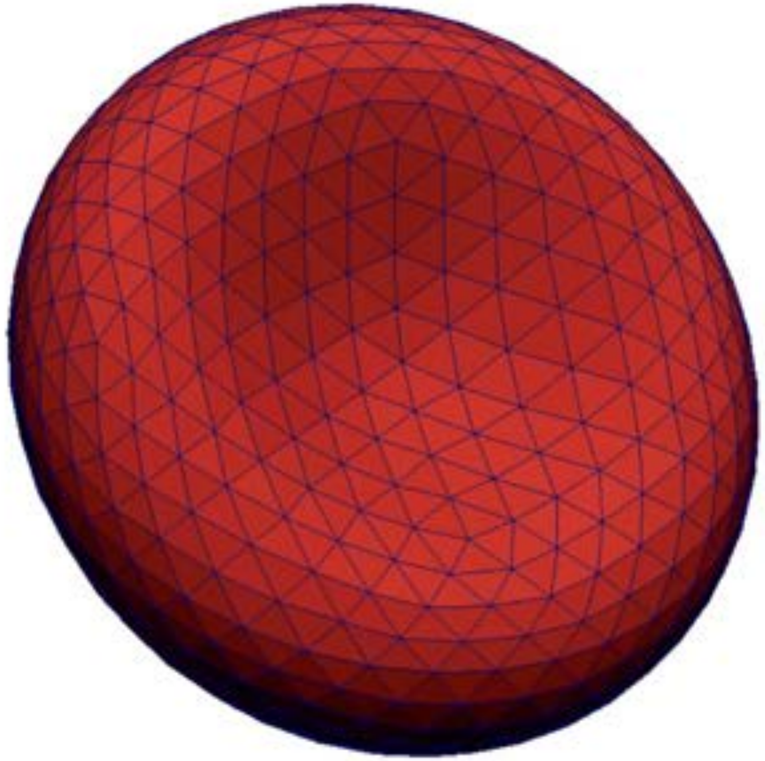
Uncertainty quantification
Defines the uncertainty on the output given various sources of error on the model input.



De Vries et al., (2020) International Journal for Uncertainty Quantification, 10 (4)

Computational cost of the cell model





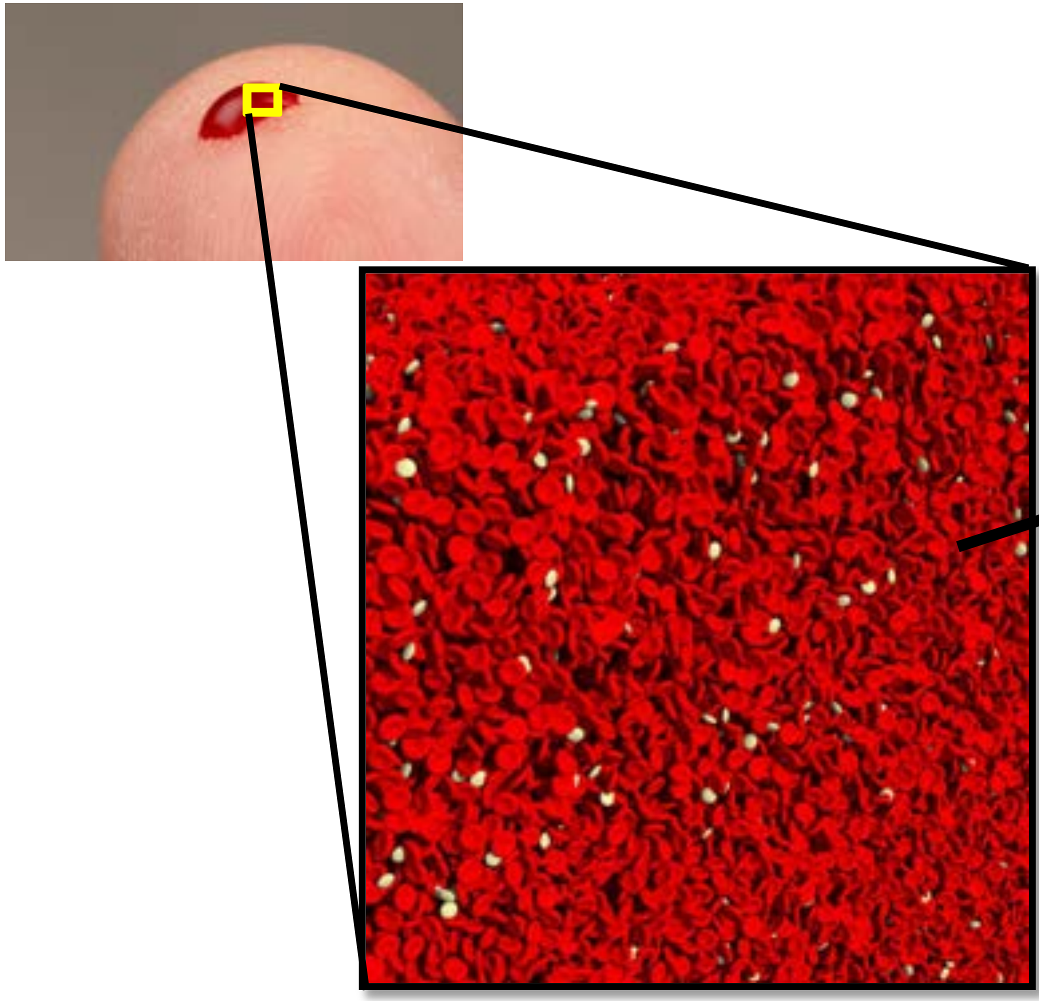
Membrane
- Area conservation
- Bending rigidity

Cytoskeleton
- Elasticity
- Bending rigidity

Inner cytoplasma
- Viscosity

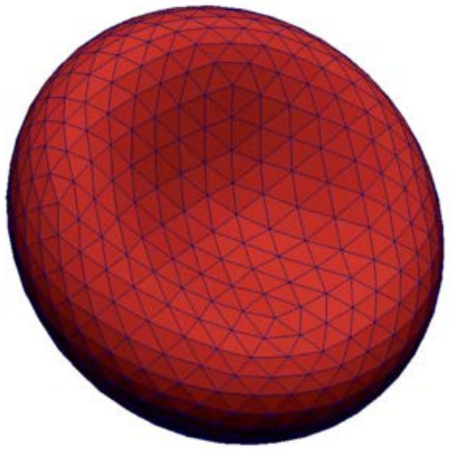
~ 5000 equations / RBC

Scales of blood – how costly is cellular resolution?
(And when do we need it?)



1 microliter of blood = 1 mm^3 = 5 million RBCs
(1 drop is ~50 microliters)

RBC
- **642 vertex**
- **1280 face**
- **1920 edge**



Membrane
- Area conservation
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Cytoskeleton
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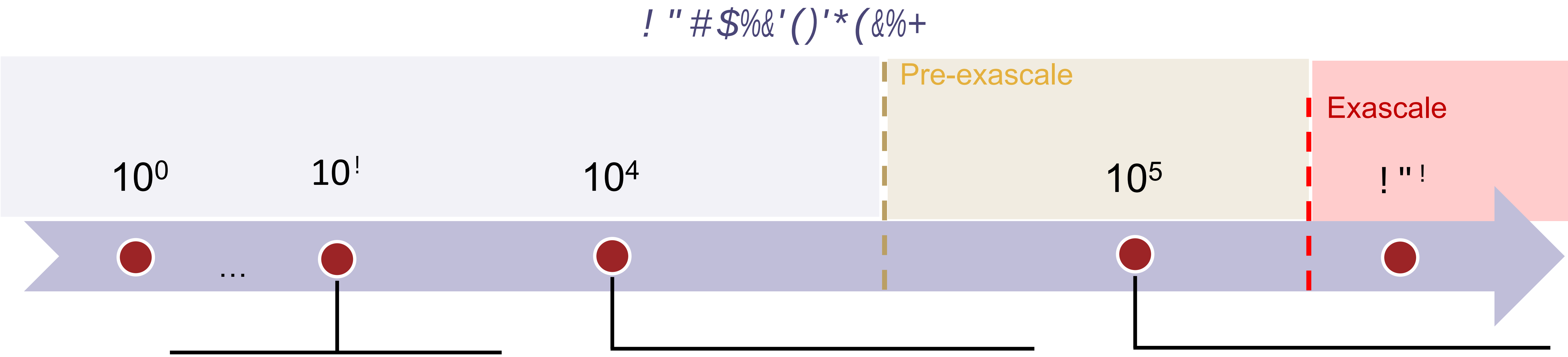
Inner cytoplasma
- Viscosity

~ **5000** equations / RBC

1. Efficiently computing 5M RBCs requires > 500k computing cores. (***Weak-scaling problem***)

2. 1 s physical time is computed for ~2-3 days on current HPC architectures.
(***Strong-scaling problem***)

Onset of challenges encountered at scale



Minor challenges
(e.g., scheduling inefficiencies).

- Software stack scalability (libraries and tools) needing new standards e.g. MPI 4.0.
- Code porting (e.g. CPU -> GPU, different HPC architectures).
- Scaling of complex codes (e.g. coupled codes).
- Scalability of I/O, "Exascale is exabytes".

- **Load-balance (static and dynamic).**
- **Energy efficiency.**
- **Resilient computing and fault tolerance.**
- **Management of complex workflows.**

HPC deployment

Superman (BME, Budapest)

Eagle (PSNC, Poznan)

Marenostrum (BSC, Barcelona)

SGI Altrix (QUT, Brisbane)

Archer2 (EPCC, Edinburgh)

Snellius and Lisa (SURF, Amsterdam)

Sanam (KACST)

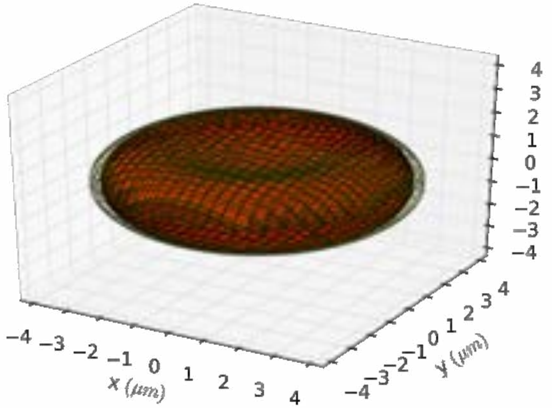
Supermuc-NG (LRZ, Munich)

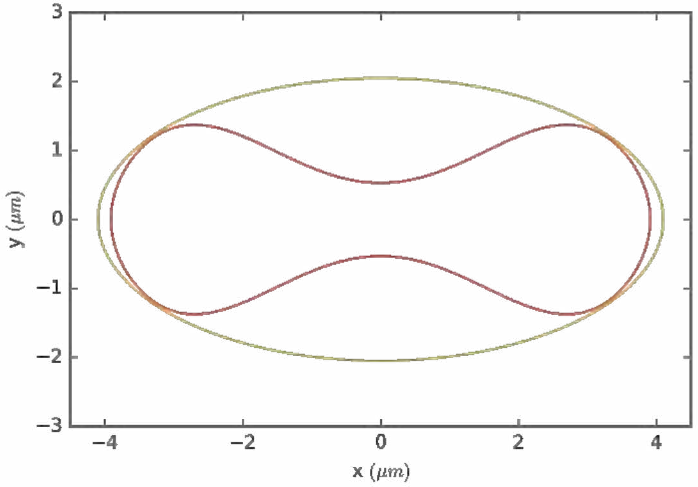
Aspire I (NSCC, Singapore)

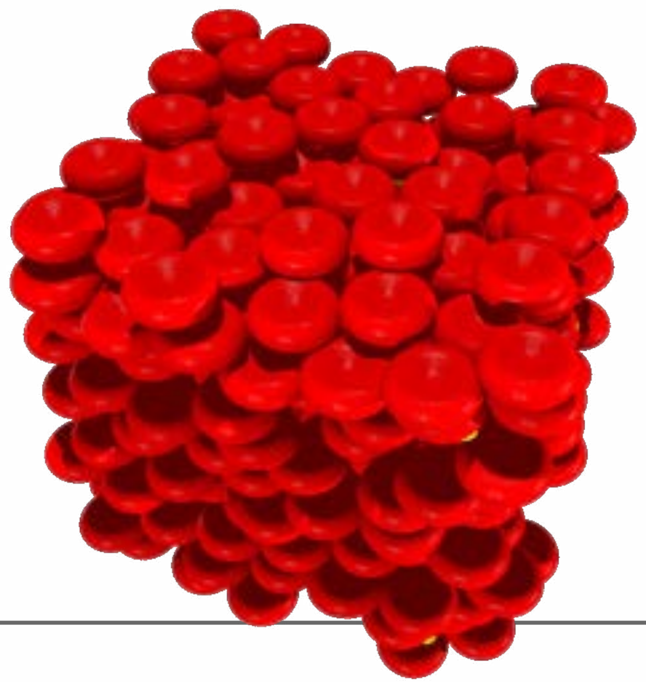
Domain decomposition and communication

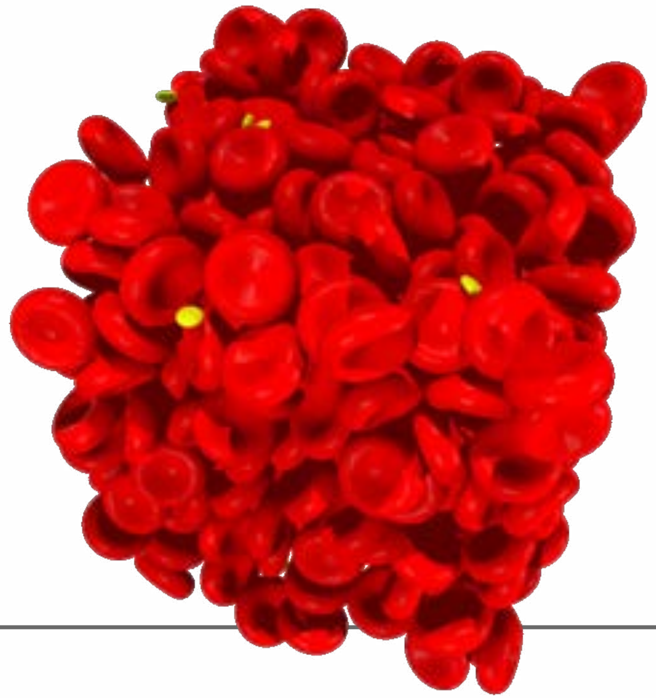
- Decomposition into rectangular domains.
- MPI communication.
- The fluid field assignment to CPUs is static.
- The cells move and passed on to be computed where the local fluid field is computed.
- This makes the fluid-structure coupling efficient.
- Two-step communication envelope.

