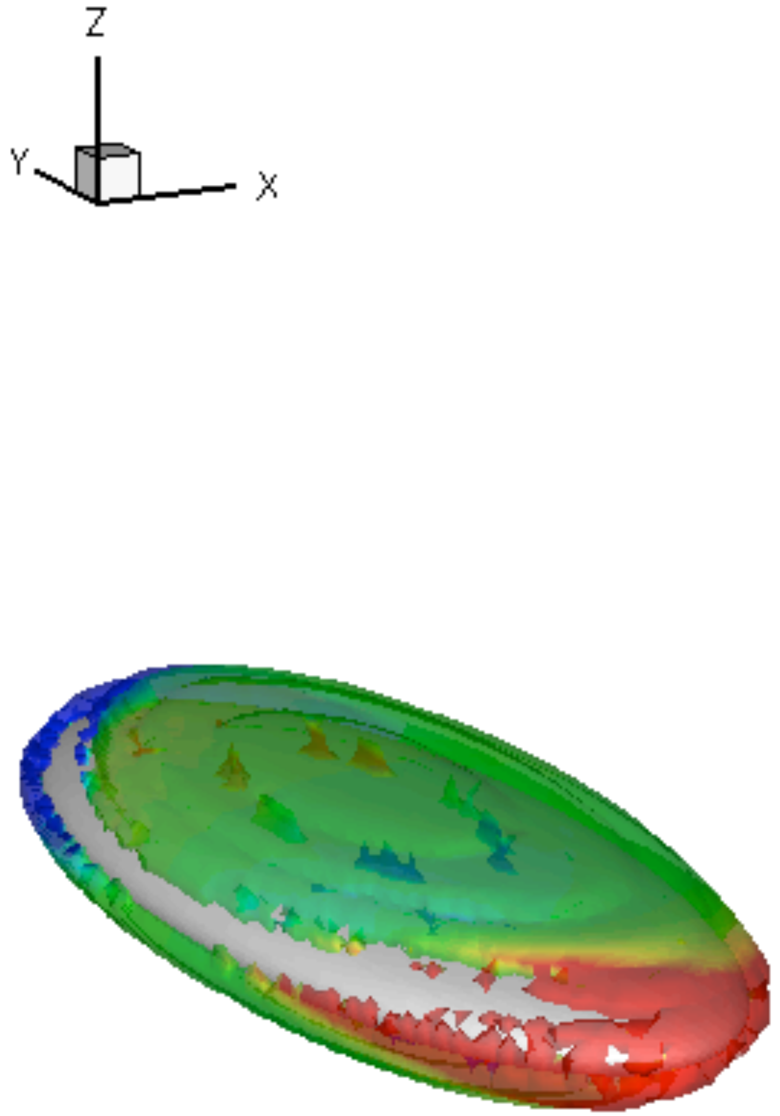
BOUNDARY CONDITIONS AND PARTICLES



BOUNDARY CONDITIONS AND PARTICLES

BC for Particle Methods

Boundary conditions and particle methods : a non-standard issue, because particles make sense only as a collection of overlapping points.

A single particle on a boundary not enough to enforce a given boundary condition at that point.

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BC for Particle Methods

IMPORTANT to allow the flow to :

- leave the computational box without non-physical artifacts (numerical issue)
- inject material in computational box
- generate vorticity and to impart forces at interfaces/solid boundaries (fluid-structure interaction, physical and numerical issue)

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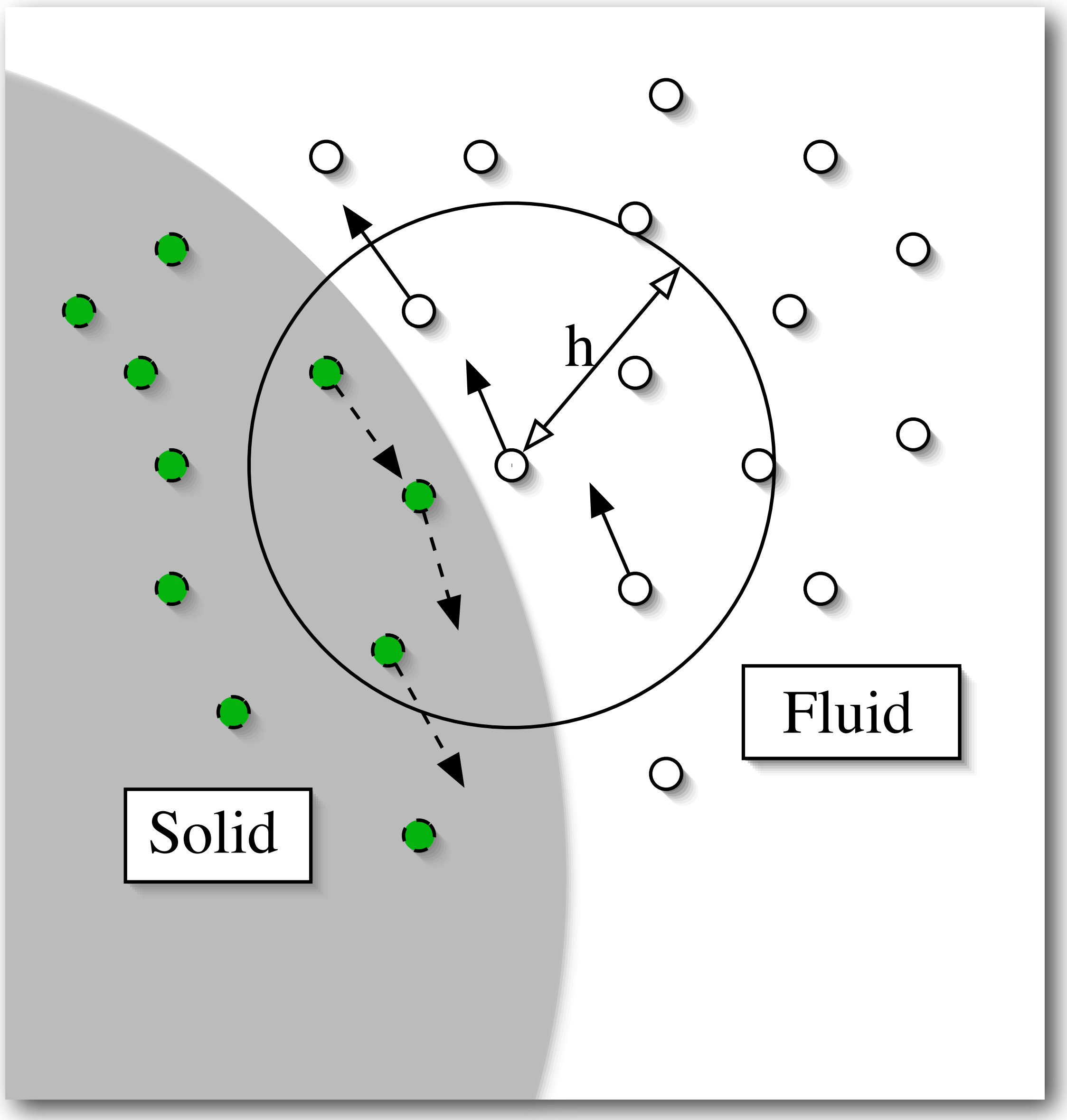
BCs using Ghost Particles

SPH methods often use the concept of ghost particles to overcome this difficulty.

Example where one wants to enforce zero flow at the boundary by using ghost particles :



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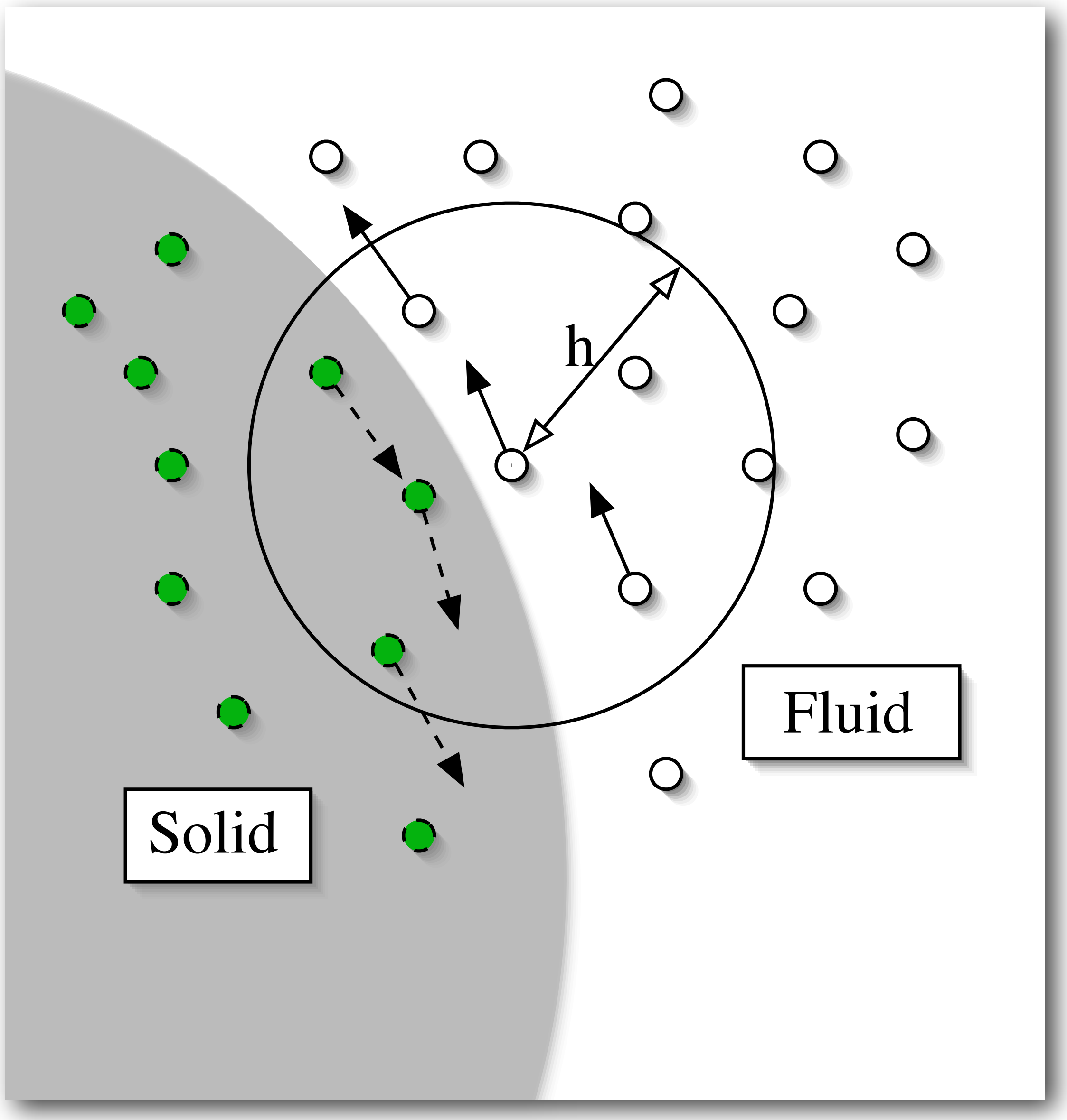

DIFFICULTY: accurate definitions of ghost particles need local mappings around interface onto half-space geometries

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BCs for Vortex Methods

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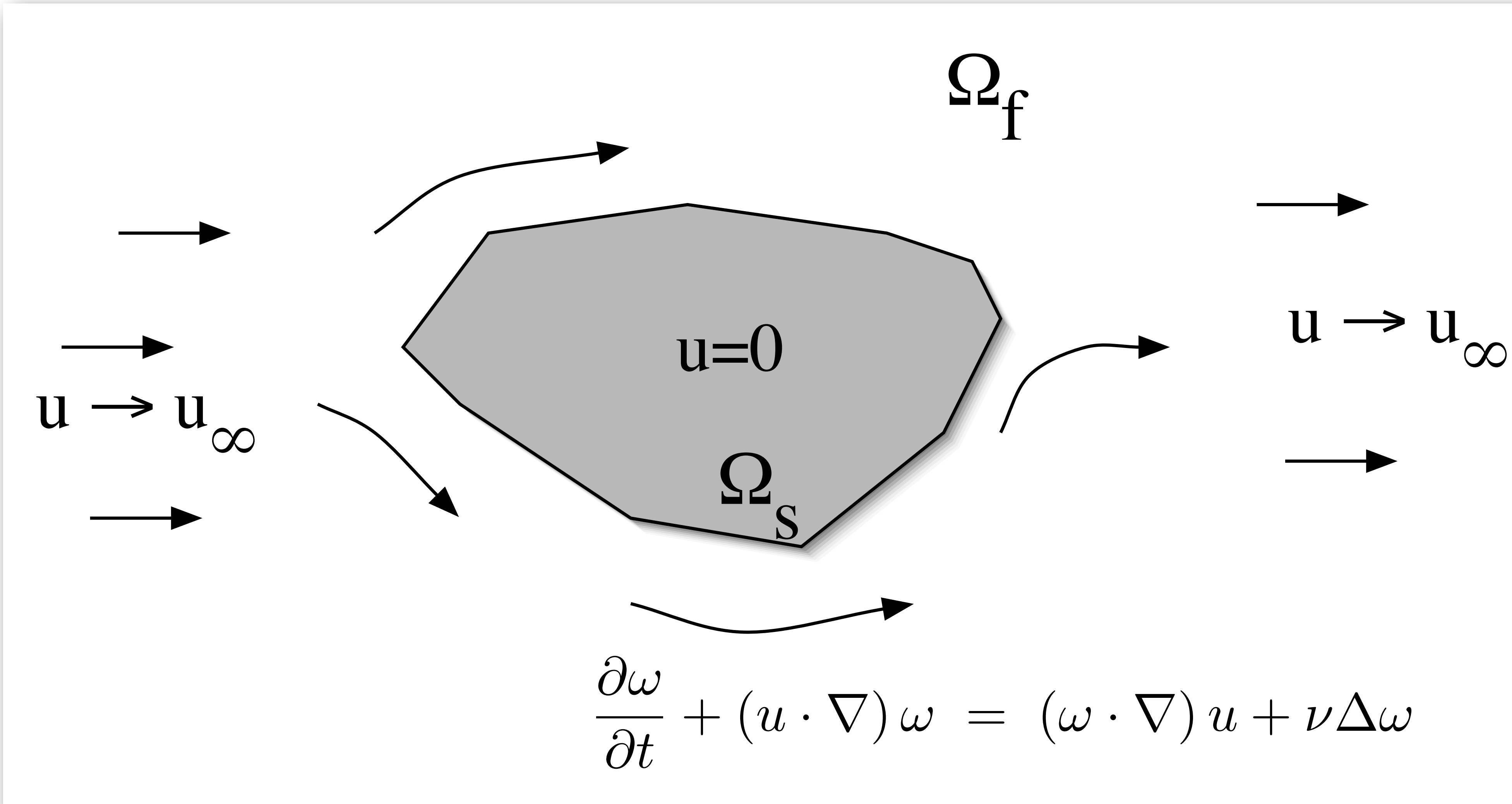
Like for all numerical methods, can deal with boundary conditions in two ways:

- using body-fitted grids (the boundary is made of specific points of a given grid used to solve for the flow)
- seeing the boundary as an immersed boundary

Vorticity BCs for No-slip Incompressible Flows



Boundary conditions appear at two levels:

- KINEMATICS : velocity from vorticity : div **u** = 0, curl **u** = ω in Ω and **u.n** = 0 on ∂Ω (no-through condition)
- DYNAMICS : advection-diffusion equation for vorticity :

$$\omega_t + (\mathbf{u} \cdot \nabla)\omega = (\omega \cdot \nabla)\mathbf{u} + \nu \Delta \omega$$ in Ω , ω = ? on ∂Ω

Kinematic Boundary Condition

Classical way to deal with the first boundary condition ($\mathbf{u}.\mathbf{n} = 0$ on $\partial\Omega$) is to look for a decomposition of the velocity field into a rotational and a potential part:

$$\mathbf{u} = \nabla \varphi + \nabla \times \psi$$

IN PRACTICE : compute first $\boldsymbol{\omega}$**,** without bothering about boundary conditions, then fix boundary conditions with φ

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Boundary Condition $\mathbf{u}.\mathbf{n} = 0$ gives $\partial\varphi/\partial n = -\partial(\nabla \times \psi)/\partial n$ on $\partial\Omega$

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div **u** =0 ⇒ $\Delta \varphi = 0$ in Ω

$\nabla \times \mathbf{u} = \omega \Rightarrow \Delta \psi = \omega$, div $\psi = 0$ in Ω.

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In a grid-free vortex method, this results in :

$$\mathbf{u}(\mathbf{x}) = \int_{\Omega_f} \mathbf{K}(\mathbf{x}-\mathbf{y})\boldsymbol{\omega}(\mathbf{y})\, d\mathbf{y} + \int_{\partial\Omega} \nabla G(\mathbf{x}-\mathbf{y}) q(\mathbf{y})\, d\mathbf{y}$$

where q is a potential to be determined from an integral equation on $\partial\Omega$

DYNAMICS - No-slip Condition

Next, enforce that *tangential* velocities are also zero at the boundary

traditional numerical recipe for vortex methods mimics the physical mechanism: vorticity produced at the boundary to prevent any slip velocity at the boundary

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FRACTIONAL STEP ALGORITHM [Chorin 1978]:

1) first substep without vorticity creation
2) compute resulting slip
3) remove this slip by injecting in the flow the appropriate sheet of vorticity

DYNAMICS - Lighthill's Algorithm

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[Koumoutsakos-Leonard 1992]

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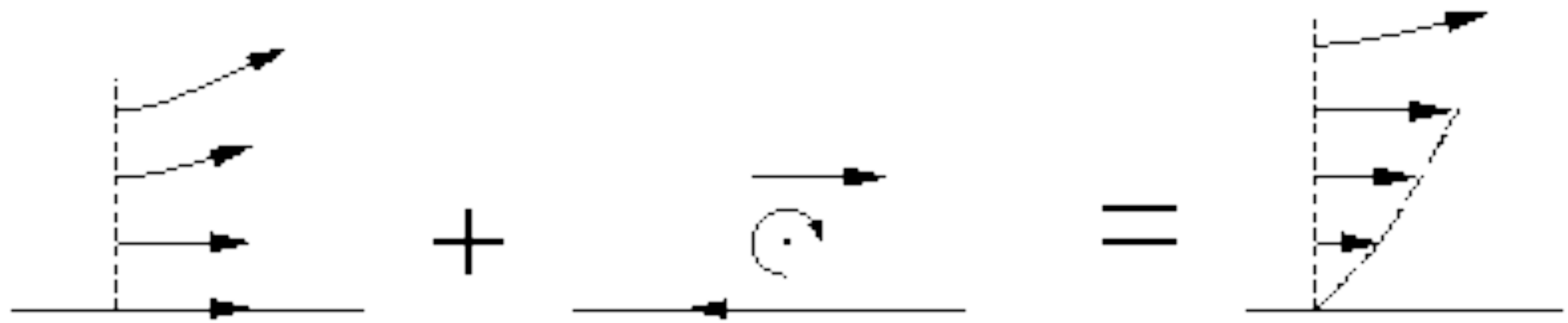


substep 2 substep 3

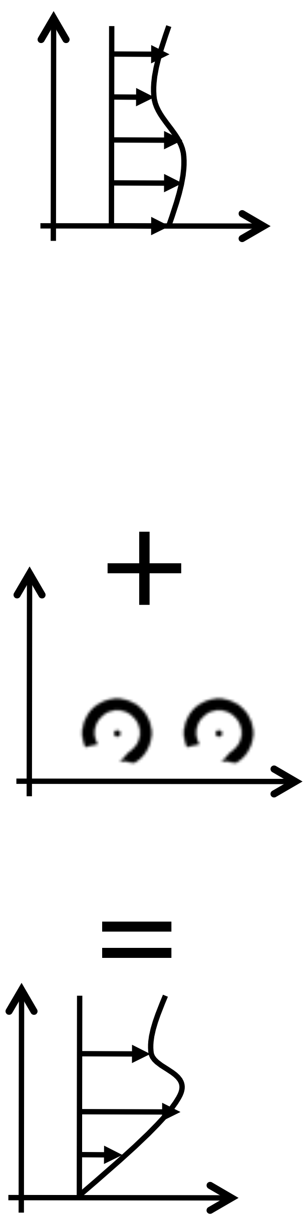
$$\frac{\partial \omega}{\partial t} - \nu \Delta \omega = 0 \qquad \Omega$$

$$\nu \frac{\partial \omega}{\partial n} = -\frac{1}{\Delta t} u \bullet \tau \qquad \partial\Omega$$

[Koumoutsakos-Leonard 1992]

3D Vorticity Flux BCs

In 3D, need boundary conditions for 3 vorticity components



After advection step computation of slip

Vorticity flux onto flow particles

$$\begin{cases} \dfrac{\partial \omega}{\partial t} - \nu \, \Delta\omega = 0 & \text{sur } \Omega \times]t_0, t_0 + \delta t[\\ \omega(t_0) = 0 & \text{sur } \Omega \\ \nu \dfrac{\partial \omega_z}{\partial n} = -\dfrac{\partial u_\theta}{\partial t} & \text{sur } \partial \Omega \times]t_0, t_0 + \delta t[\\ \nu \left(\dfrac{\partial \omega_\theta}{\partial n} + \kappa \omega_\theta \right) = -\dfrac{\partial u_z}{\partial t} & \text{sur } \partial \Omega \times]t_0, t_0 + \delta t[\\ \omega_r = 0 & \text{sur } \partial \Omega \times]t_0, t_0 + \delta t[\end{cases}$$

case of flow past a cylinder
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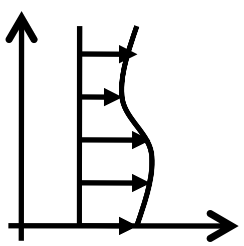

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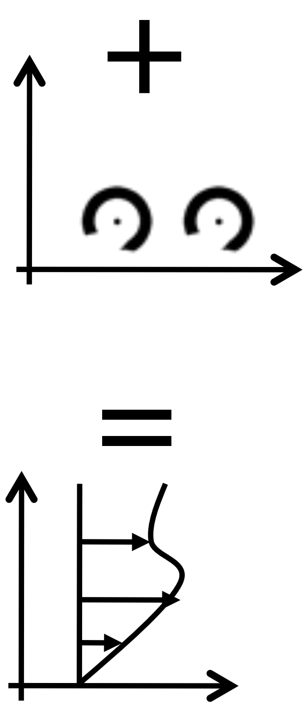

