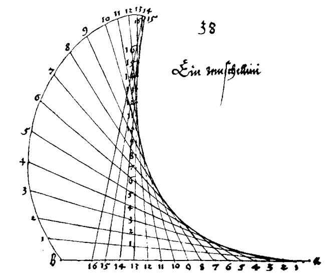
Drug Permeation through Skin: A Challenging Application for High Performance Scientific Computing

Modeling Natural Barriers
September 28 - October 1 2015
Bad Wildbad

Michael Heisig, Arne Nägel, Gabriel Wittum
G-CSC, Goethe-University, Frankfurt am Main



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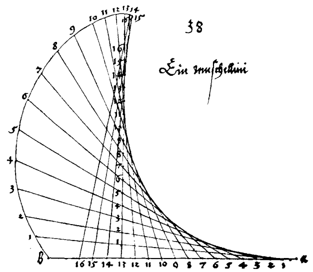
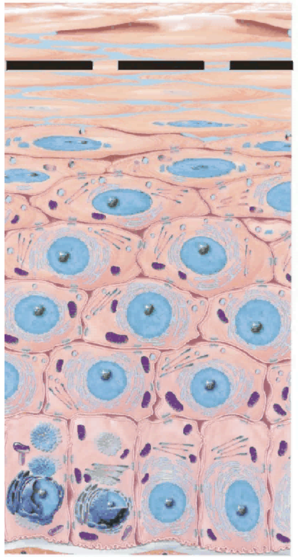
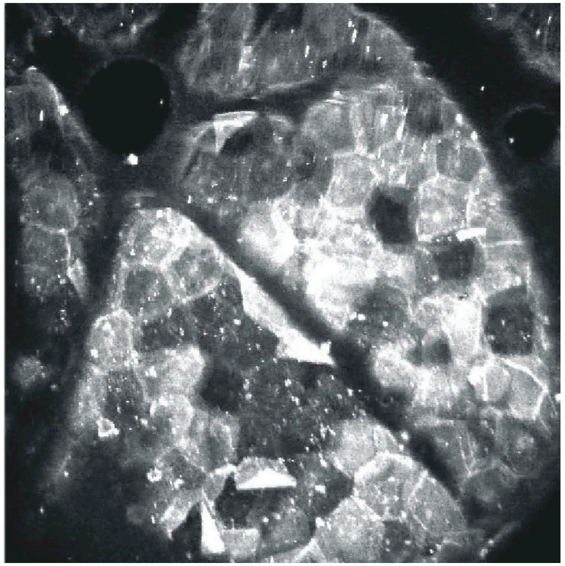


Motivation

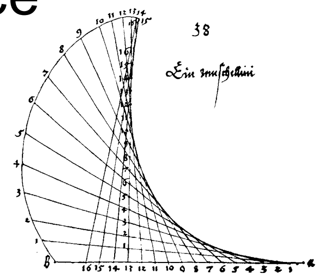
1) **Scientific motivation**: We have learnt so much about structure...

Courtesy of Roger Wepf, ETH

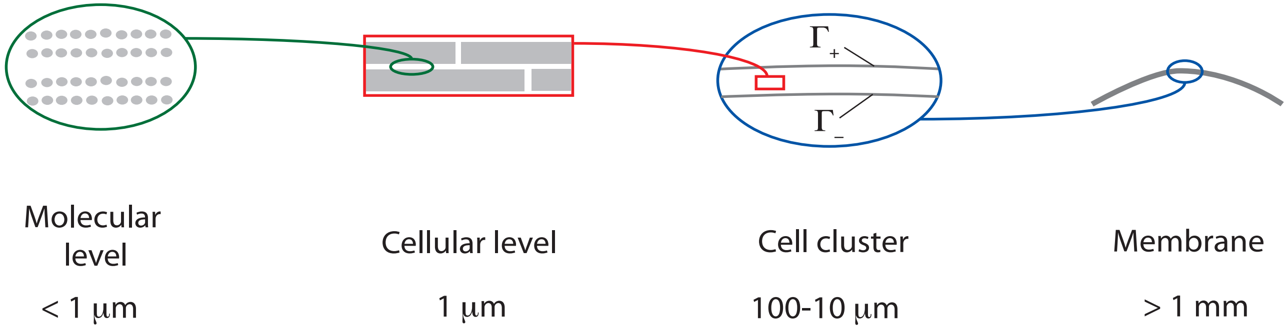
... why not use this information?

2) **Personal motivation**: Real interdisciplinary research is, when two fields interact, learn from each other and then advance mutually



Multiscale Character and Modelling Perspectives:

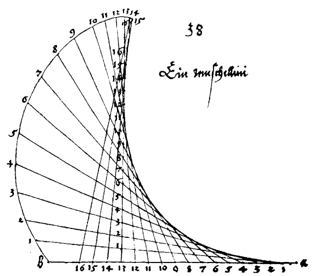
Micro scale **Macro scale**



Mechanistic approach (*bottom-up*):
- Effects emerge from small to large scales
- Based on first-principles
- Function-related parameters

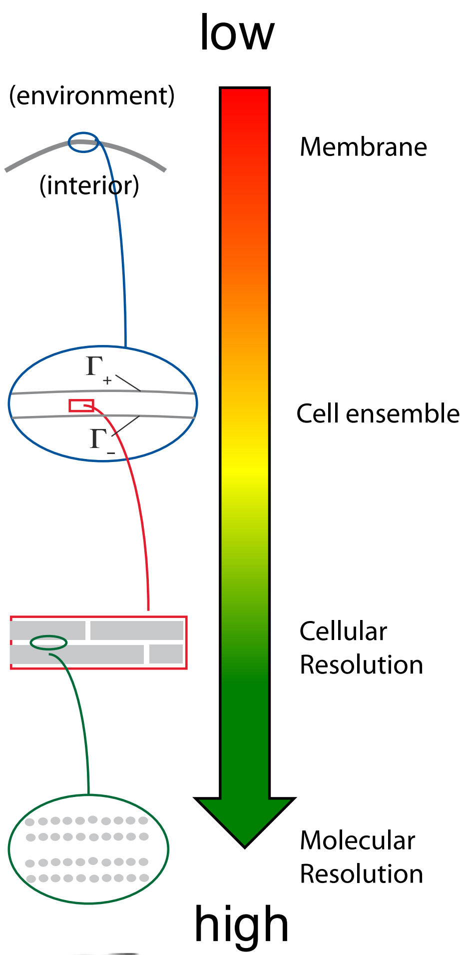
Descriptive approach (*top-down*):
- Simple description (e.g. linearization,..)
- Based on observations
- Apparent (fitted) parameters

Trade-off problem:
Need to balance accuracy and simplicity of description!



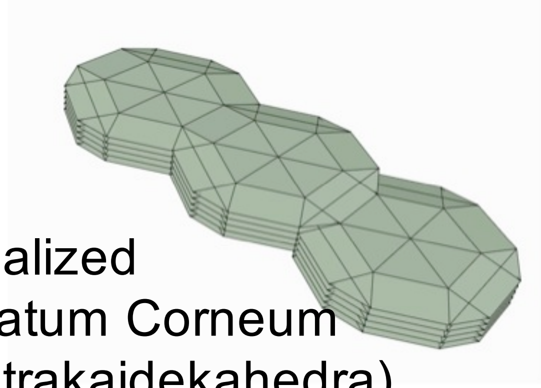
Different Modeling Approaches

Level of detail



Type of model	Time	Space	Response time
Quantitative Structure-Permeability Relationship	✗	✗	Instant
Compartmental models (ODE)	✓	✗	Seconds
Macroscopic Models (PDE)	✓	✓ (often 1D)	Minutes
Microscopic Models (PDE)	✓	✓ (2D, 3D)	Hours
Molecular Dynamics			

Motivation: Microscopic Modelling of Stratum Corneum

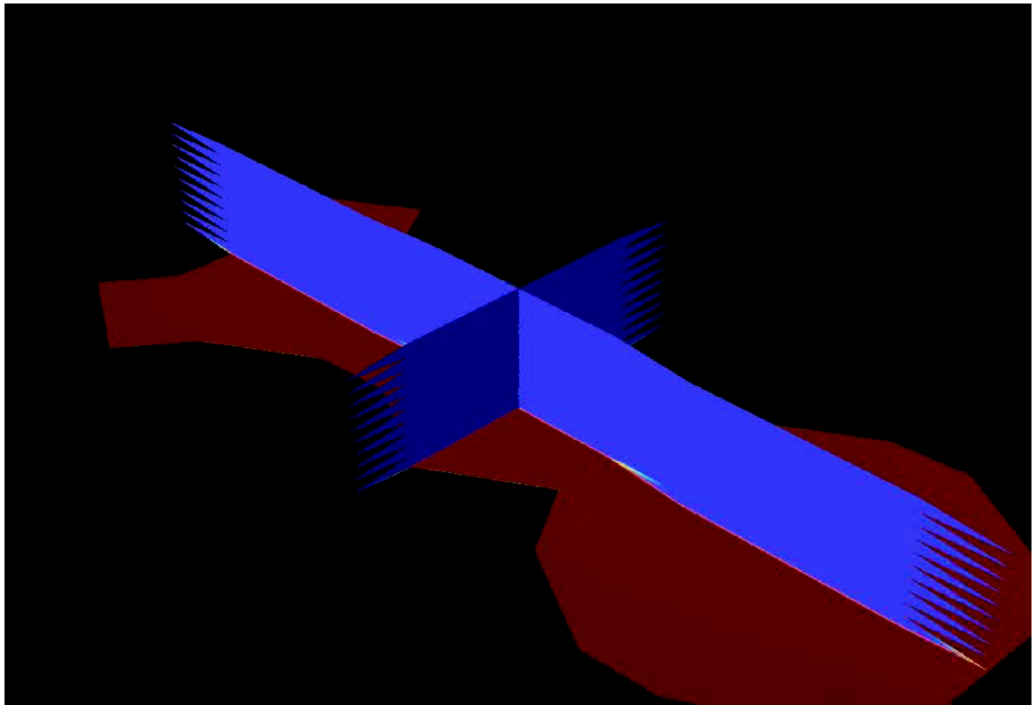


Idealized
Stratum Corneum
(Tetrakaidekahedra)

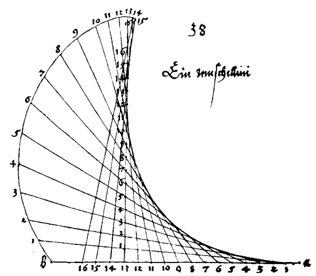
$$\partial_t(Ku) + \partial_x[-DK\partial_x u] = 0$$

Diffusion equation
(e.g. piecewise constant coefficients)

Morphology + Function = Effect



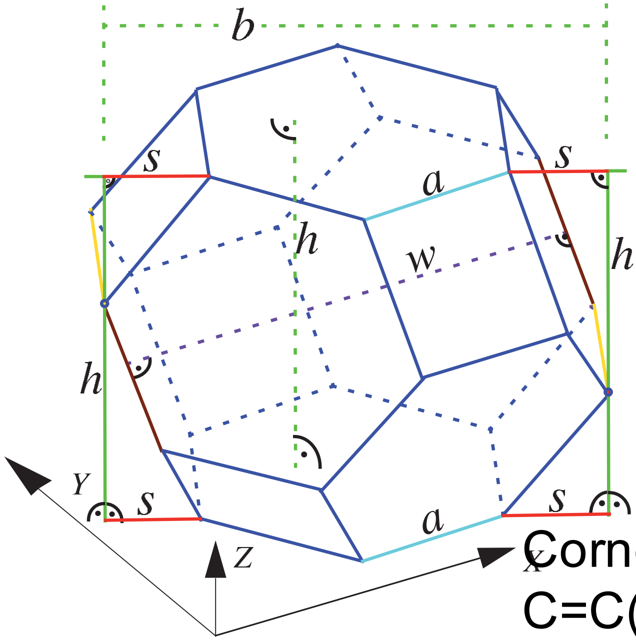
Corneocyte
sponge effect



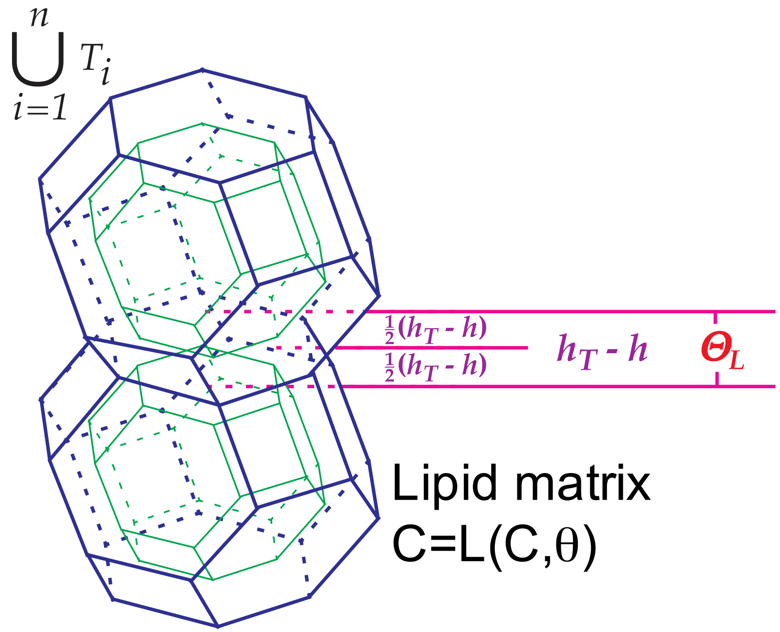
Outline

1. Introduction
2. Transport in Stratum Corneum
3. Transport in the viable Epidermis
4. Mechanical Properties and Swelling

Using Tetrakaidekahedra as a Cell Template

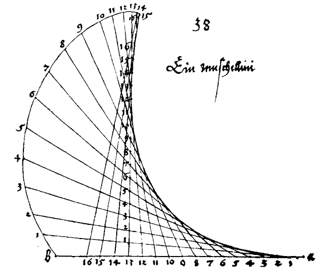


Corneocyte cell
C=C(a,h,w)