How to initialize cells?









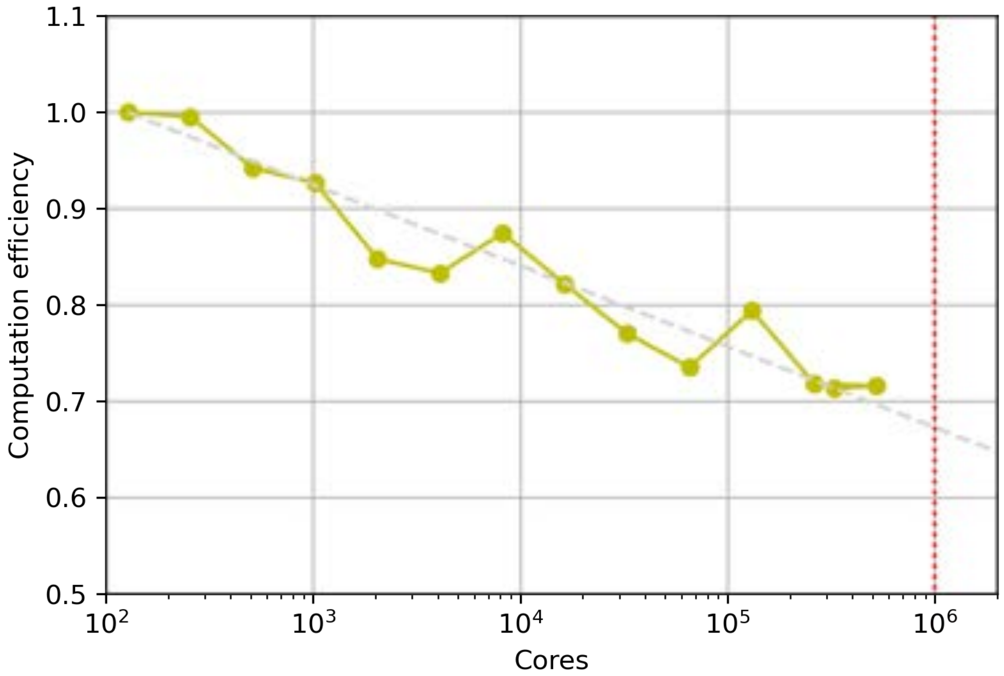
Simulation to initialize cells

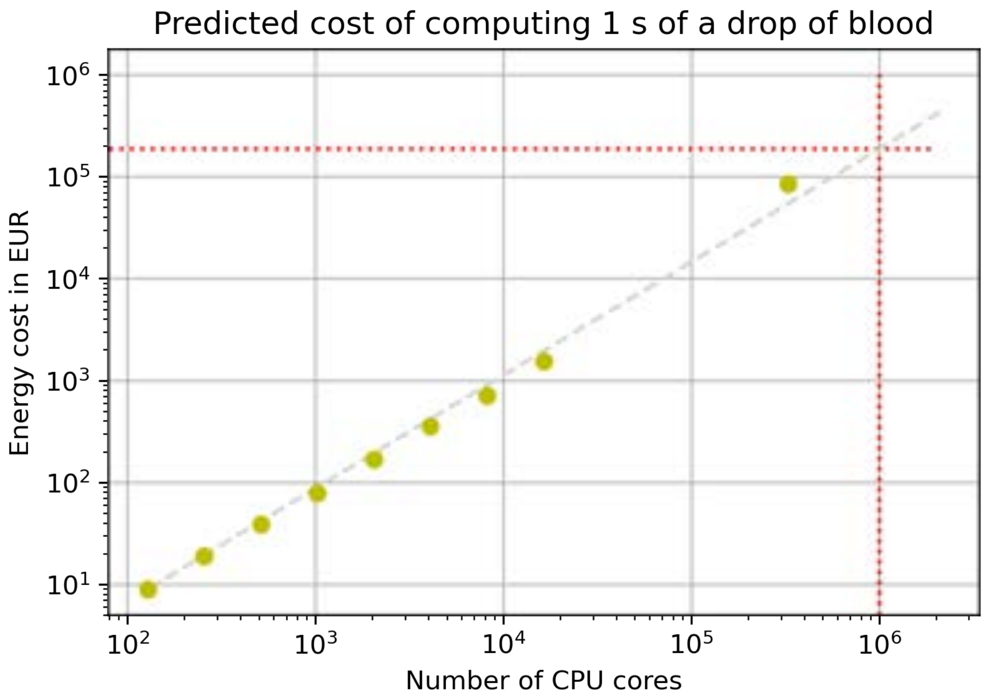
- We neglect deformation, and cover the cells with shape-fitted ellipsoids.
- Positioning based on the force-bias method:

$$\vec{F}_{ij} = \boldsymbol{\delta_{ij}} p_{ij} \frac{\vec{r}_j - \vec{r}_i}{|\vec{r}_j - \vec{r}_i|}$$

- New cell-types are easy to add.
- Fast computation, position millions of cells on the scale of minutes.
- Code is significantly improved in the upcoming release (2.6)

Performance and energy usage at scale
(up to 330,000 cores)





- Computational efficiency above 70% with 330,000 cores (~1M cells).
- Energy usage is measured from short simulations. (No checkpointing, no load-imbalance).
- Cost projected to *1 s* simulations.

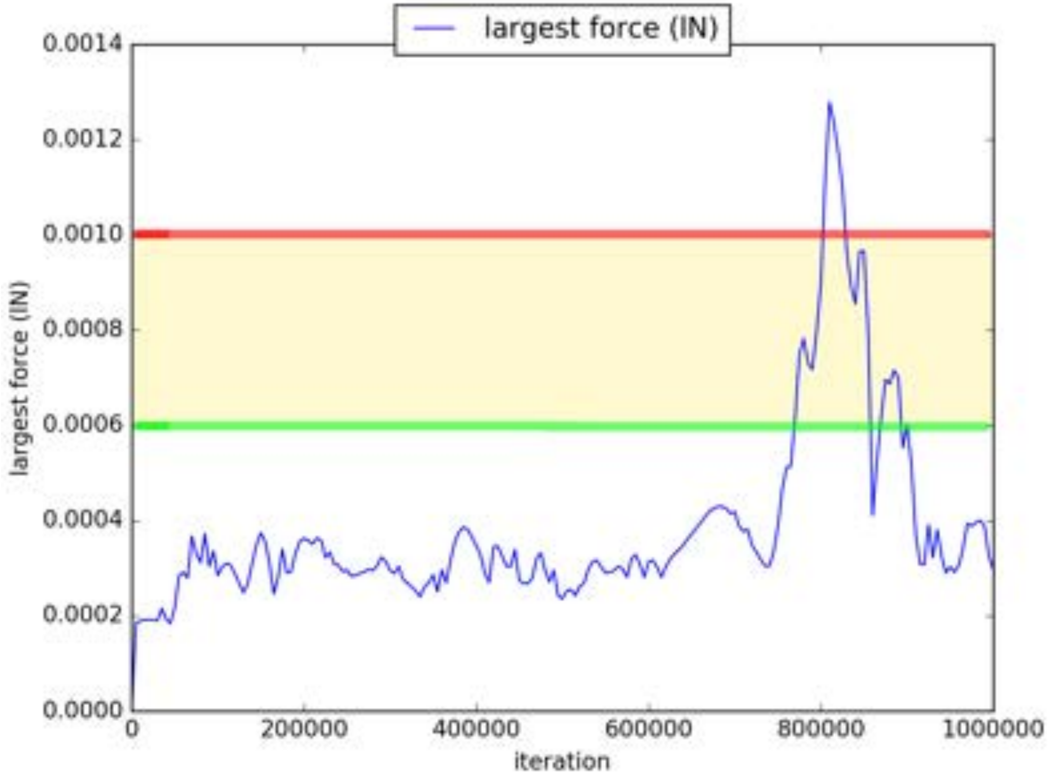
Dynamic time-step size using separable time-scales

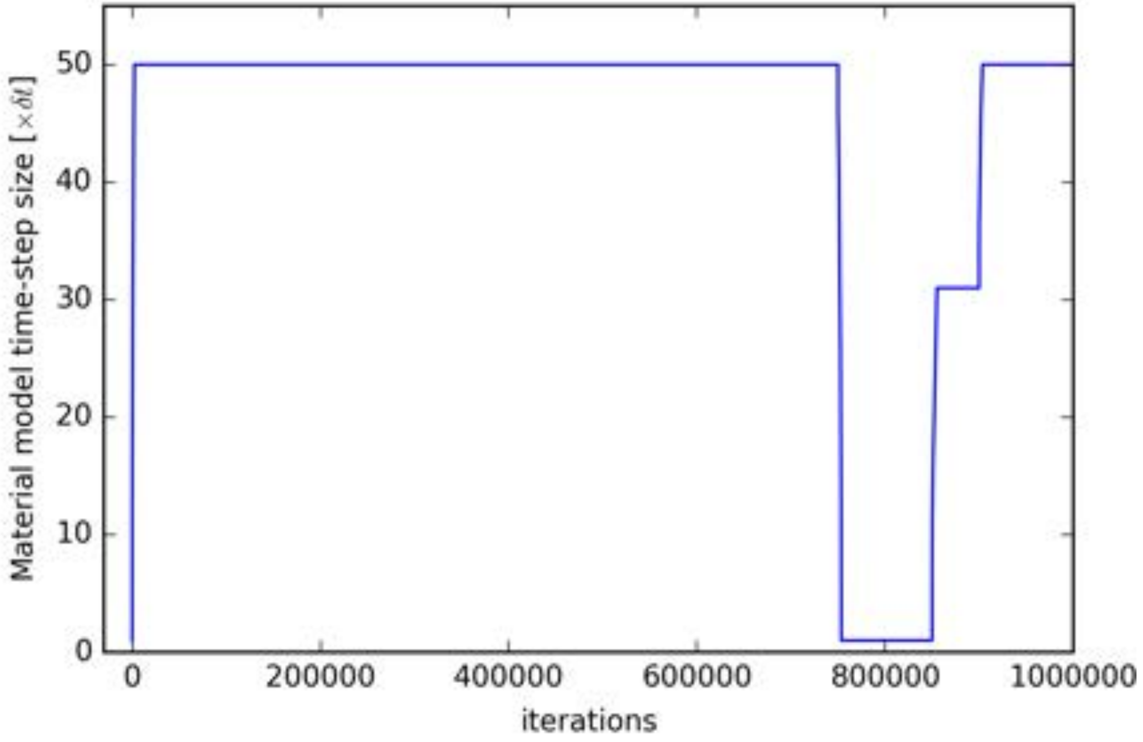
Time steps:

- Fluid field (LBM): **dt** ~ 1e-8 s
- FSI coupling (IBM): **dt** ~ 1-6 dt
- Material model (DEM): **dt** ~ 1-100 dt

dt ≤ dt ≤ dt

dt:

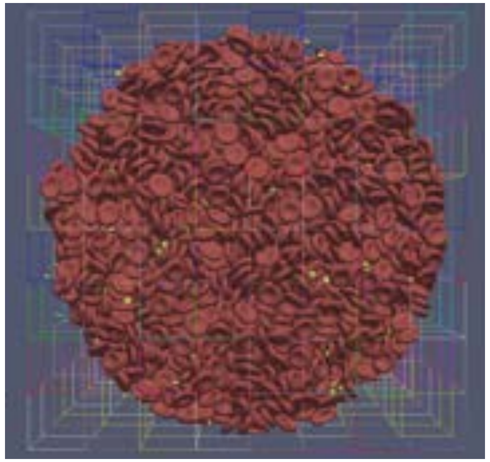




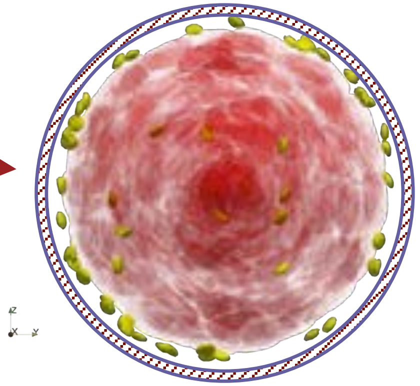
Static and dynamic load-imbalance

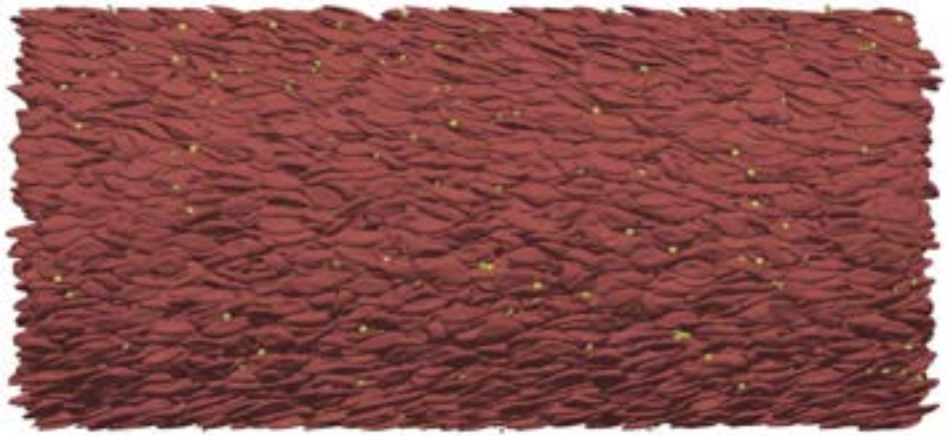
Sources of load-imbalance

- **Static** due to the geometry
  (Can be mitigated through a single domain decomposition step)