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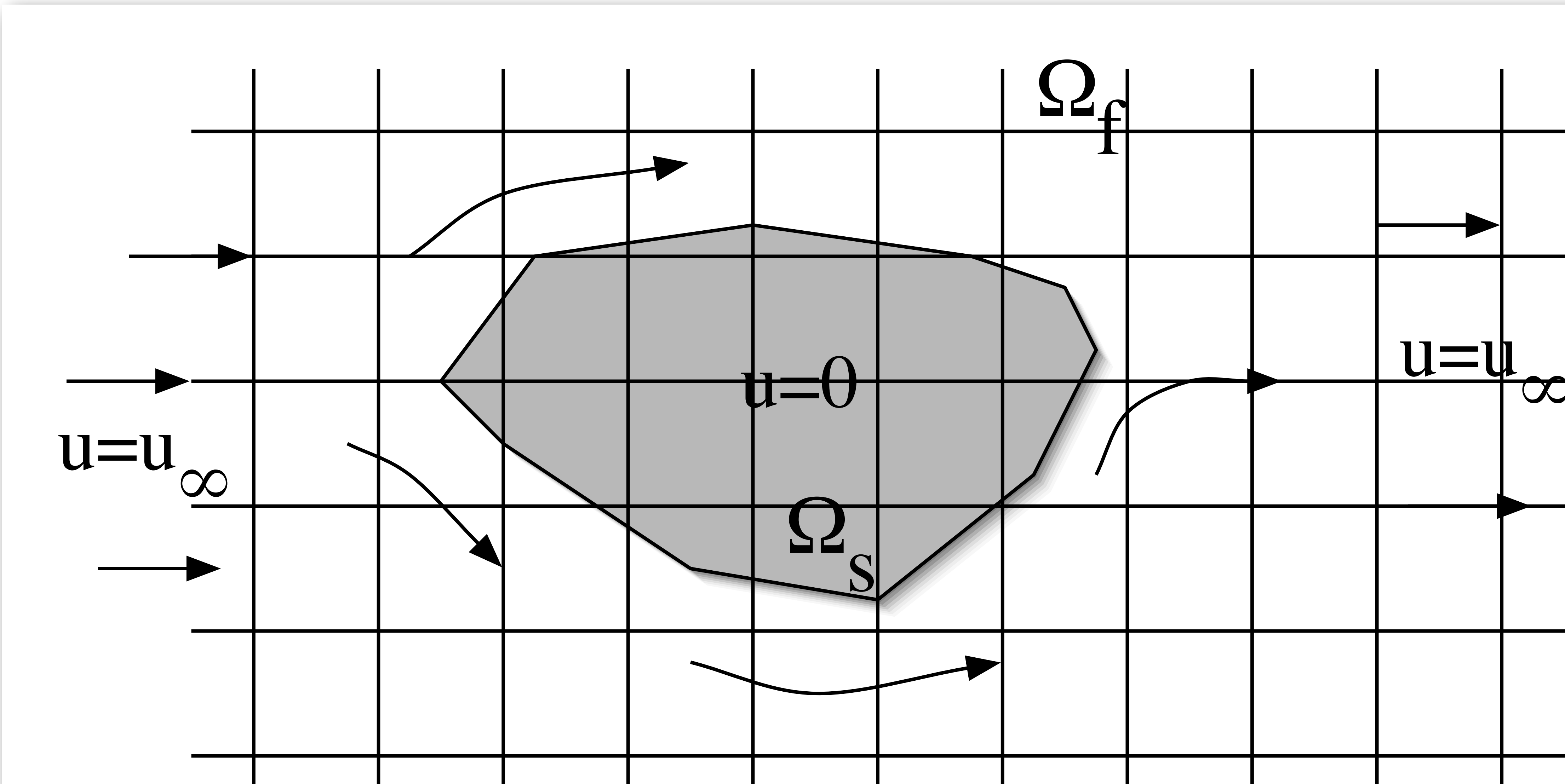
case of flow past a cylinder [Cottet-Poncet 2003]

difficulty: requires local coordinate system on the surface

IMMERSED BOUNDARIES

Obstacles, walls, objects .. are part of the flow



The case of a rigid body with prescribed velocity

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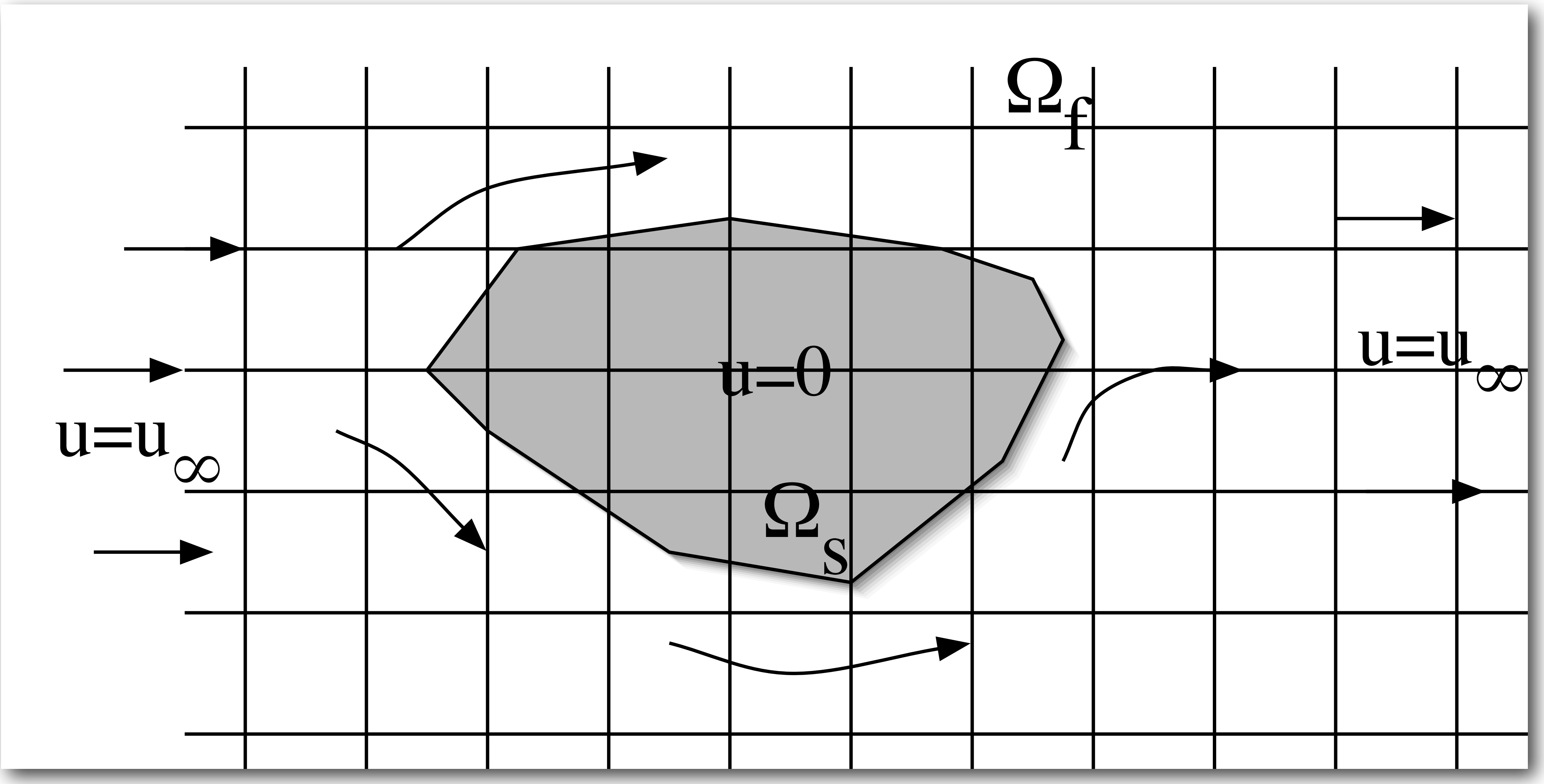

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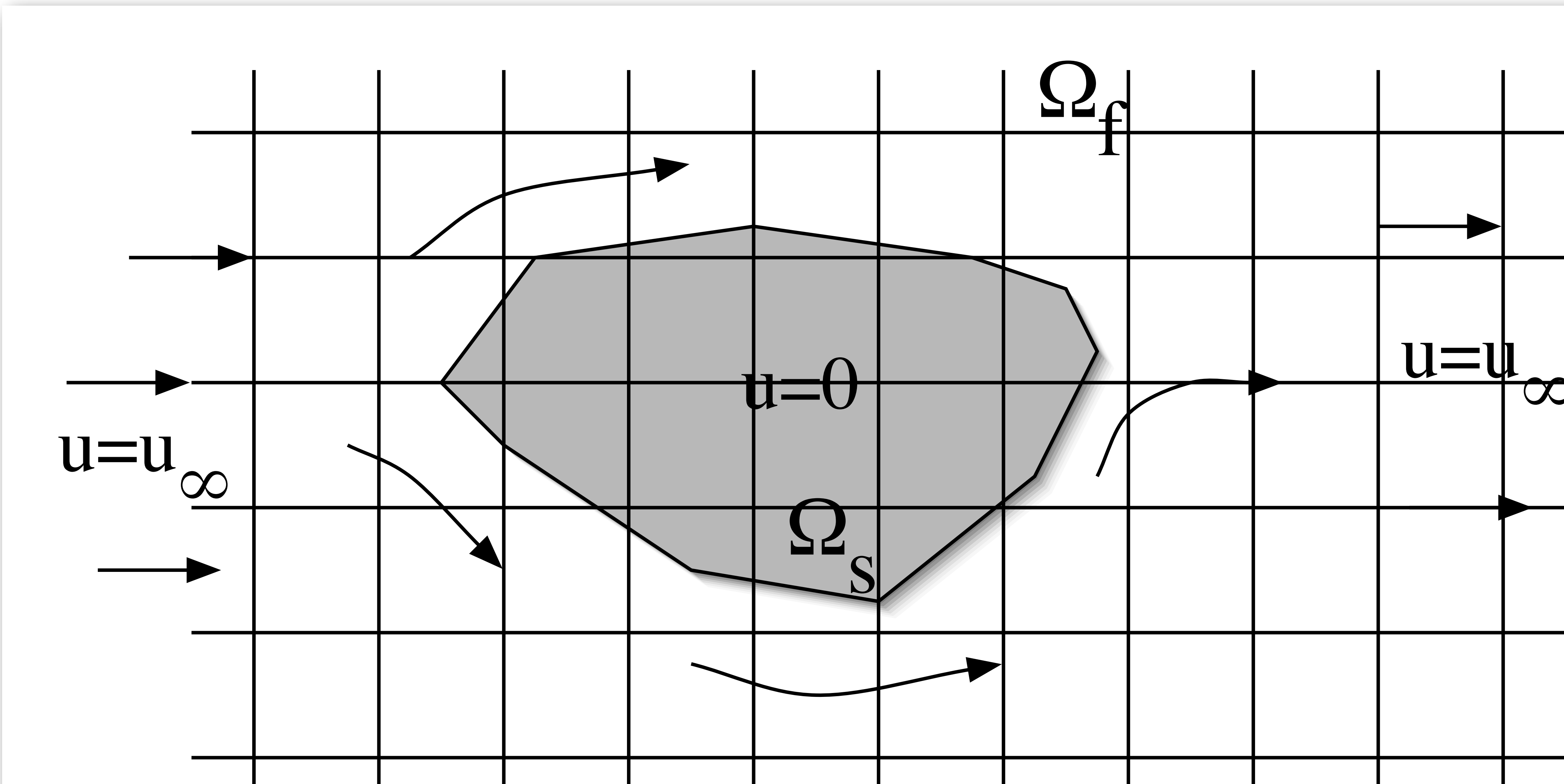
- elastic membrane



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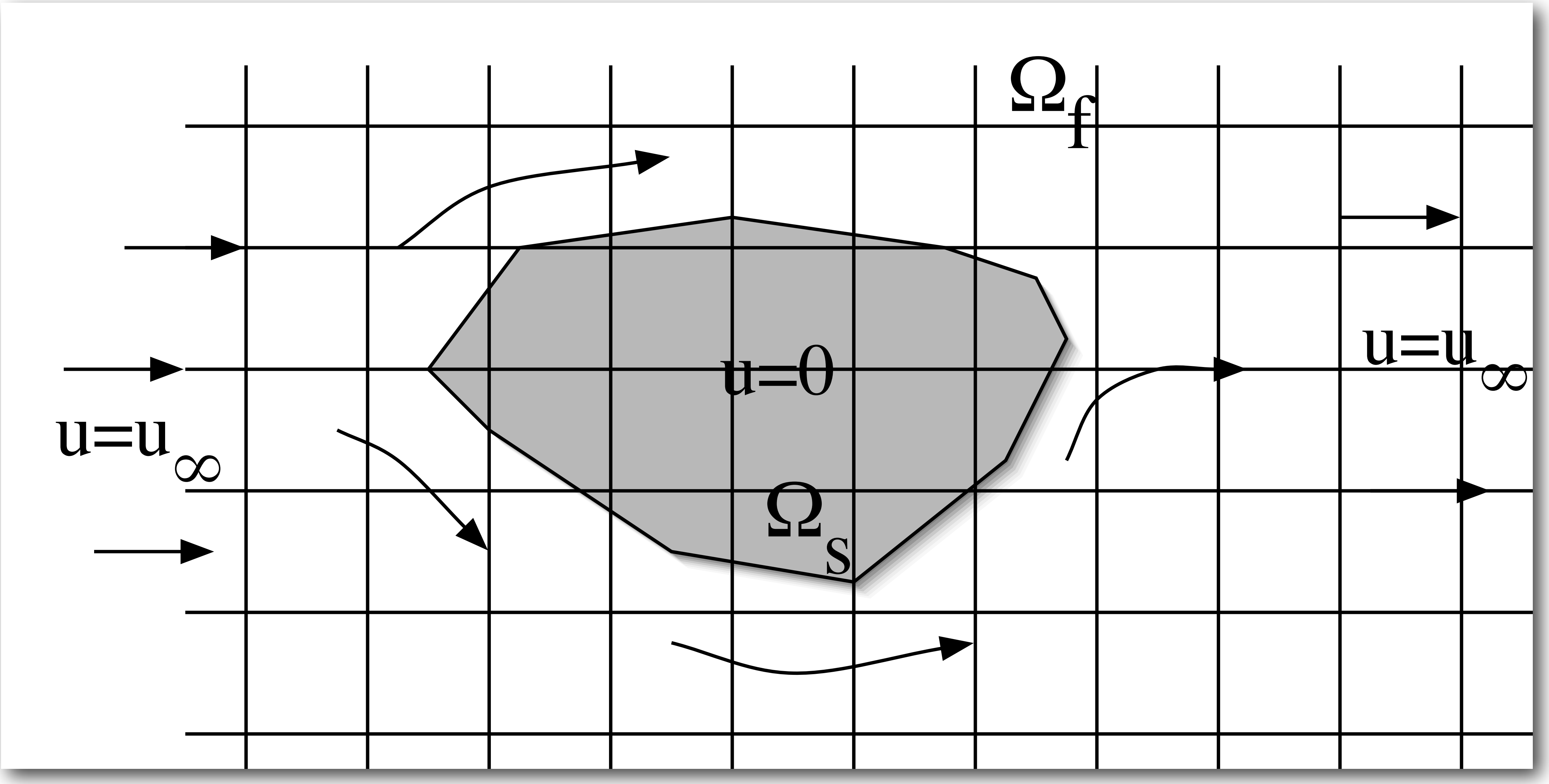

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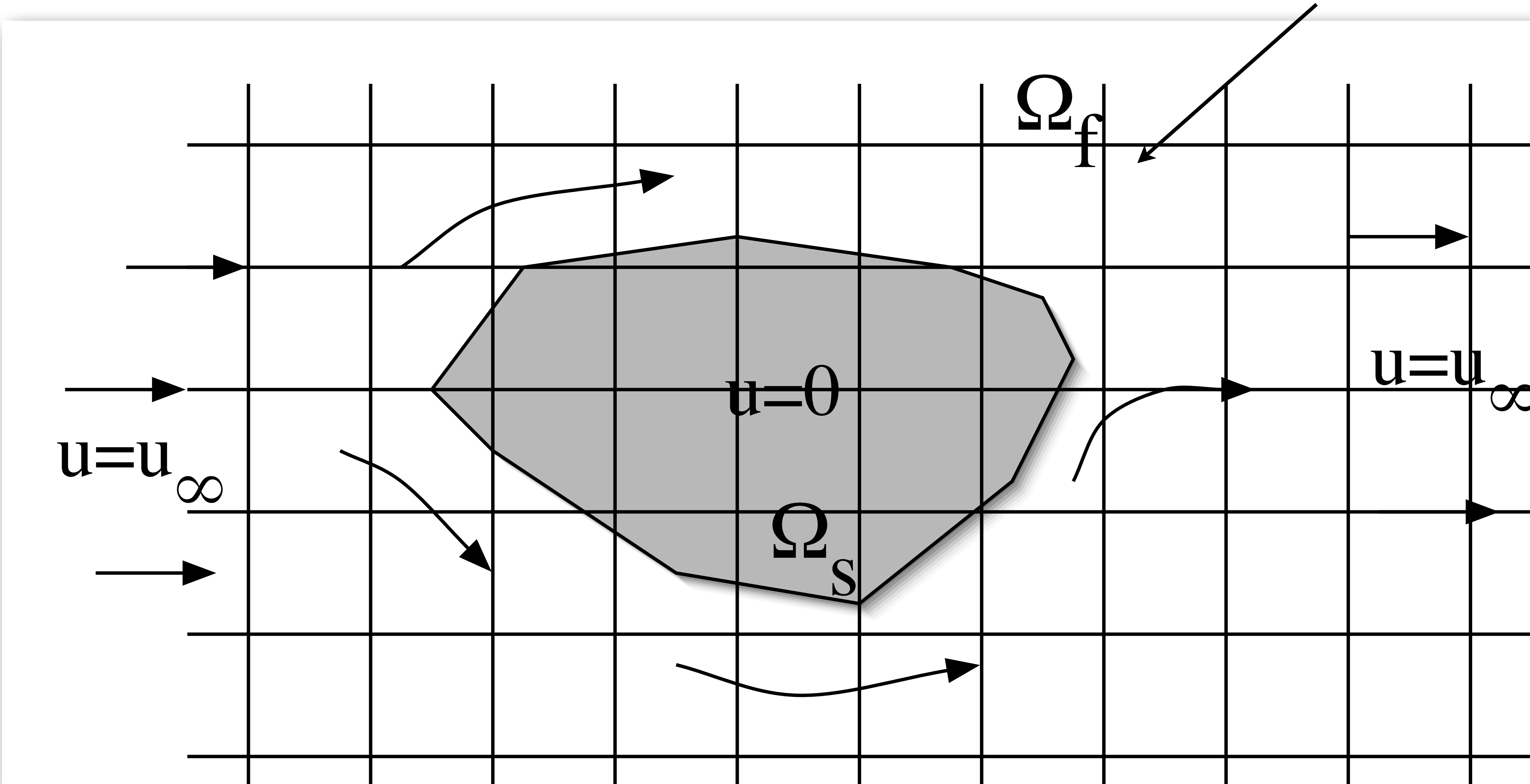
grid where particles are initialized/ created/remeshed



The case of a rigid body with prescribed velocity


BOUNDARIES + ALGORITHMS

COUPLING AND BOUNDARY CONDITIONS

Atomistic:

Molecular Dynamics

$$m\frac{d^2r}{dt^2} = F$$

+ Fc

m : mass r : position F : force

Boundary Conditions

Continuum:

Navier- Stokes Eqs.

$$\frac{D\mathbf{u}}{Dt} = -\frac{1}{\rho}\nabla P + \nu\nabla^2\mathbf{u}$$

$$\frac{D\rho}{Dt} = \rho\nabla\cdot\mathbf{u}$$

+ Fa

u : velocity, P : pressure, ρ : density, ν : viscocity

Boundary Conditions = Coupling

$$\rho \frac{D\mathbf{u}}{Dt} = \nabla \cdot \boldsymbol{\sigma} \; + f (\text{enforces b.c.})$$

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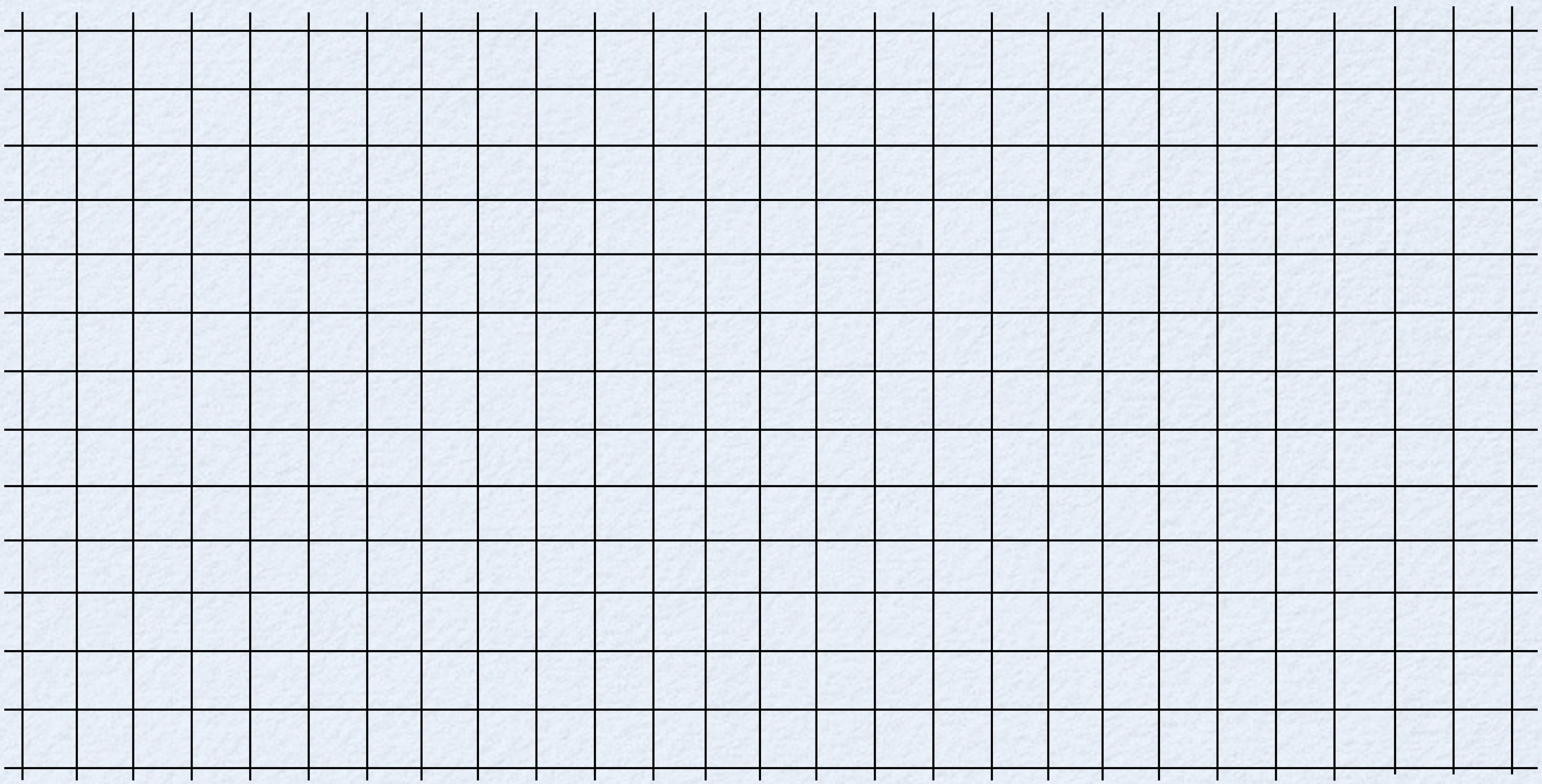

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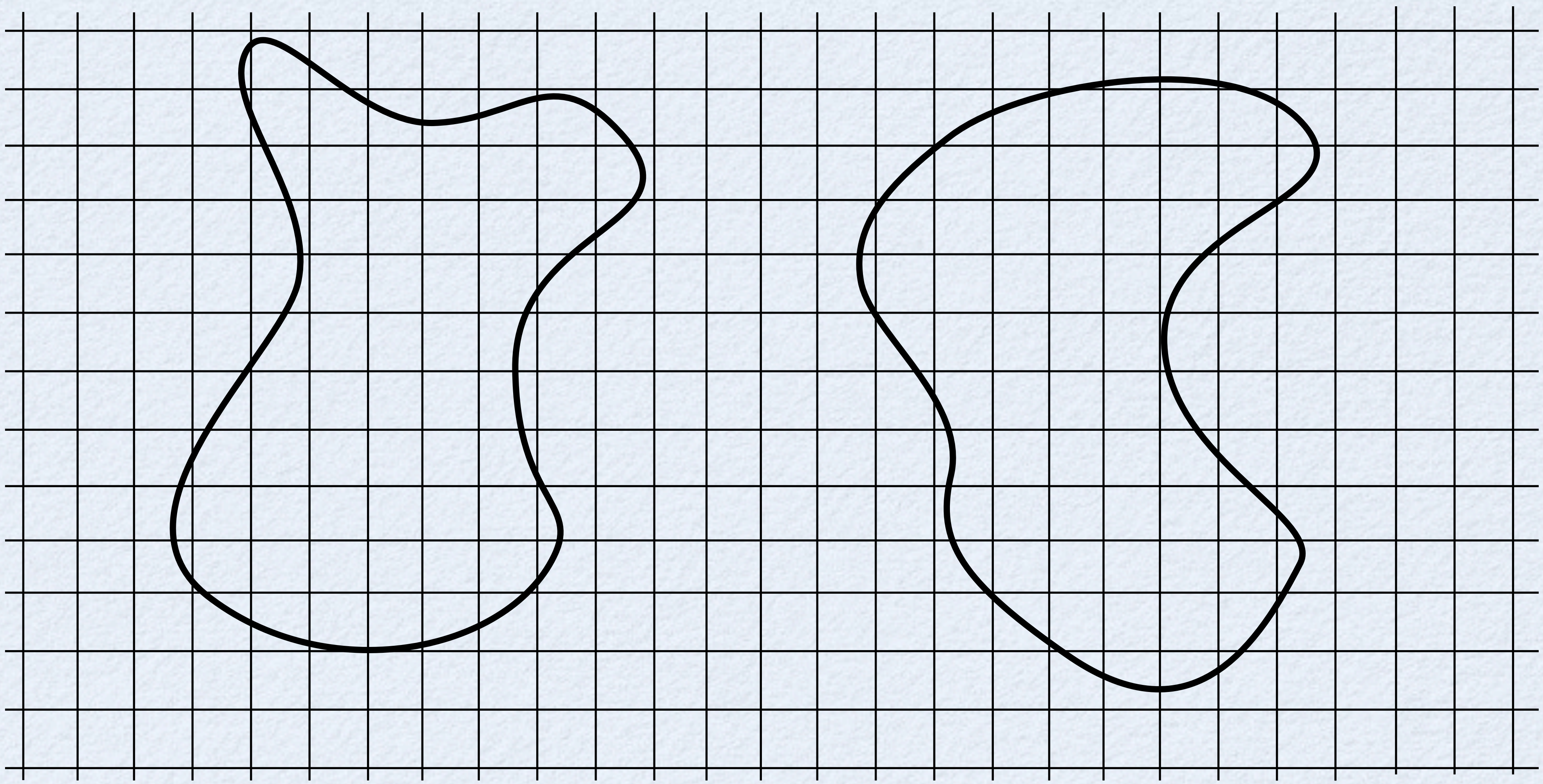