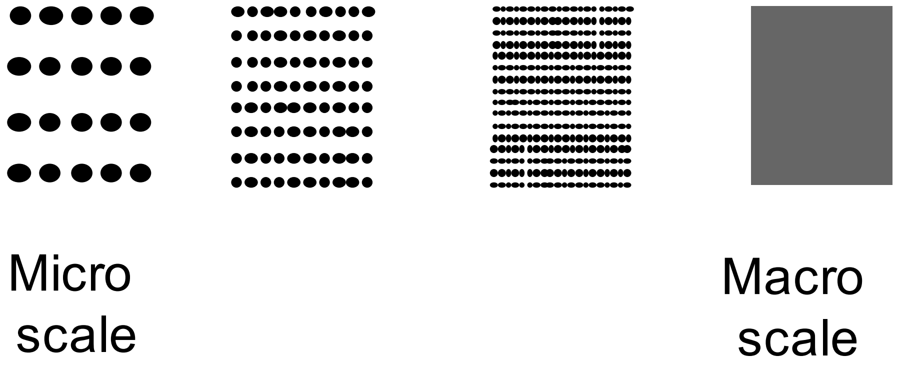
Lipid matrix
C=L(C,θ)

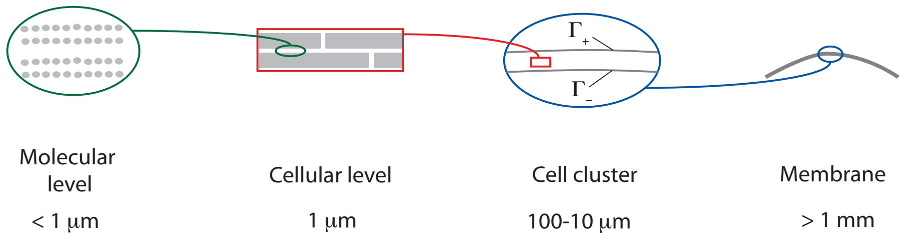
- TKD = Polyhedron with 14 faces
- Goes back to Keppler (dense packings, foam cells)
- Configuration $\mathscr{C}$: Corneocyte cell C, lipid matrix L ➔



Homogenization

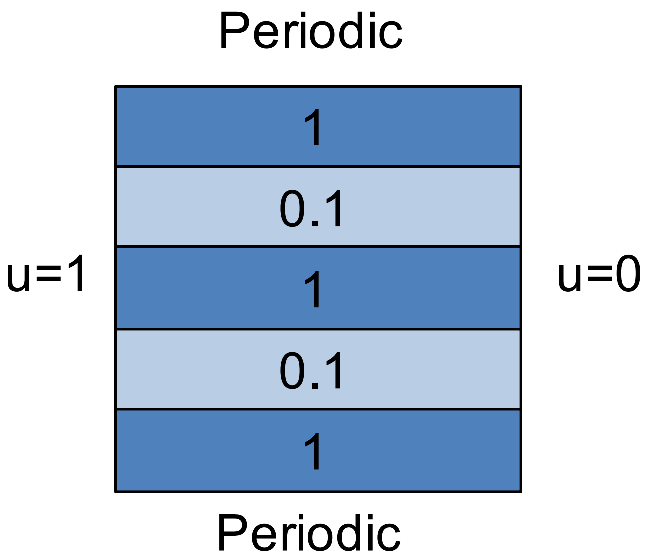
Idea: Obtain information about macro scale process from micro scale process





Homogenization – Example:

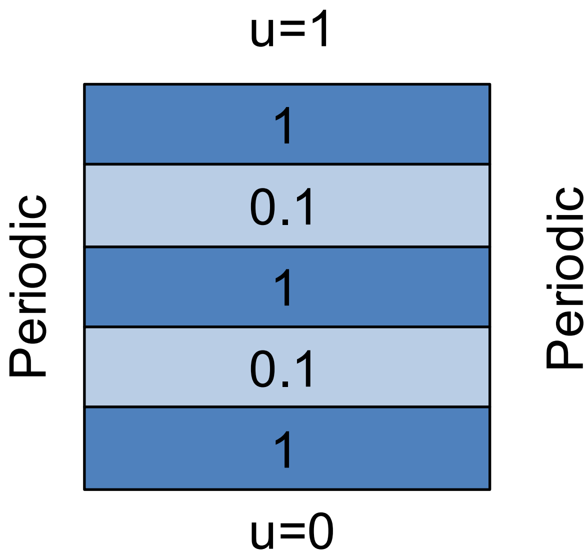
a) Lateral Diffusion ➔



$$\overline{D}_{||} = \frac{1}{L}\int_0^L D(x)\,dx$$
$$= 0.6 * 1 + 0.4 * 0.1$$
$$= 0.64$$

Results in **anisotropic** diffusion tensor: $\mathbb{D} = \begin{pmatrix} \overline{D}_{||} & 0 \\ 0 & \overline{D}_{\perp} \end{pmatrix}$

b) Transversal Diffusion 🡇

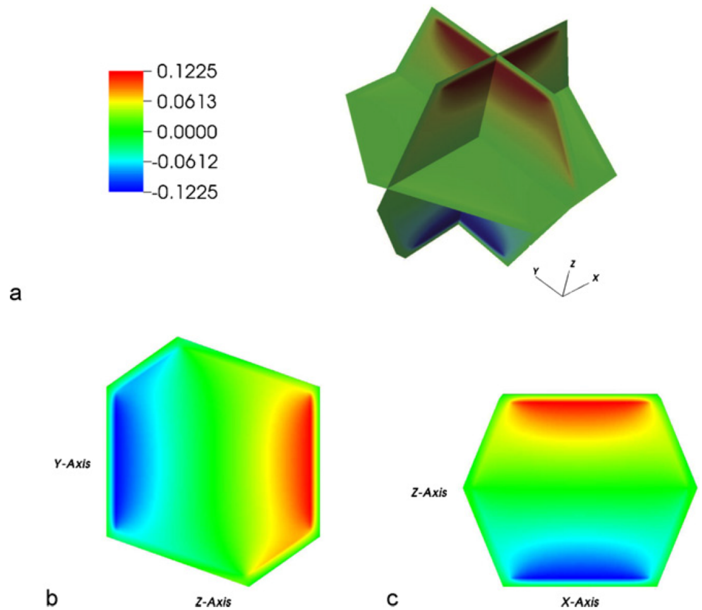


$$\left(\overline{D}_{\perp}\right)^{-1} = \frac{1}{L}\int_0^L D(x)^{-1}\,dx$$
$$= (0.6 * 1 + 0.4 * 10)^{-1}$$
$$= (4.6)^{-1} \approx 0.21$$

Homogenization applied to

Method of Asymptotic Expansion (e.g., Bensoussan, Lions, Papanicolaou,1978)

- Requires solution of d=3 cell problems
- Simple for diffusion problems

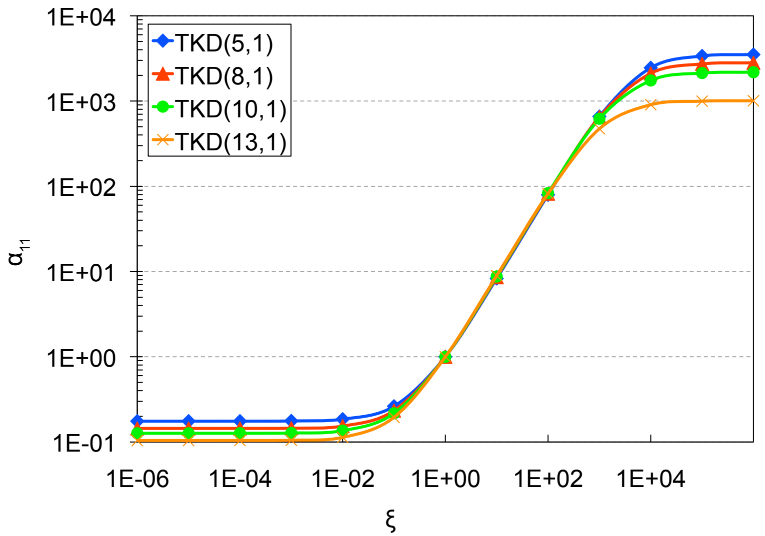


For Cuboid model:
Rim, Pinsky, van Osdol,
J Membrane Sci, 2007

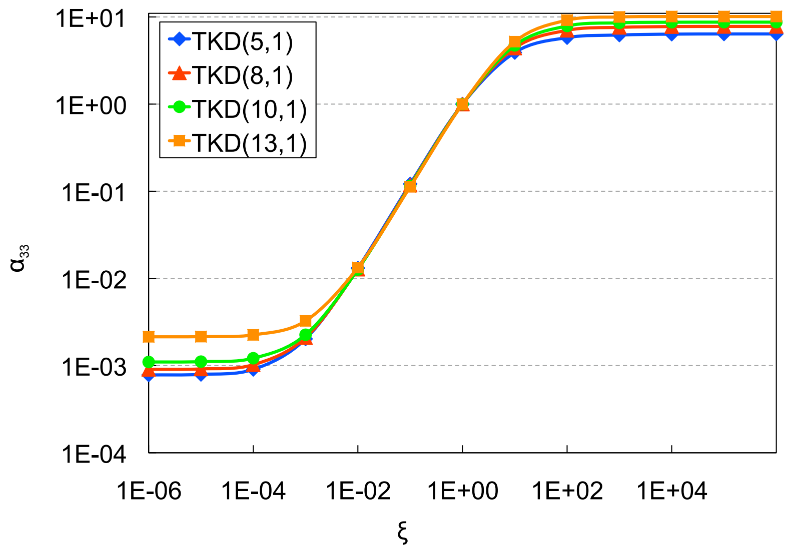
For TKD: Muha, N', Stichel, Grillo, Heisig, Wittum,
J Membrane Sci, 2010

Homogenization of Tetrakaidekahedra

Lateral ➔



Transversal 🡣



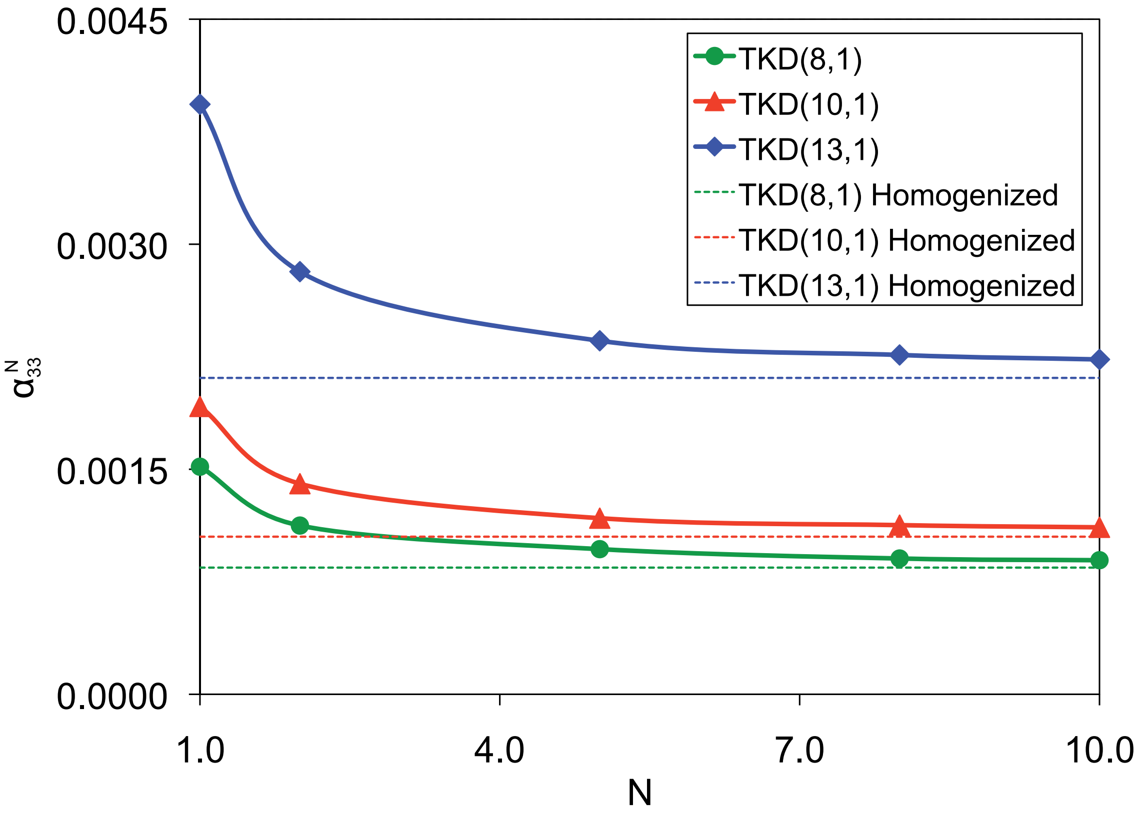
Results:

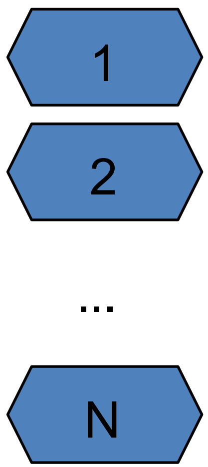
- Diagonal diffusion tensor
- Separate coefficients for lateral/transversal direction
- Dependent on effective diffusivity (sigmoidal)