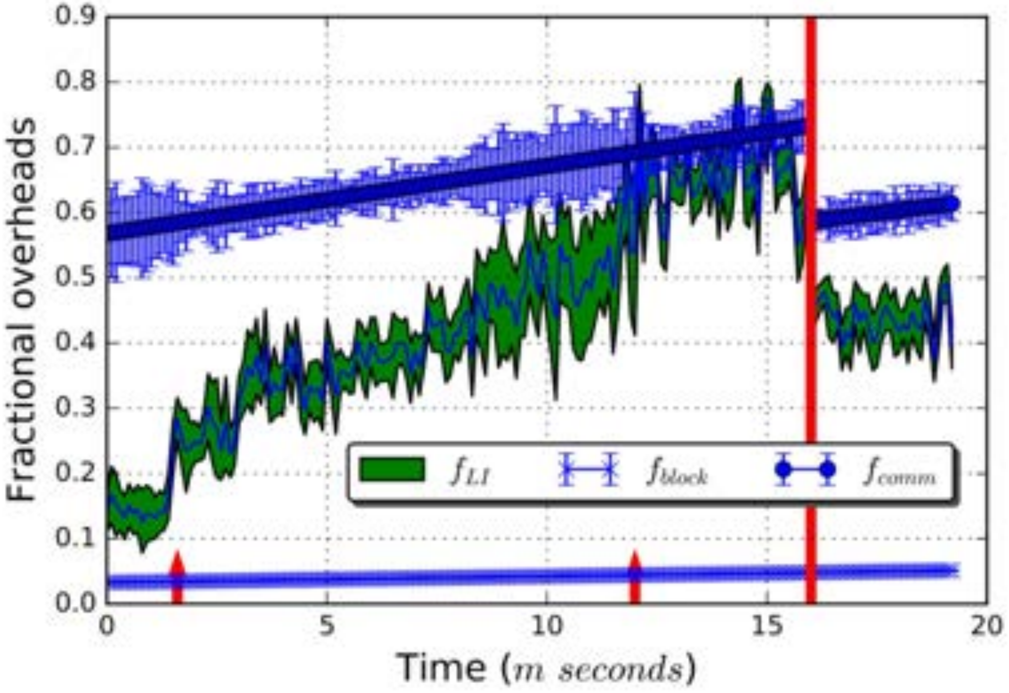


- **Dynamic** due to the movement of the cells
  (Requires rebalancing again and again in a dynamic system)



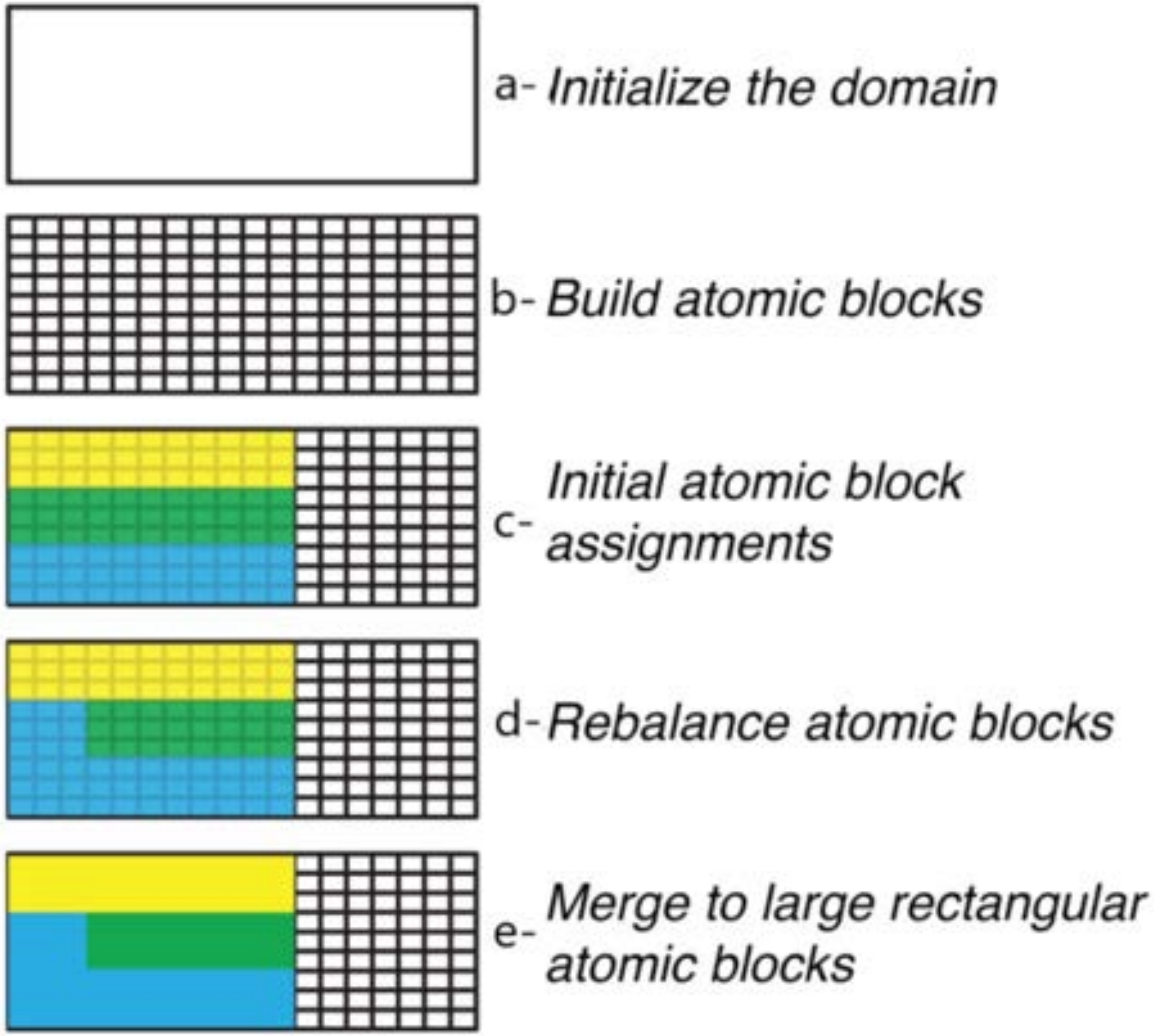


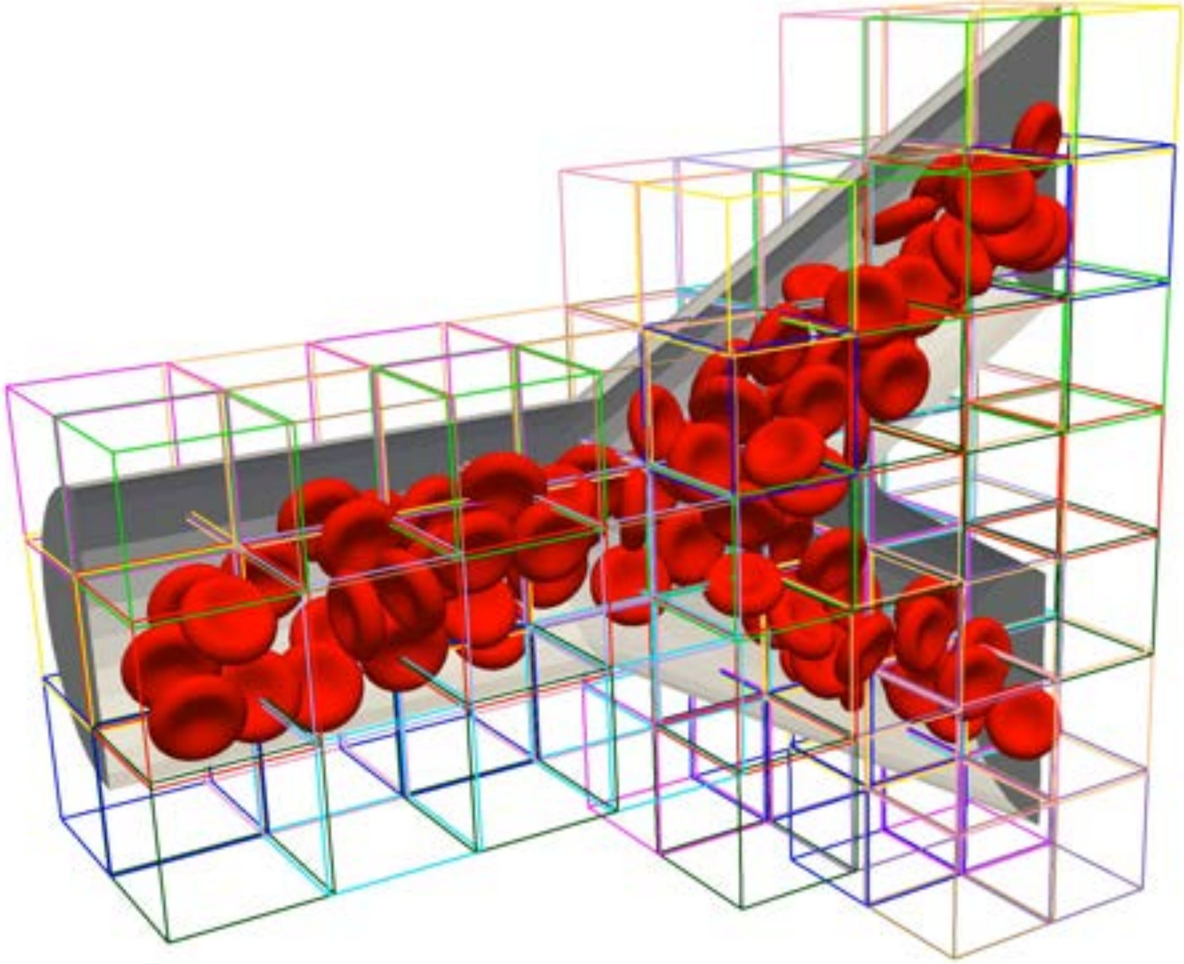
Dynamic rebalancing



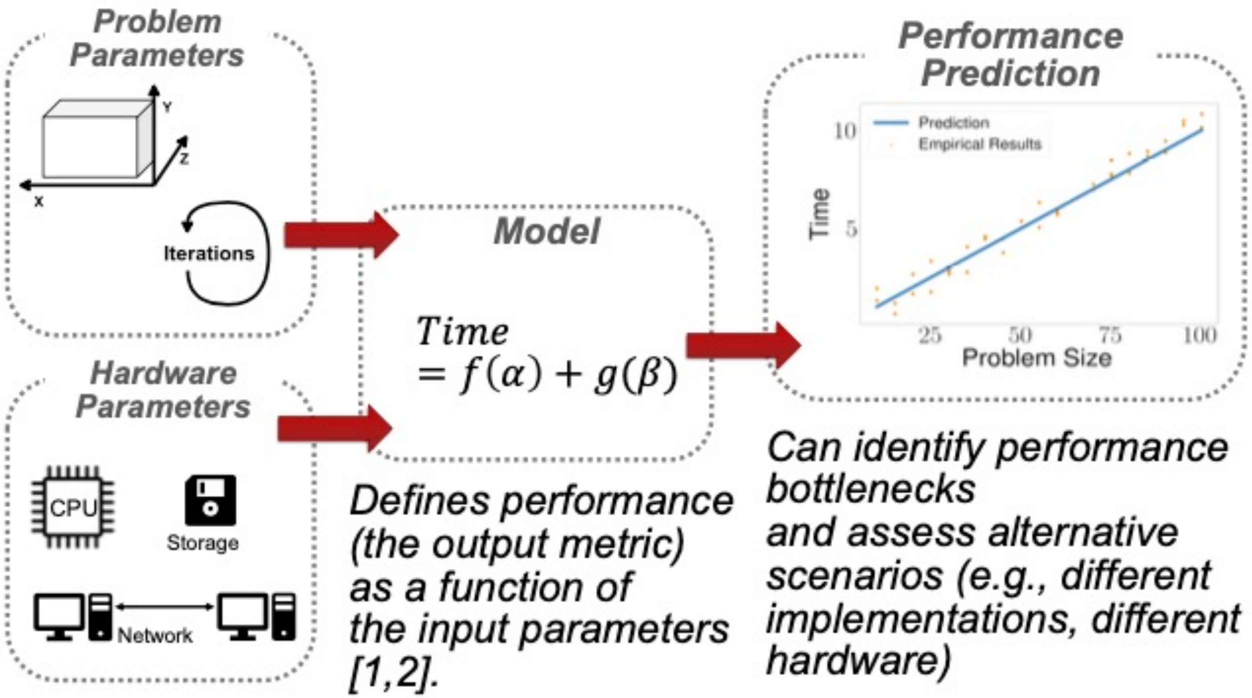
Rebalancing also has an associated cost (both compute time and space)!