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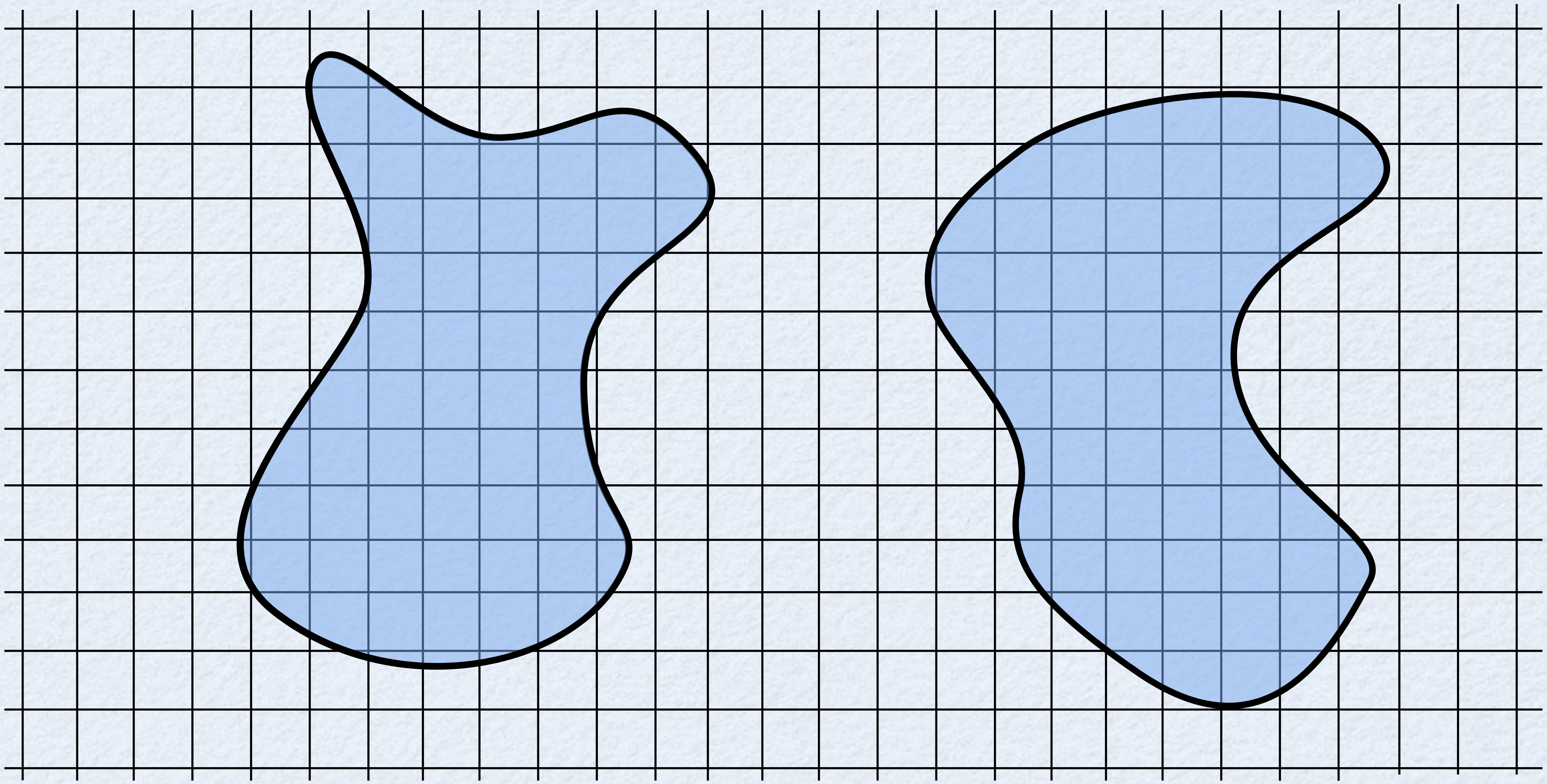

$$\rho \frac{D\mathbf{u}}{Dt} = \nabla \cdot \boldsymbol{\sigma} + f(\text{enforces b.c.})$$

Penalization Method: $f(\mathbf{x}) = \lambda \chi_S (\mathbf{u}_S - \mathbf{u})$

- **Enforce boundary velocity by a bodyforce f in Momentum Equation**

$$\rho \frac{Du}{Dt} = -\nabla p + \nabla . \tau + f$$

$$= f_{i,part} + f_{i,boundary}$$

I. IMMERSED BOUNDARY METHOD for SPH

- **Enforce boundary velocity by a bodyforce f in Momentum Equation**

$$\rho \frac{Du}{Dt} = -\nabla p + \nabla . \tau + f$$

- Approximate Material Derivative at time step i and solve for f

$$\rho_i \frac{u_{i+1} - u_i}{\Delta t} = -\nabla p_i + \nabla . \tau_i + f_i \Rightarrow f_i = \rho_i \frac{u_{i+1} - u_i}{\Delta t} - \left(-\nabla p_i + \nabla . \tau_i \right)$$

- Desired Velocity field on the boundary $u_{i+1} = u_{desired}$

$$u_{i+1} = u_{desired} \Rightarrow f_i = \rho_i \frac{u_{desired} - u_i}{\Delta t} - \left(-\nabla p_i + \nabla . \tau_i \right)$$

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Boundary Conditions : A Particle-Mesh Operation

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- **Compute part of forcing term on the particles**

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$$f_{i,boundary} = \rho_i \frac{u_{desired}}{\Delta t} + f_{i,part,interpolated}$$

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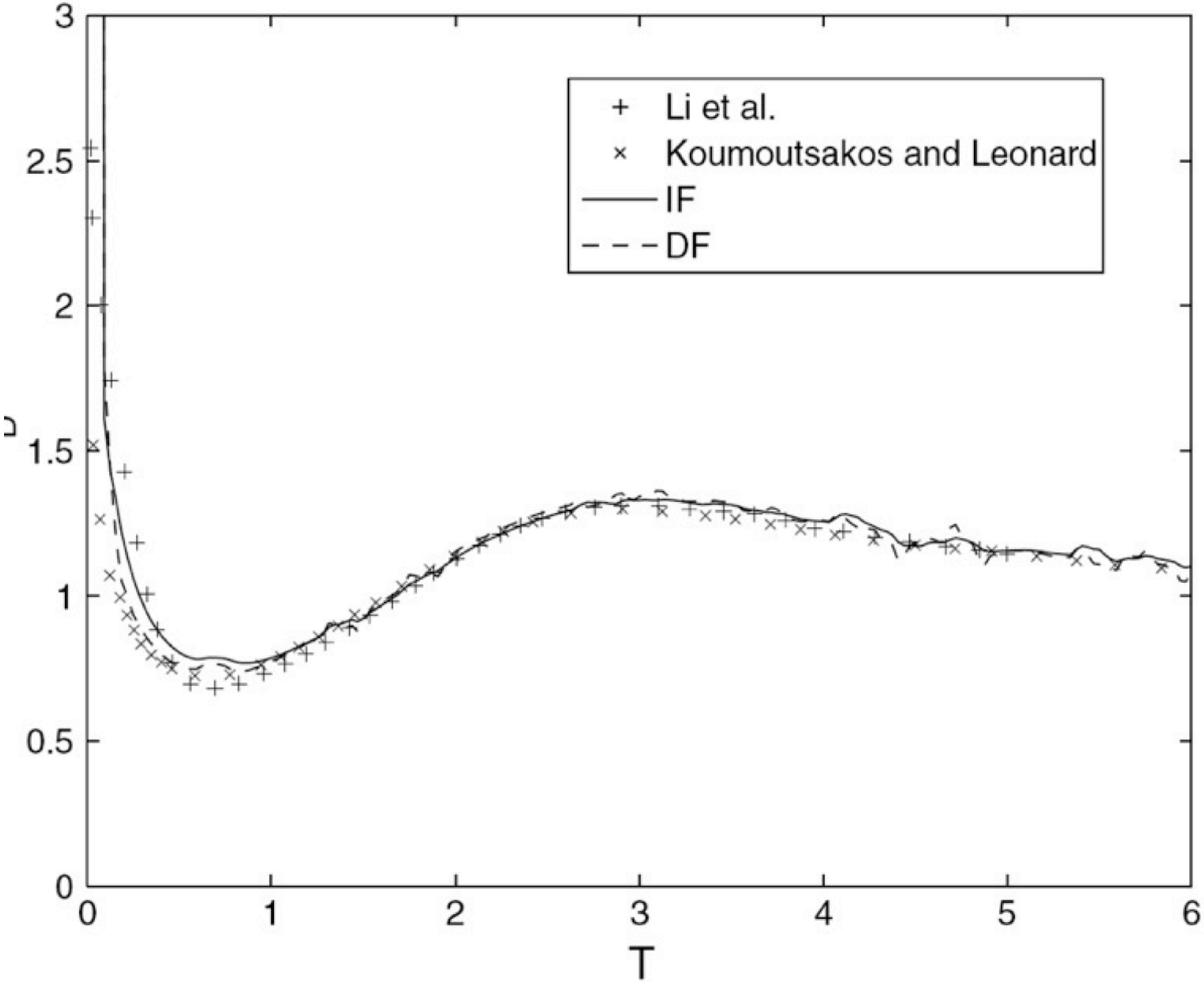
S. Hieber and PK., Immersed Boundary Method for SPH, J. Comp. Physics, 2008

A. Dupuis, P. Chatelain, and PK., Coupling lattice Boltzmann and molecular dynamics for dense fluids. Phys. Rev. E, 75: 046704, 2007

Lattice Boltzmann and Impulsively Started Cylinders

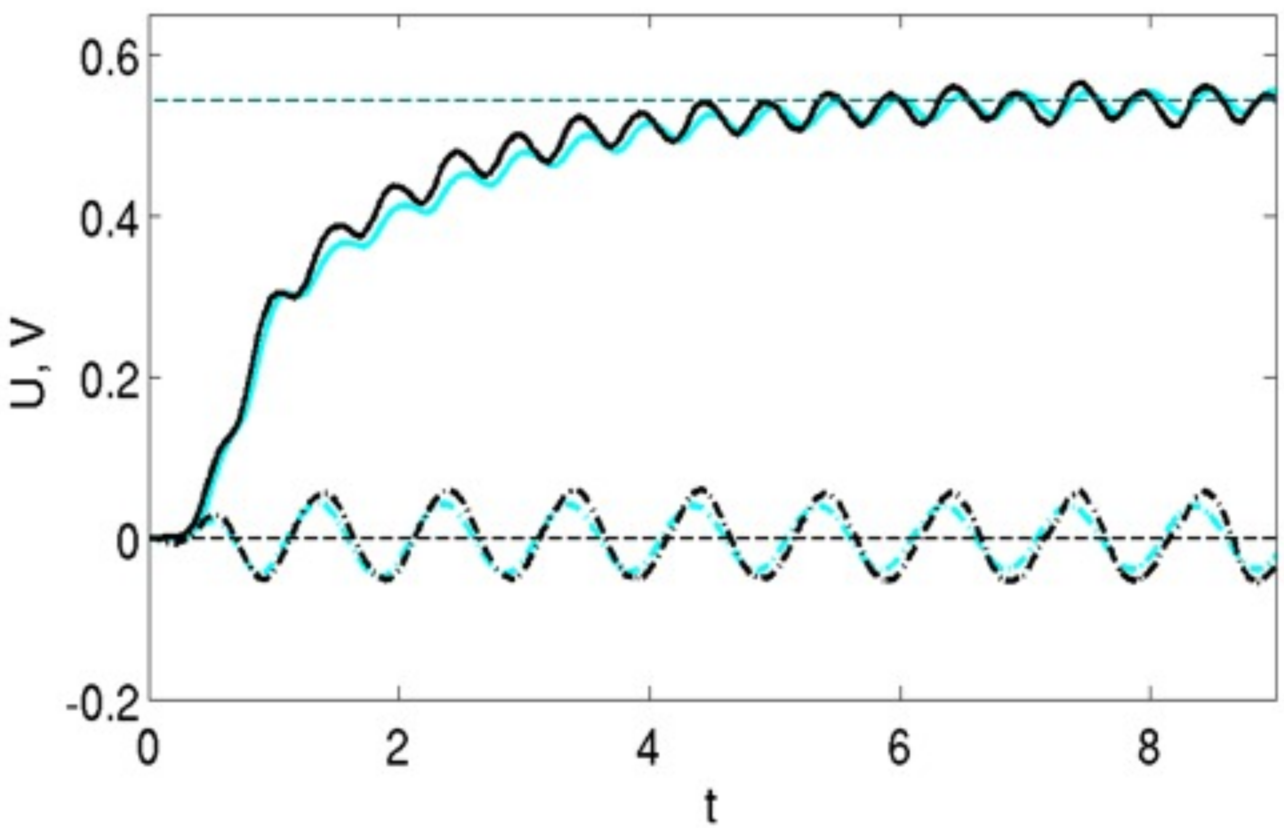


A. Dupuis, P. Chatelain, PK, An immersed boundary–lattice-Boltzmann method for the simulation of the flow past an impulsively started cylinder, J. Computational Physics, 227, 2008

Results on Swimming

Finite Volume (Kern & Koumoutsakos, J. Exp. Biology, 2007)

Particle + IBM (Hieber & Koumoutsakos, JCP, 2008)



Longitudinal and lateral velocity

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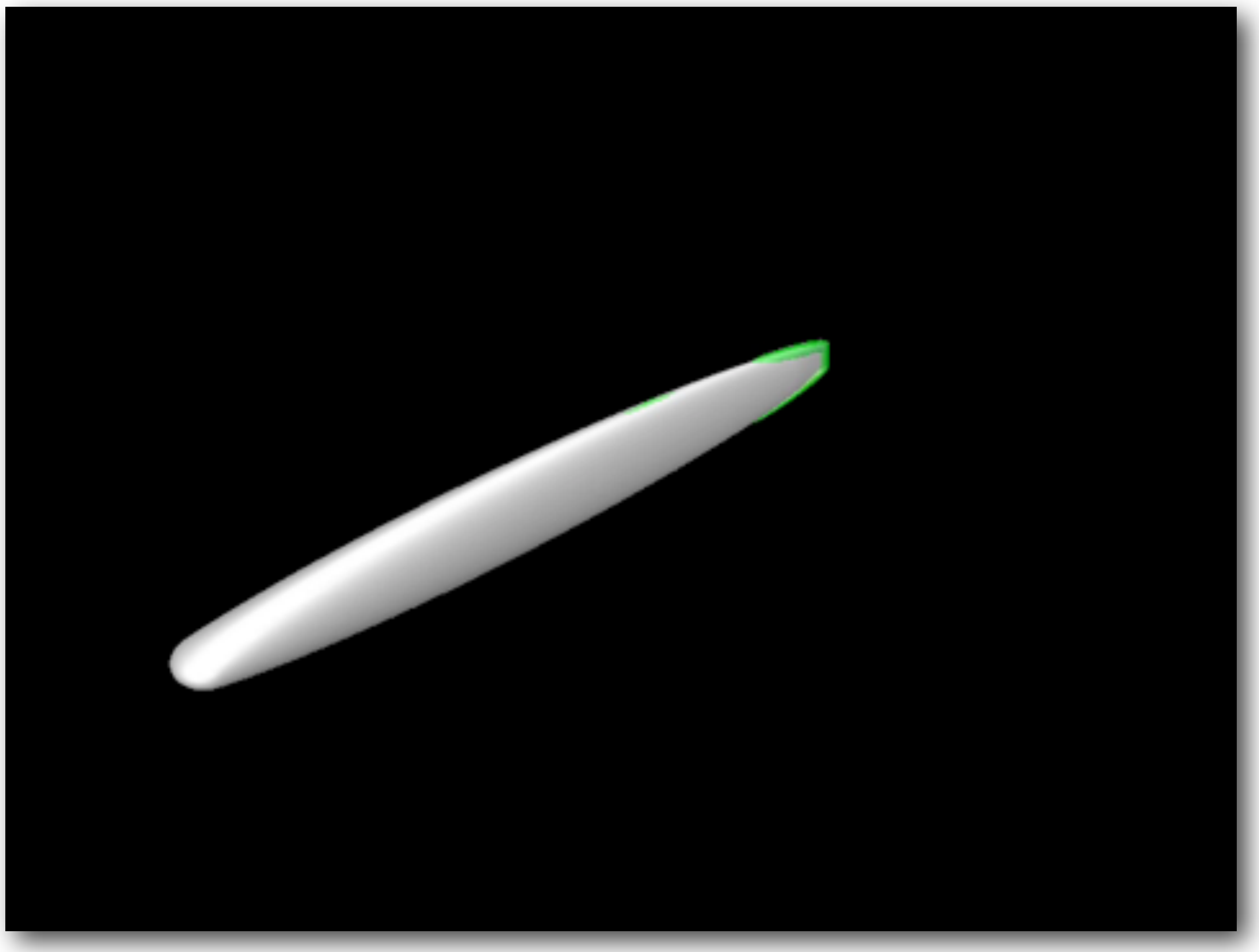

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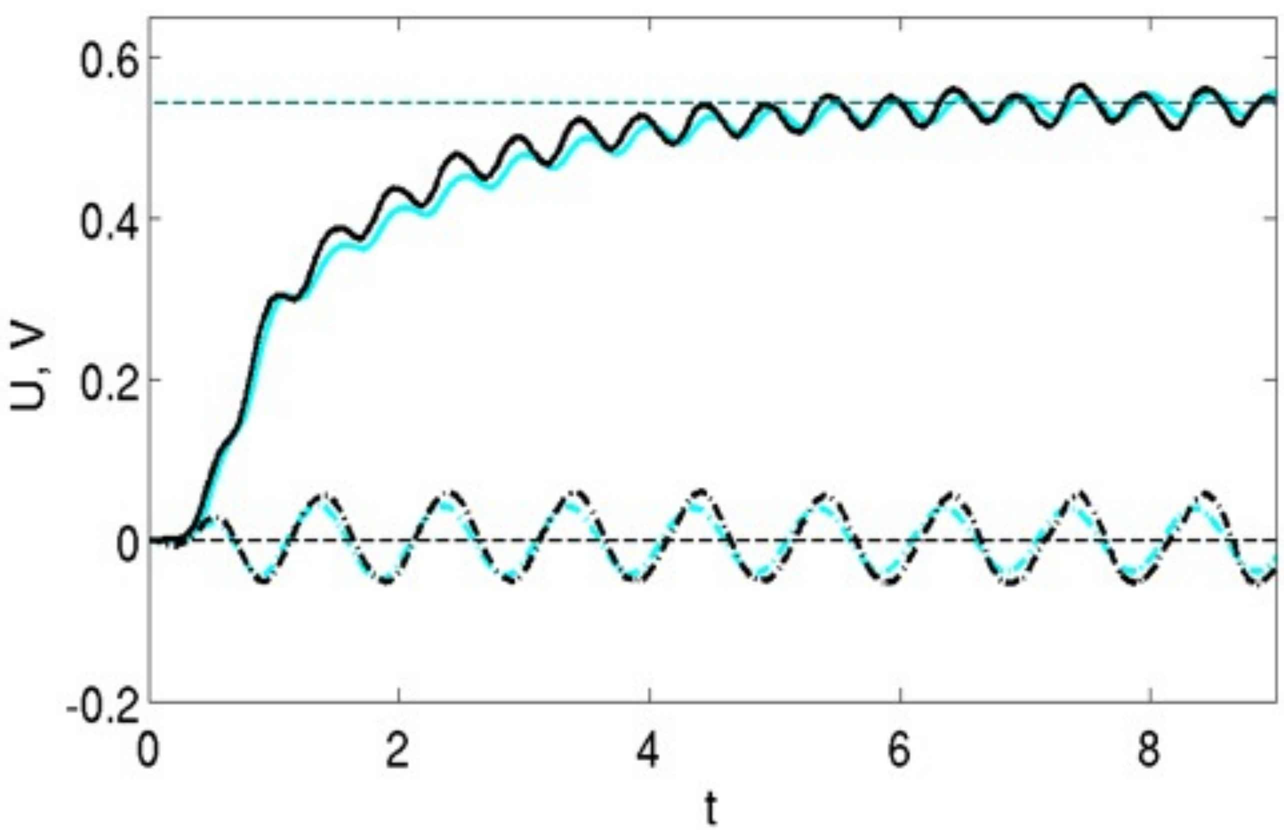

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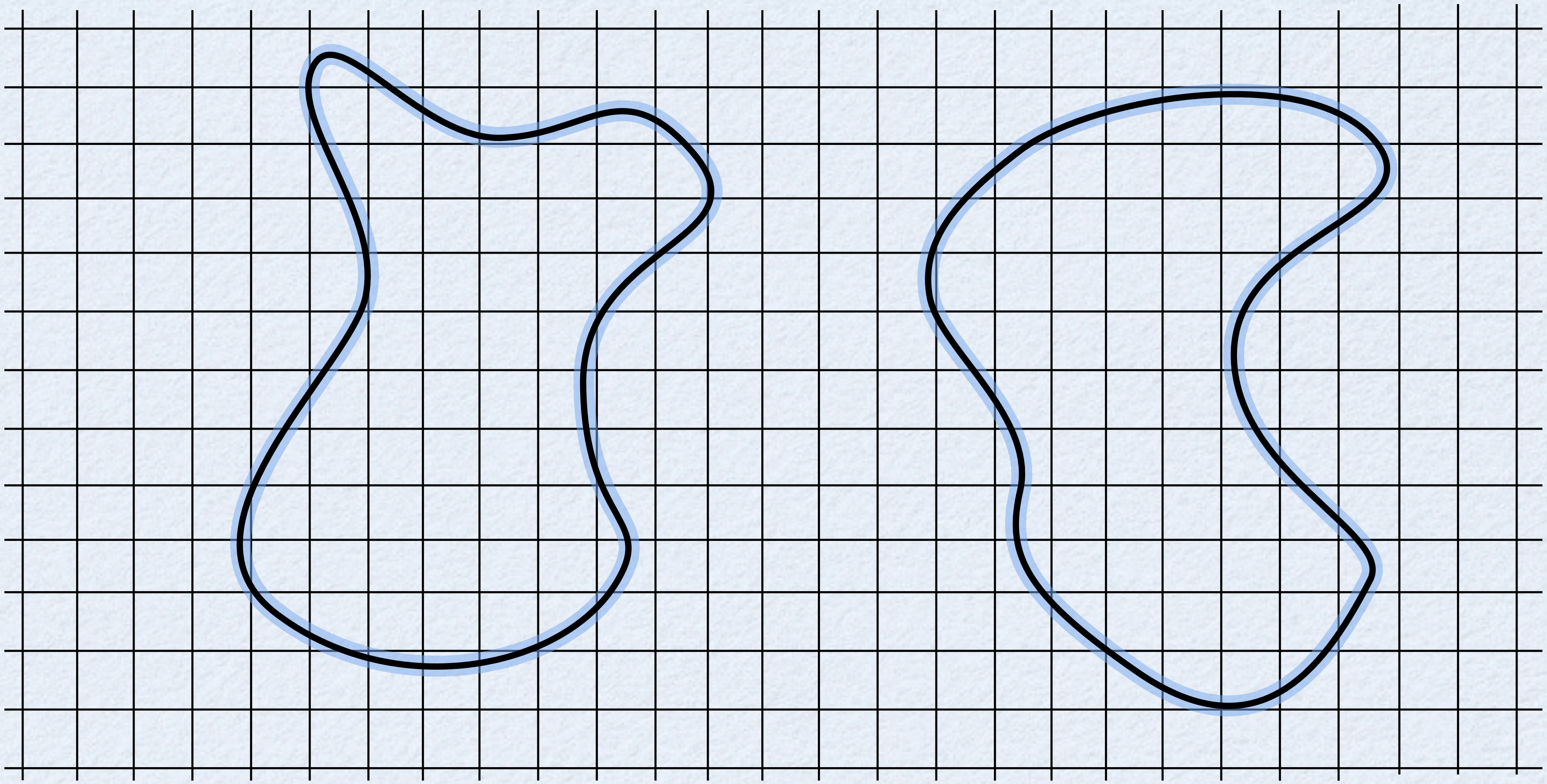

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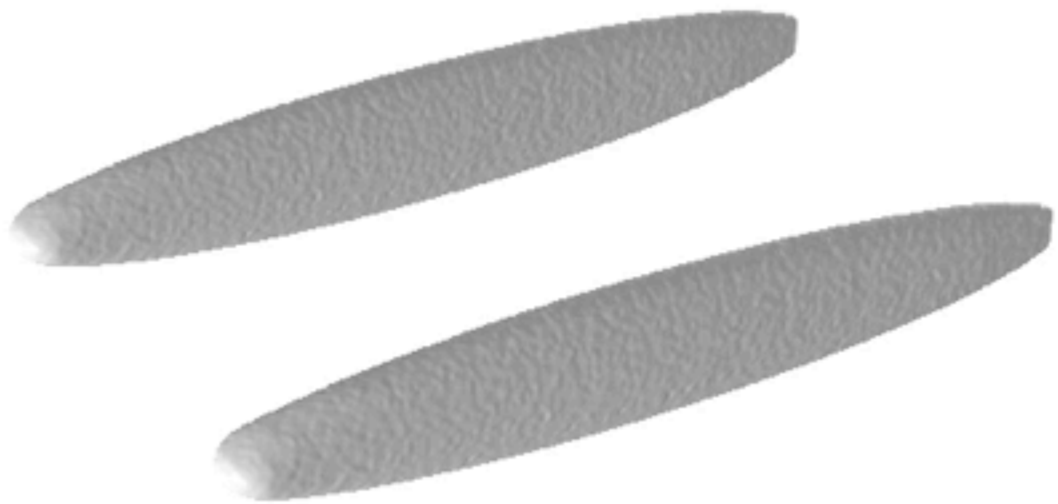
P. Angot, C. H. Bruneau, and P. Fabrie,, Numer. Math. , 1999