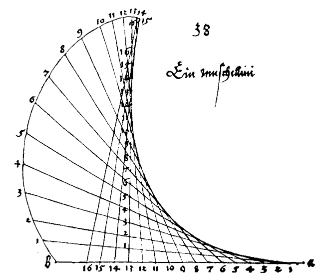
$$\mathbb{D} = D_{lip} \begin{pmatrix} \alpha_{11}(\xi) & 0 & 0 \\ 0 & \alpha_{11}(\xi) & 0 \\ 0 & 0 & \alpha_{33}(\xi) \end{pmatrix}$$

$$\xi = \frac{D_{COR}}{D_{LIP}} K_{\mathrm{COR/LIP}}$$

Validity of the approximation



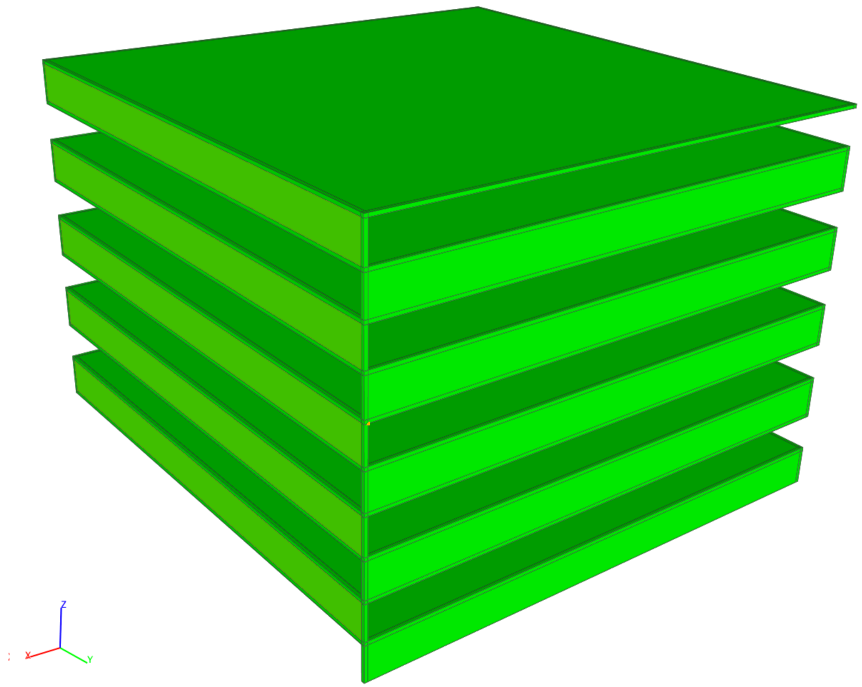




Transport in Stratum Corneum

Joint work with Andreas Vogel, Sebastian Reiter

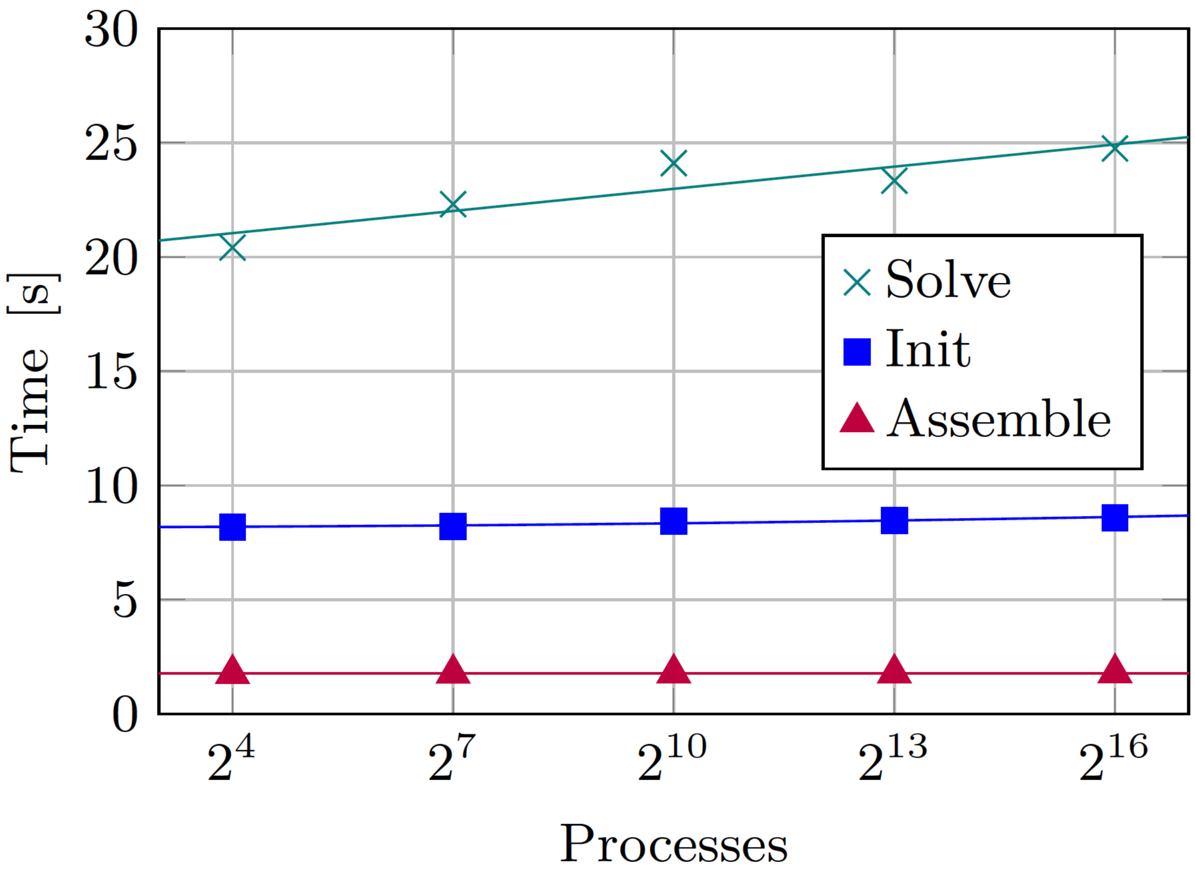
Example: Computation for a Cuboid Membrane



Diffusion through a biphasic brick-and-mortar medium (3D) w/ jumping coefficients:

$D_{LIP} = 1$,
$D_{COR} = 0.001$,
$K_{LIP} = K_{COR} = 1$

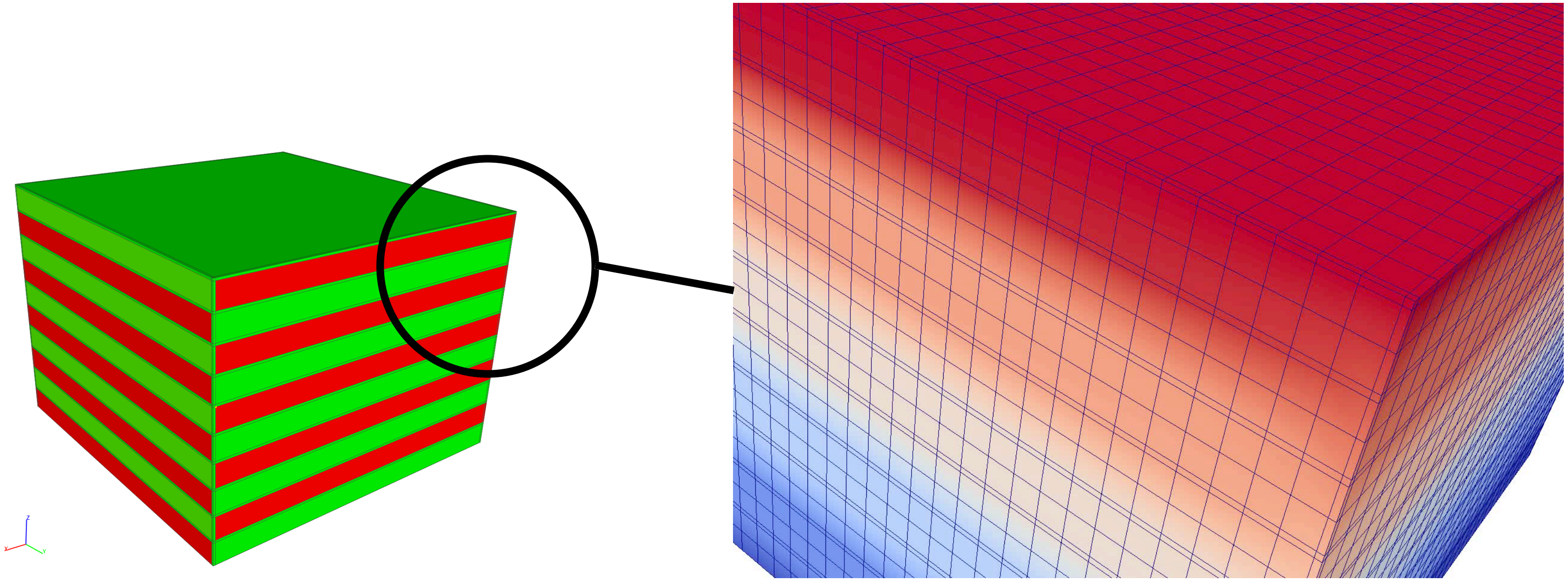
Computational effort



p	L	DoF	n_{gmg}
16	6	290,421	25
128	7	2,271,049	27
1024	8	17,961,489	29
8192	9	142,869,025	29
65536	10	1,139,670,081	29

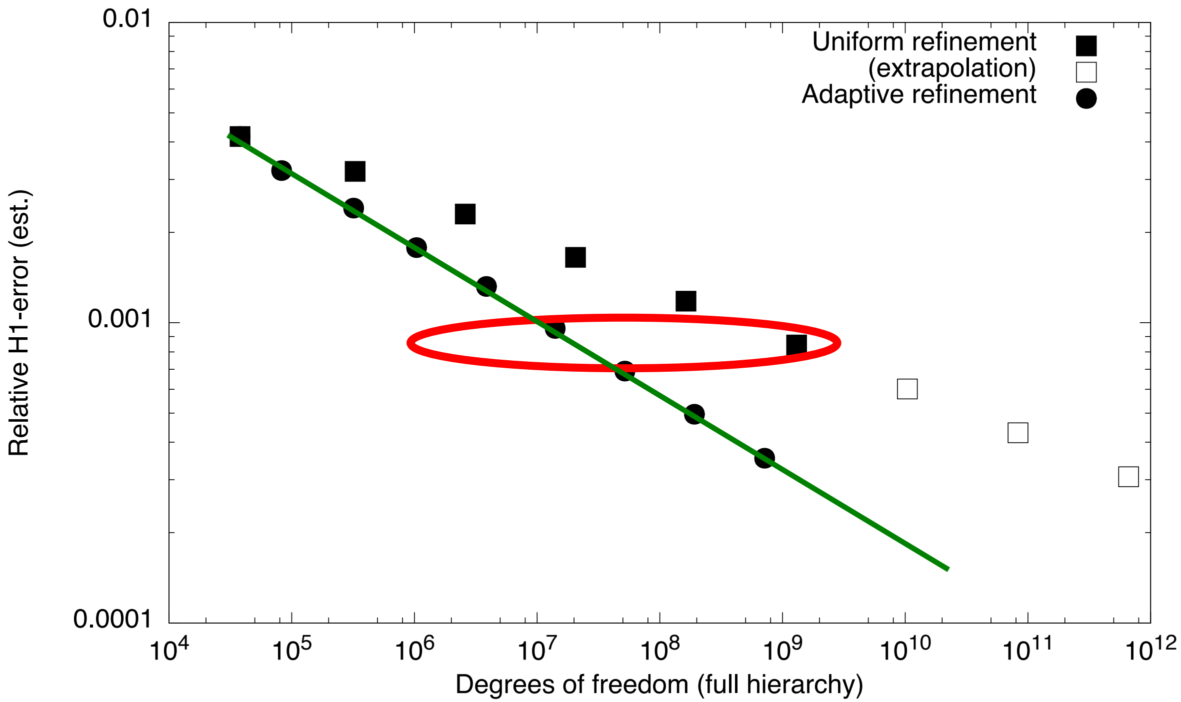
Kernel	Model for time [s]
Solve	$19.75 + 0.32 \cdot \log_2 p$
Init	$8.17 + 0.002 \cdot \log_2^2 p$
Assemble	1.78

Reducing Computational Effort by Adaptive Refinement (Verfürth, Zienkiewicz, ...)