Dynamic load-balancing via domain decomposition and fusion

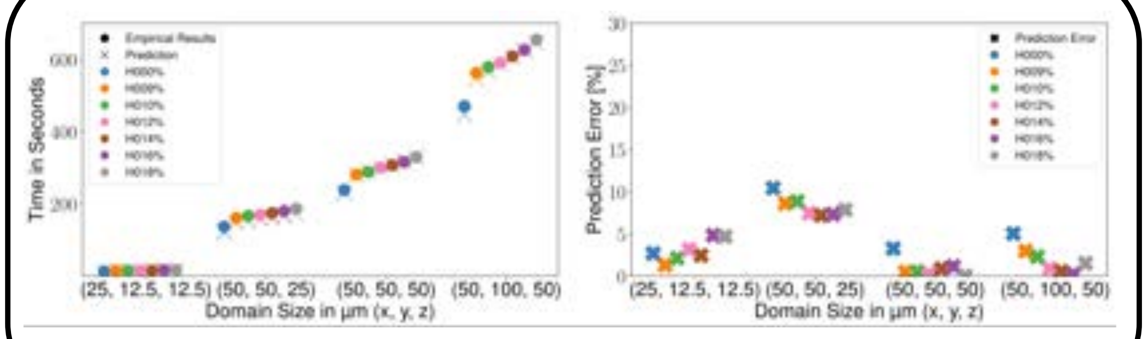




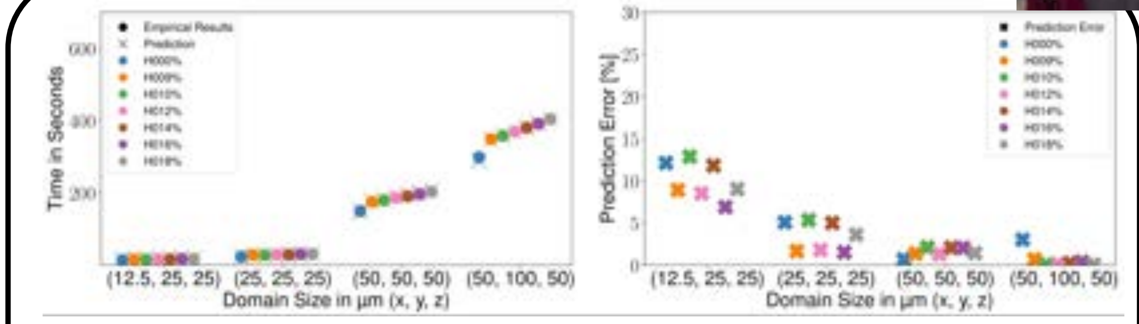
Performance and energy modelling



- **Predict performance** and energy cost of simulations on upcoming exascale machines.
- Provide **trigger** for dynamic load-balancing.
- **Identify bottle necks** and drive further optimisation.

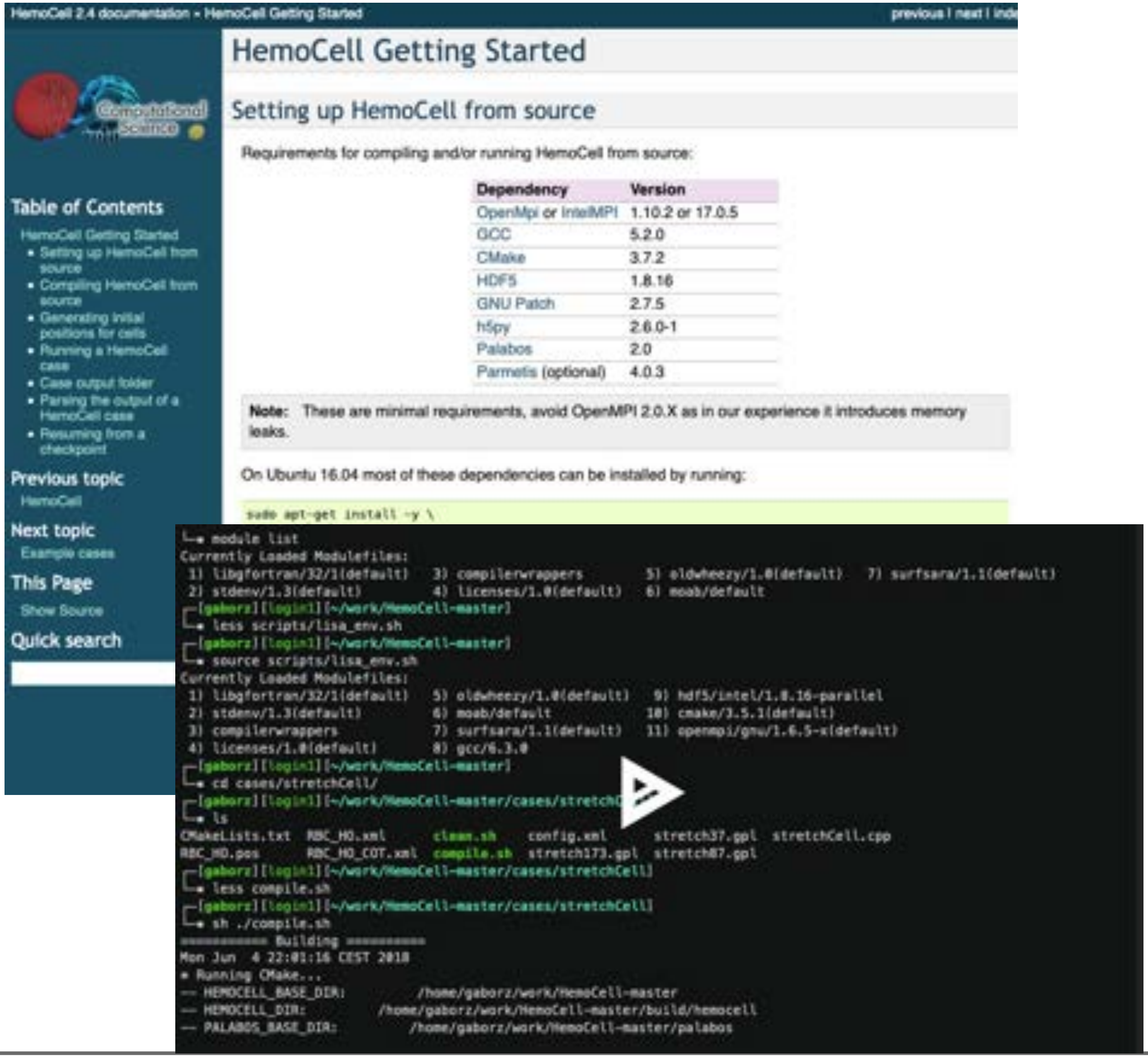


Snellius



DAS6

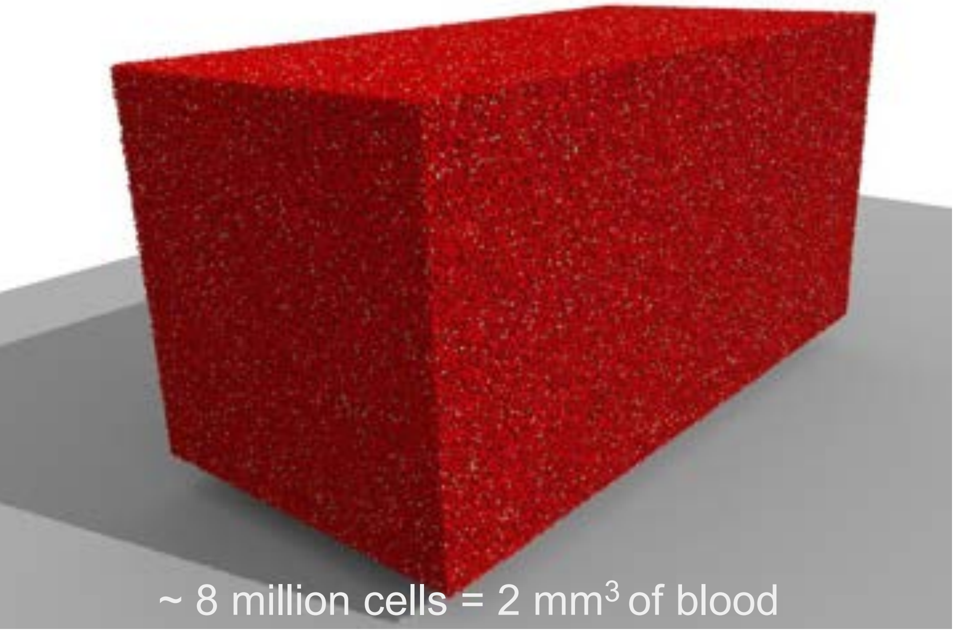
Easy deployment



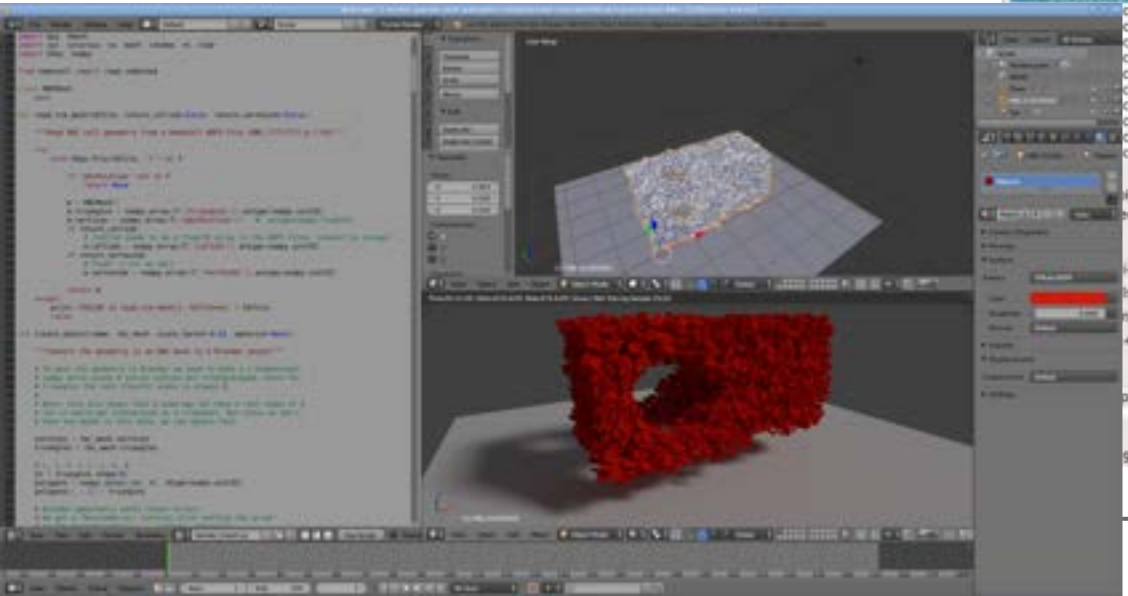
User resources

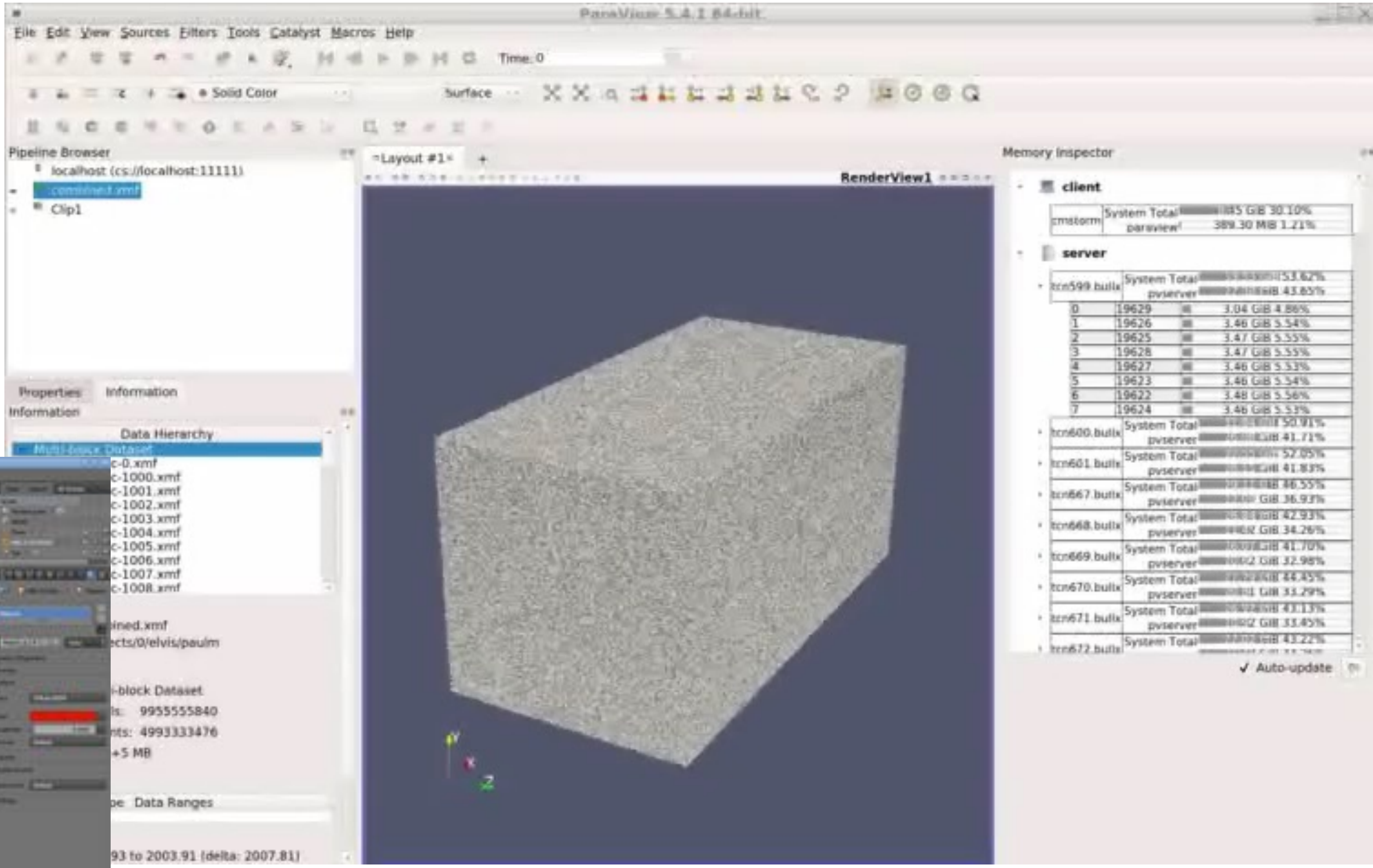
- Documentation, example cases: https://www.hemocell.eu/user_guide/index.html
- Recorded terminal sessions:
  - MareNostrum: https://asciinema.org/~bczaja
  - Snellius&Lisa: https://asciinema.org/~gzavo
- Prepared module script for several HPCs
- Deployment tools are being added for upcoming releases (SPACK, EasyBuild)
- Videos on CompBioMed YouTube channel