Immersed Boundary: $f(\mathbf{x}) = \kappa \delta_S (\mathbf{x}_S - \mathbf{x})$

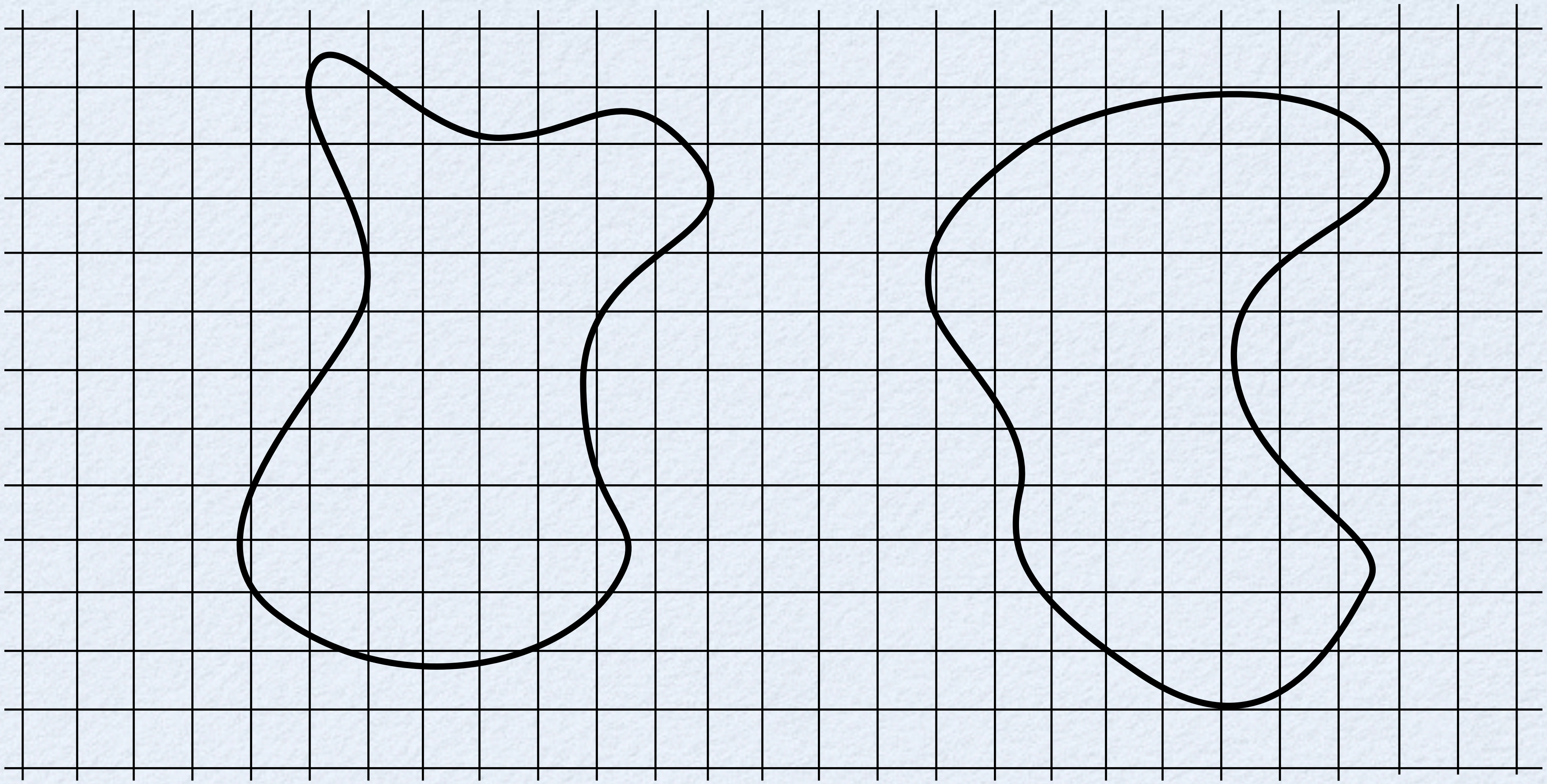
C.S. Peskin, J. Comput. Phys., (1977)

FISH SCHOOLING



2 FISH (OBVIOUSLY)

Boundary Conditions = Coupling



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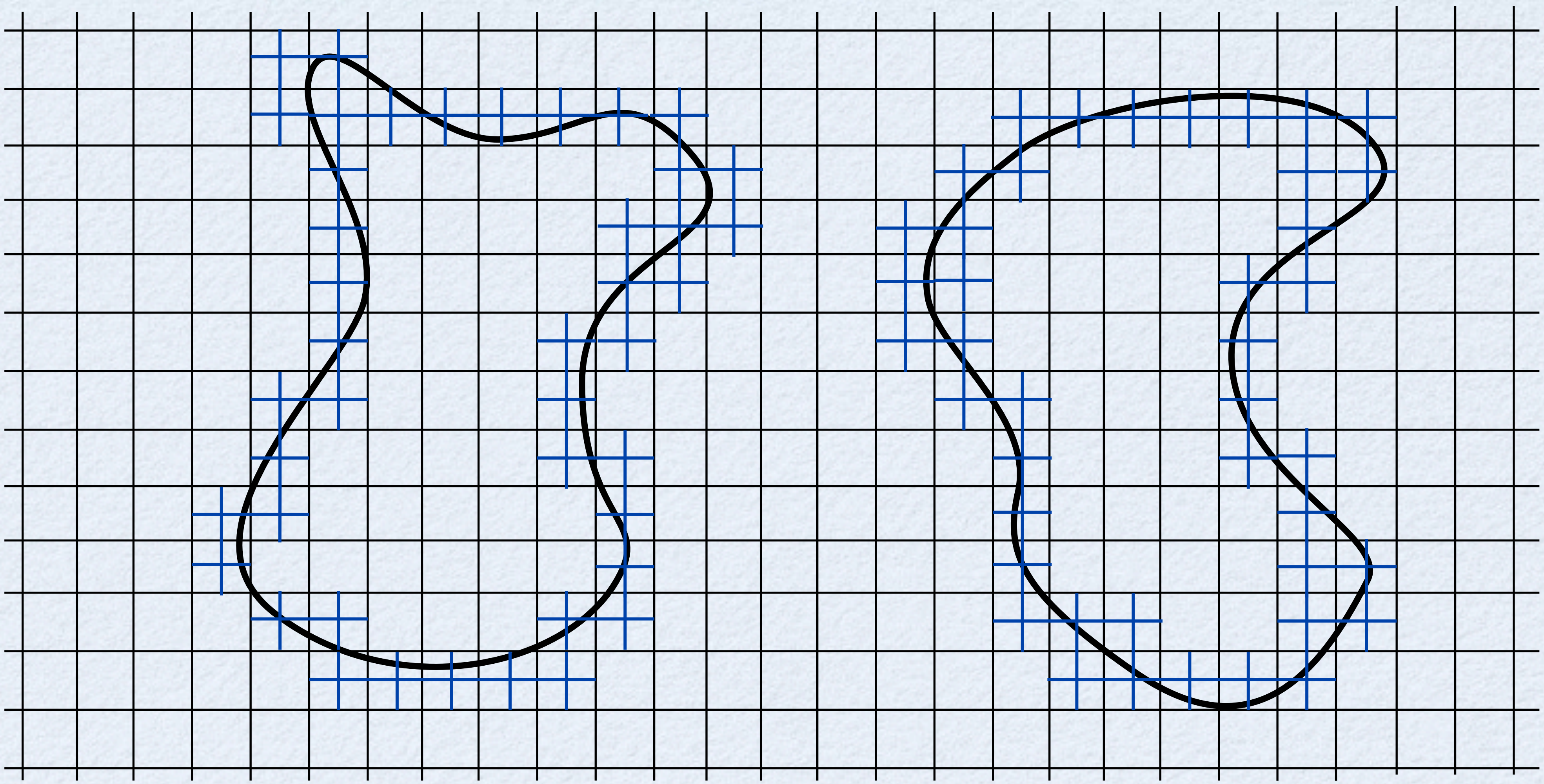

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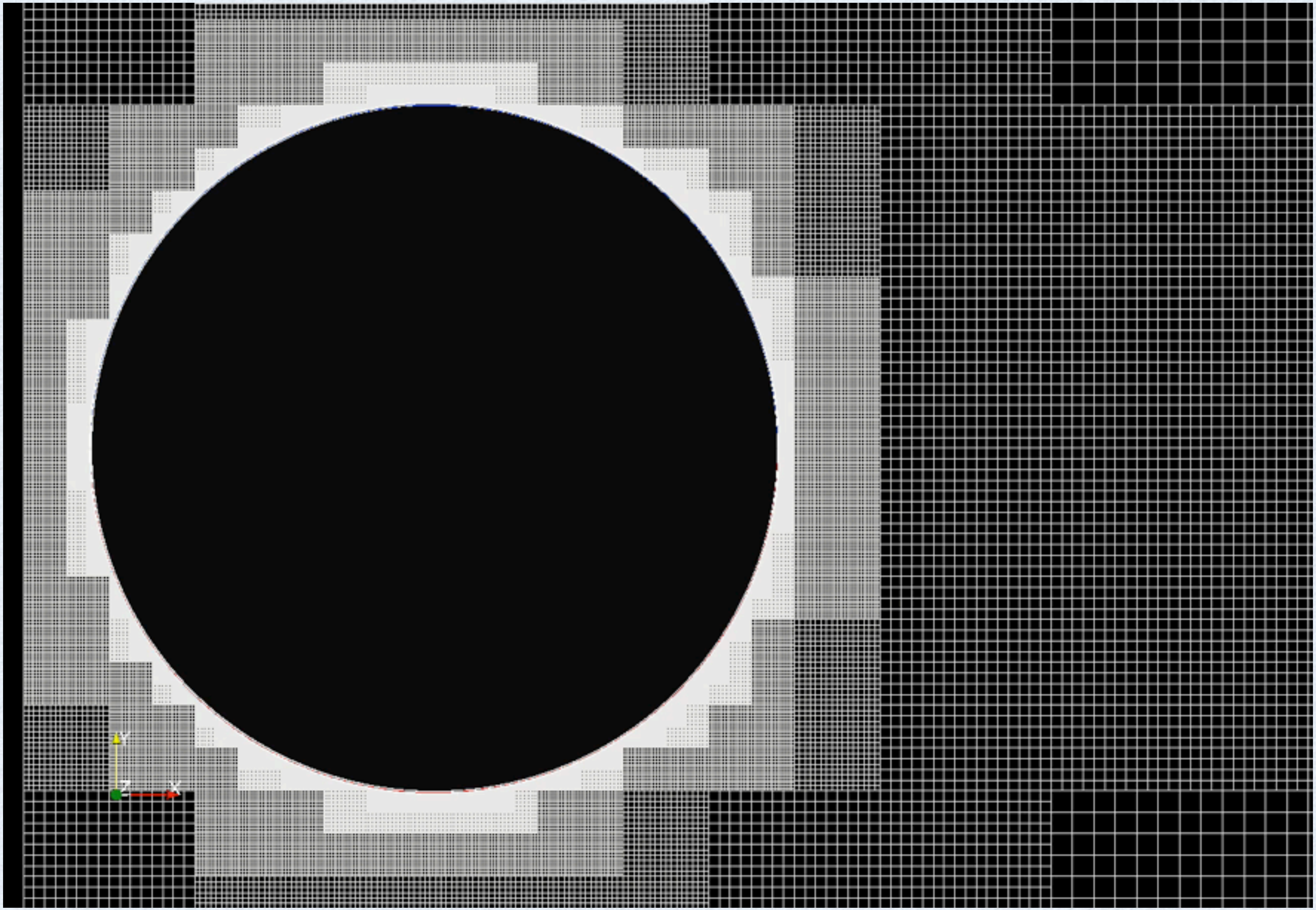
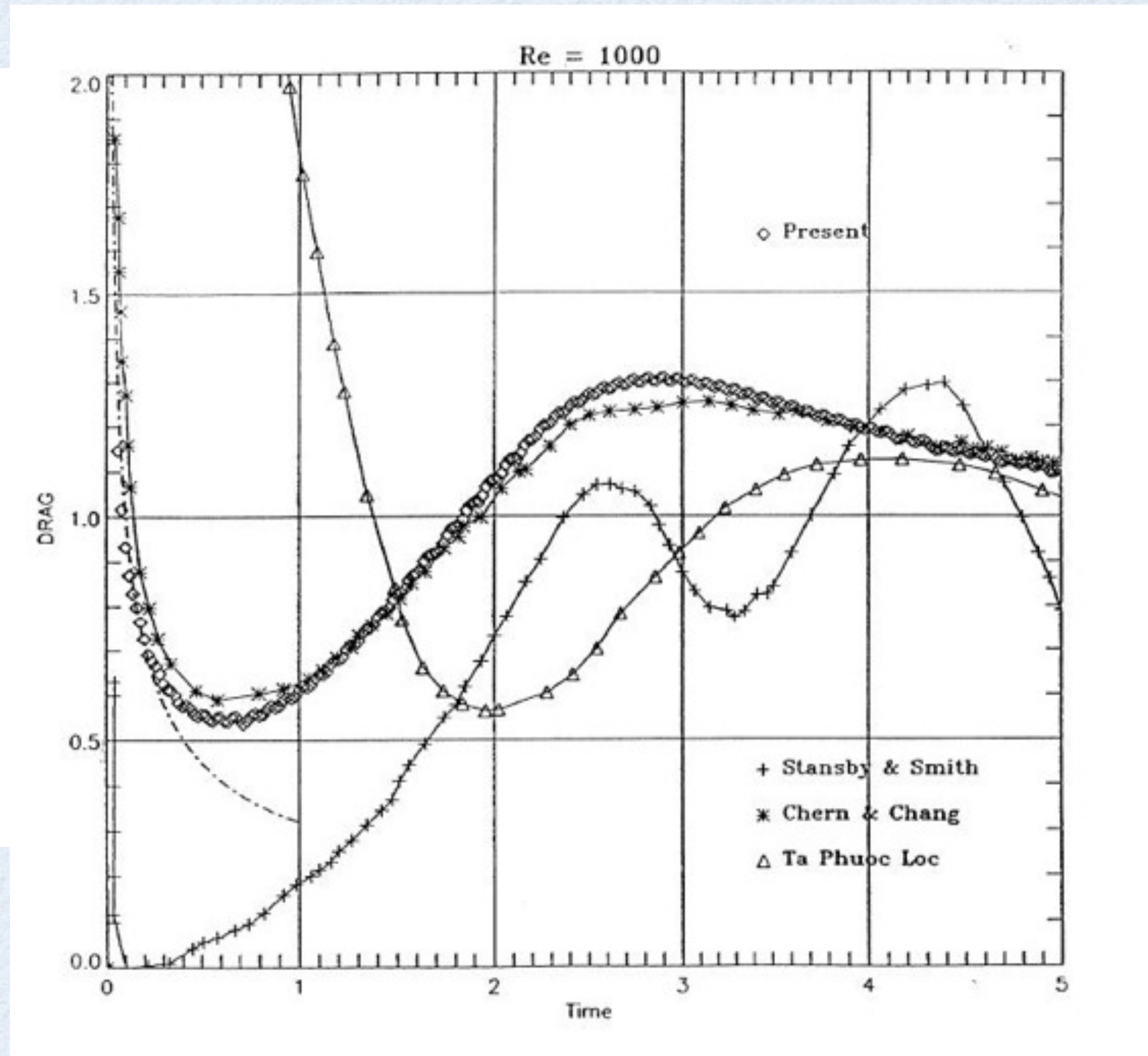
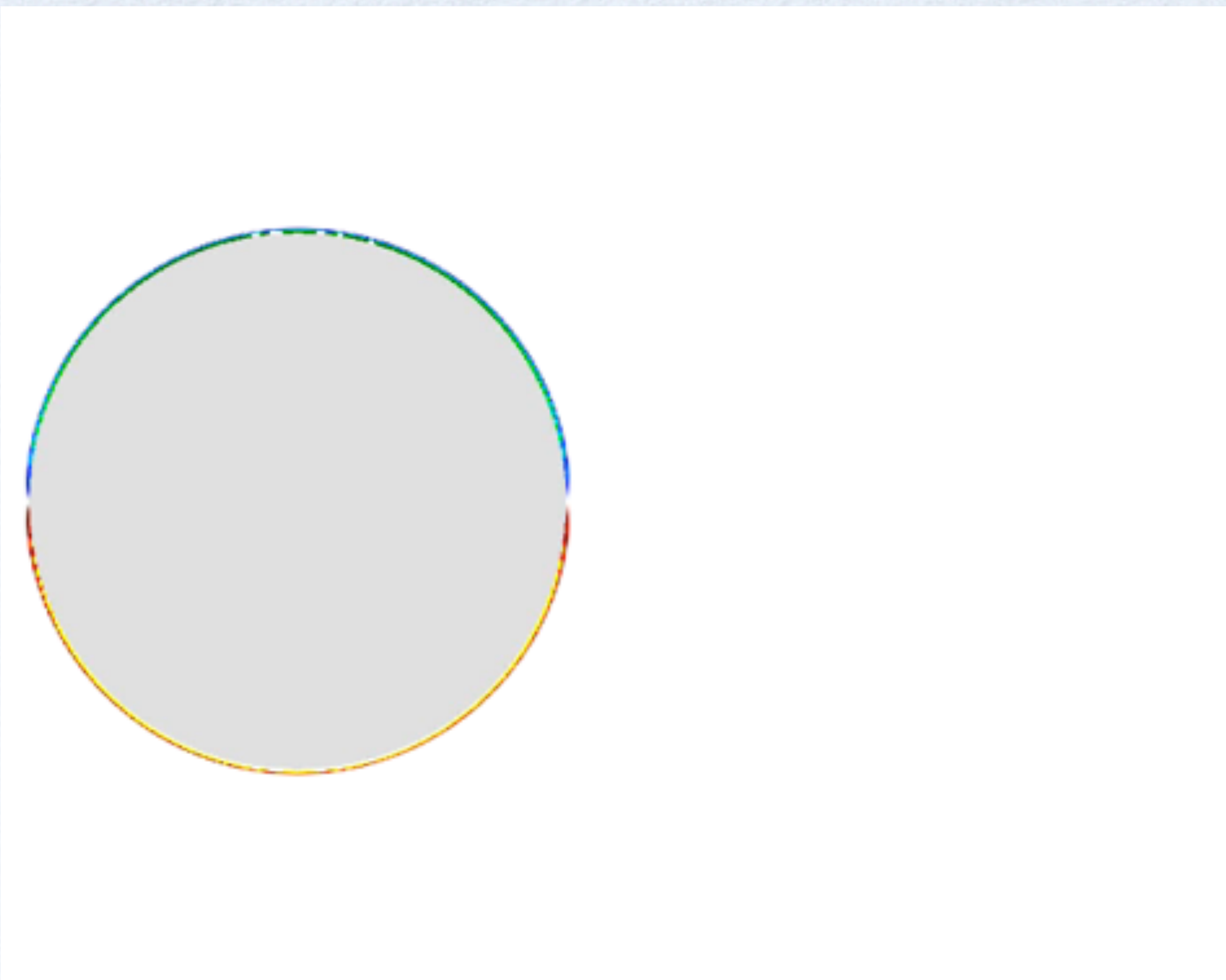
Re 9500 : Multiresolution + Multicores + (multi)GPUs

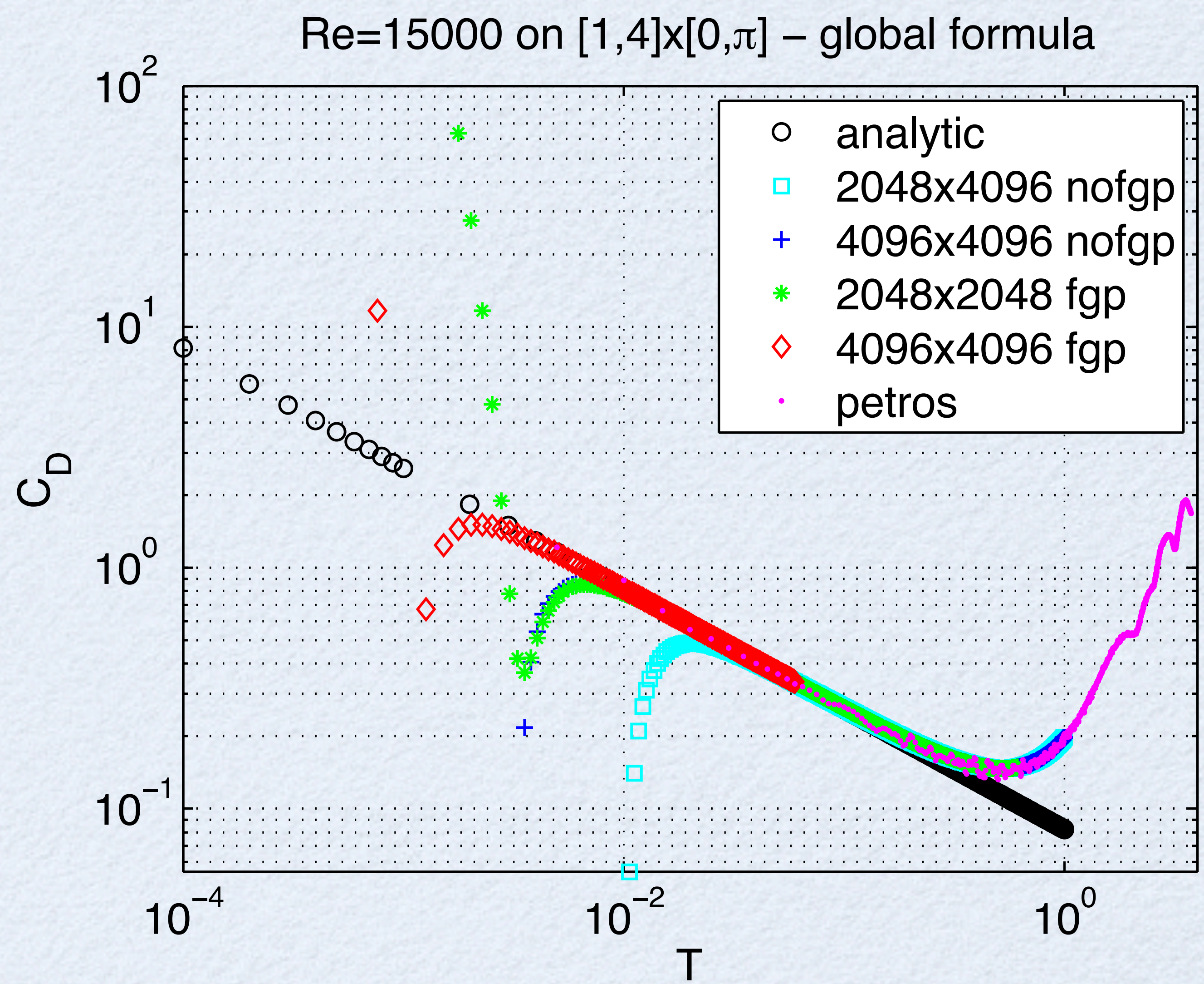


Benchmark : The Impulsive Started Cylinder

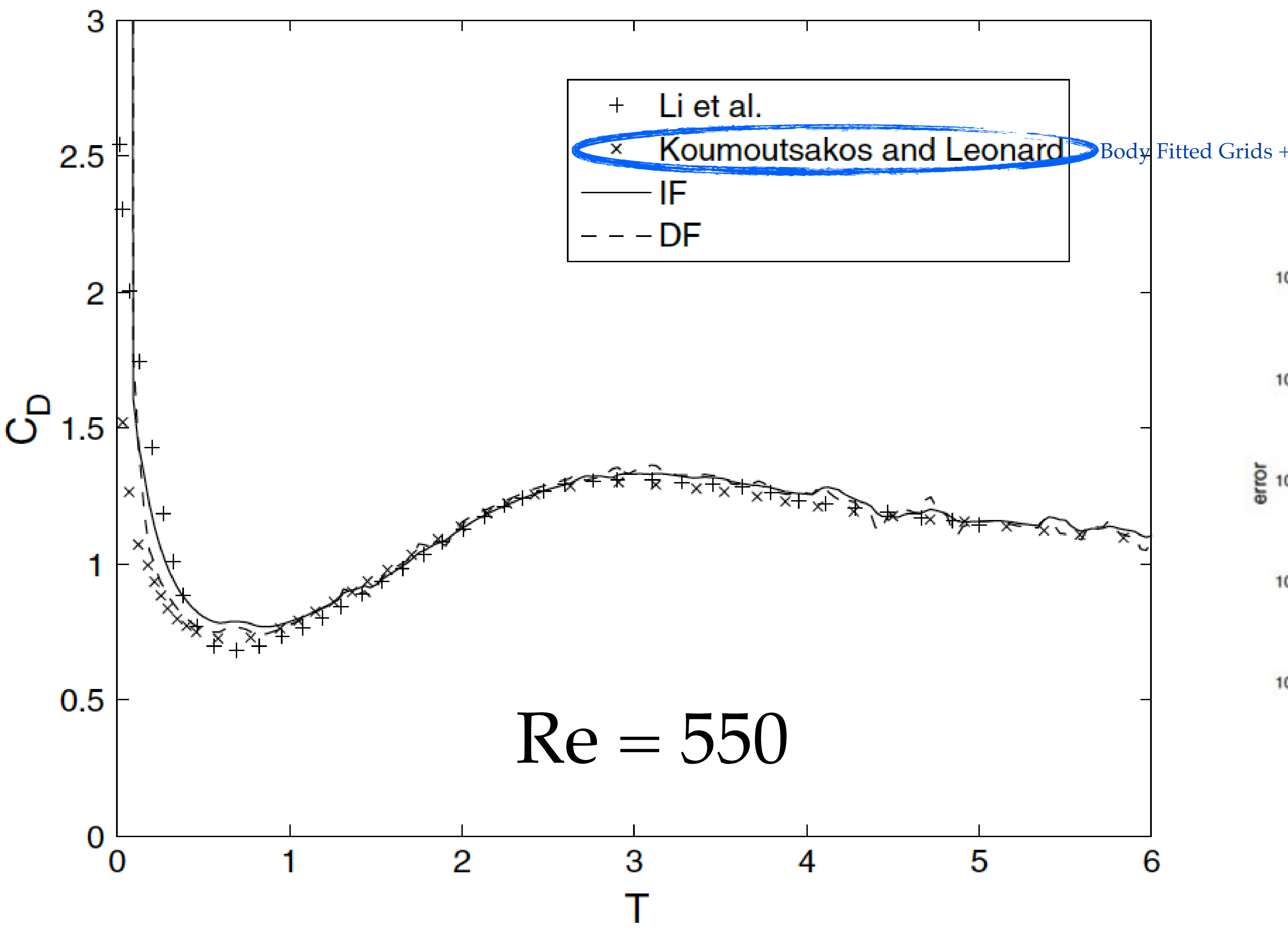


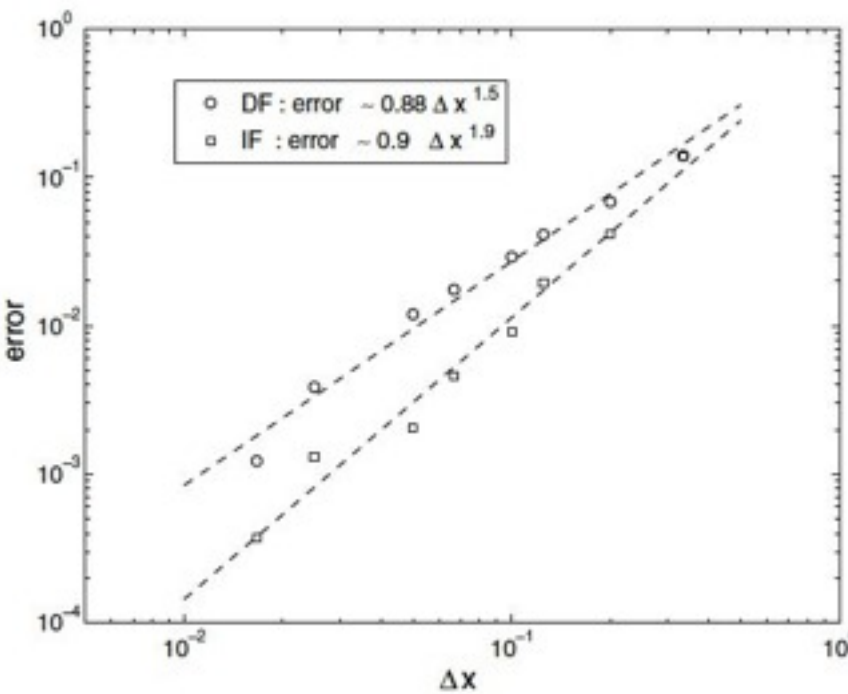
Benchmark : The Impulsively Started Cylinder