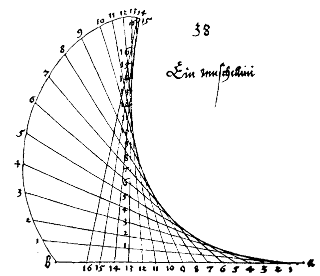


Singularities in the corners
➔ Refine the mesh only in this area
➔ Reduce number of degrees of freedom

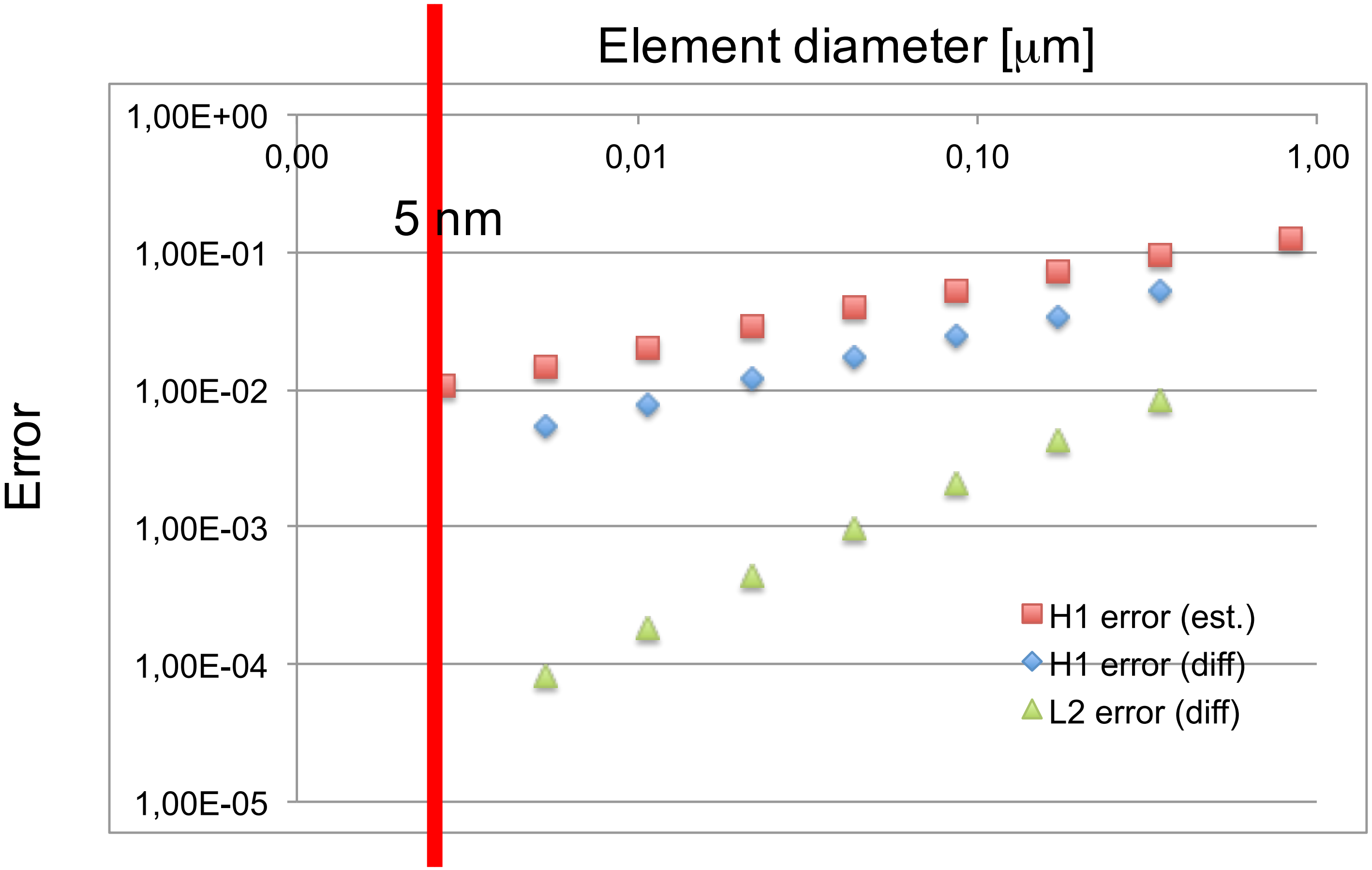
Uniform vs. Adaptive refinement (steady state problem)



- 64 K processes vs. 1K processes
  (approx. identical wall clock time on JuQueen, JSC Jülich)
- Larger gain of accuracy per dof w/ adaptivity (still counting...)

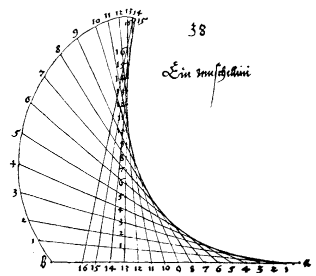


Order of Convergence

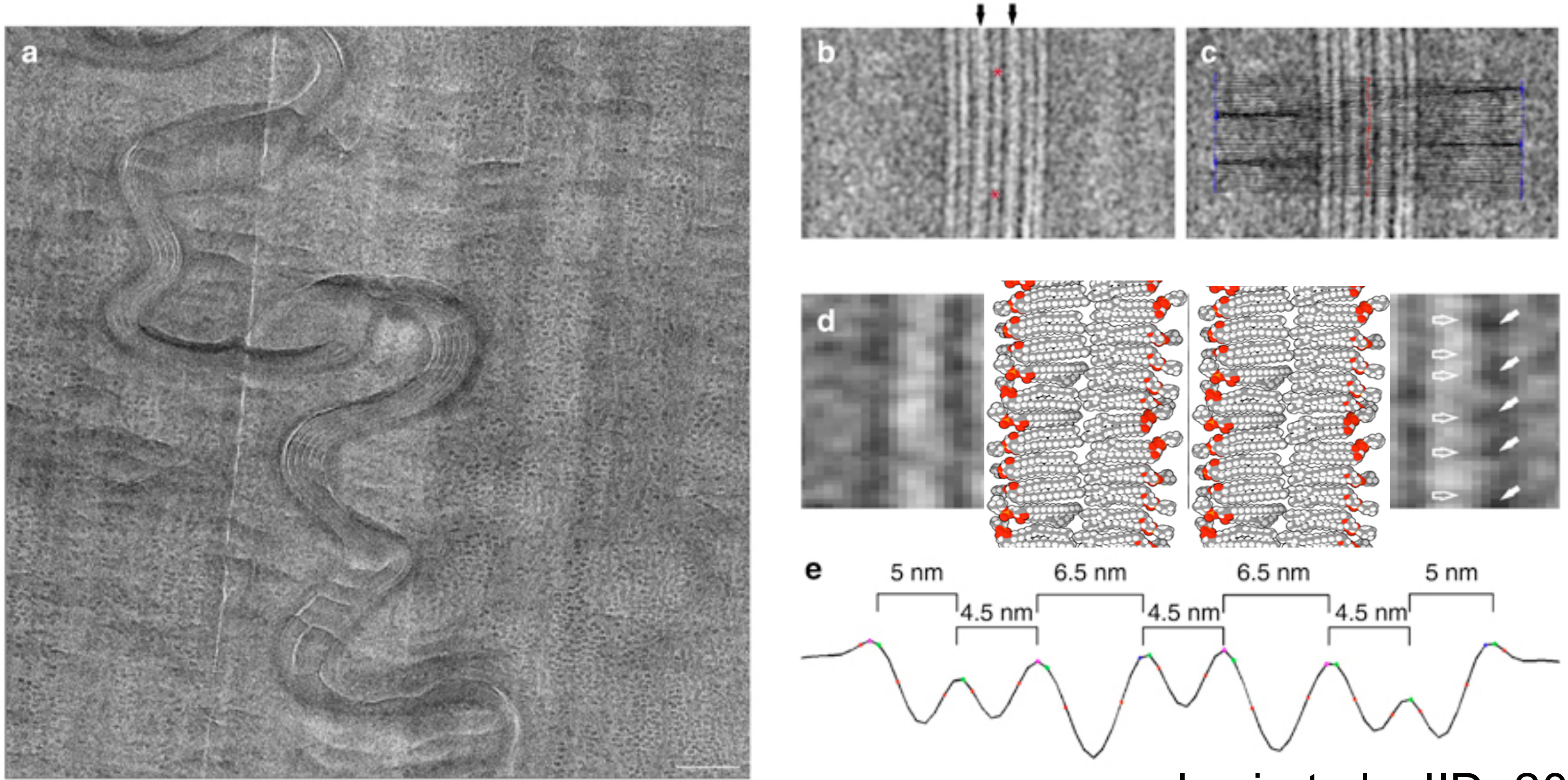


Error proportional to element diameter h:

H1-Error ~ $O(h^{1/2})$ and L2-Error ~ $O(h)$



Subscale model for stratum corneum lipids



Iwai et al., JID, 2012

- The **discretization** reaches the level of **molecular resolution**
- Need a new model (describing morphology+function)

Anisotropic diffusion in lipid bilayers - Two options:

- **Constitutive relations/ measurements**

- DLAT= 100*DTRANs (maybe 10000)

Permeability of Fluid-Phase Phospholipid Bilayers: Assessment and Useful Correlations for Permeability Screening and Other Applications

JOHANNES M. NITSCHE,[1] GERALD B. KASTING[2]

[1]Department of Chemical and Biological Engineering, University at Buffalo, The State University of New York, Buffalo, New York 14260-4200

[2]James L. Winkle College of Pharmacy, University of Cincinnati Academic Health Center, Cincinnati, Ohio 45267-0004

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- **Molecular Dynamics (**Yesterday afternoon)

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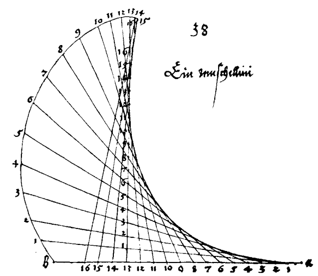
ELSEVIER

Breaching the skin barrier — Insights from molecular simulation of model membranes ☆

CrossMark

Rebecca Notman [a], Jamshed Anwar [b,*]

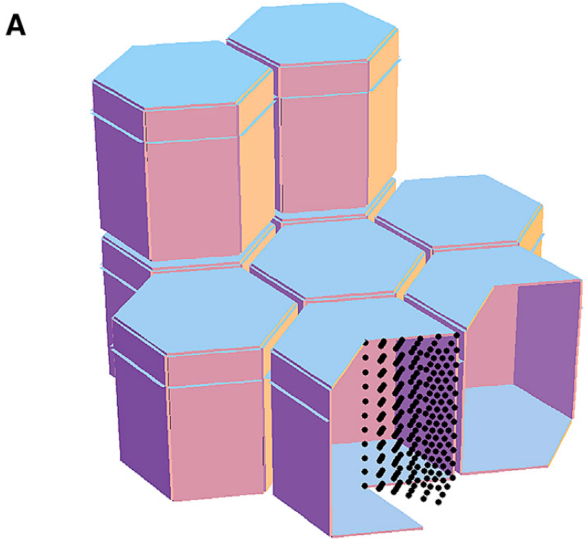
[a] Department of Chemistry and Centre for Scientific Computing, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, UK
[b] Computational Biophysics Laboratory, Institute of Life Sciences Research, University of Bradford, BD7 1DP, UK

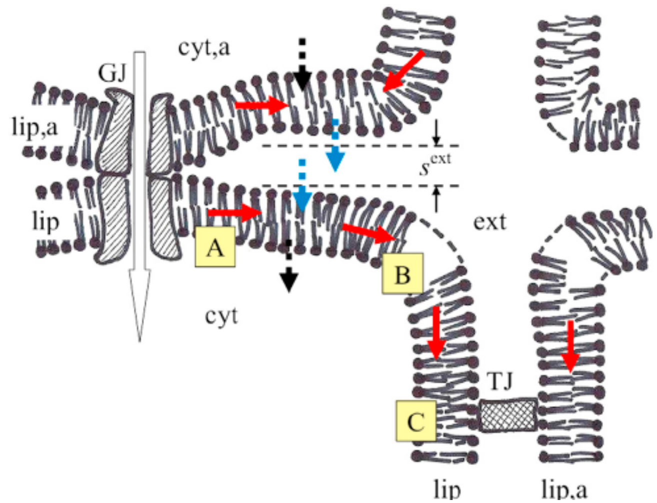


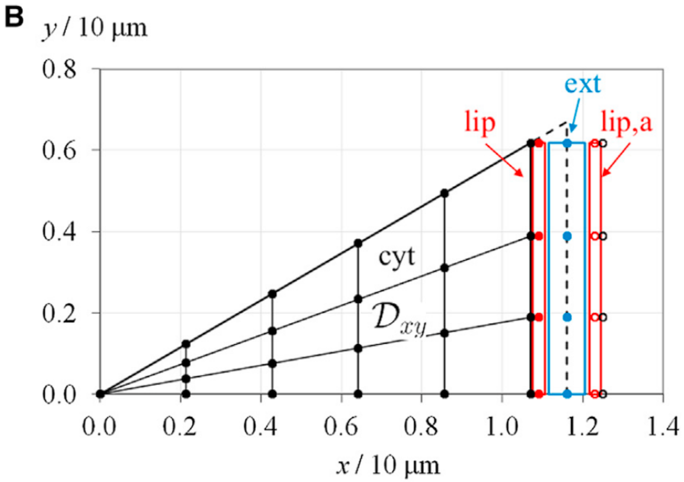
Transport in the viable epidermis

Joint work with
Johanna Brandner, Christian Börnchen@UKE, Hamburg
Markus Knodel, Rebecca Wittum @ G-CSC

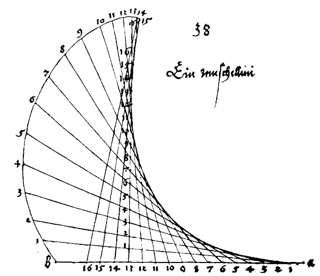
Cellular scale model:
Nitsche and Kasting, Biophys J, 2013





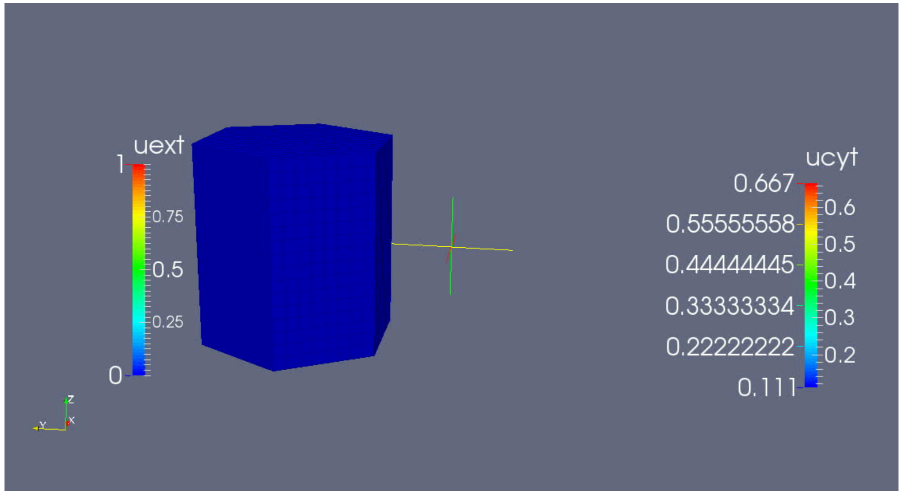


- Transport in cytosol, lipid membrane, intracellular space
- Gap Junction/Tight Junctions
- ➢ Effective Diffusivity (z-direction)