Visualization (Blender, ParaView), data analytics

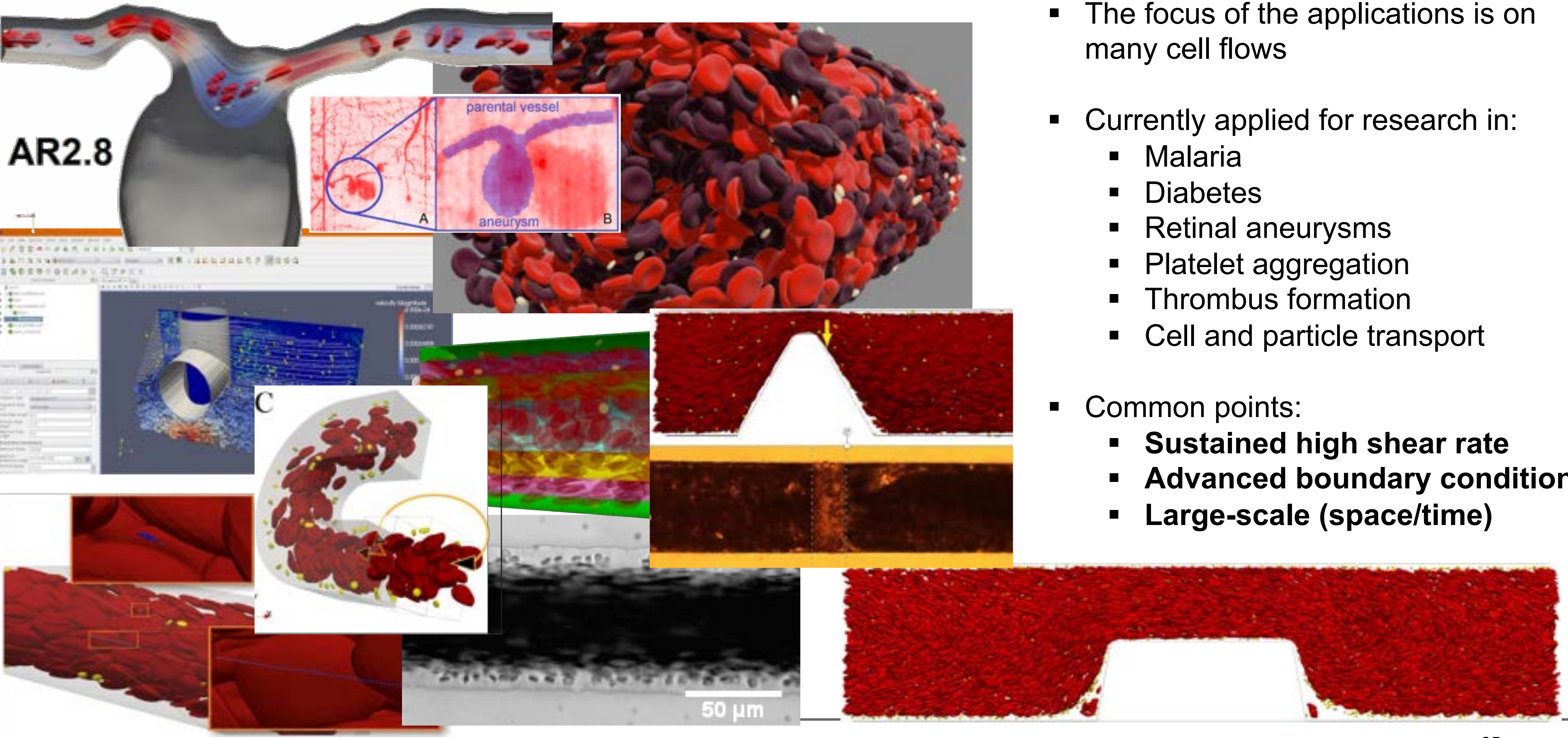


~ 8 million cells = 2 mm^3 of blood





HemoCell applications

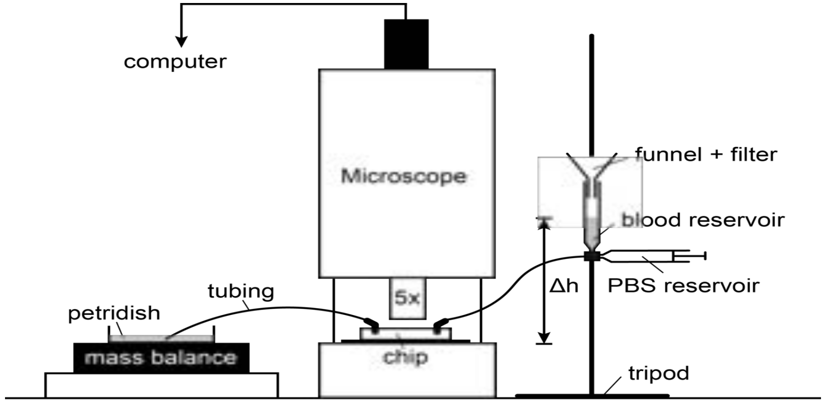


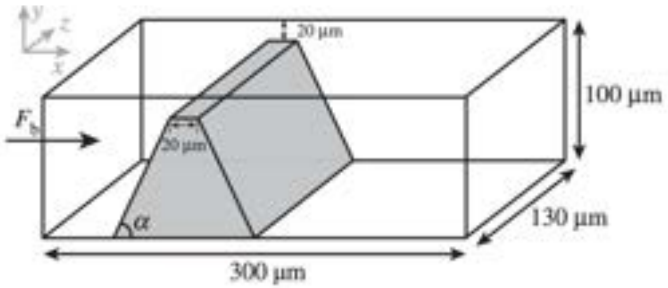
- The focus of the applications is on many cell flows
- Currently applied for research in:
  - Malaria
  - Diabetes
  - Retinal aneurysms
  - Platelet aggregation
  - Thrombus formation
  - Cell and particle transport
- Common points:
  - **Sustained high shear rate**
  - **Advanced boundary conditions**
  - **Large-scale (space/time)**

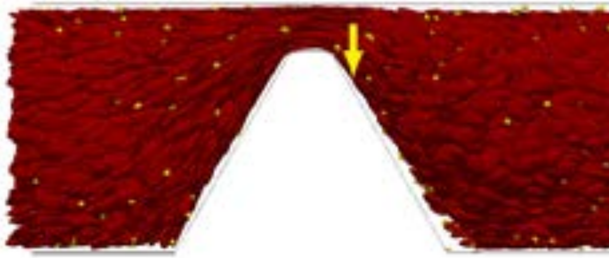
Initiation of high-shear thrombus formation

What are the necessary conditions?

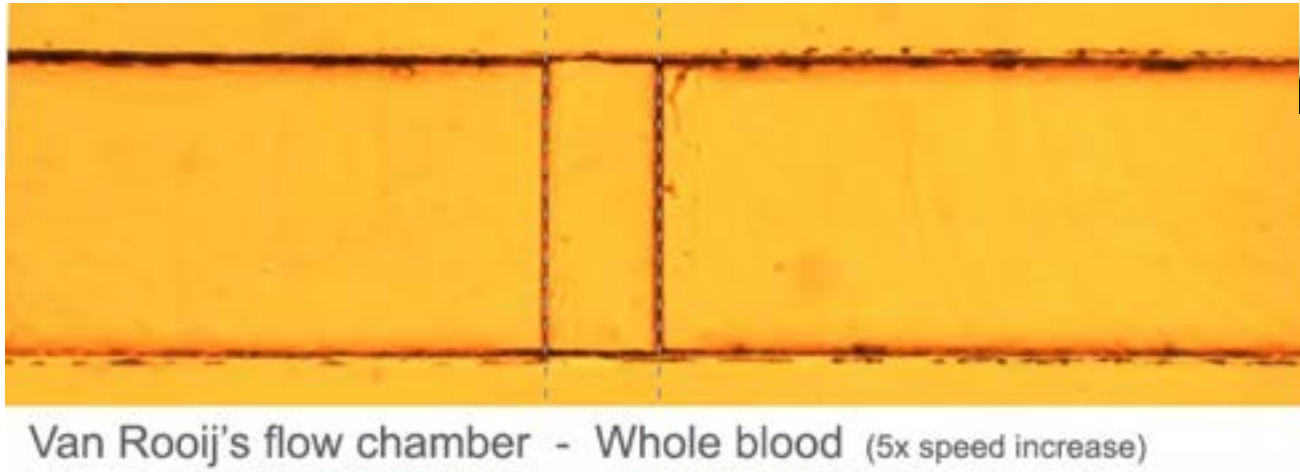
- Combination of *in vitro* measurements and *in silico* computations.
- The simulations inform us about the detailed flow conditions (mechanics).
- **Necessary** conditions:
  - High-shear
  - Available platelets
- **Preferred** conditions:
  - Large CFL

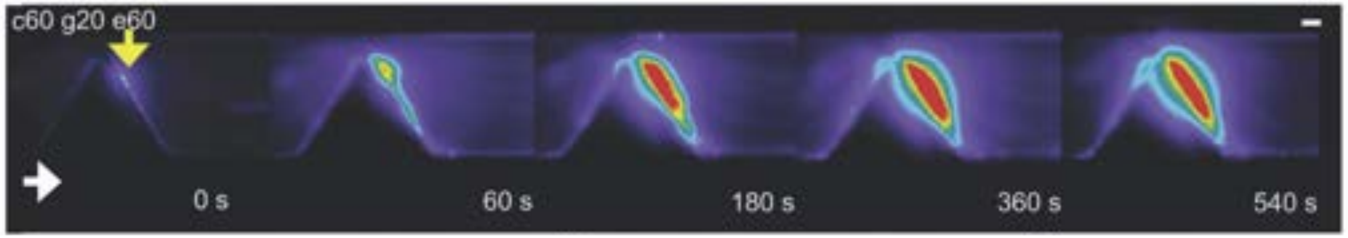






van Rooij, et al. (2019). J Royal Soc. Interface, 16(159), 20190148.
van Rooij et al. (2020). Scientific reports, 10(1), 1-11.

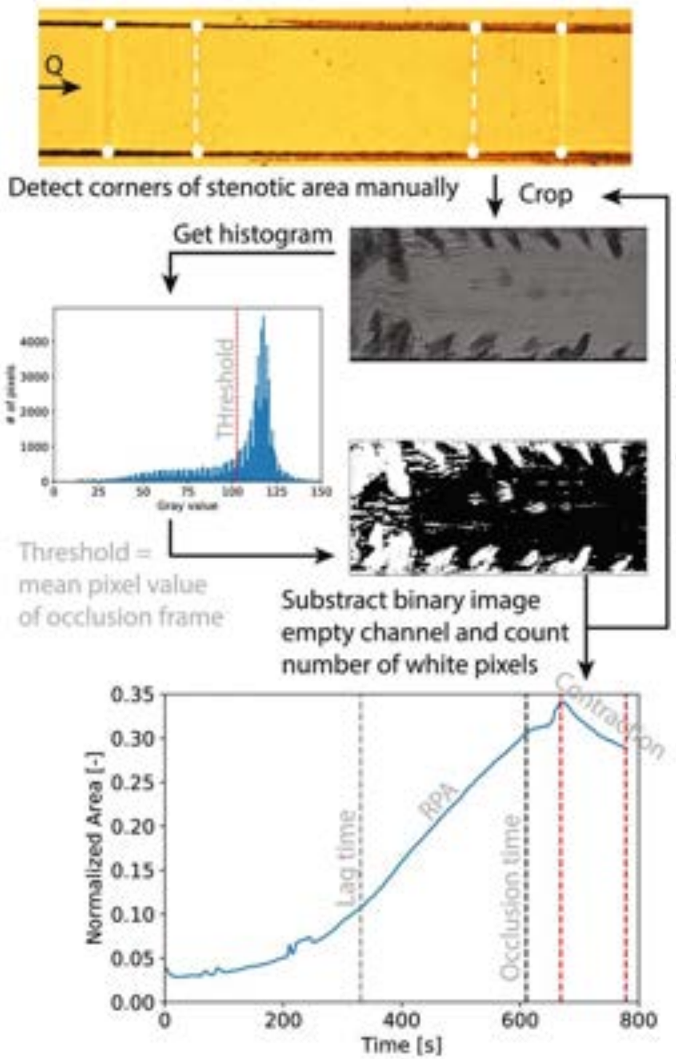


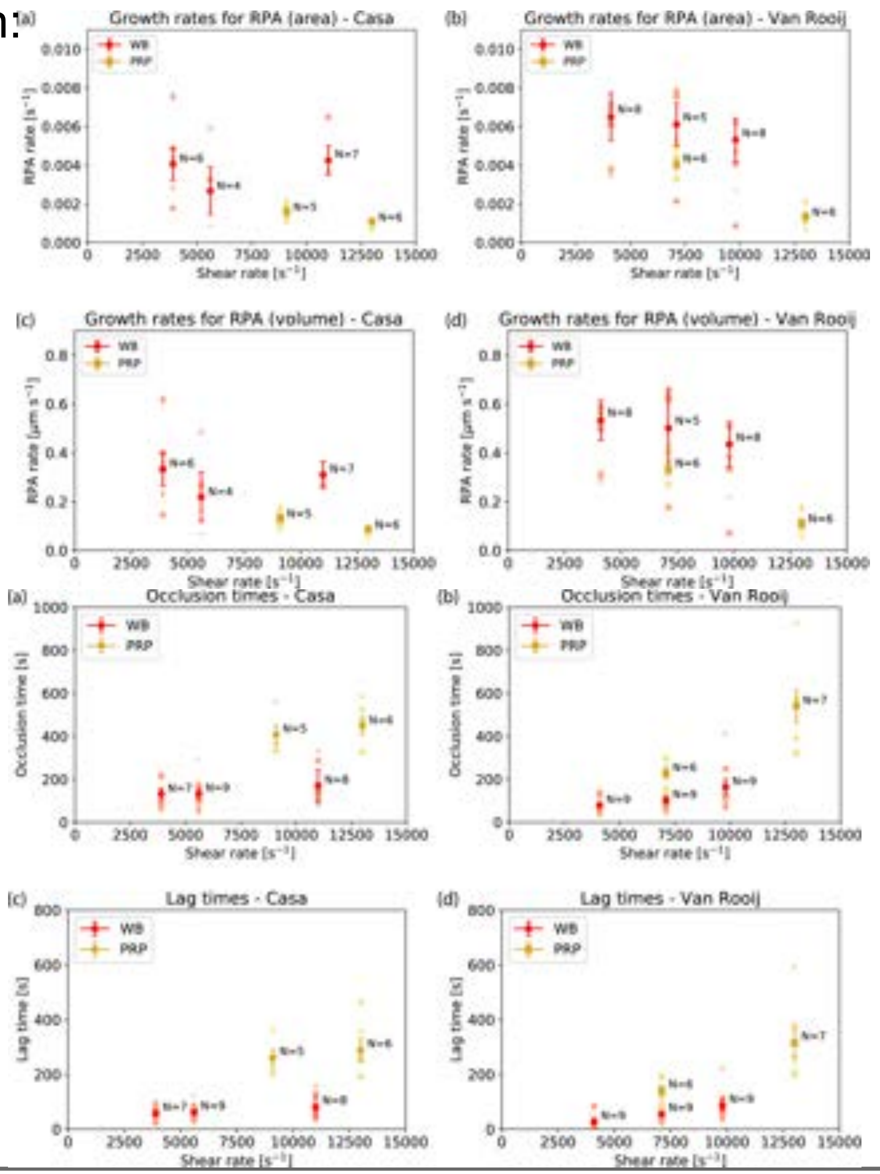


Tovar-Lopez and Nesbitt et al., Lab Chip, 2010, 10, 291-302

HemoCell explains the role of platelet availability

Experiments for aggregation information:

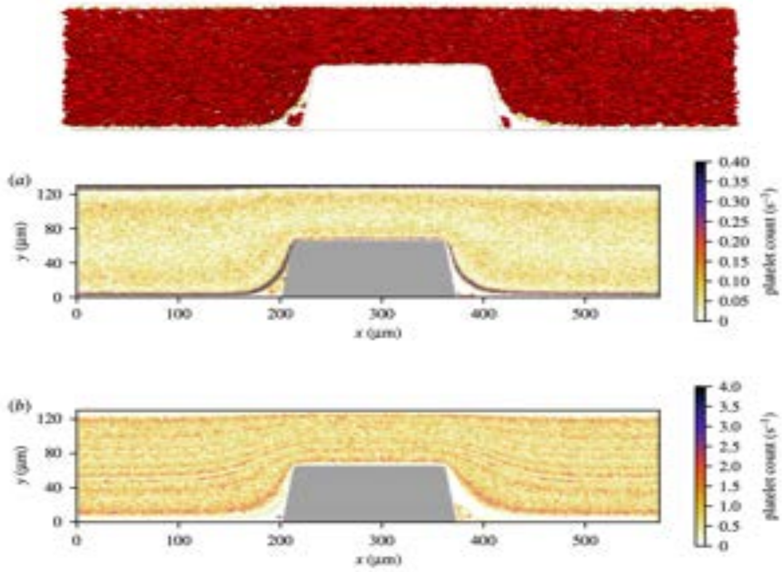




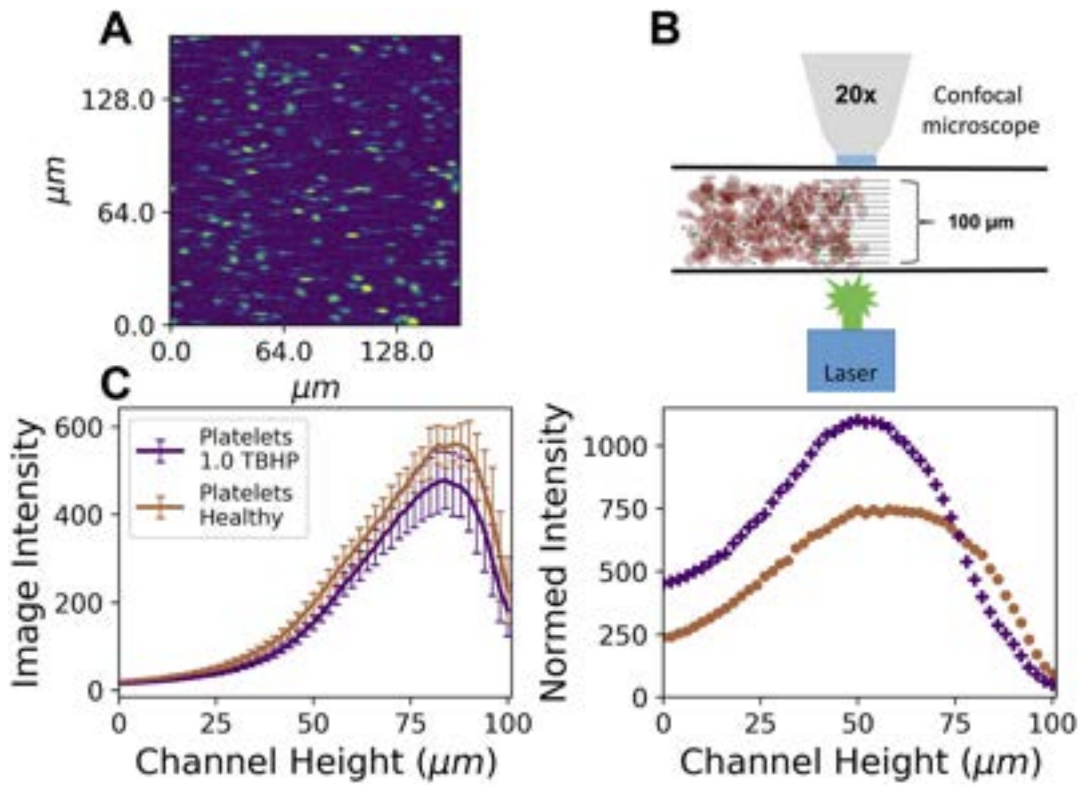
van Rooij et al. (2021). Interface focus, 11(1), 20190126.

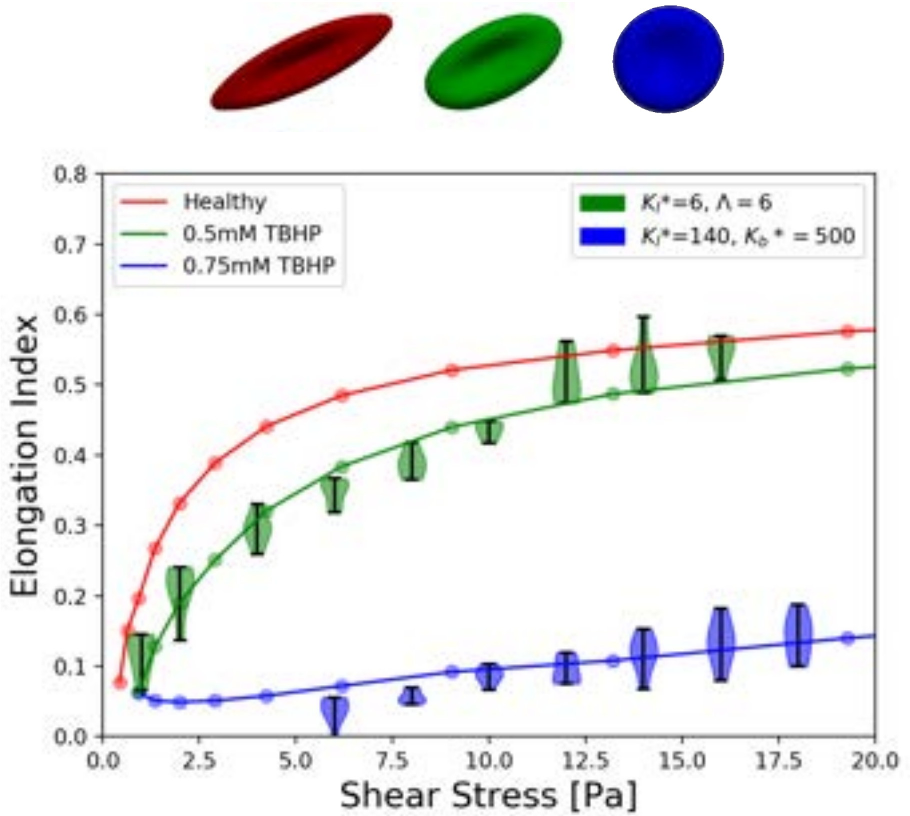
Simulation for conditions
(e.g., shear rate, platelet availability):

- **Higher platelet availability (margination) facilitates** all stages leading to occlusion.
- **Shear rate** acts as a critical **threshold**.



Effect of diabetic RBCs on cellular transport





- Chemically rigidified RBCs model diabetic cells, where the **deformability is a controllable** parameter.
- Due to the **limited experimental observation depth**, the results are **complemented by simulations**.

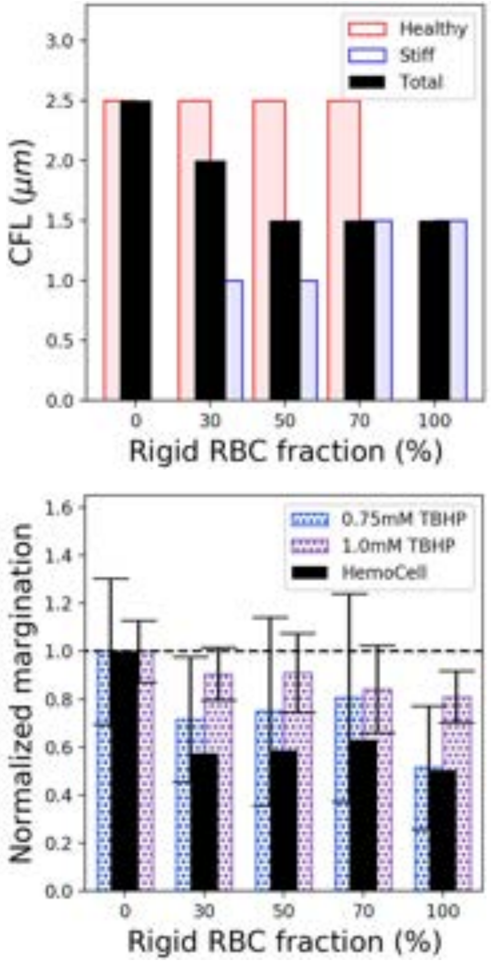
Note: *the diabetic model underwent the same validation and UQ as the healthy cell model.*

Czaja, et al. (2020). PLOS Comp. Biology 16.3 (2020): e1007716.

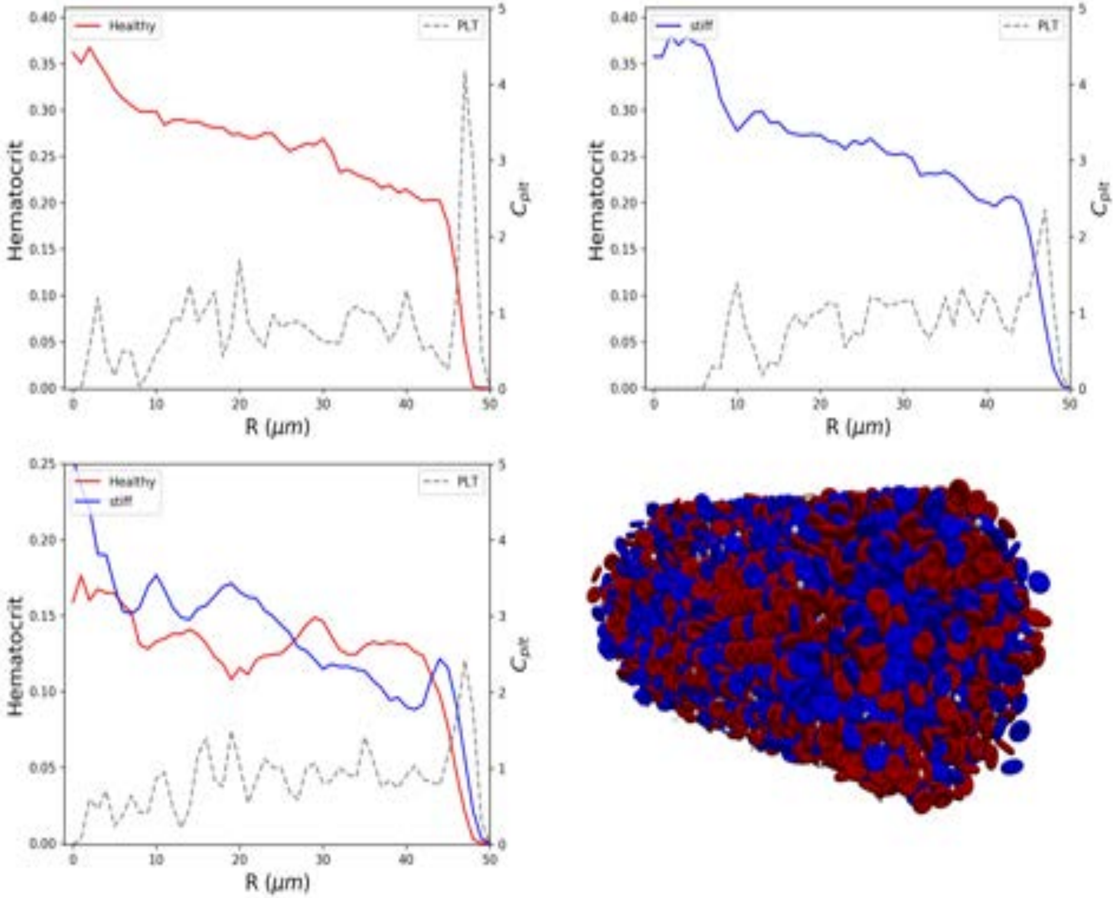
HemoCell explains the mechanism of cellular transport

Outcomes:

Experiments with limited data availability:



Simulations with fine-grained details:

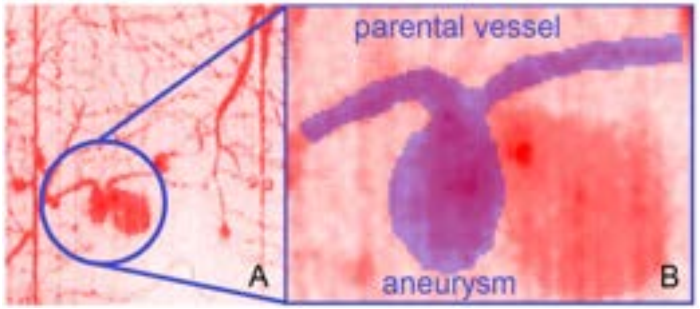


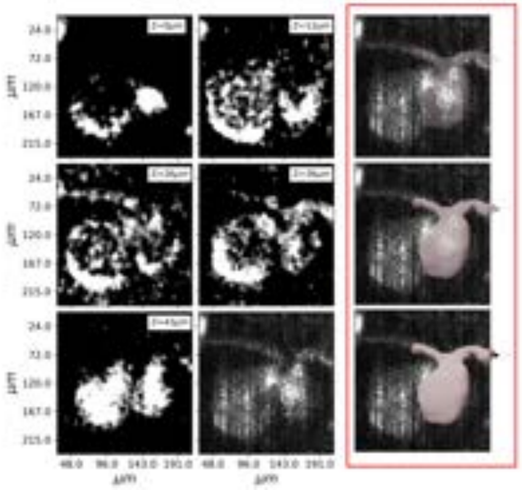
- The **direction** of the margination **does not change**.
- The **intensity** of margination is **disrupted** (reduced deformability).
- **Reduced CFL size**: diabetic cells are pushed closer to the wall (less lift force).