Lattice Boltzmann + Immersed Boundaries





Convergence Rate

Dupuis A., Chatelain P., Koumoutsakos P., An Immersed Boundary-Lattice Boltzmann Method for the Simulation of the Flow Past an Impulsively Started Cylinder, **J. Computational Physics**, 227, 9, 4486-4498, 2008

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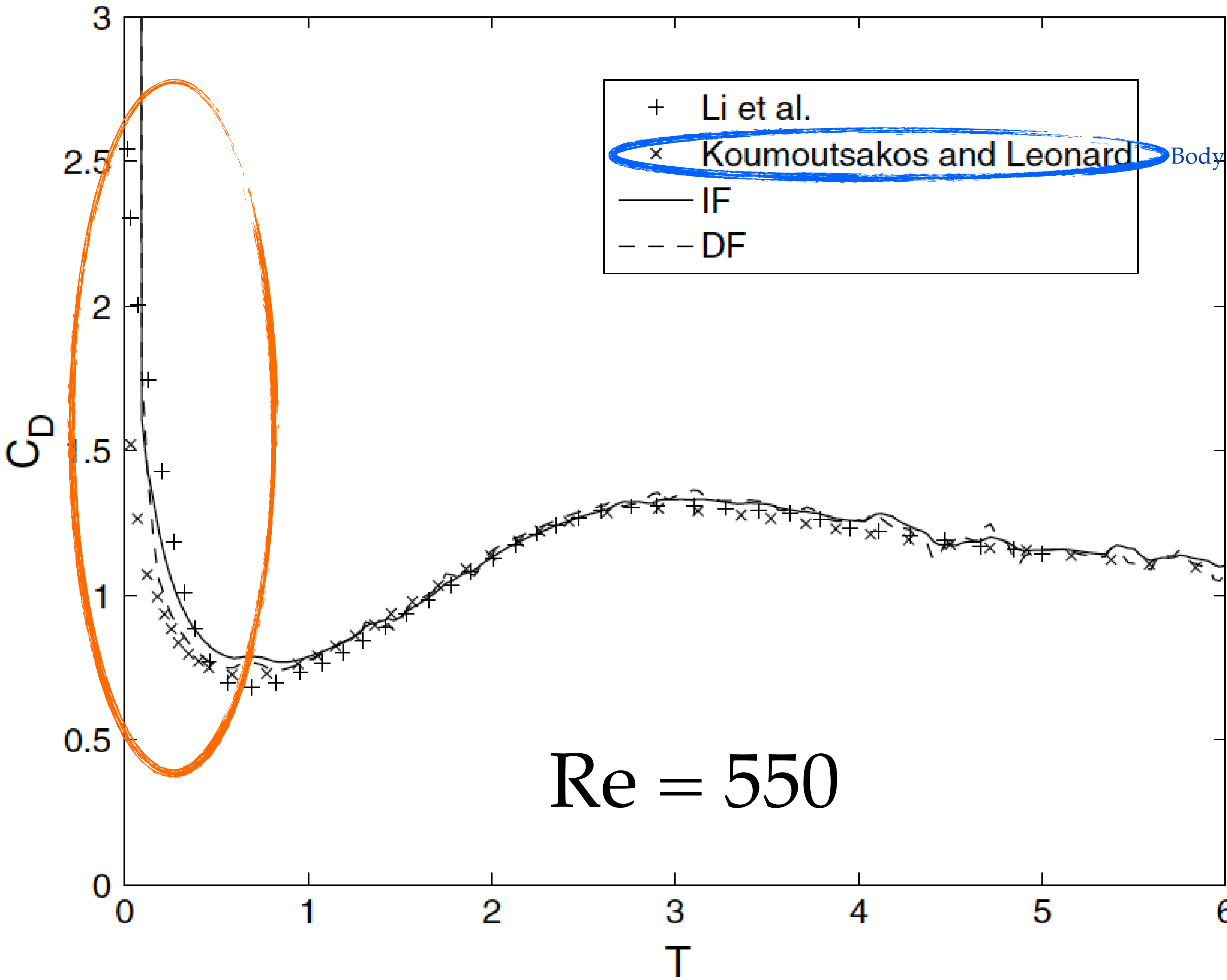

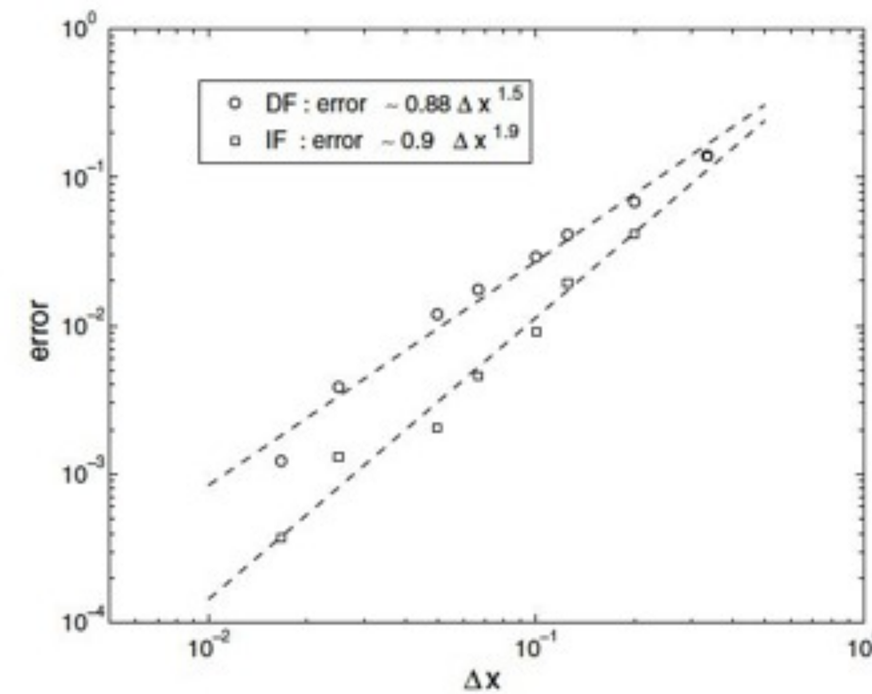

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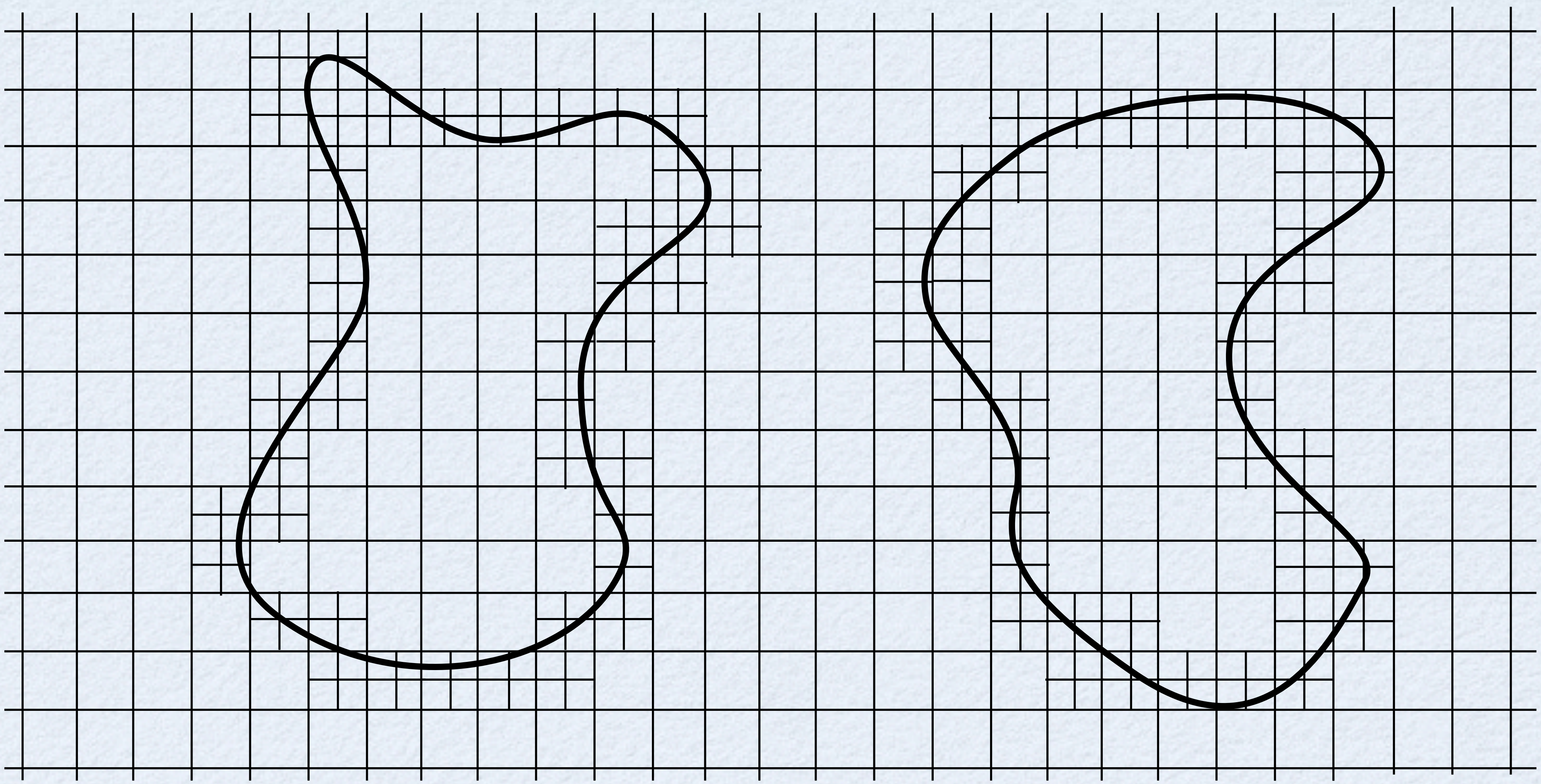
Boundary Conditions = Coupling



$$\rho \frac{D\mathbf{u}}{Dt} = \nabla \cdot \boldsymbol{\sigma} \; + f(\text{enforces b.c.})$$

Multiphysics/Multiscale

$$f(\mathbf{x}) \approx F(\text{Atomistic Simulations})$$

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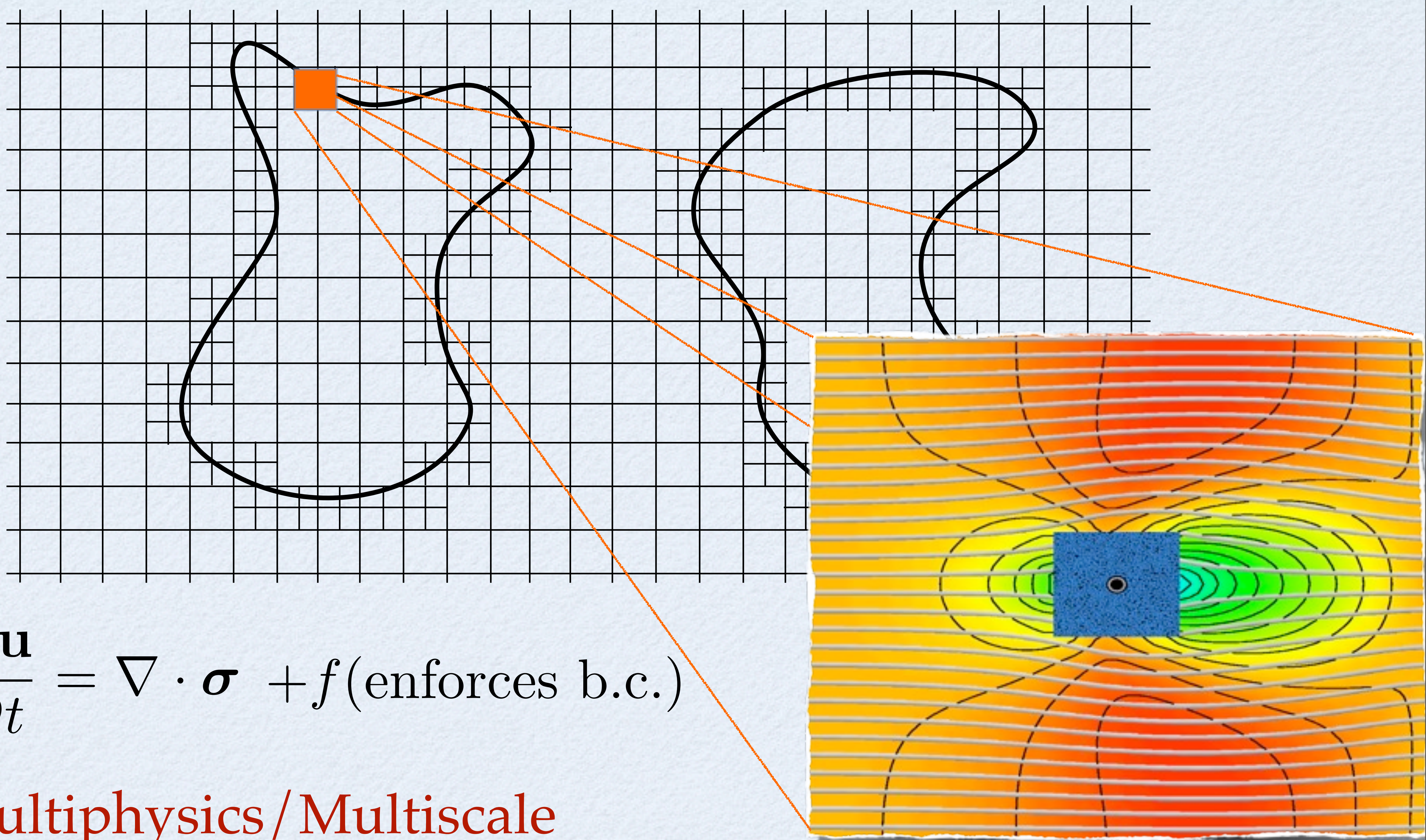

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Schwarz DD for Liquids

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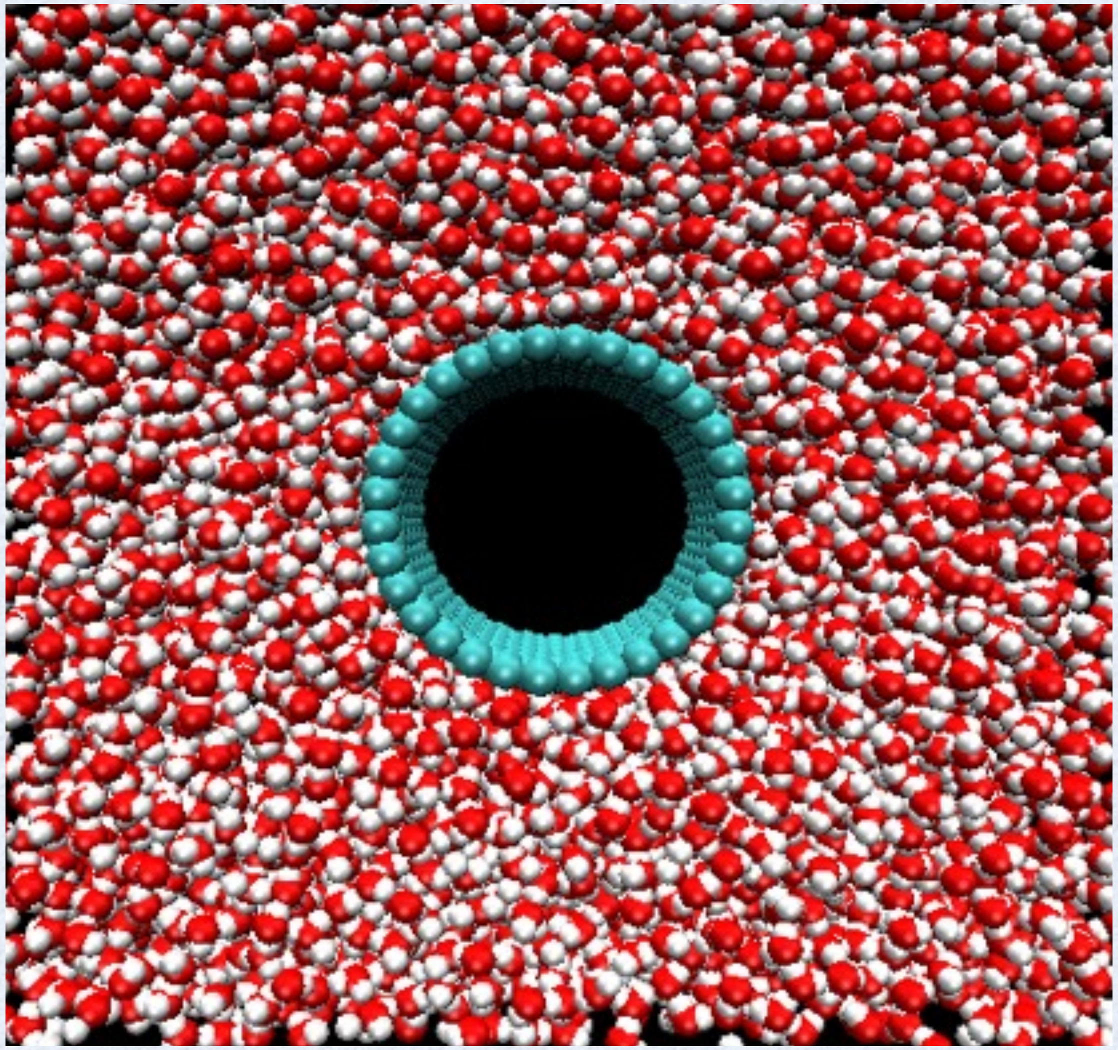

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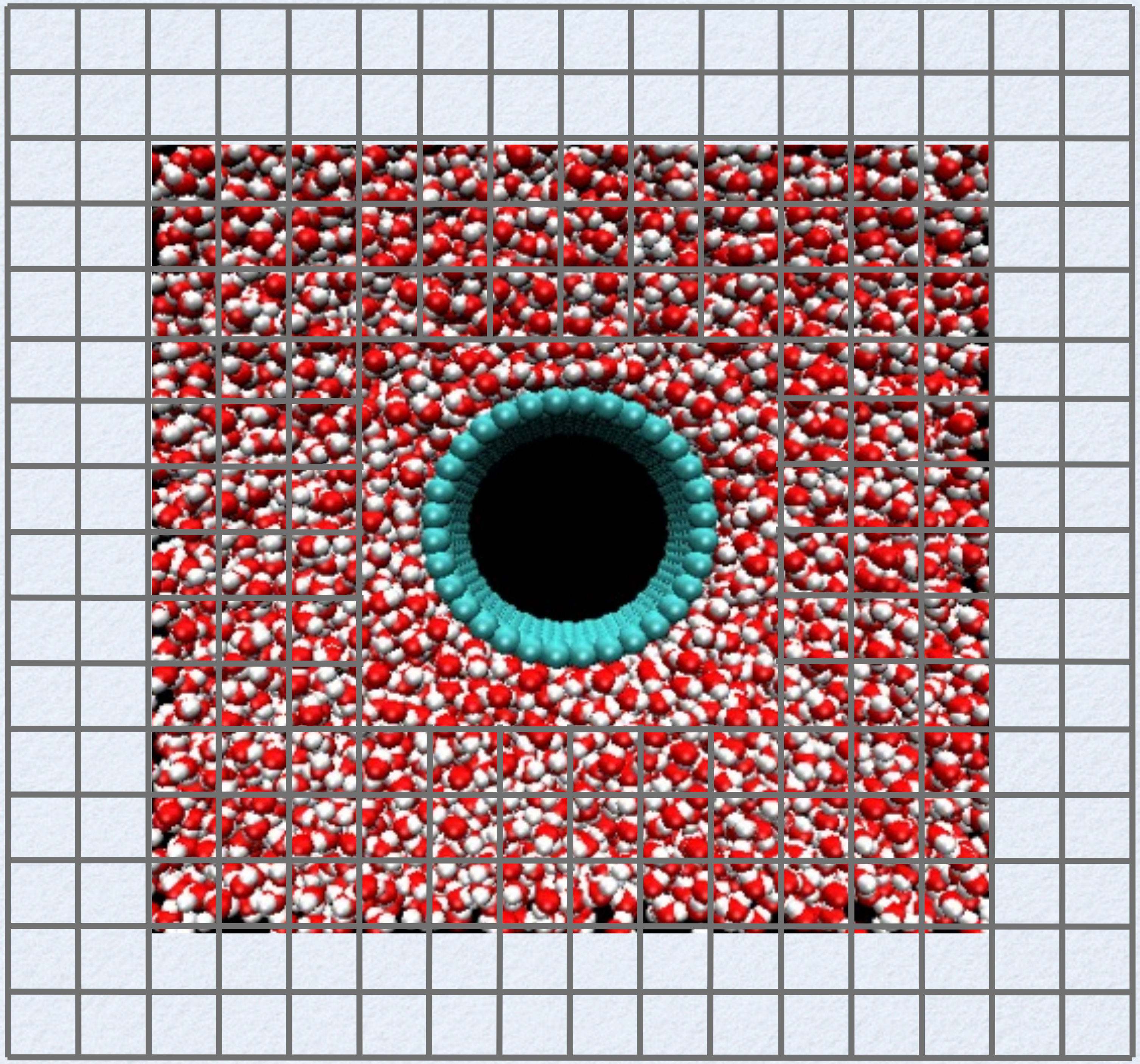

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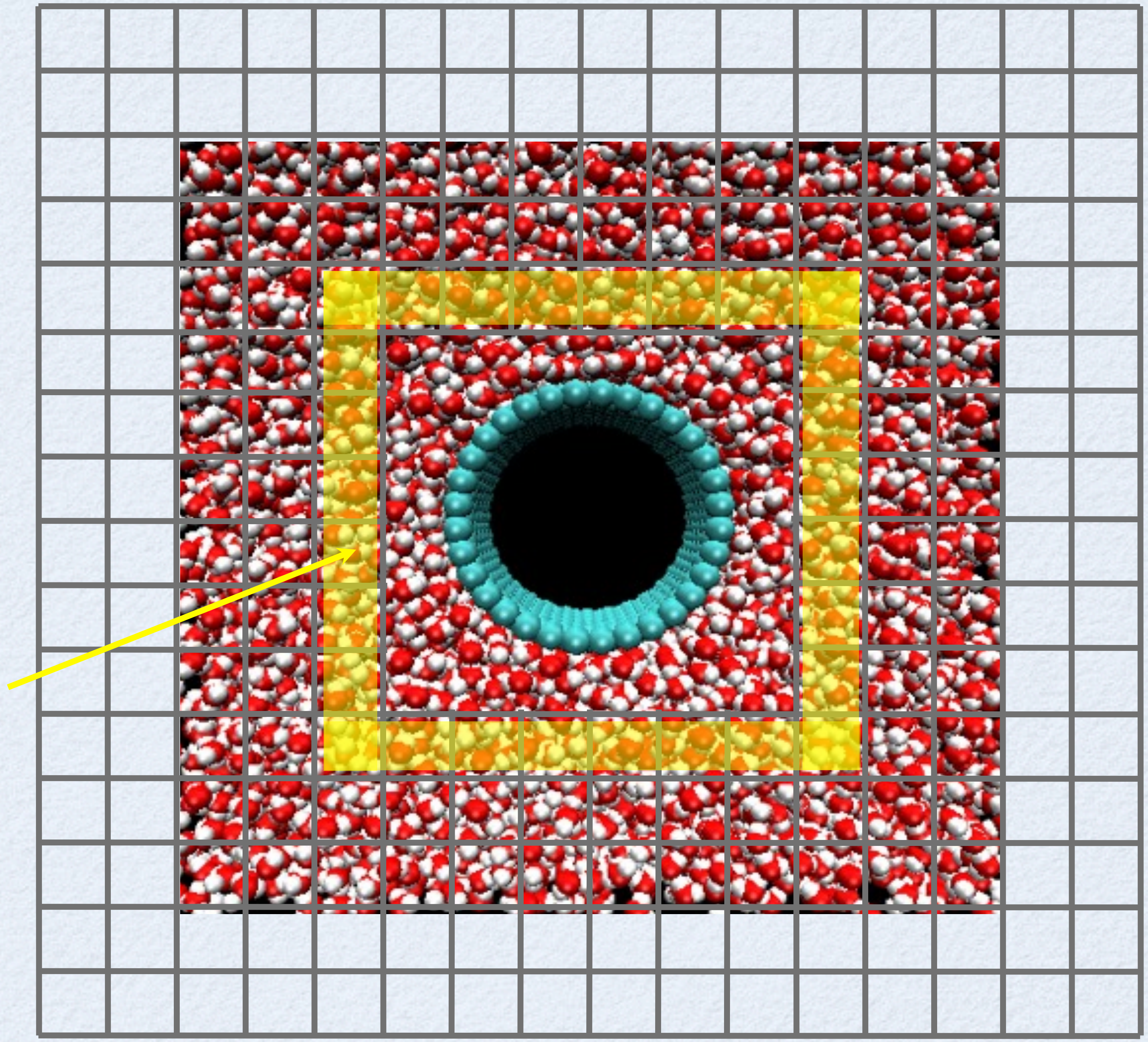