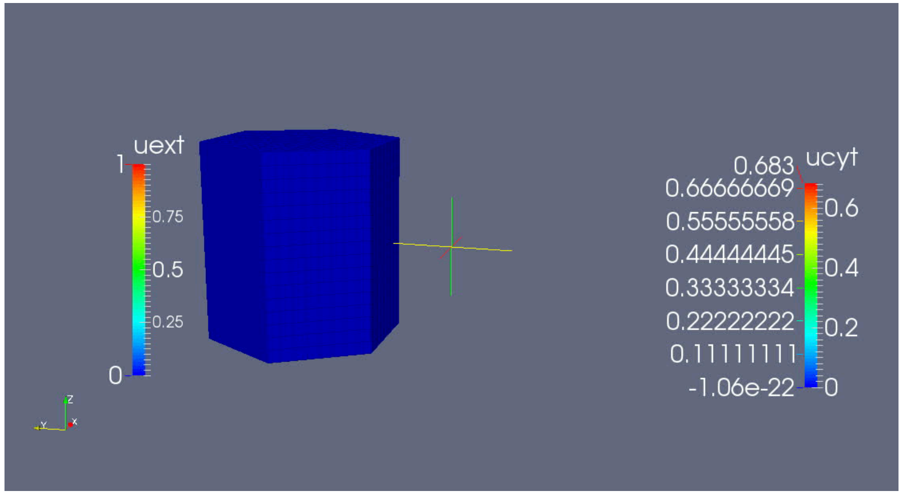


Transient simulation for viable epidermis (R. Wittum)

- Non-homogenized 3D model
  following Nitsche and Kasting, Biophys J, 2013

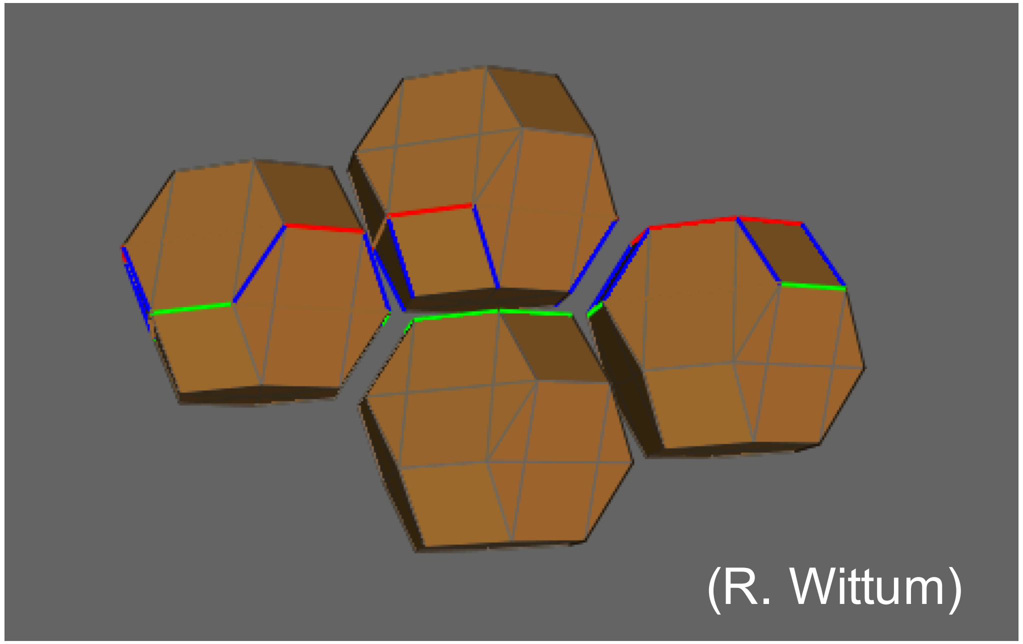


Fast diffusion in cytosol



Slow diffusion in cytosol

Open question: Tight Junction on real 3D structures



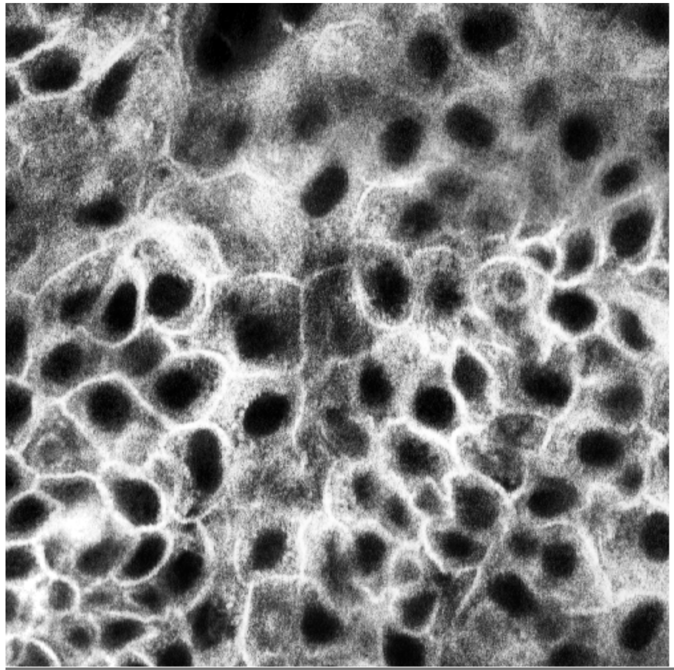
Towards cell ensembles: Reconstructed Epidermis

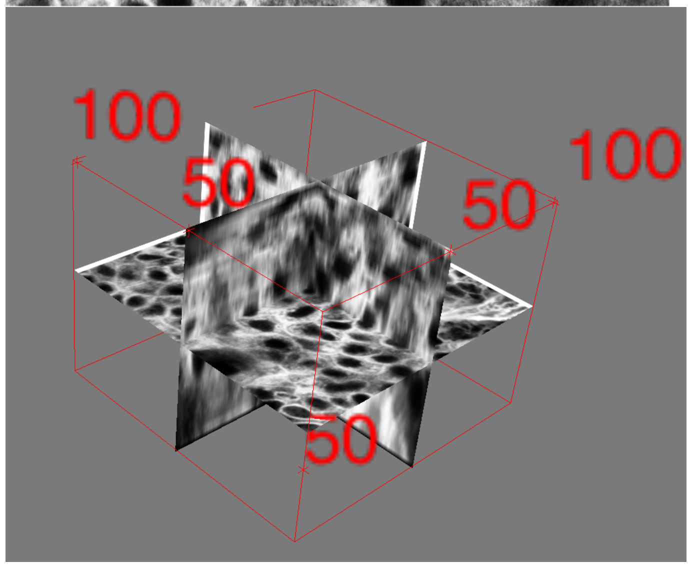
1. Obtain image data
   (stacks of microscopy data)

2. Reconstruct
   a. Cell Nuclei
   b. Cell Membranes

3. Generate Volume meshes

4. Run simulations





Images courtesy of
C. Börnchen and J. Brandner
(UKE Hamburg)

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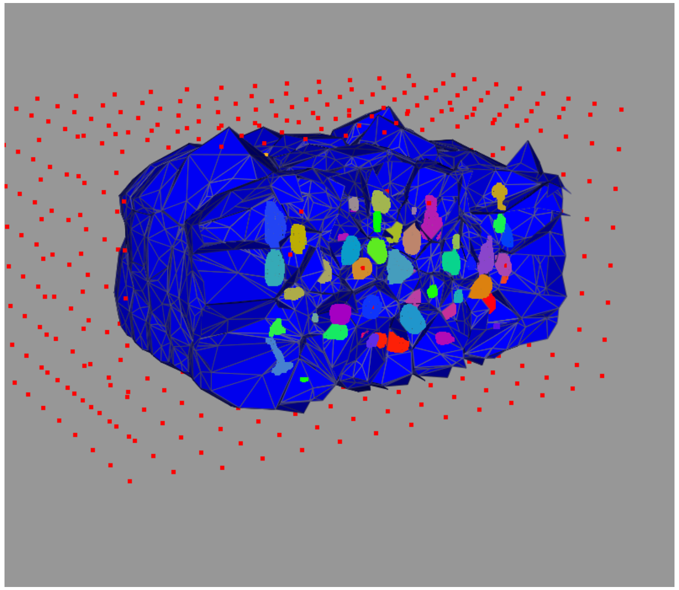

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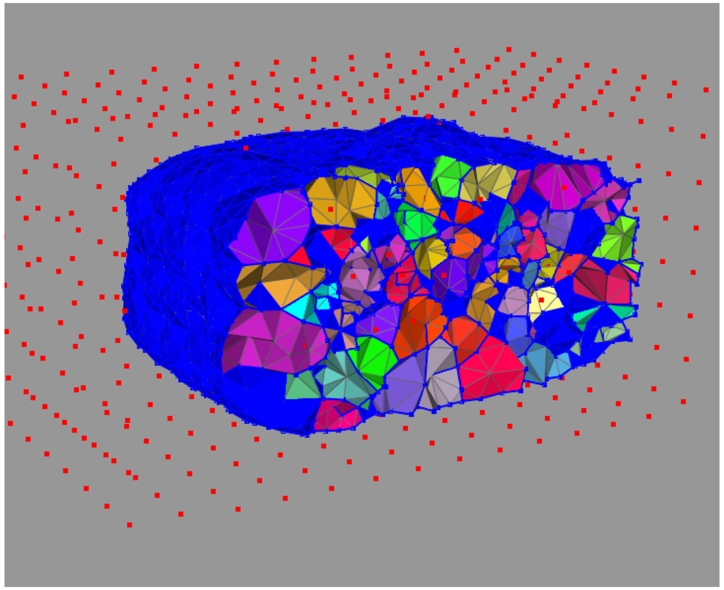
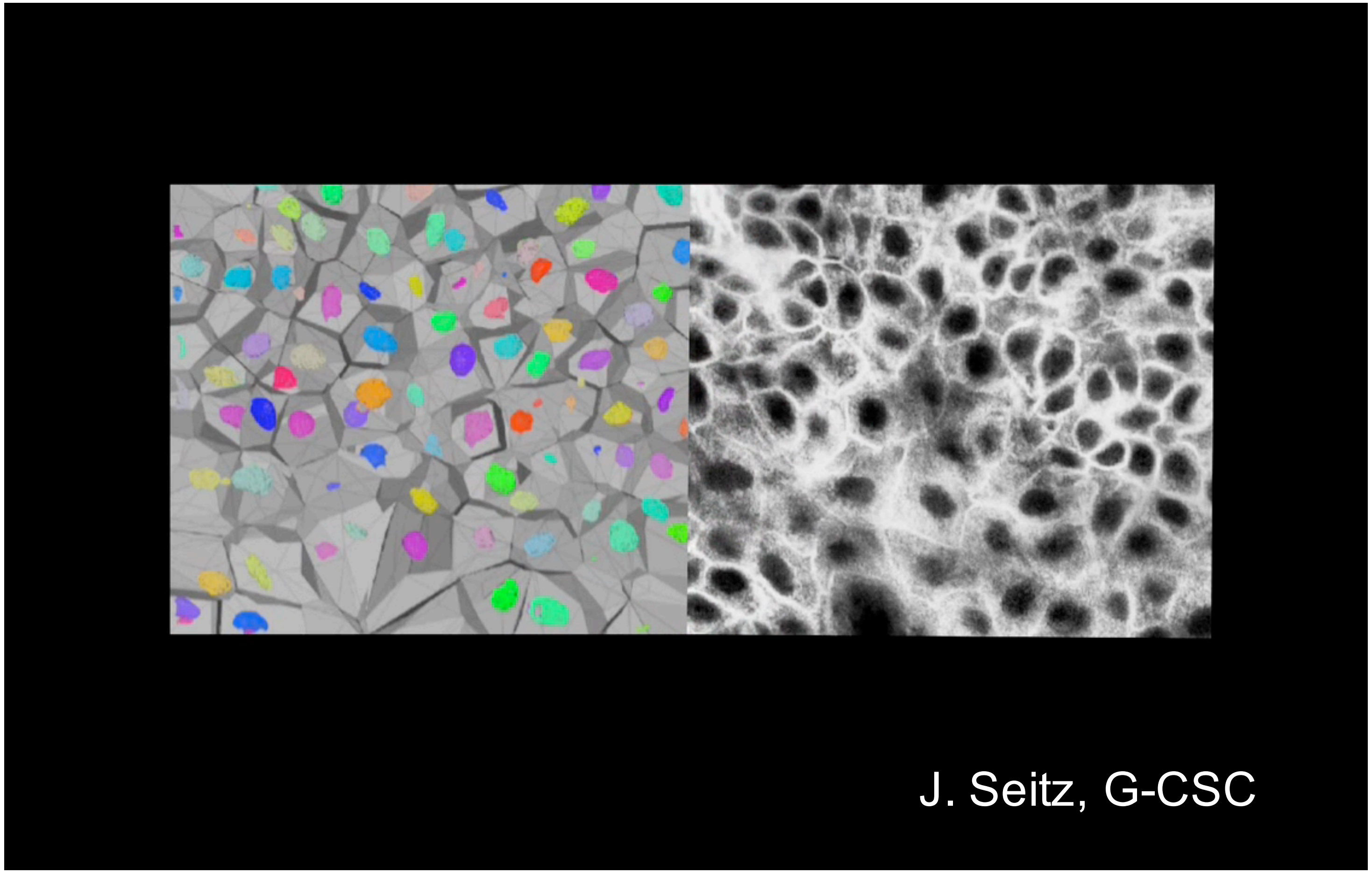