Czaja, et al. (2020). PLOS Comp. Biology 16.3 (2020): e1007716.

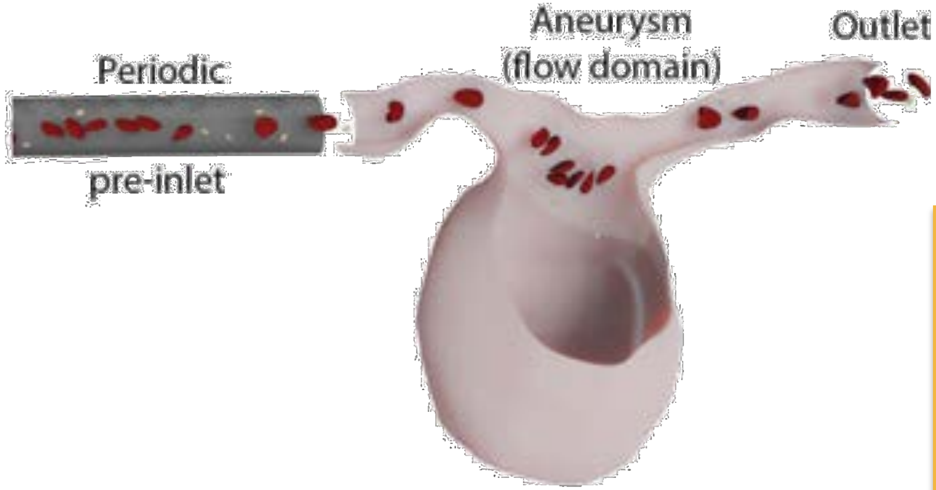
Transport in pulsatile flow inside micro-aneurysms
(diabetic retinopathy)

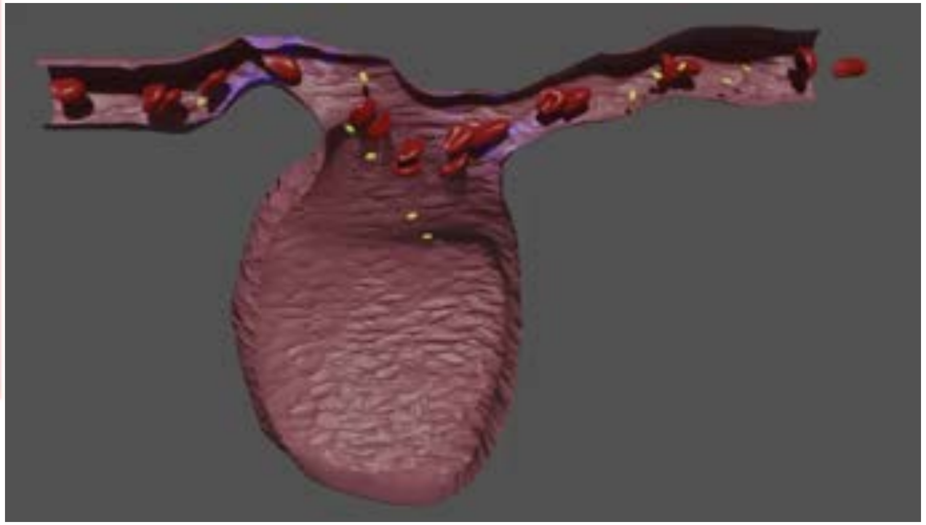
Medical imagery:
Adaptive Optics combined with Optical Coherence Tomography (AO-OCT)





Simulation of pulsatile flow:



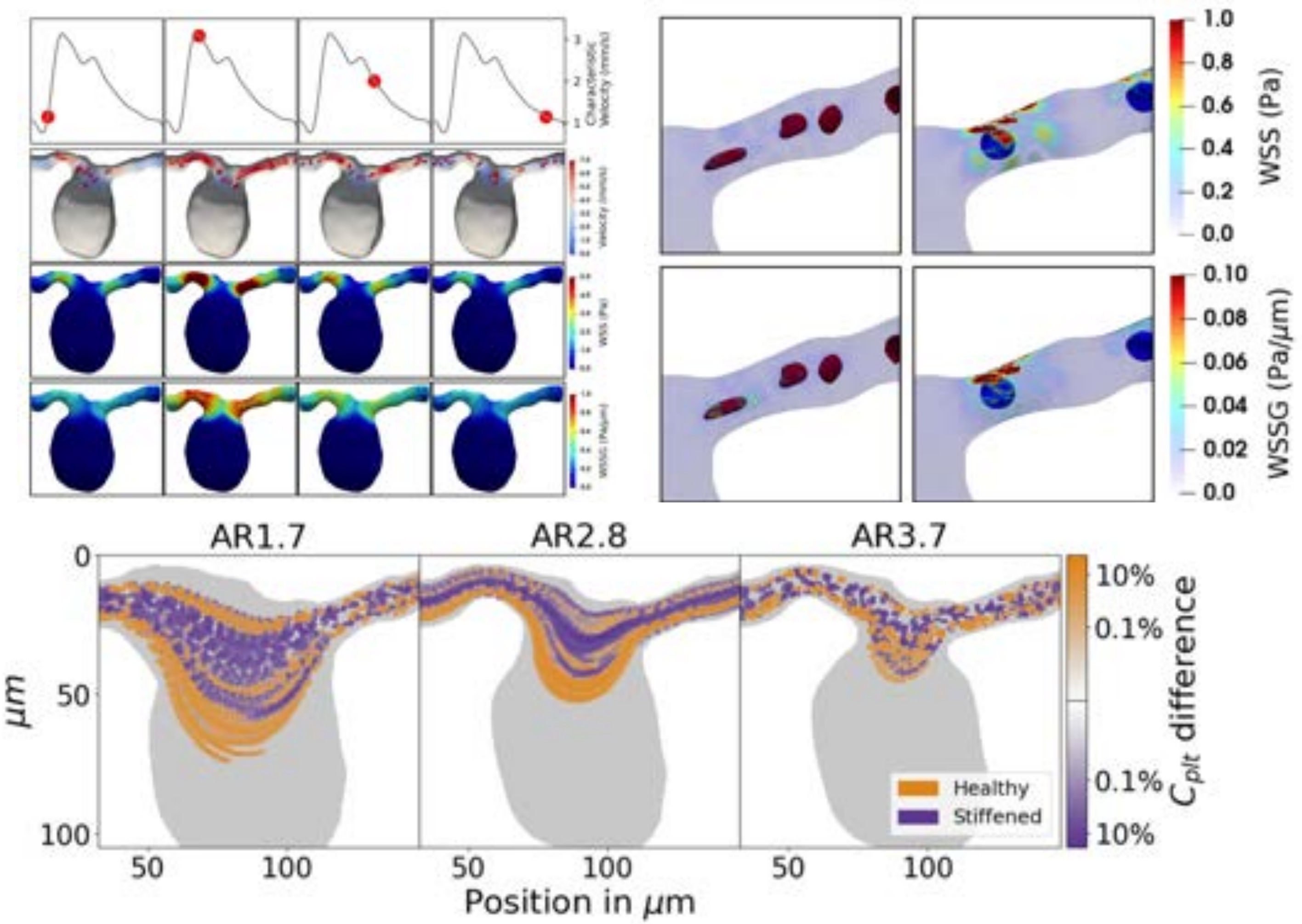


- The combination of **Adaptive Optics combined** with **Optical Coherence Tomography** allows for **3D patient specific geometry**, which is a unique feature.
- The availability of validated diabetic cell models allow the in-depth investigation of cellular transport in already developed microaneurysms.

Czaja, Benjamin, et al. Computer Methods in Biomechanics and Biomedical Engineering (2022): 1-19.

Transport in pulsatile flow inside micro-aneurysms
(diabetic retinopathy)

Simulation results for a full cardiac cycle:



Czaja, Benjamin, et al. Computer Methods in Biomechanics and Biomedical Engineering (2022): 1-19.

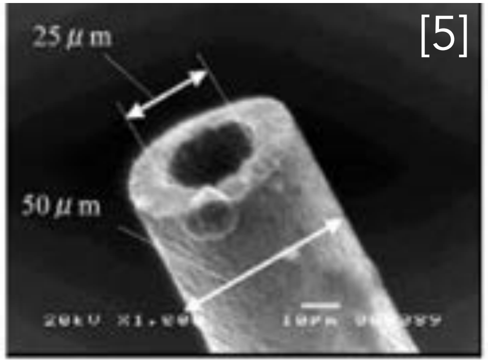
Outcomes:

- Healthy RBCs promote PLT penetration to the aneurysm.
  Might be a beneficial mechanism to facilitate closure of the saccular regions.
- Diabetic RBCs rarely penetrate the sac.
  This implies that RBC filled aneurysms might indicate an already "leaky stage" in development. (But not yet rupture). Possible clinical indicator.
- Diabetic cells give much more mechanical stimuli on the endothelial cells.
  This might have a role in the formation of the aneurysms (to be investigated).

Vessel puncture by microneedle

Fascicle tip of female mosquito labium

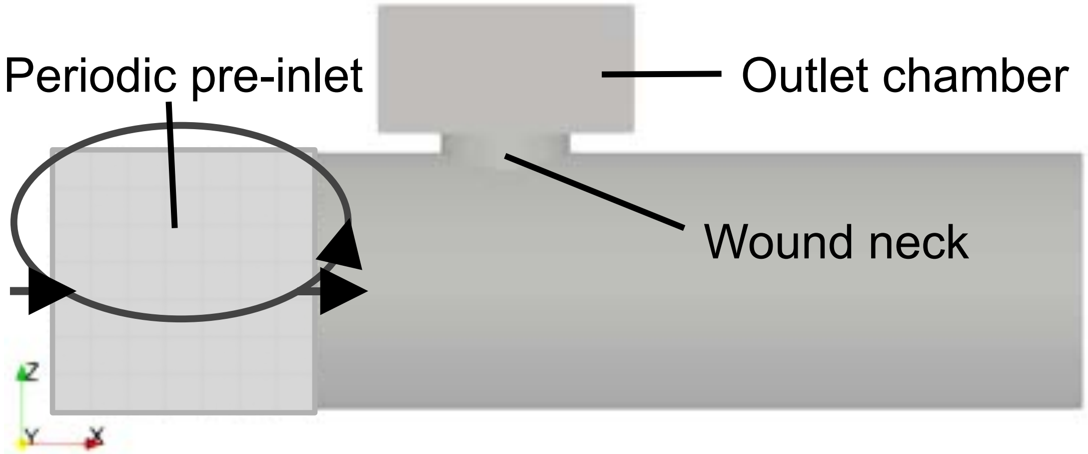
Microneedle development



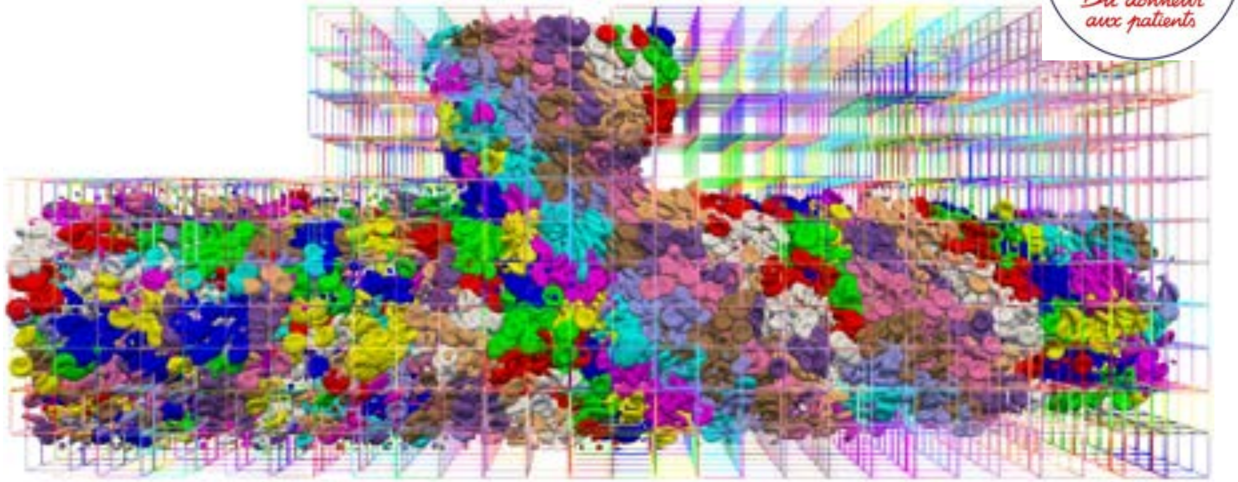
Clinical relevance:
- minimally invasive
- painless