Measure
A→C

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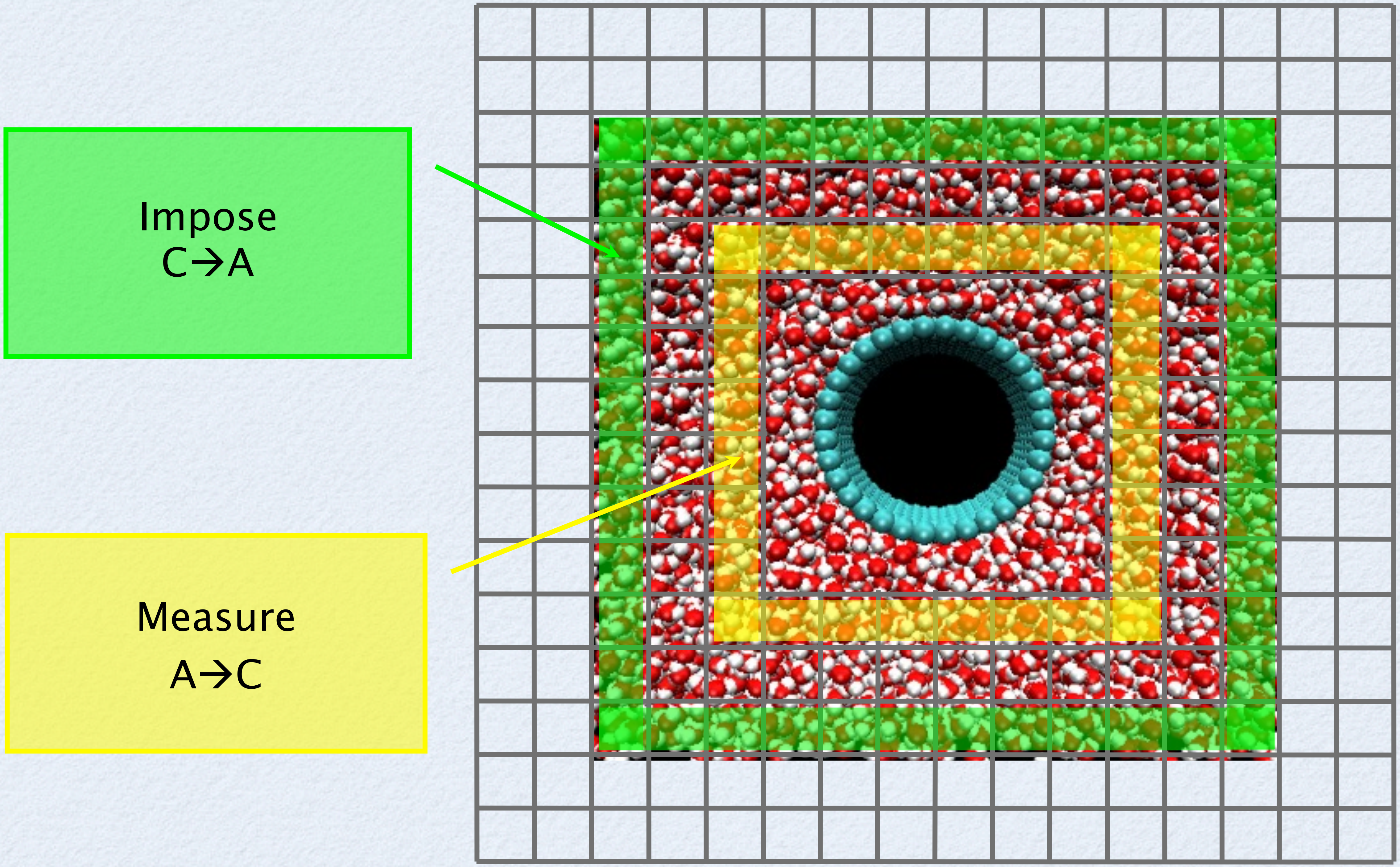

- Iterate, until the solution in the overlap region converges.
- Conservative scheme - transport coefficients in A and C match

Bridging FLUX & SCHWARZ DD Algorithms

Dupuis A., Kotsalis E.M, Koumoutsakos P., Coupling Lattice Boltzmann and Molecular Dynamics Models for Dense Fluids, **Physical Review E**, 75, 046704, 2007

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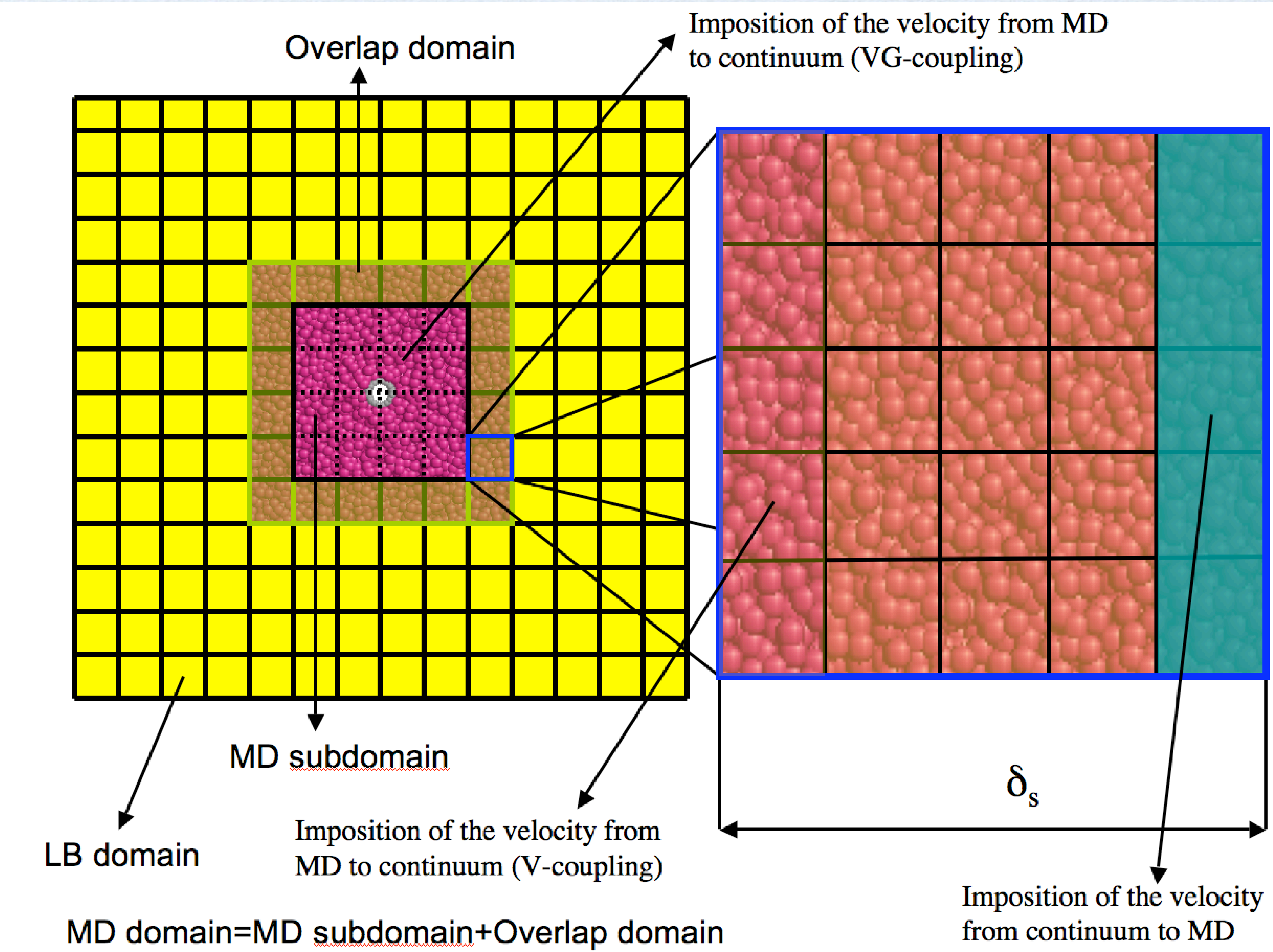

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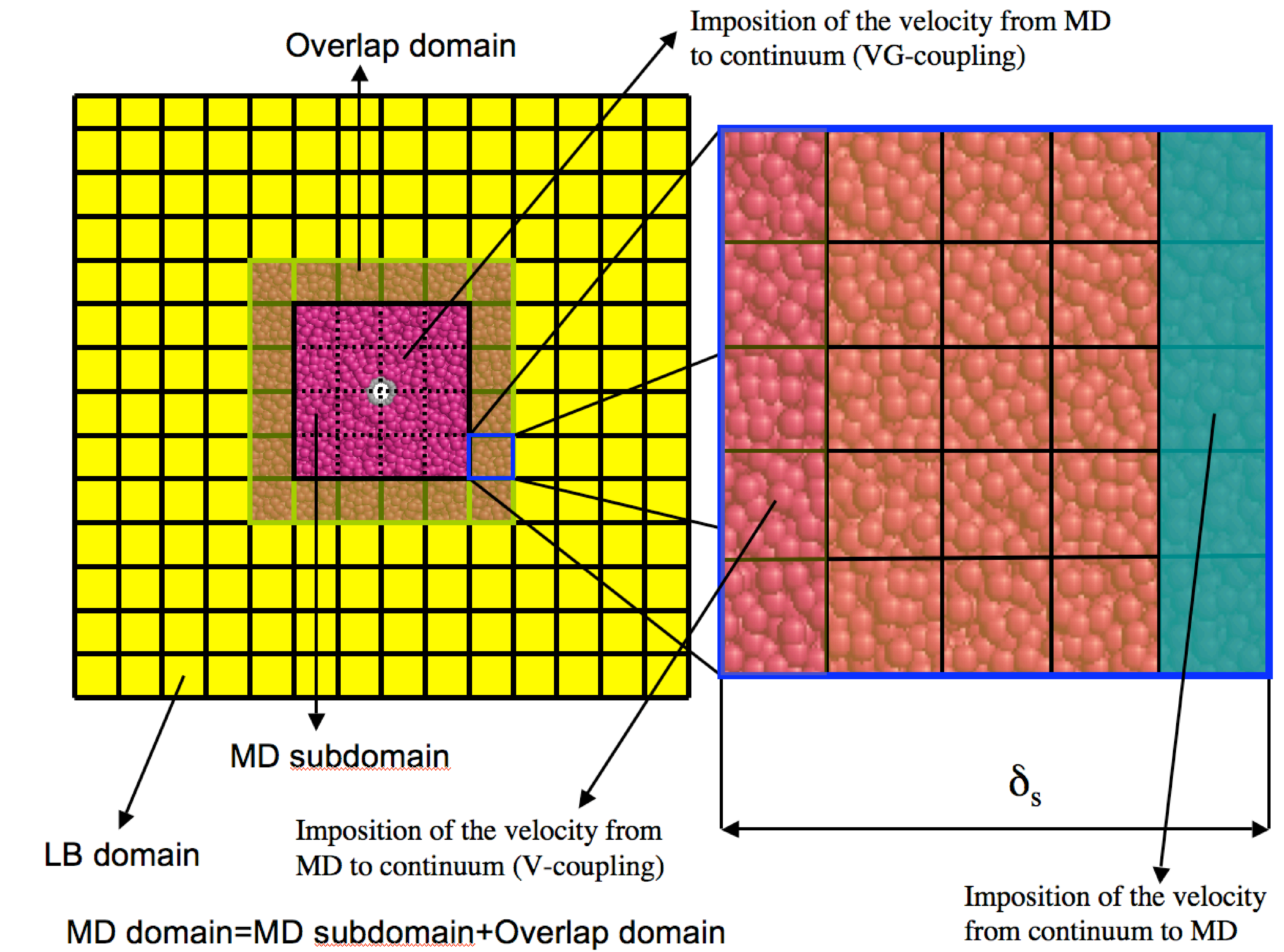

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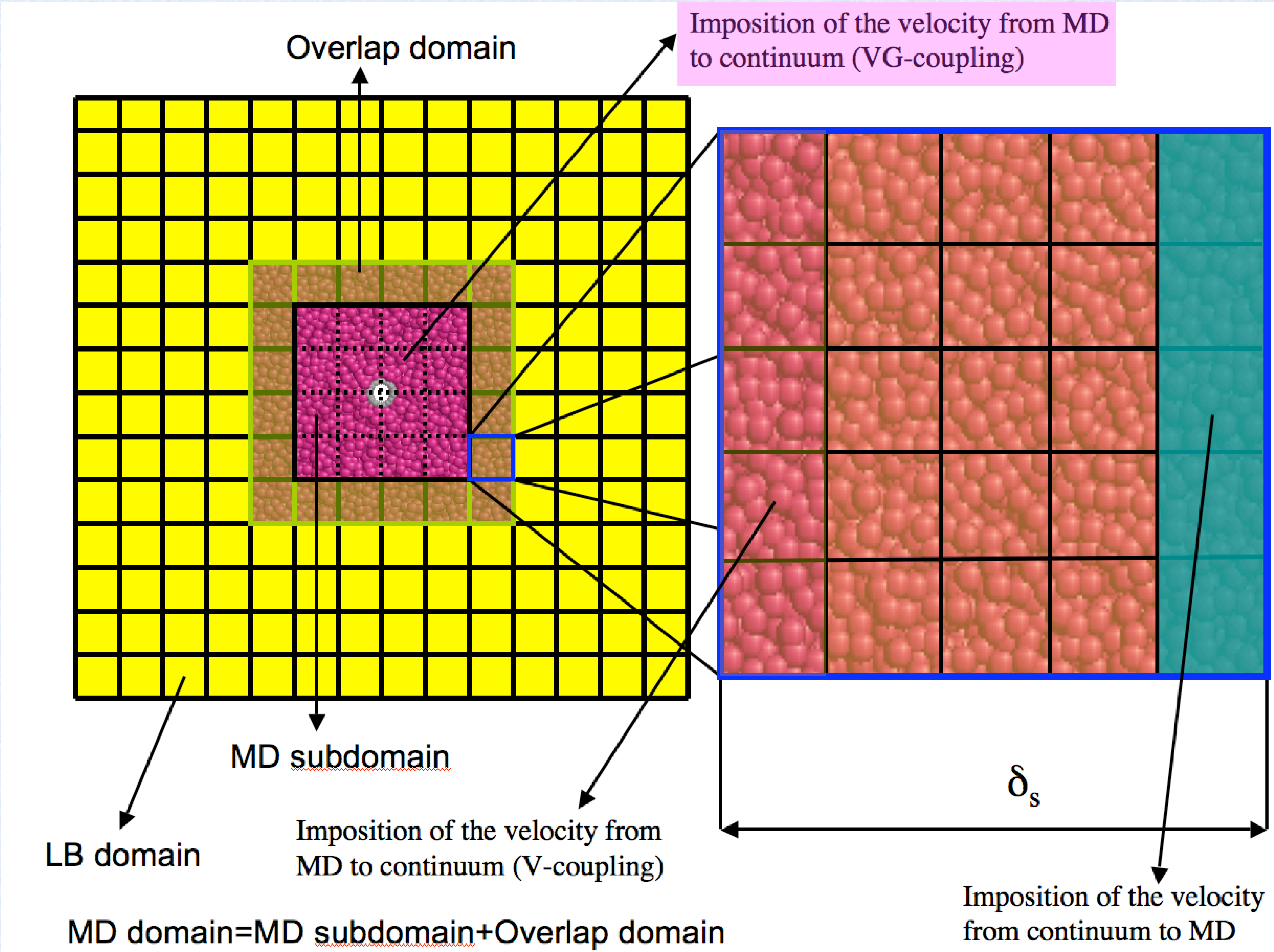

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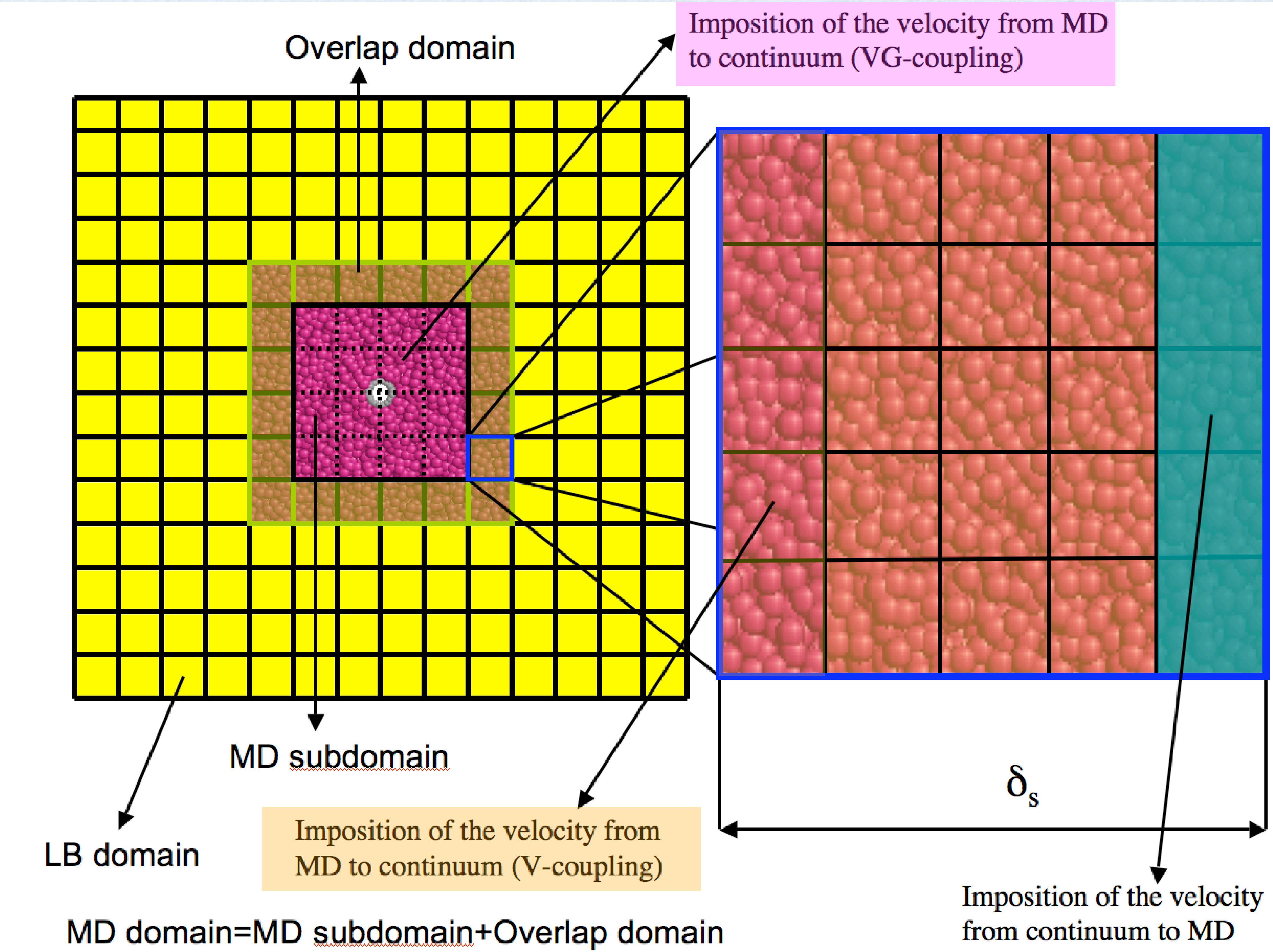
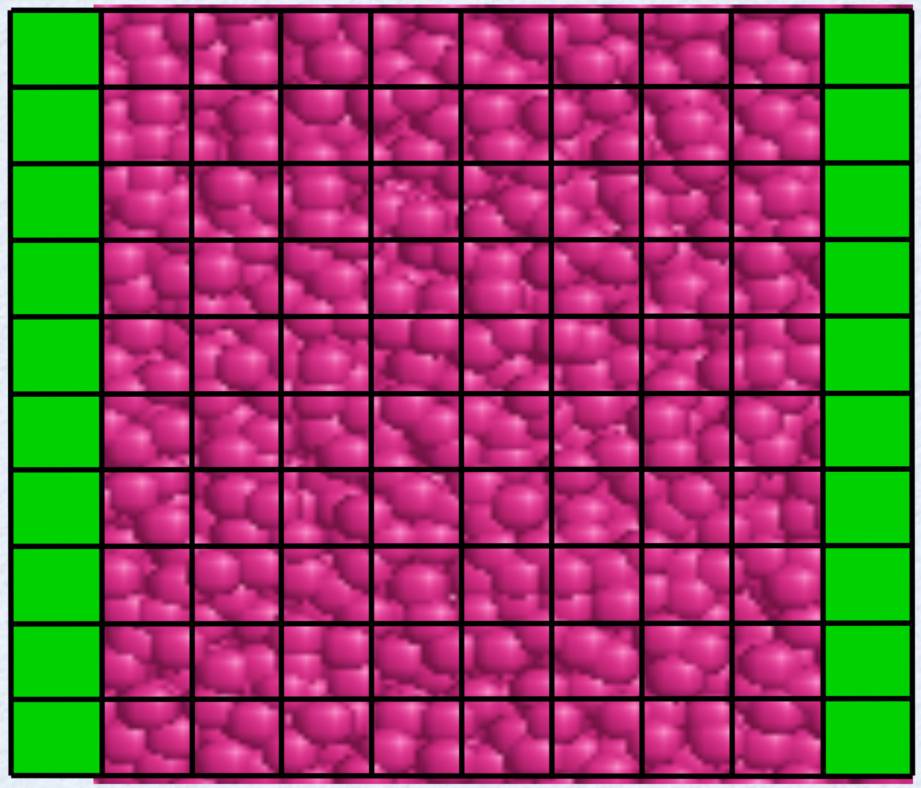
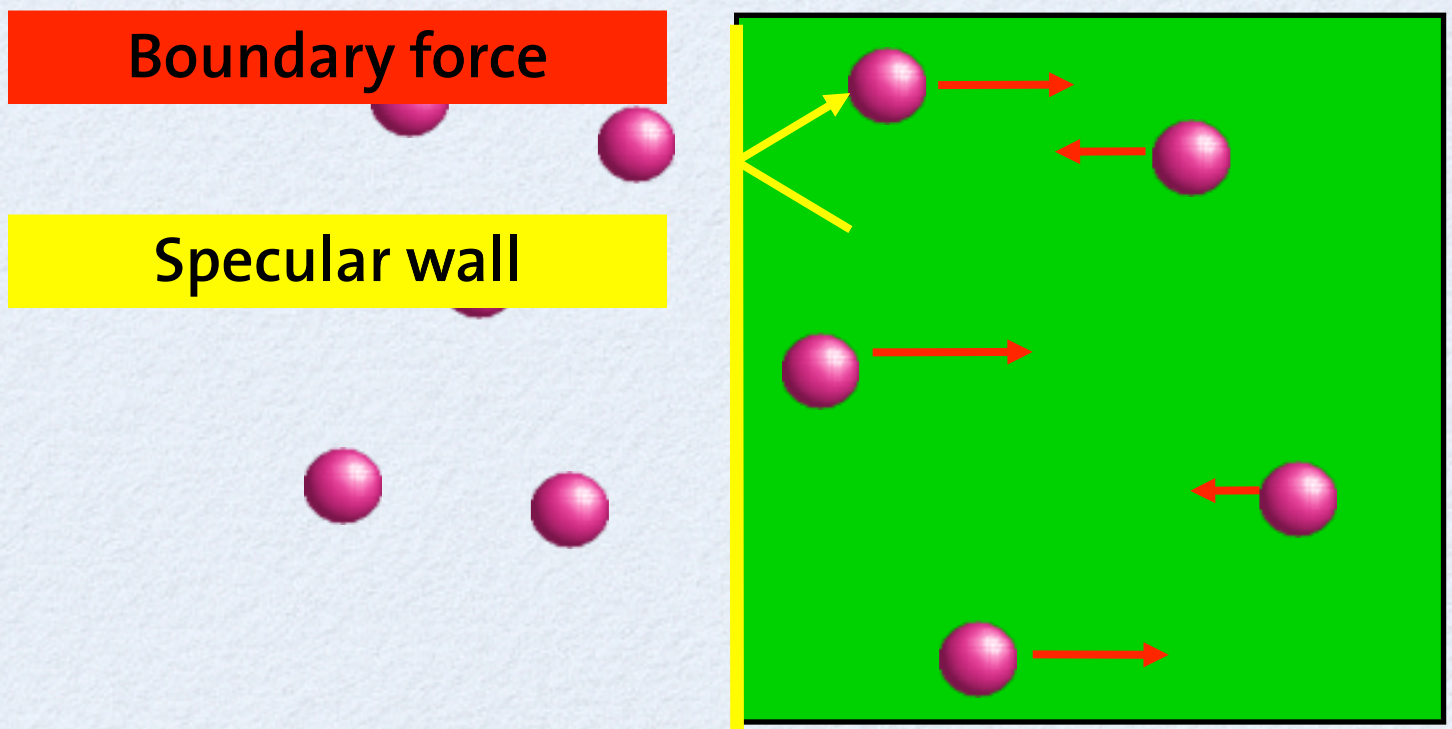