Comparison: Reconstruction vs. Image



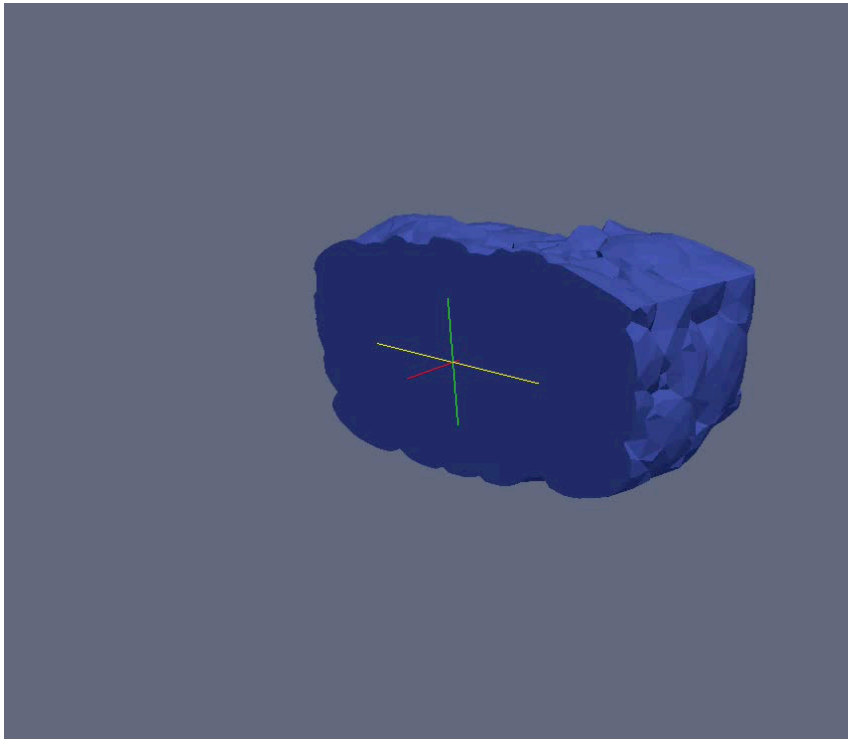
Towards cell ensembles: Reconstructed Epidermis

1. Obtain image data
   (stacks of microscopy data)

2. Reconstruct
   a. Cell Nuclei
   b. Cell Membranes
      (Voronoi diagram)

3. Generate Volume meshes

4. Run simulations
   (w/ cellular scale model)

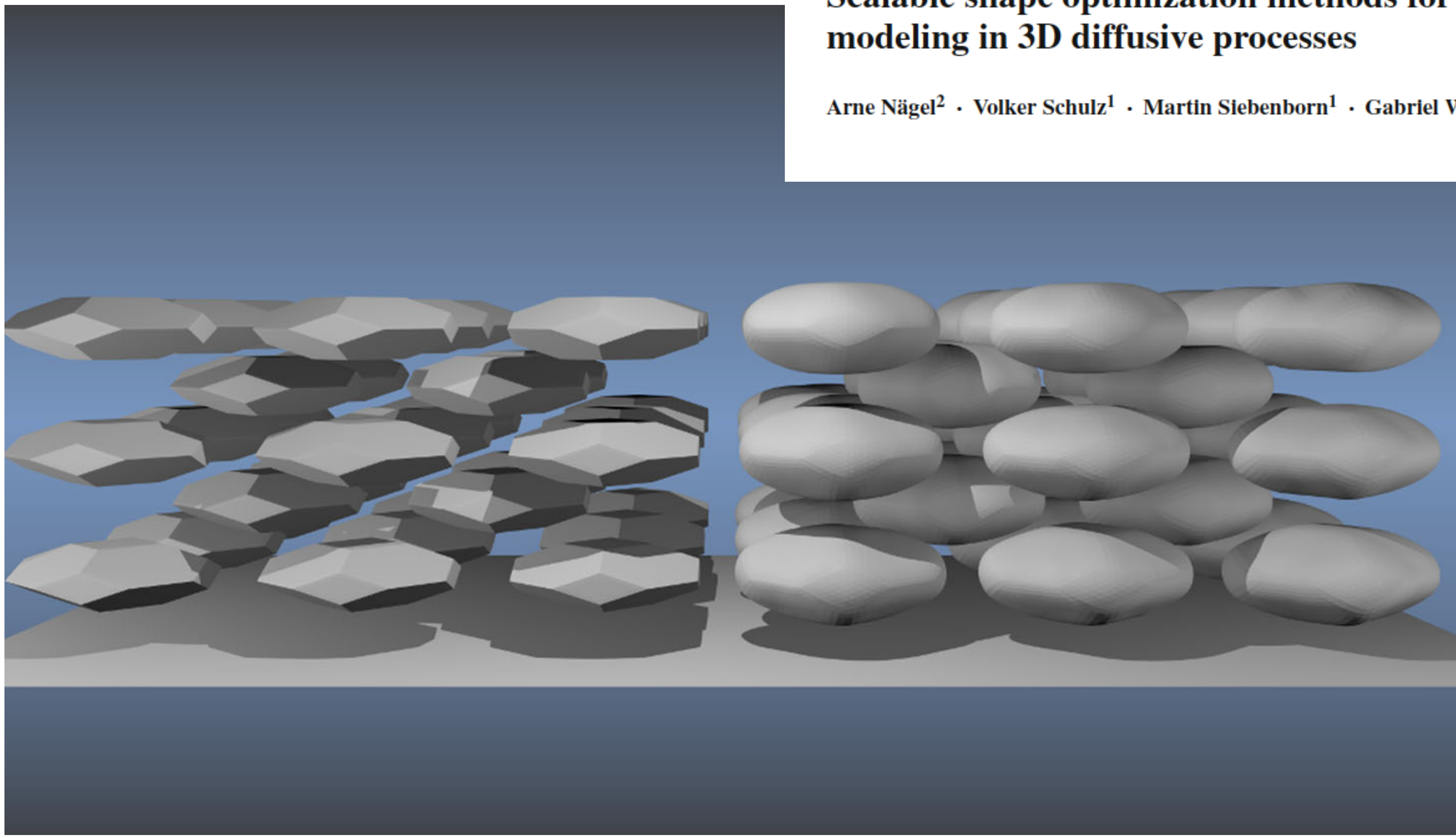


Optimization as a Tool for Cell Reconstruction:

Comput Visual Sci
DOI 10.1007/s00791-015-0248-9

Scalable shape optimization methods for structured inverse modeling in 3D diffusive processes

Arne Nägel[2] · Volker Schulz[1] · Martin Siebenborn[1] · Gabriel Wittum[2]

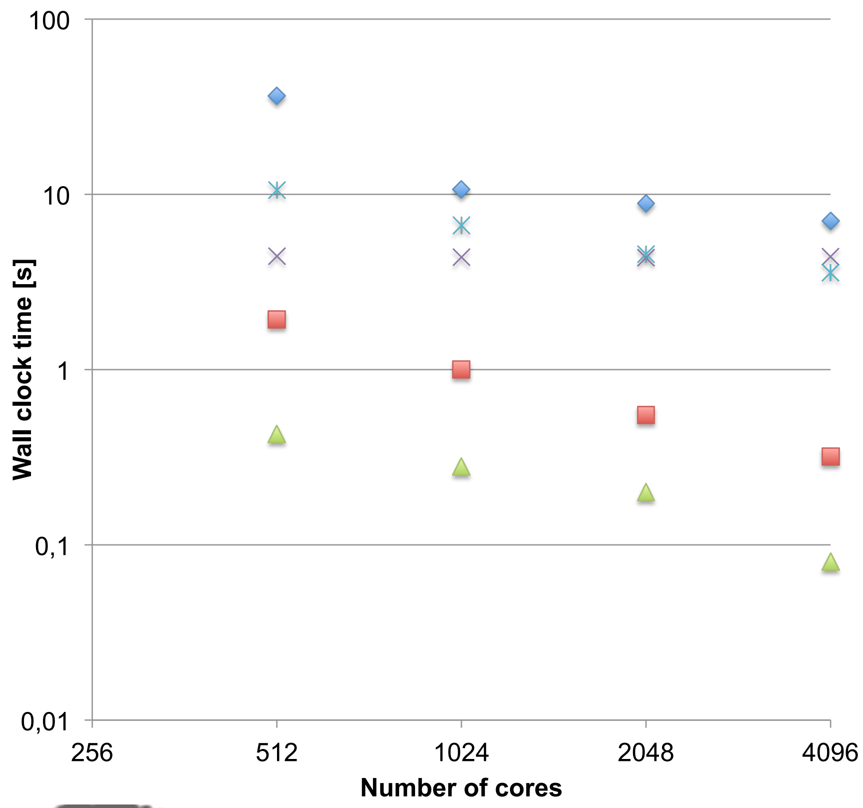


Optimize a shape w.r.t. an objective (imaging data)

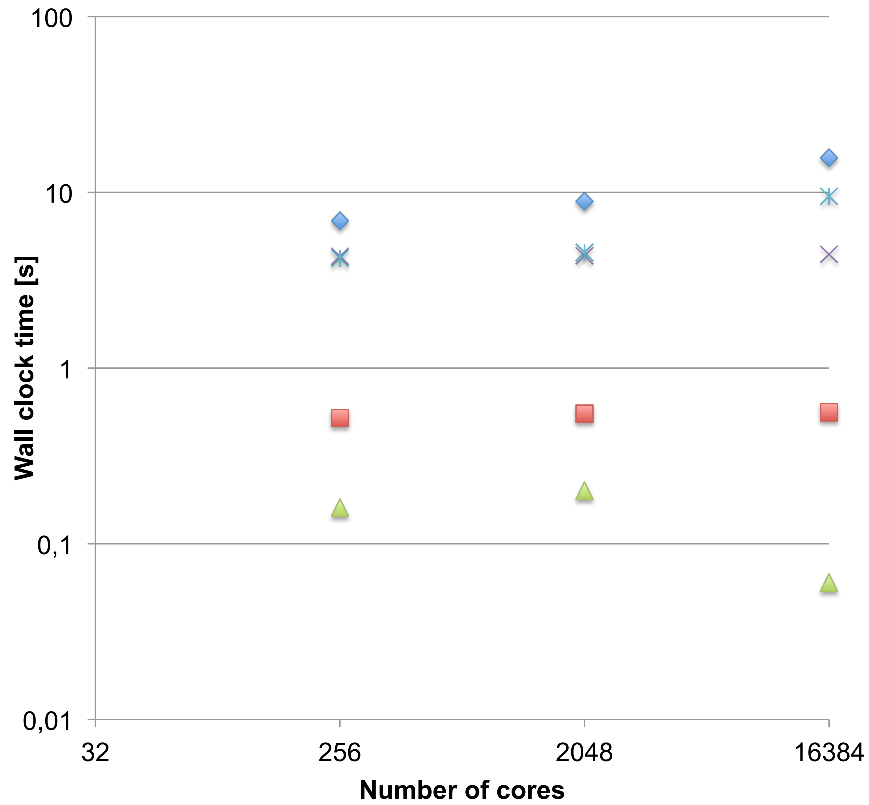
Scalability

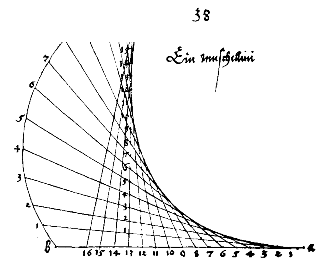
Parabolic problems (VOLUME)
Objective (VOLUME)
Gradient (SURFACE)
Laplace-Beltrami (SURFACE)
Deformation (VOLUME)

Strong Scalability
(constant work, more workers)

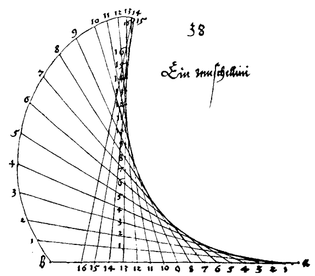


Weak Scalability
(more work, more workers)