Application:
- blood drawing
- drug injection
- glucose monitoring

HemoCell setup



Domain decomposition



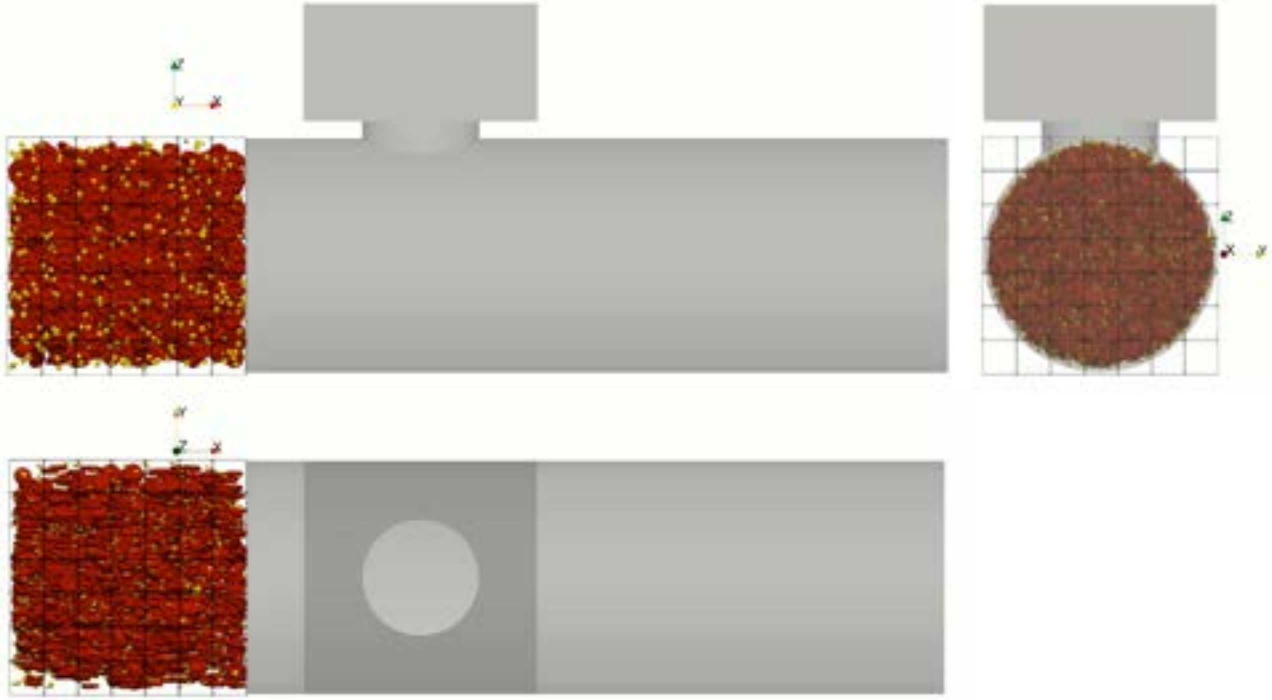
[3] Print K., 2018-01-09, https://bit.ly/3zAX19V

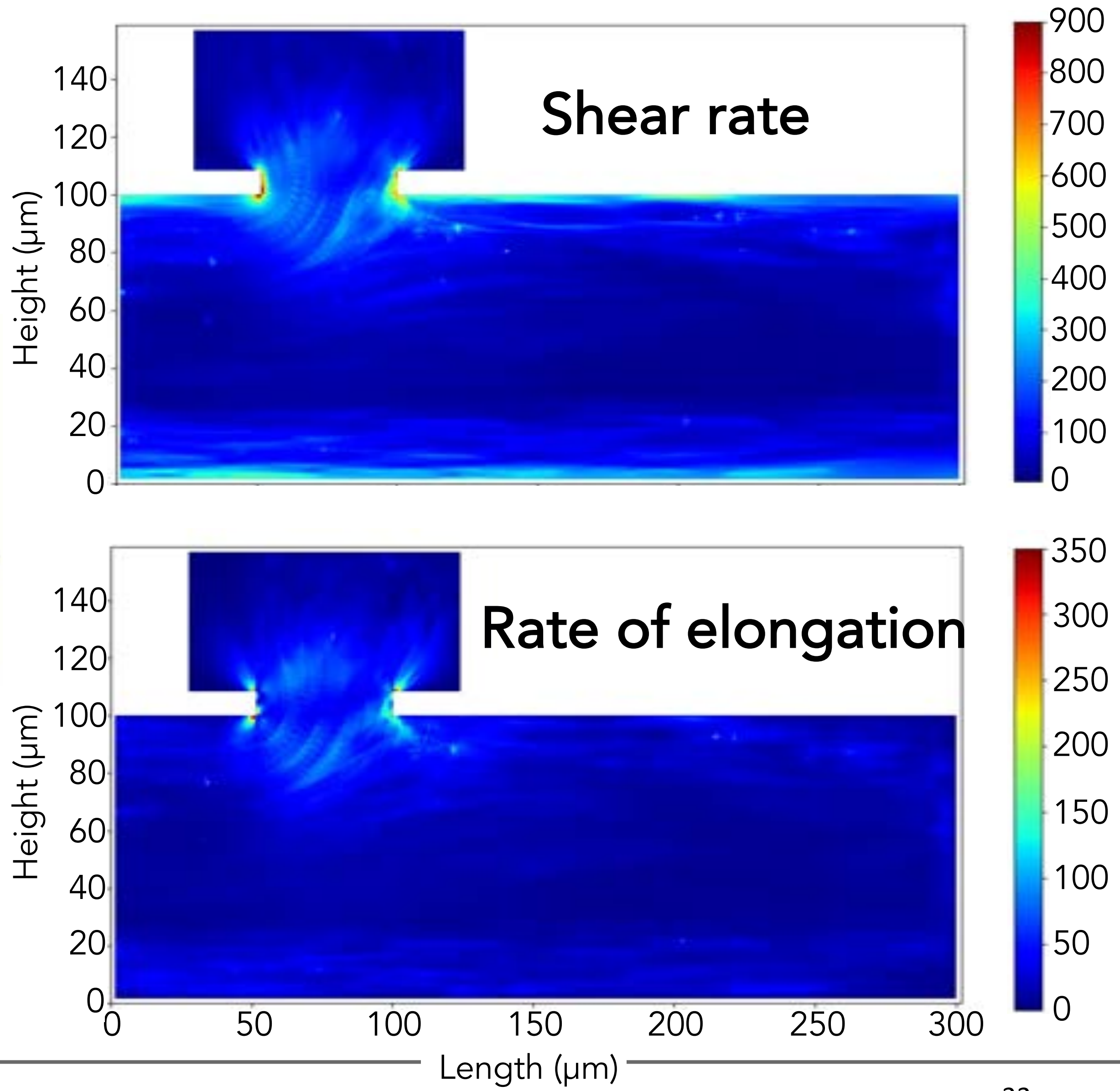
[4] Ramasubramanian et al., *Bioinsp. Biomim*, 2008, **3**, 10pp

[5] Chakraborty et al., *Journal of Applied Physics*, 2008, **103**, 114701

Simulation results – work in progress

100 μm diameter vessel
25 μm diameter puncture
Re = 0.75
Hematocrit: 25%





Next steps in development, enabled by the largest scales

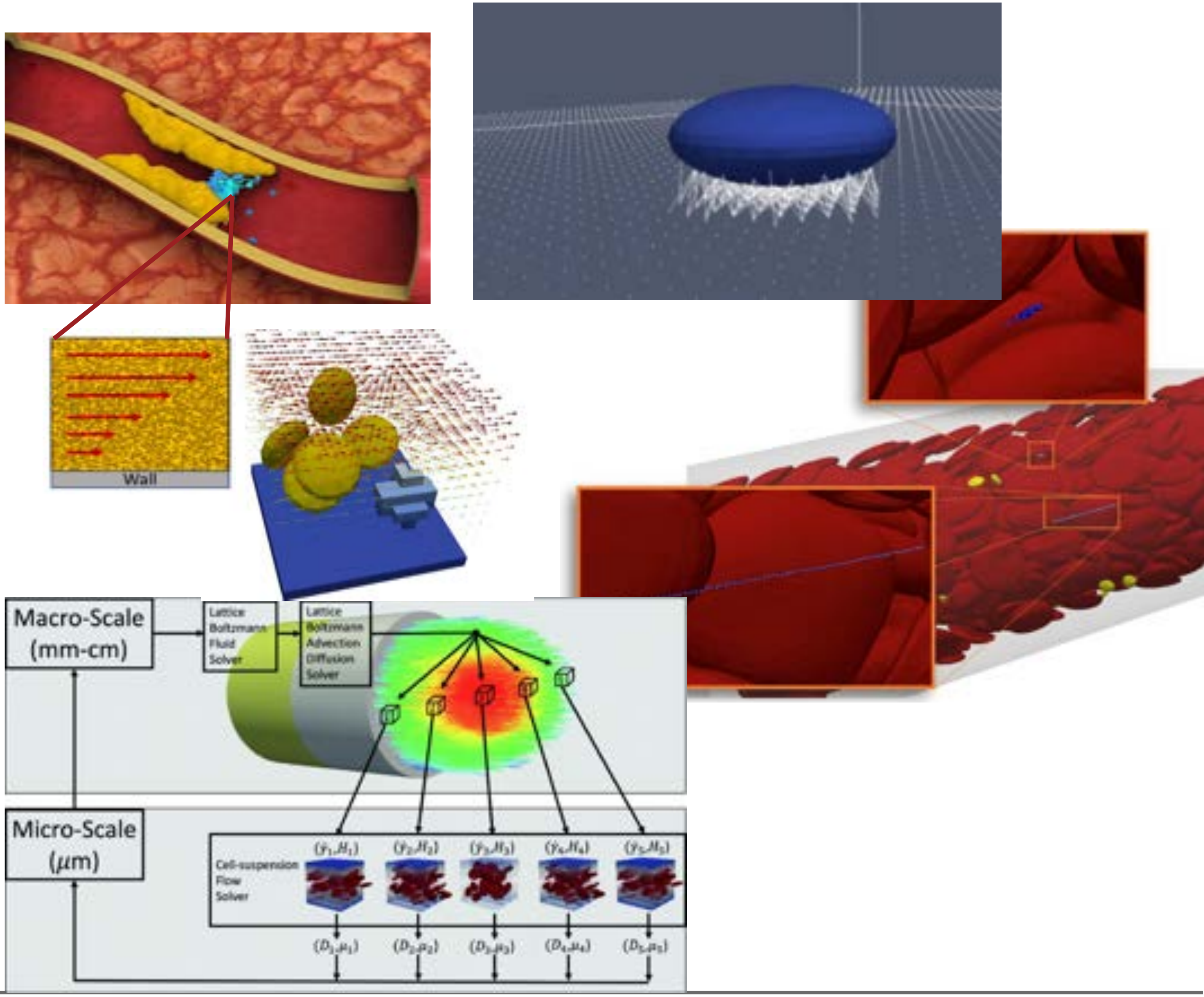
Integrating more biological processes

- Thrombus formation
  Platelet binding, build-up of thrombus in pathologic scenarios, in the presence of chemicals.

- Sub-cellular processes
  Protein mechanics, uncoiling of vWF, other components of pharmacological importance.

- Multi-scale models joining the various scale of blood.
  Important to capture micron-scale processes that influence the final organ-scale outcomes on clinical time-scales.

This is happening now!



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Q&A

To pose a question, you can write your question in the “Questions” tab

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 823712

Thank you for participating!

…don't forget to fill in our feedback questionnaire…

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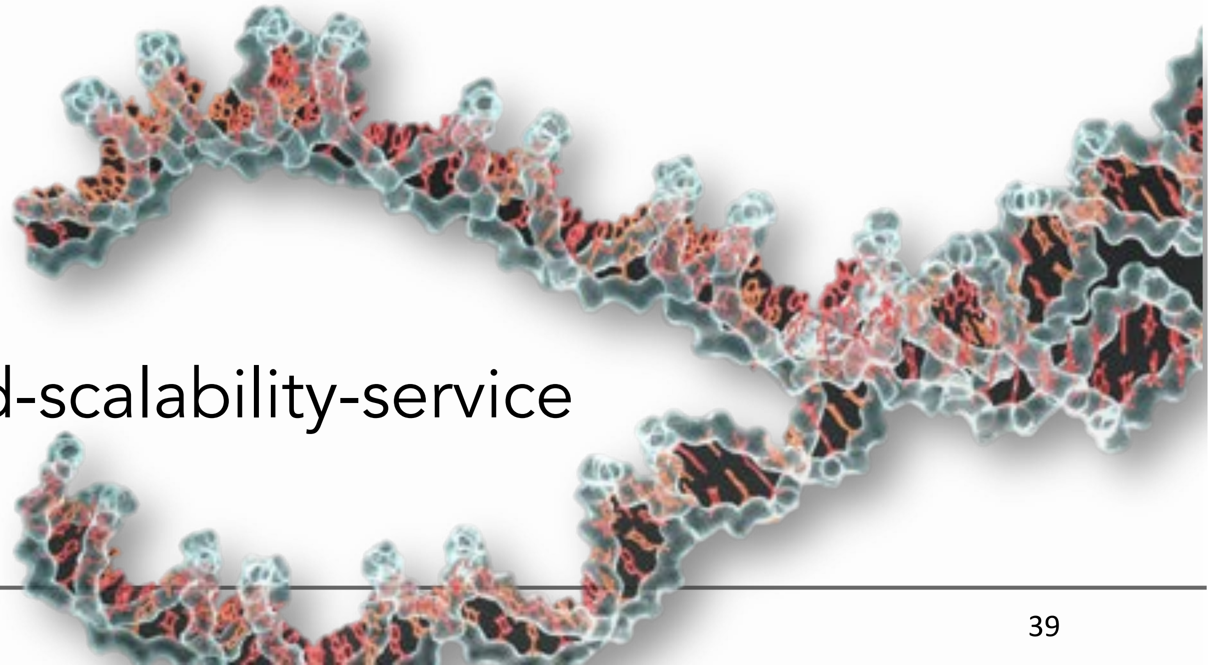

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Collaboration	• Join teams and collaboratively work on shared goals, projects, concerns, problems or topics
Safe space	• A pre-competitive space where experts from academia, industry, and regulatory agencies can ask for and exchange advices

More than 500 experts have already joined the community and its channels

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