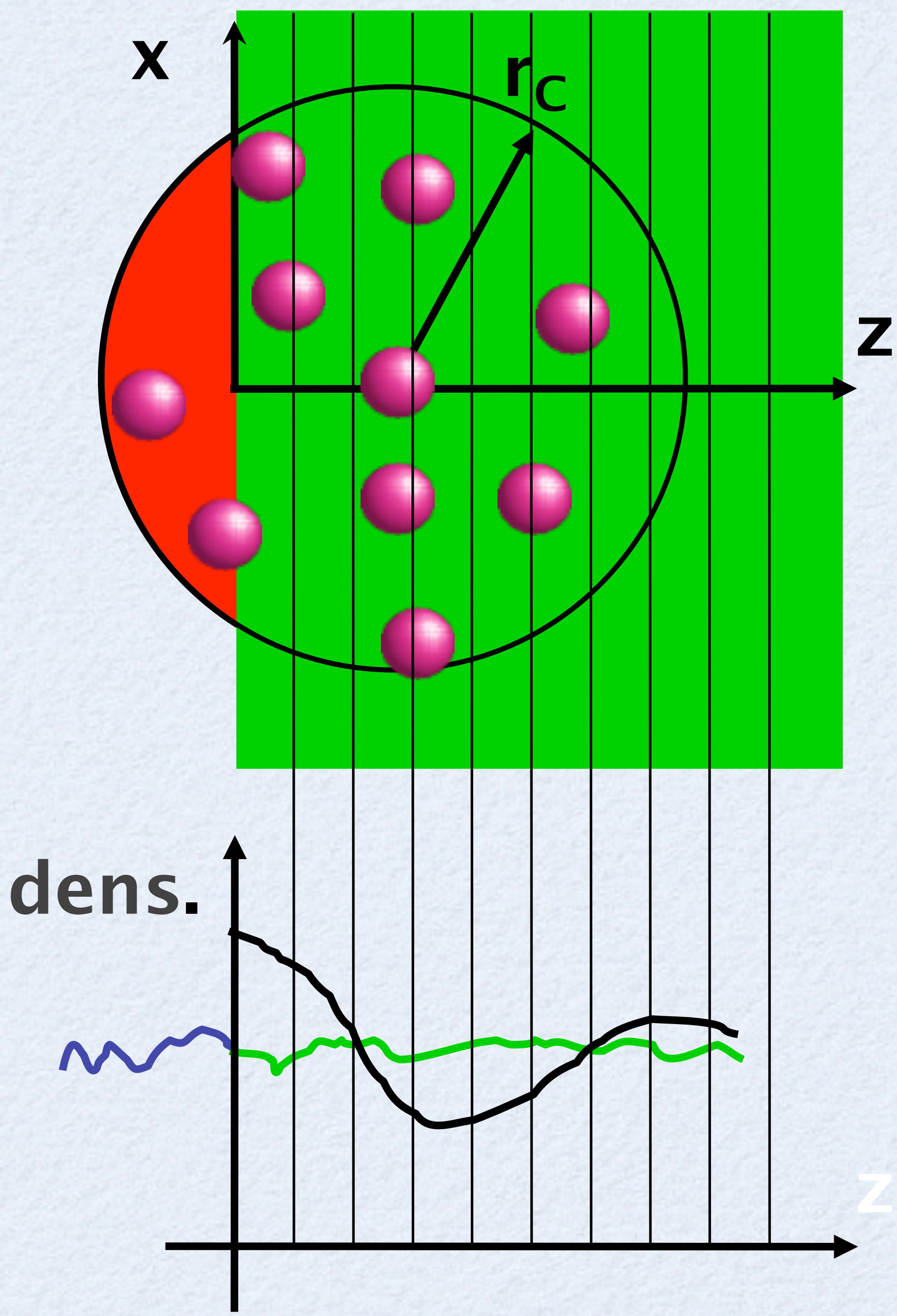
TEST 1 : EQUILIBRIUM Non-Periodic MD





NON_PERIODICITY & BOUNDARY FORCE

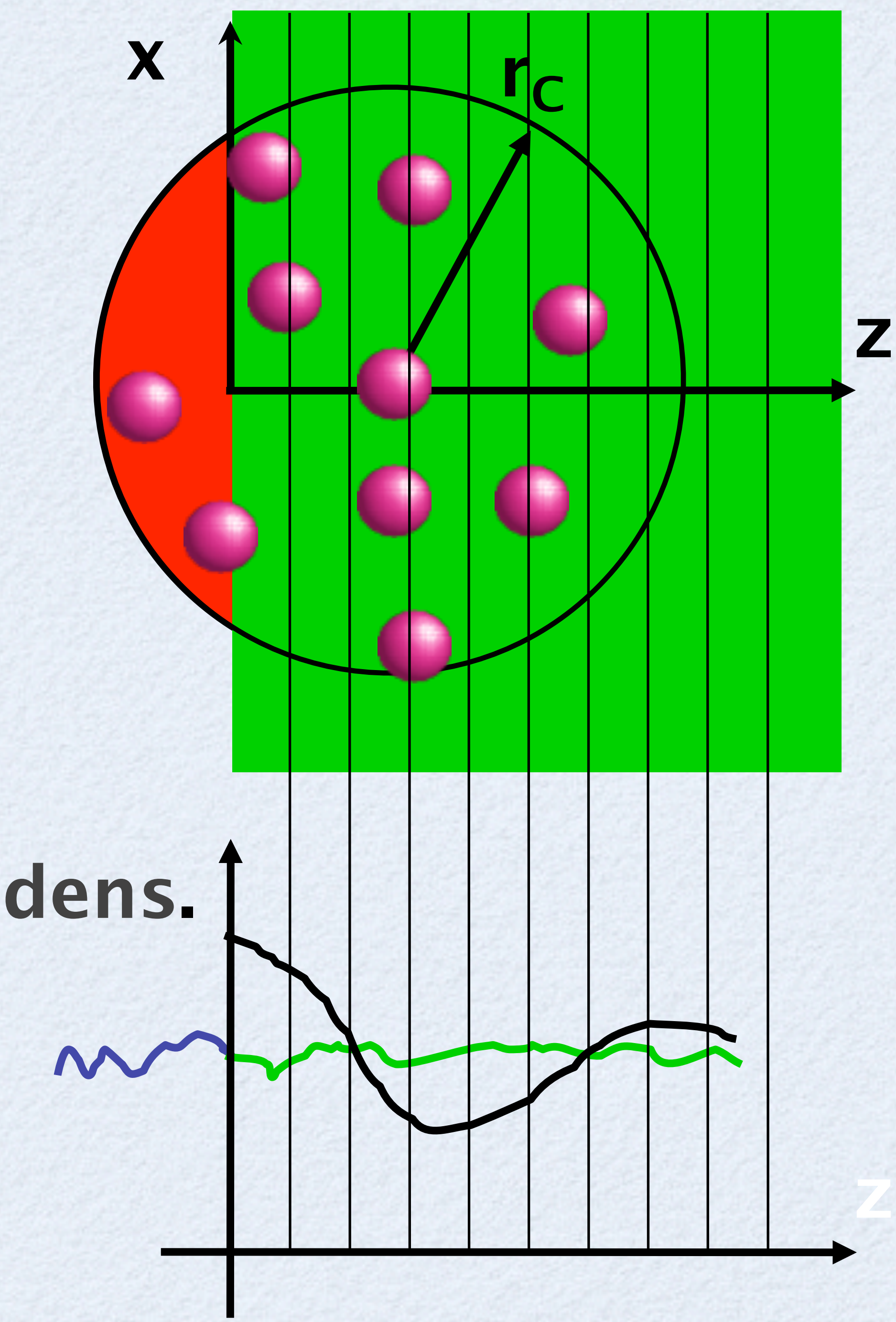
How can we account for the particles in the red domain?



NON_PERIODICITY & BOUNDARY FORCE

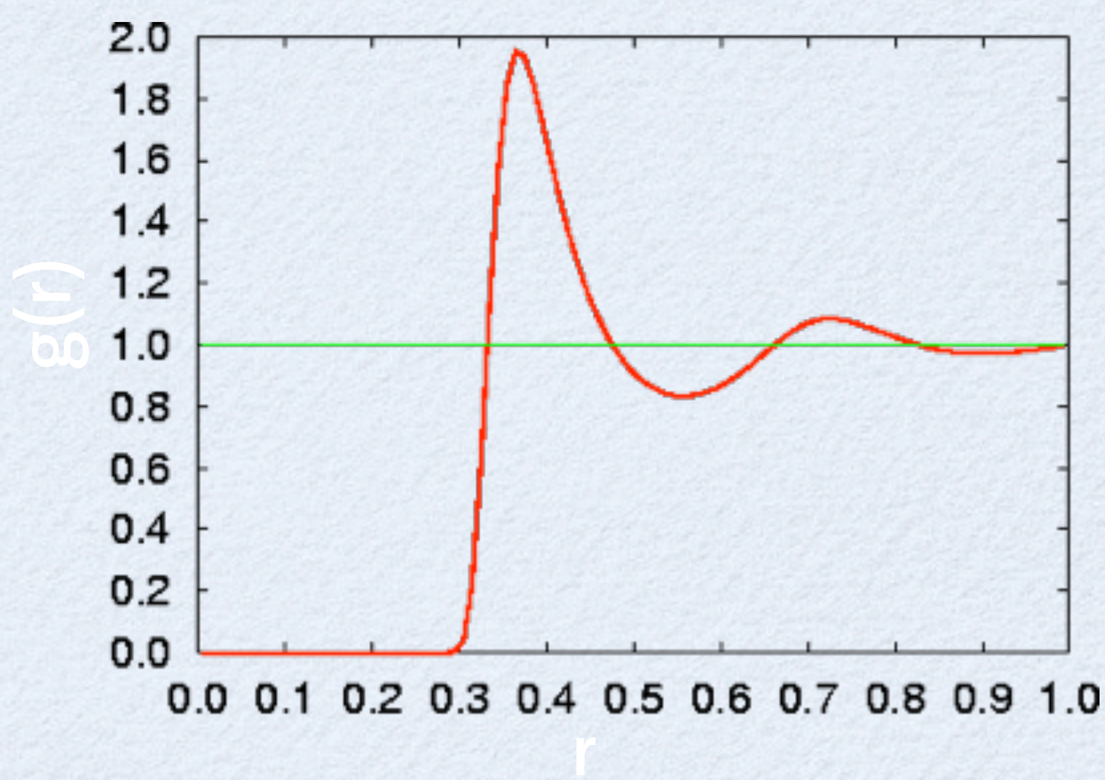
How can we account for the particles in the red domain?

Take fluid structure into account: g(r)



$$\rho(r) = \int_0^r 4\pi r'^2 \rho g(r') dr'$$

$$F_m(z) = -2\pi\rho \int_{\text{red}} g(r) \frac{\partial U(r)}{\partial r} \frac{z}{r} x dx dz$$

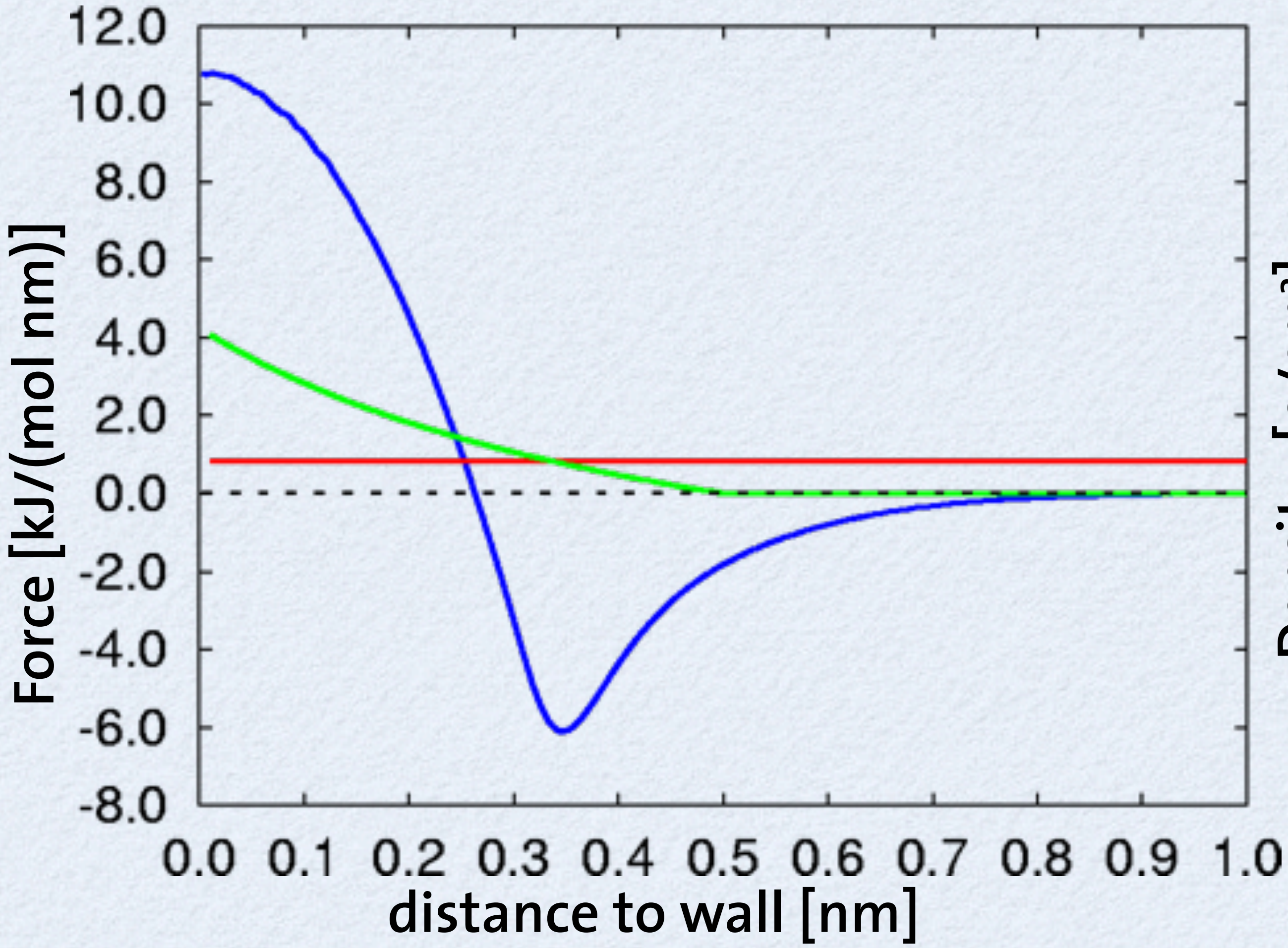


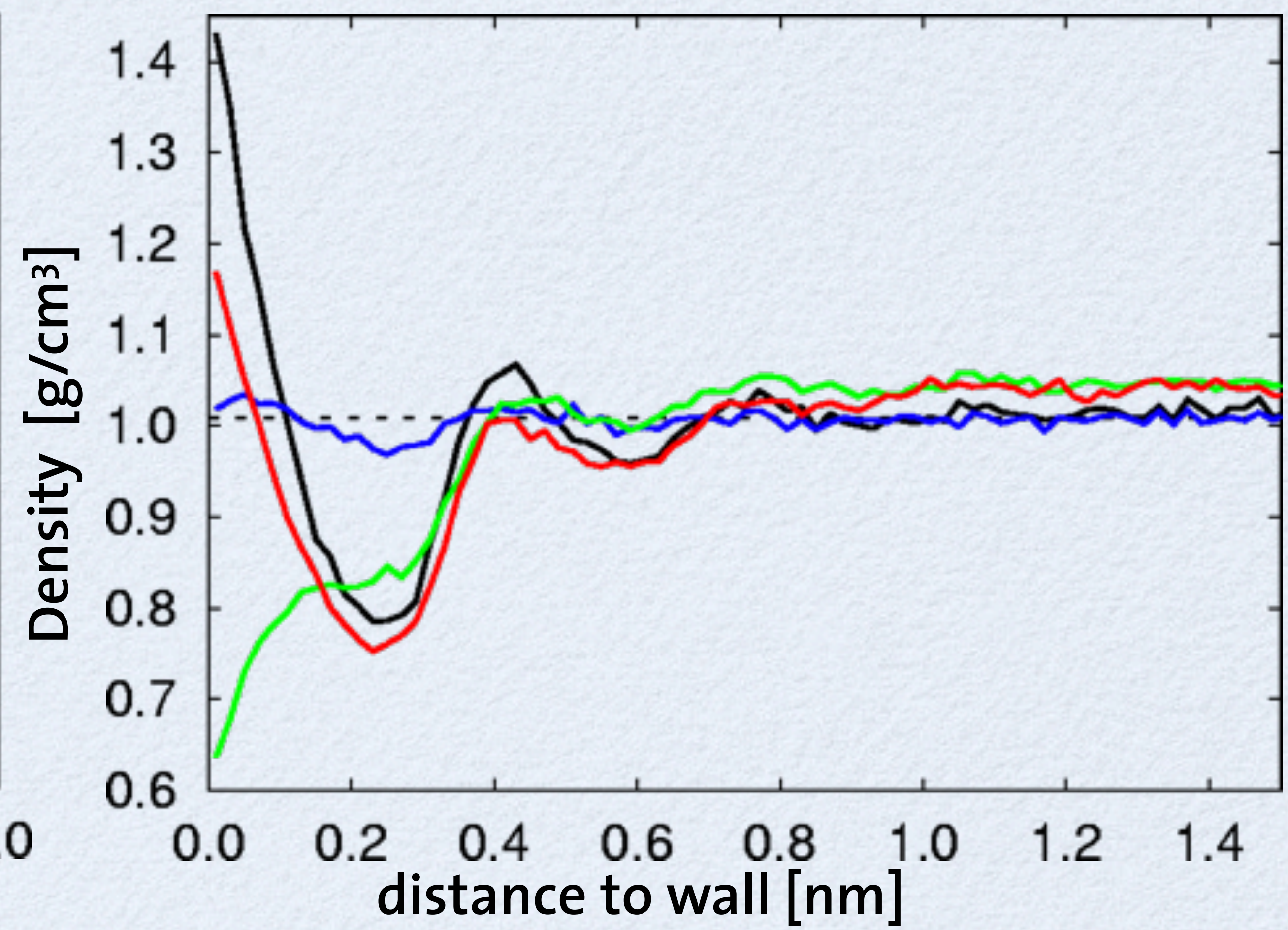
215 K
1.0 gcm^{-3}

A comparison of Forces

No force

Uniform distribution (O'Connell 1995[A])





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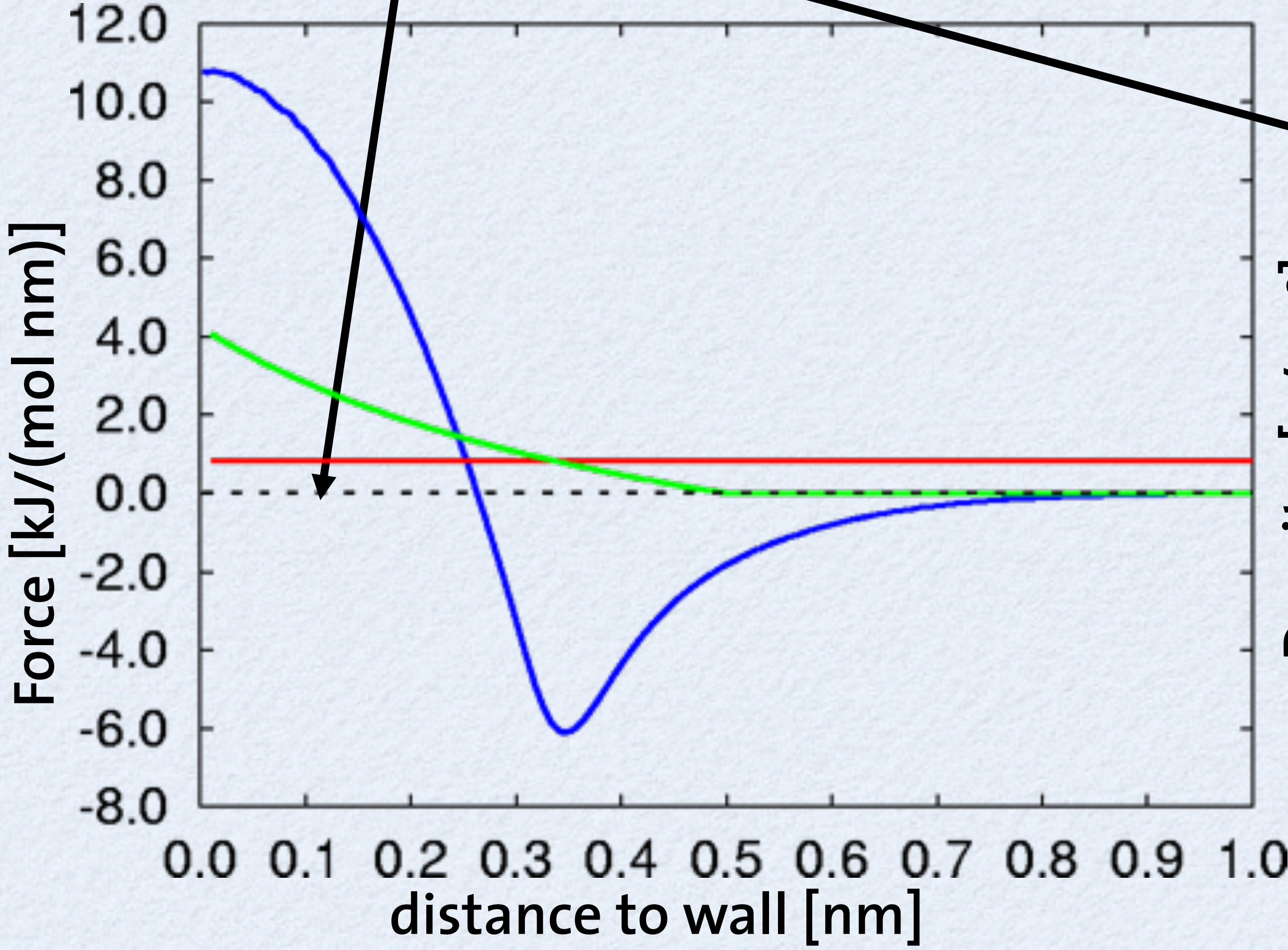