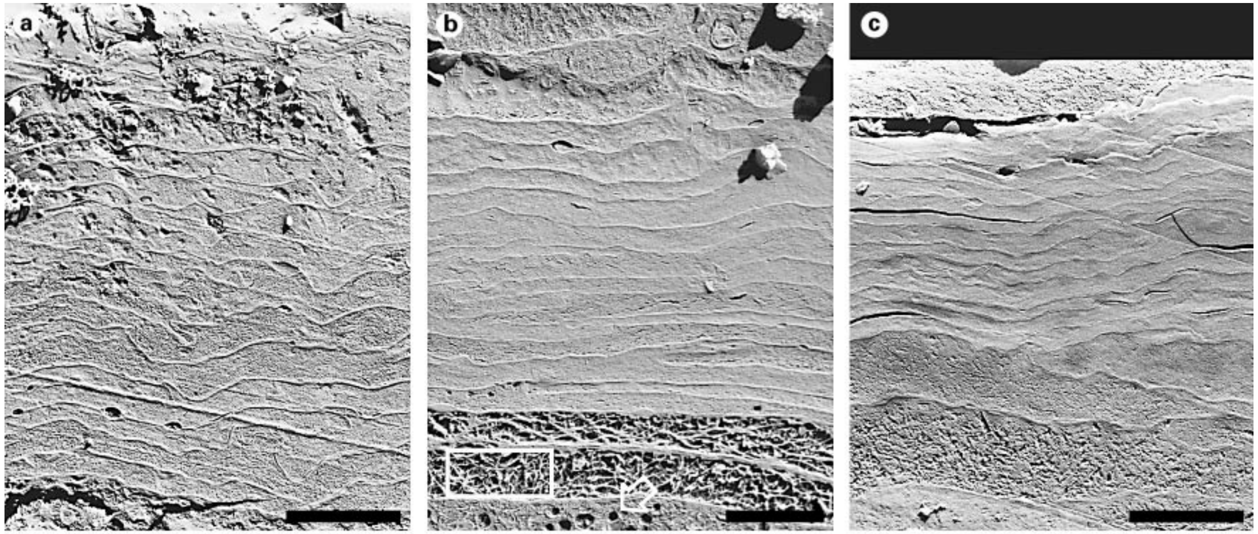




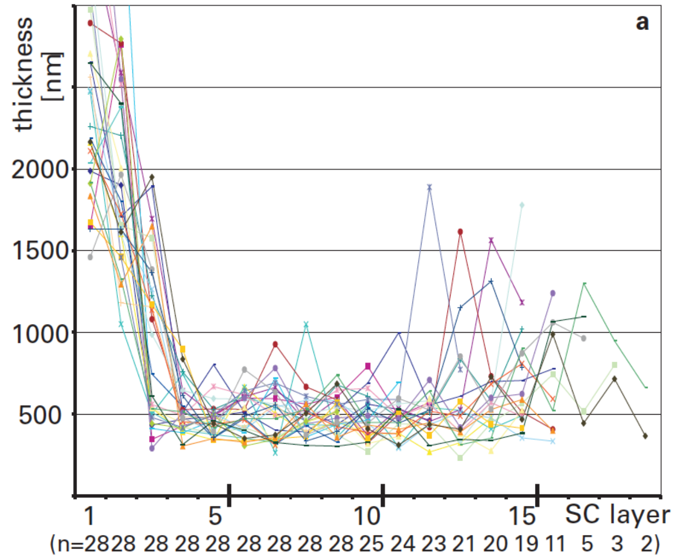
Mechanical Properties and Swelling

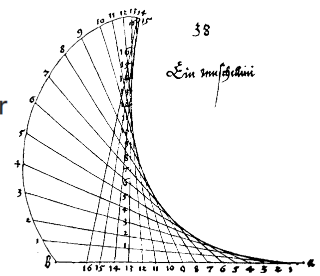


Motivation: Swelling



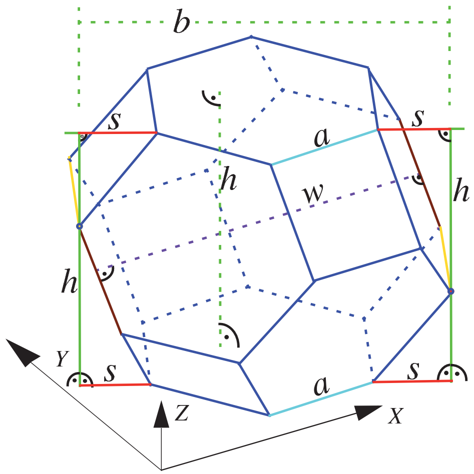
T. Richter et al,
Skin Pharmacology and
Physiology, 2004





Modelling swelling

A.) Static model



- Based on geometric considerations
- Omitting some functional details

B.) Dynamic Model:

Momentum of mixture : $\nabla[\sigma - pI] - F\Phi_f(z_0c_0 + \sum_i z_i c_i)\nabla\Psi = 0$

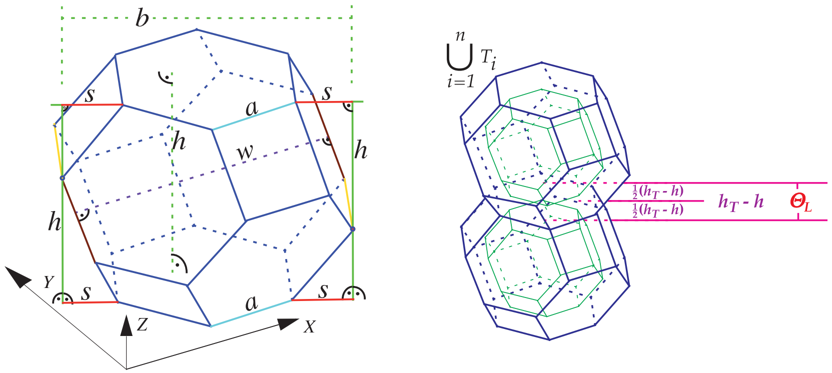
Mass of mixture : $\partial_t(\nabla \cdot \vec{u}) + \nabla \cdot [-\Phi_f \kappa(\nabla p + \frac{F}{RT}(\sum_i z_i c_i)\nabla\Psi)] = 0$

Mass of component i : $\partial_t(\Phi_f c_i) + \nabla \cdot [-\Phi_f D_i(\nabla c_i + c_i \frac{z_i F}{RT}\nabla\Psi)] = 0$

Charges : $\nabla \cdot [-\epsilon\epsilon_0 \nabla\Psi] = F(z_0c_0 + \sum_i z_i c_i)$

- Based considerations from physics
- Continuity of mass, momentum etc

Static Swelling:



We create a configuration $\mathscr{C}$= (C,L) from $\mathscr{C}_0$= (C_0,L_0) as follows

1. The corneocyte volume decreases/increases by α:

$$V(C) = \alpha V(C_0)$$

2. The volume of the lipid bilayer remains constant:

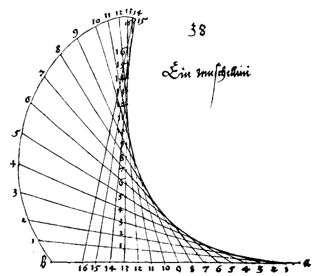
$$V(L) = V(L_0)$$

3. The area of the cornified envelope remains constant:

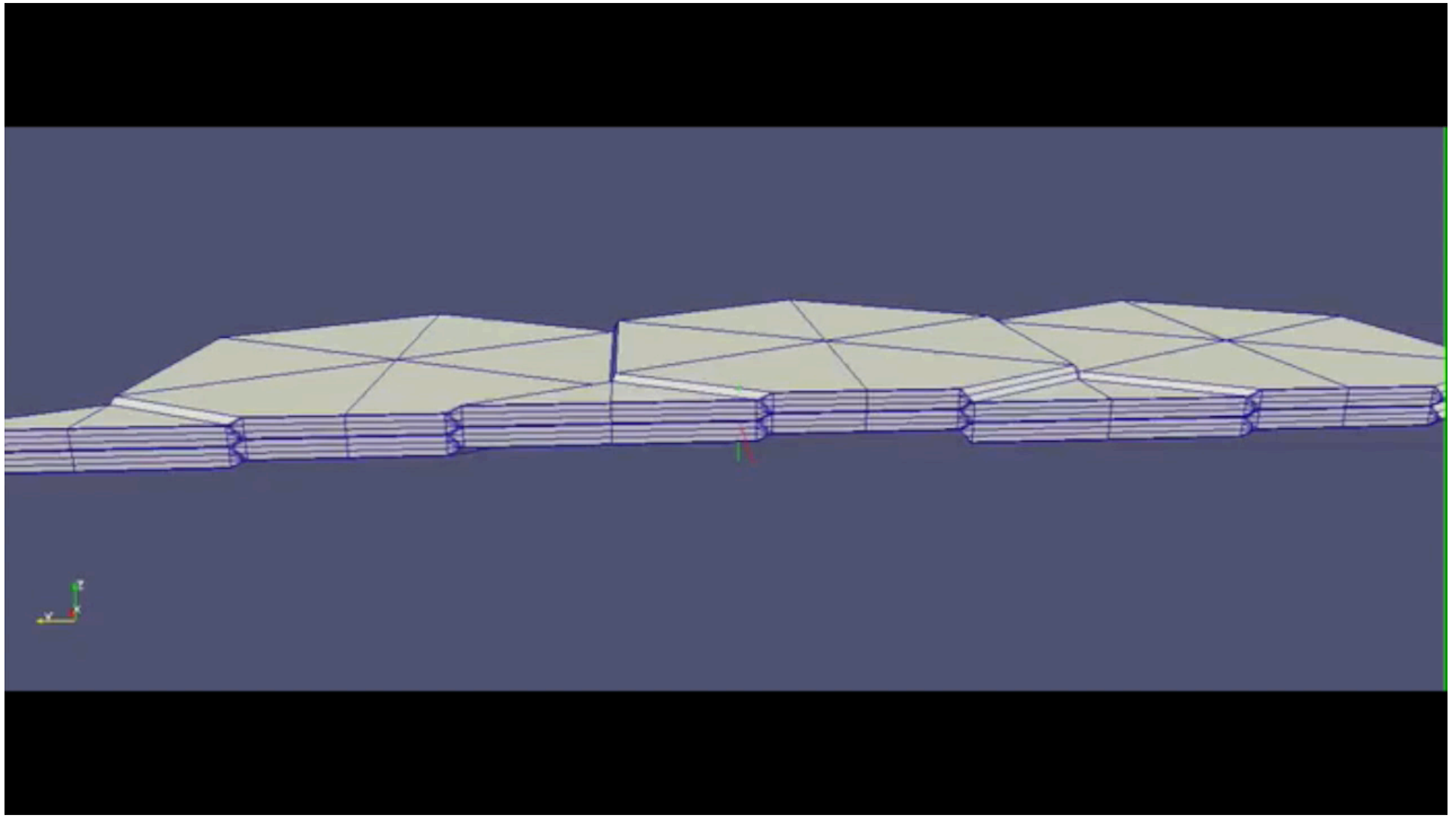
$$A(\partial L \cap \partial C) = A(\partial L_0 \cap \partial C_0)$$

4. We have an evolution:

$$\dot{\alpha}(t) = f(\alpha), \alpha(0) = 1$$

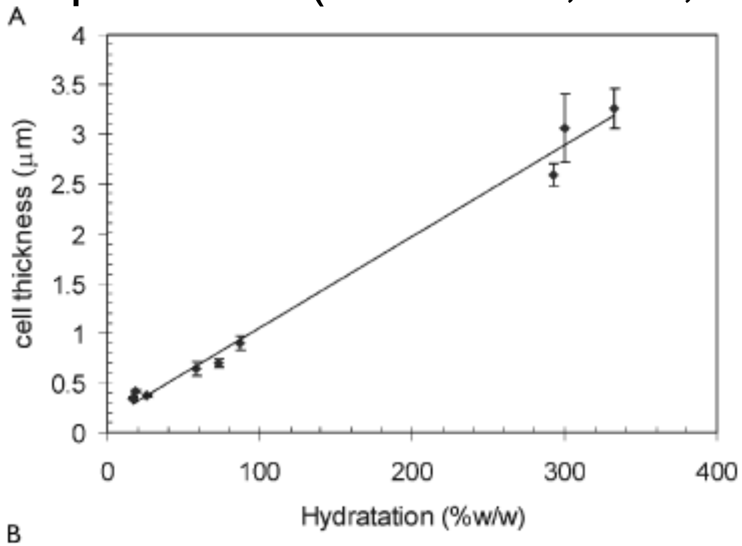


Static Swelling Results

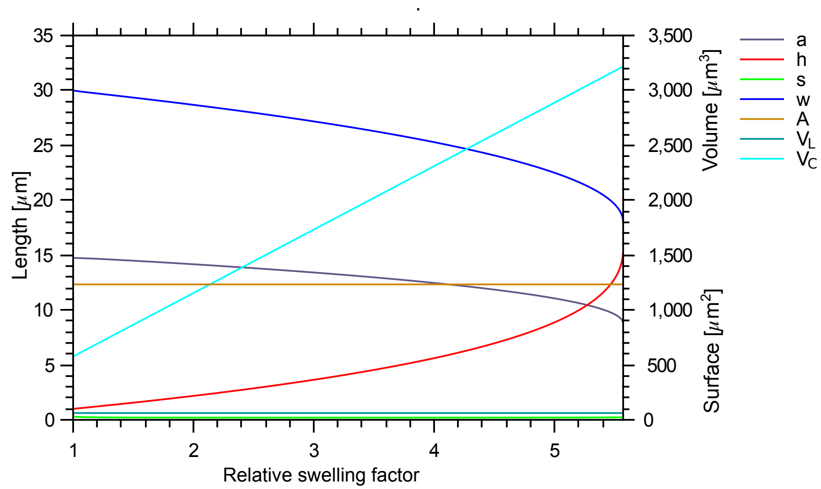


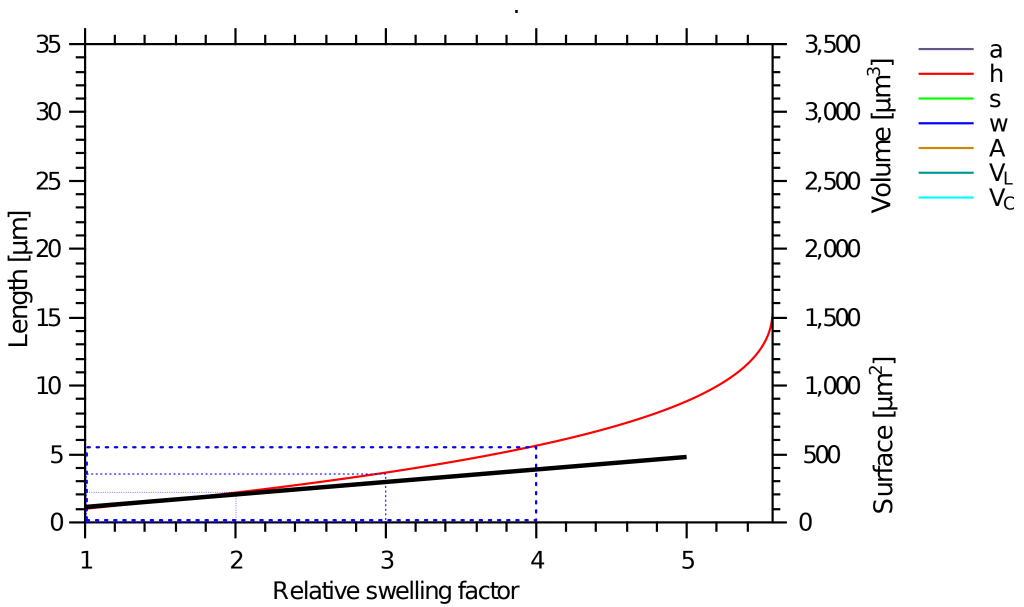
Static Swelling: Results

Experiment (Bouwstra, JID, 2003)

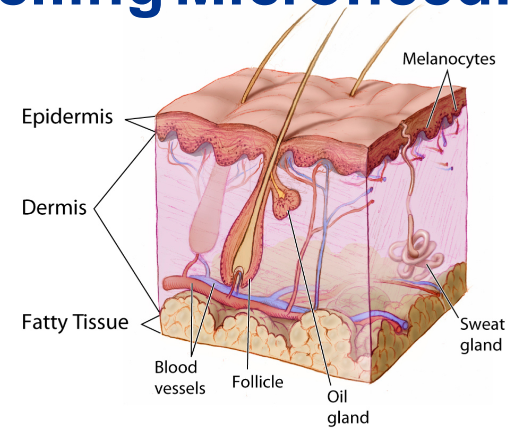


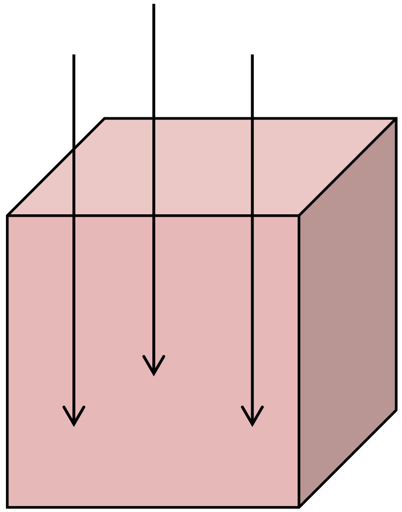
Simulation (Scherer, 2012)





Coupling Flow and Mechanics: Modelling Microneedle Injection





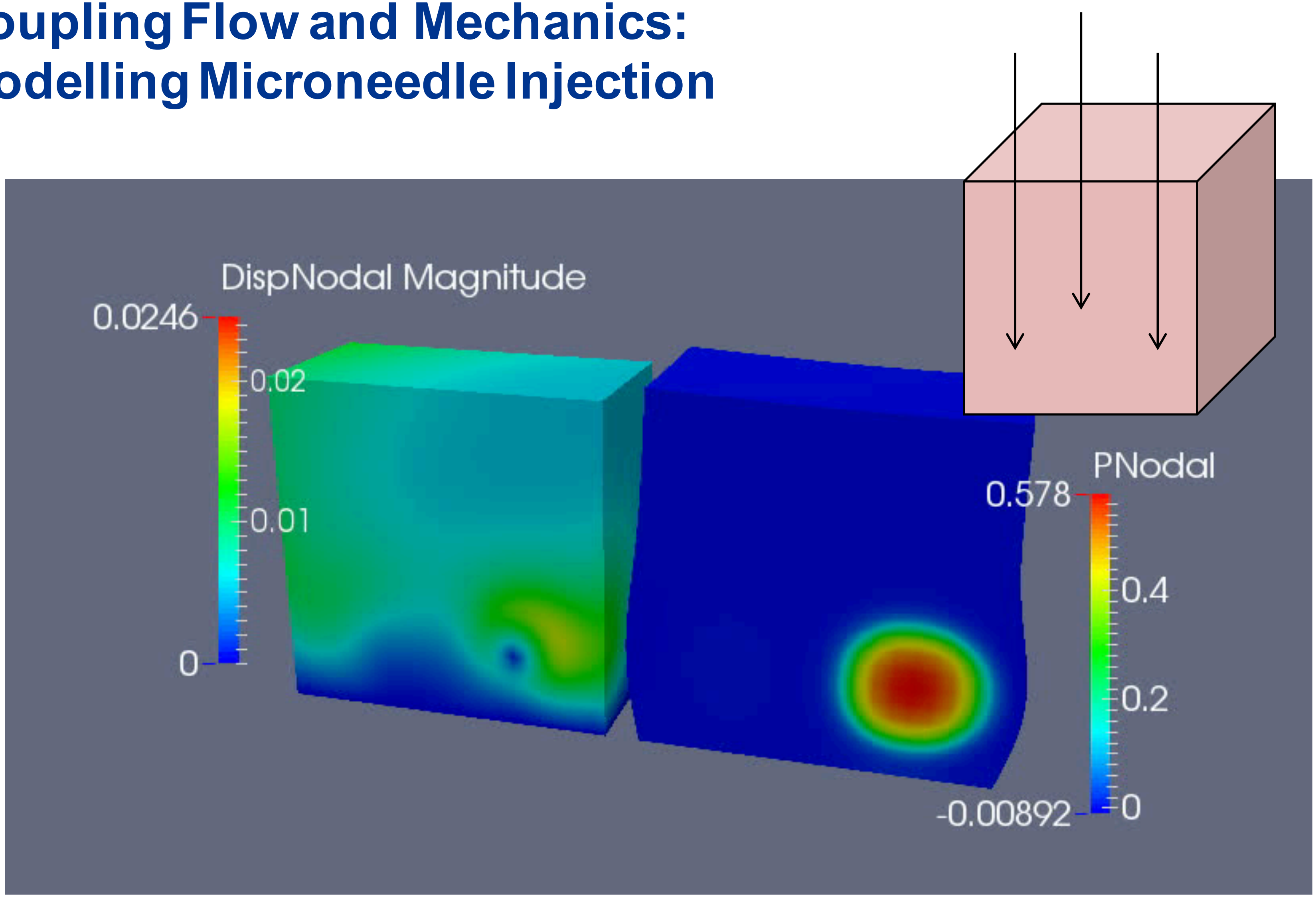
Deformation of a fluid filled medium is described by quasi-static Biot system (Biot, 1941) by displacement $\mathbf{u}$, hydrostatic pressure p :

$$\begin{aligned} \nabla \cdot [\boldsymbol{\sigma} - \alpha p \mathbf{I}] &= \mathbf{r} \\ (\Phi p + \alpha \nabla \cdot \mathbf{u})_t + \nabla \cdot [-\kappa \nabla p] &= q \end{aligned}$$

Mechanical stresses given by

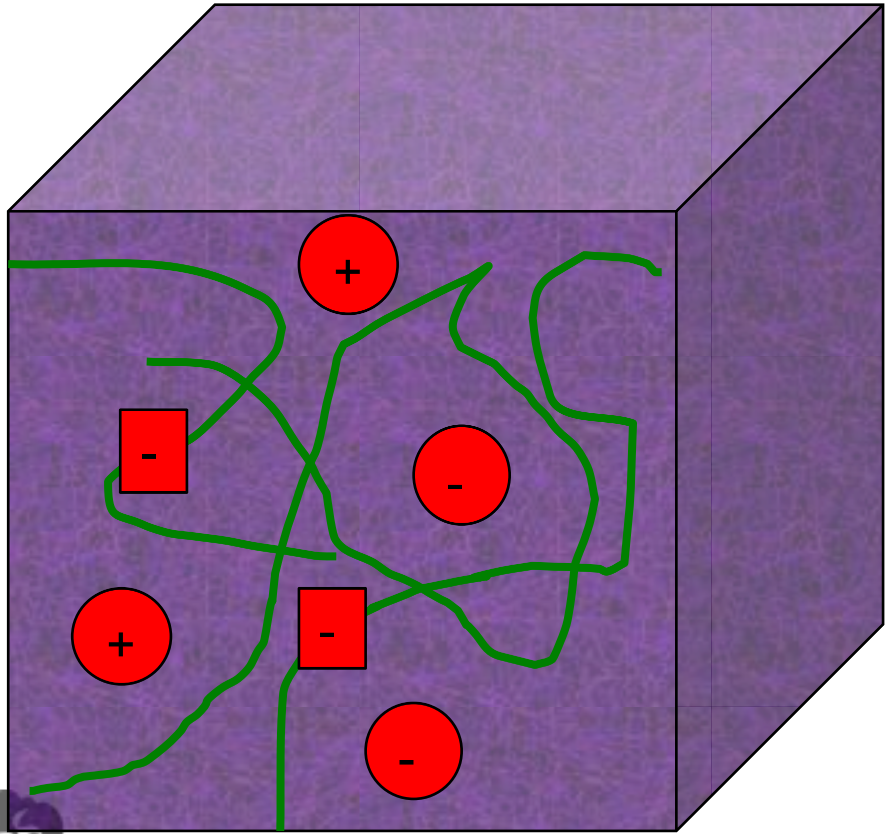
$$\boldsymbol{\sigma} := \lambda \, \mathrm{tr}\,(\boldsymbol{\epsilon}) \boldsymbol{I} + 2\mu \, \boldsymbol{\epsilon}, \qquad \epsilon_{ij} := \frac{1}{2}\left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}\right)$$

Coupling Flow and Mechanics: Modelling Microneedle Injection



Components of a hydrogel

Swelling Model for Hydrogels (e.g., Lai et al, 1991; Huyghe & Janssen, 1997, ...):



Two phases:

- Solid phase: w/ network of macromolecules (polymer)
- Fluid phase: w/ water and solvents (water+ions)

Hydrogel Swelling Model
(e.g., Lai et al, 1991; Huyghe & Janssen, 1997, ...):

Featuring 3+n phases:

Momentum of mixture : $$\nabla[\sigma - pI] - F\Phi_f(\quad \sum_i z_i c_i)\nabla\Psi = 0$$

Mass of mixture : $$\partial_t(\nabla \cdot \vec{u}) + \nabla \cdot [-\Phi_f \kappa(\nabla p + \frac{F}{RT}(\sum_i z_i c_i)\nabla\Psi)] = 0$$

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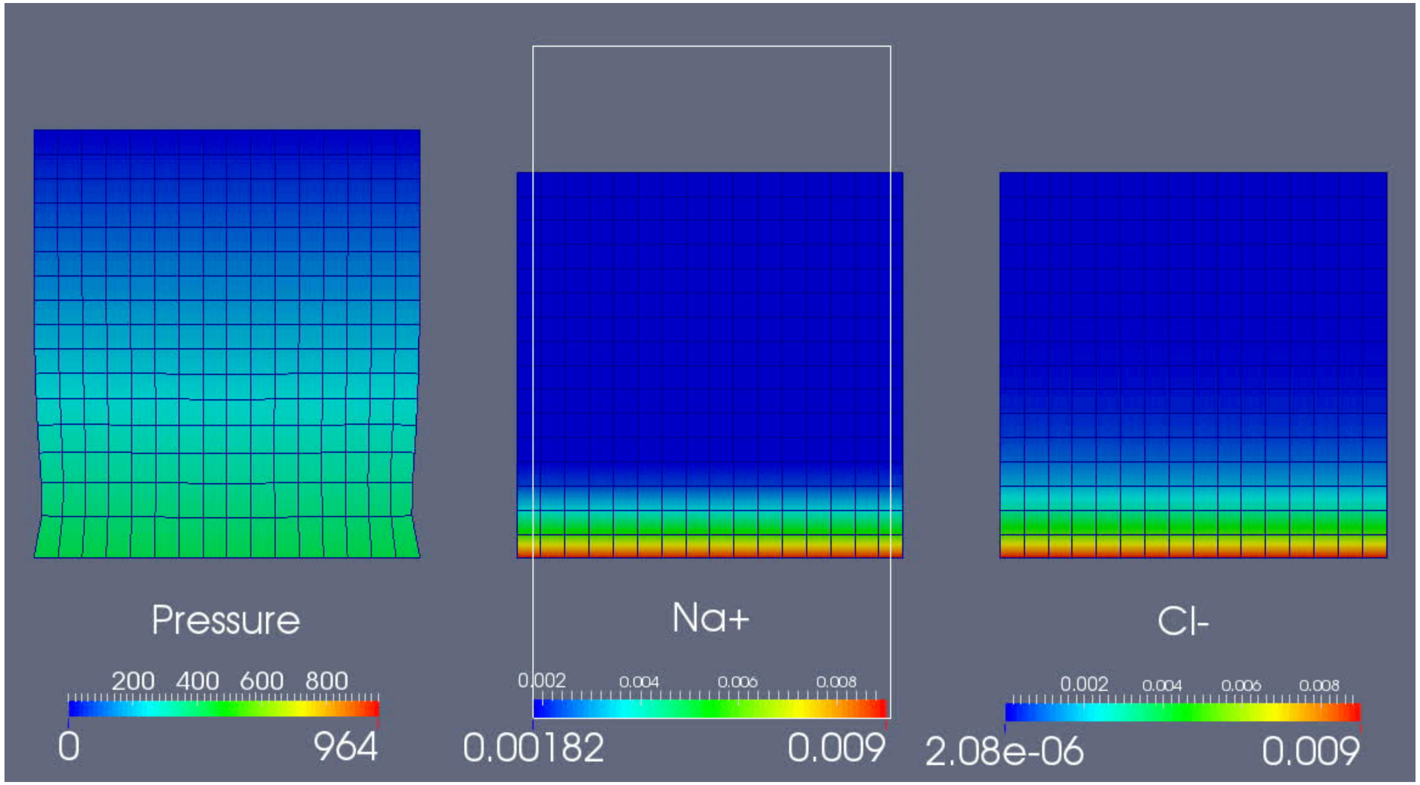
Charges : $$\nabla \cdot [-\epsilon\epsilon_0 \nabla\Psi] = F(z_0 c_0 + \sum_i z_i c_i)$$

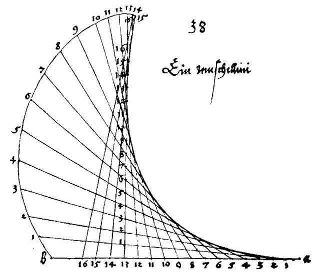
- Deformation of solid phase u
- Pressure of fluid phase p
- Fixed (positive) charges, n mobile (ionic) substances,
- Electric potential (w/ assumption of electro-neutrality)

Dynamic Swelling Model: Quantitative Results



➔Innermost cells show strongest swelling (e,g., Richter, 2004)

➔Welcome: Discussion on material properties (mechanics),driving forces, charge distribution, ...



Summary

- The skin is an organ with an inherent multi-scale structure
- A bottom up approach is feasible: Properties observed macroscopically likely to depend on microscopic features.
- Large number of cells can be addressed by supercomputing (only?). This drives development of new scalable algorithms.
- The work in the field advances both (i) our understanding of the skin as well as (ii) mathematical methods.

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