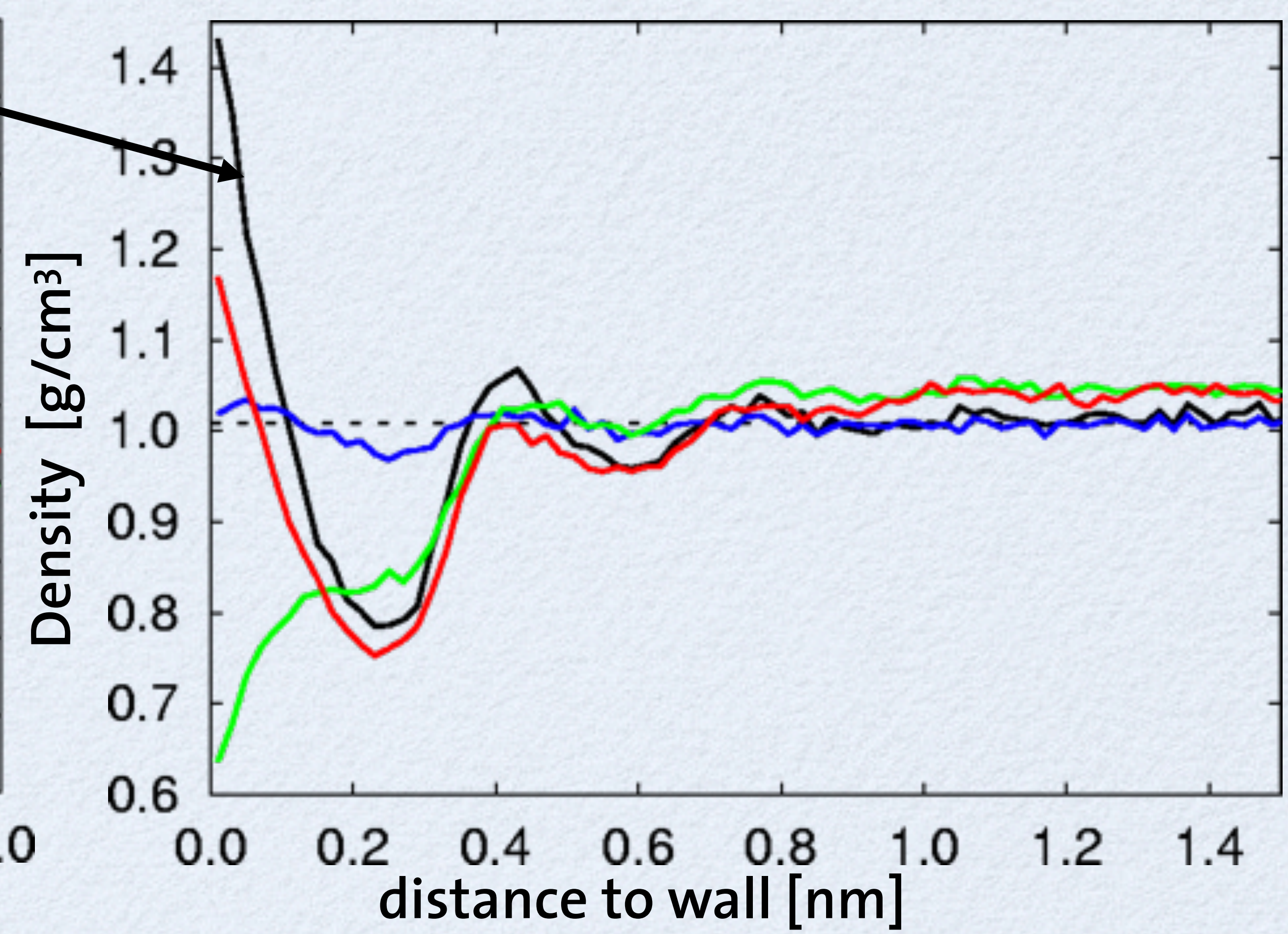

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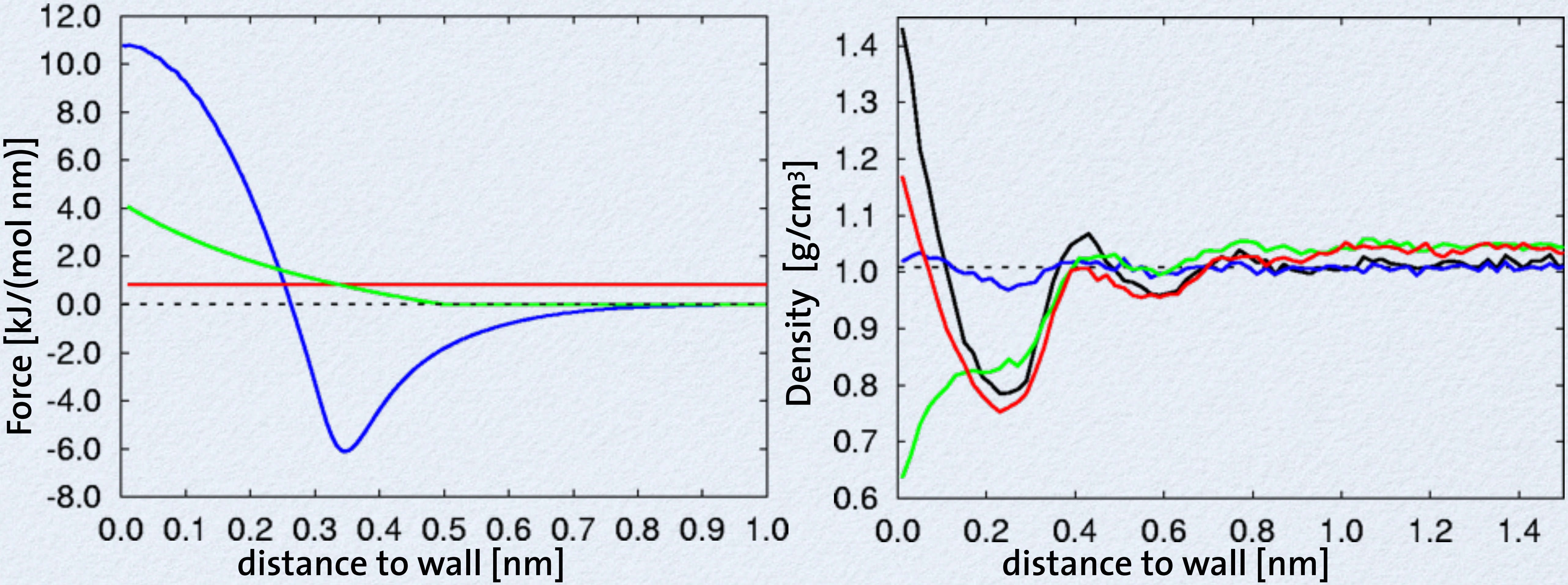

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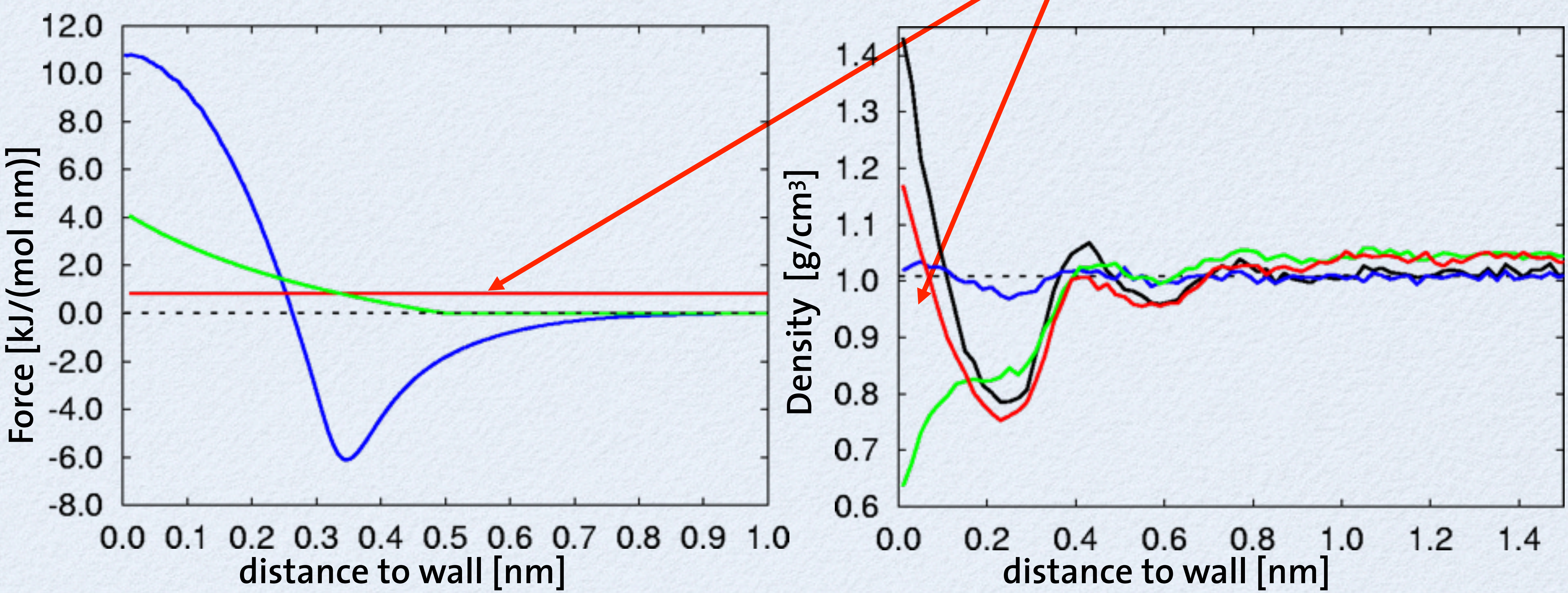

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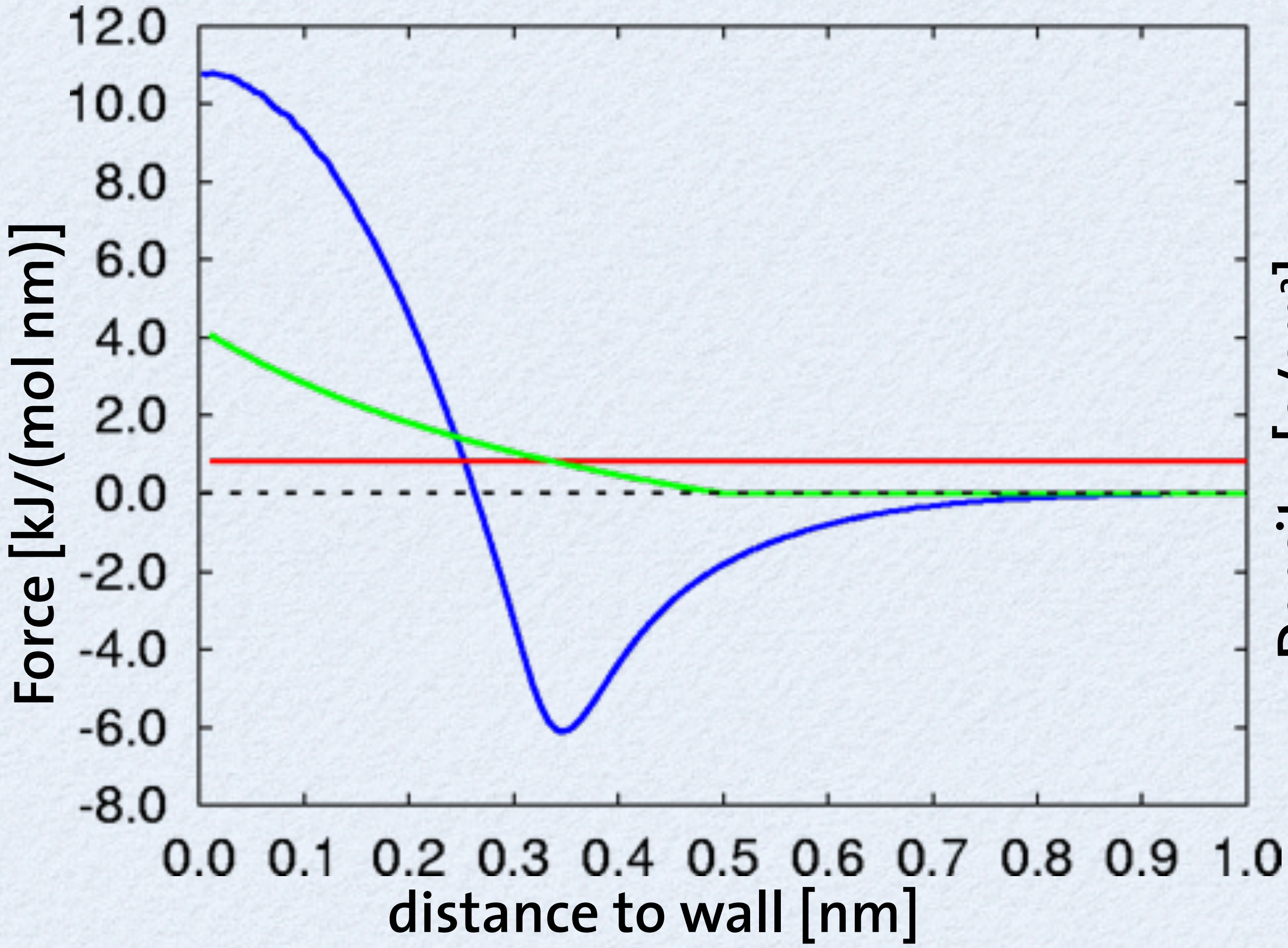

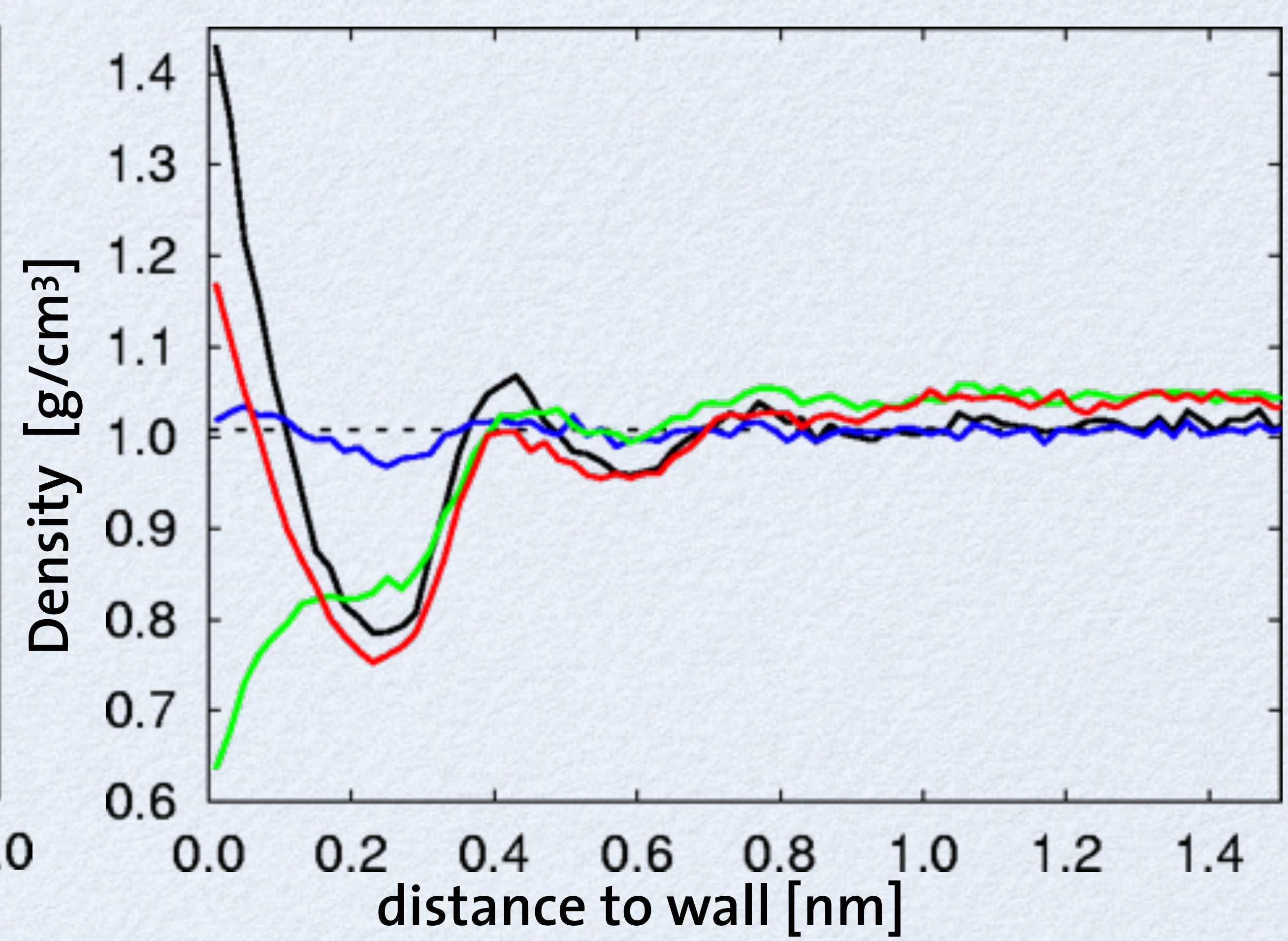

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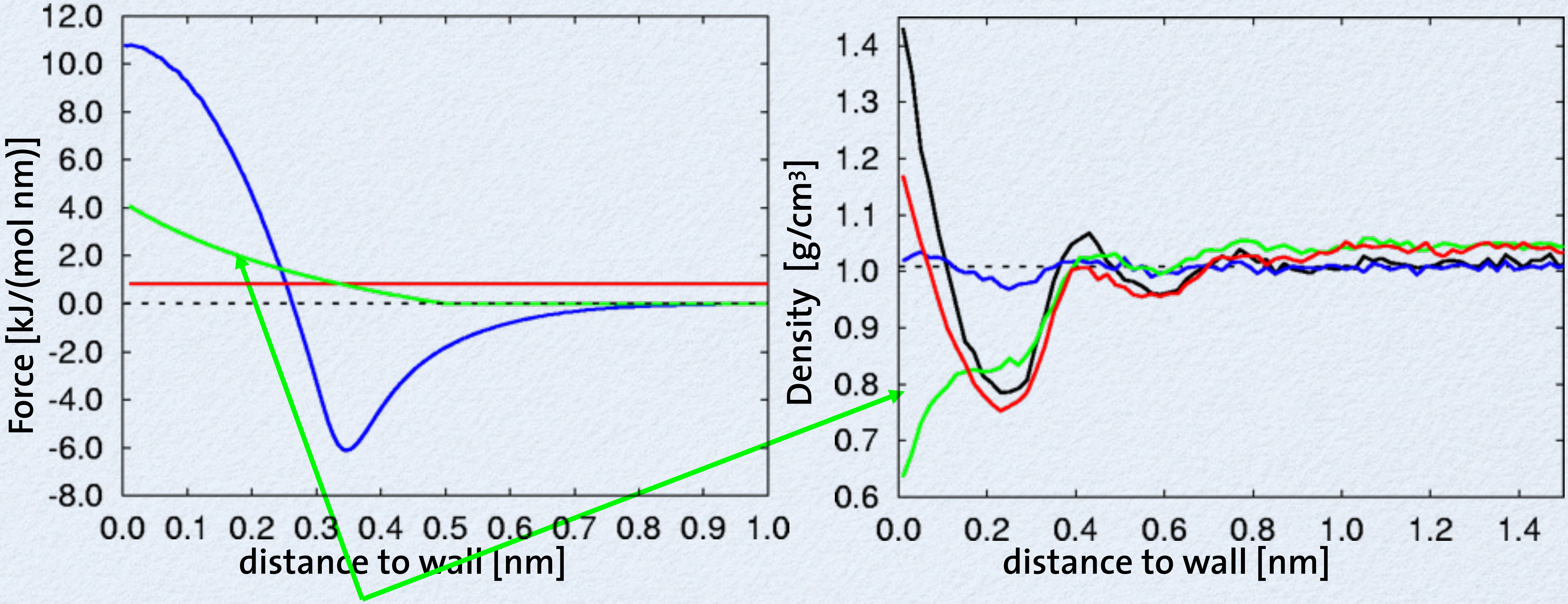

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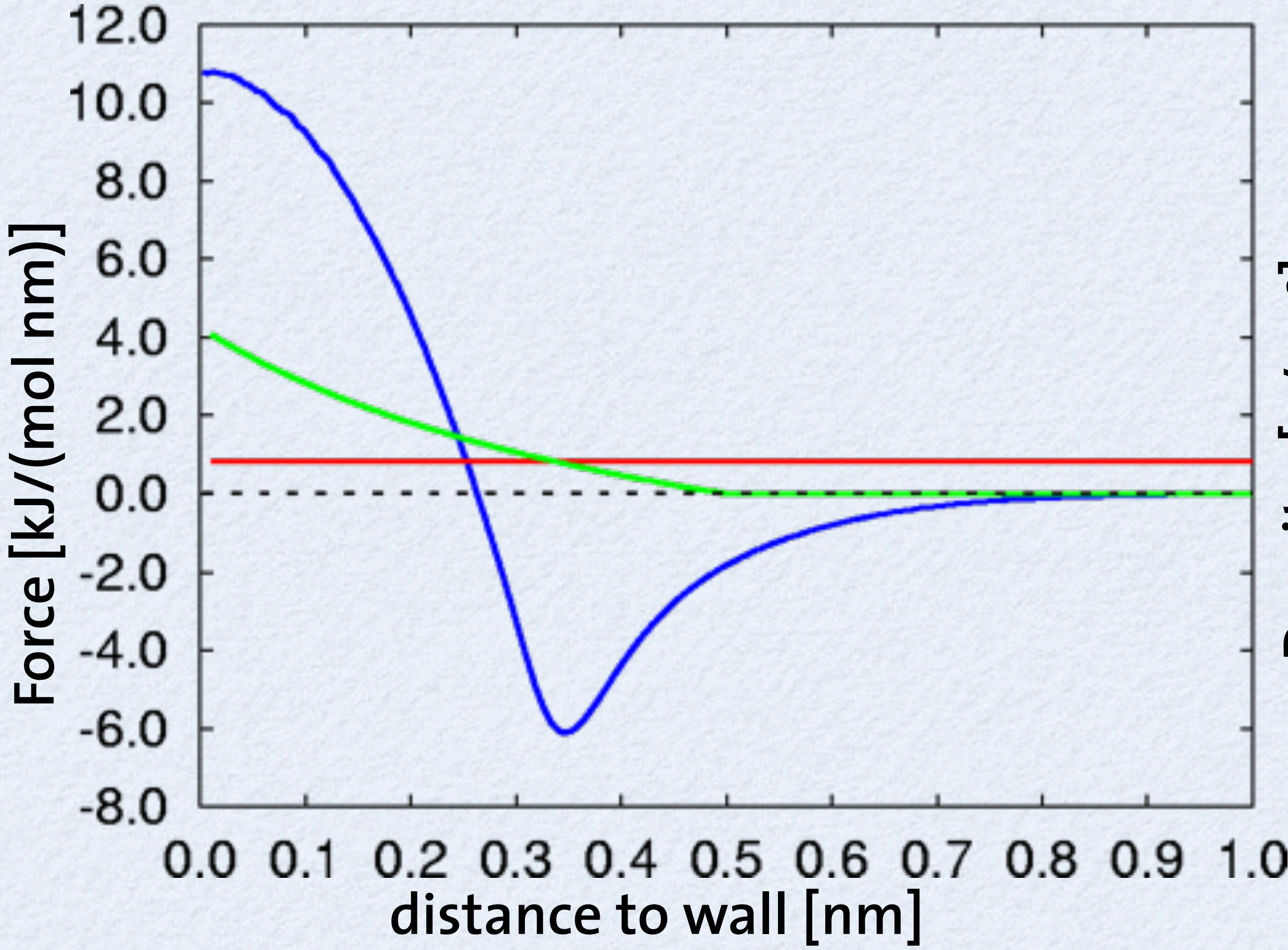

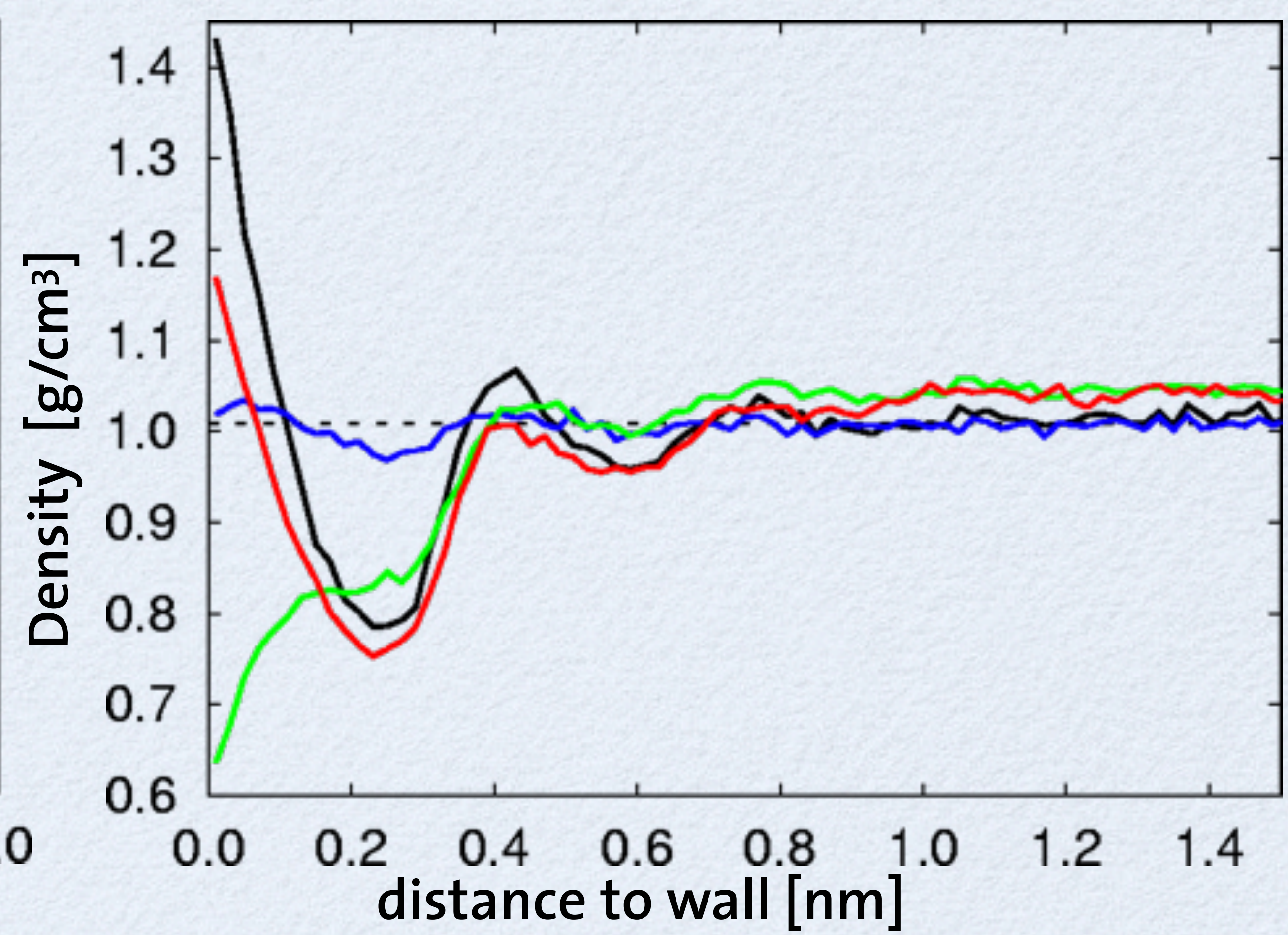

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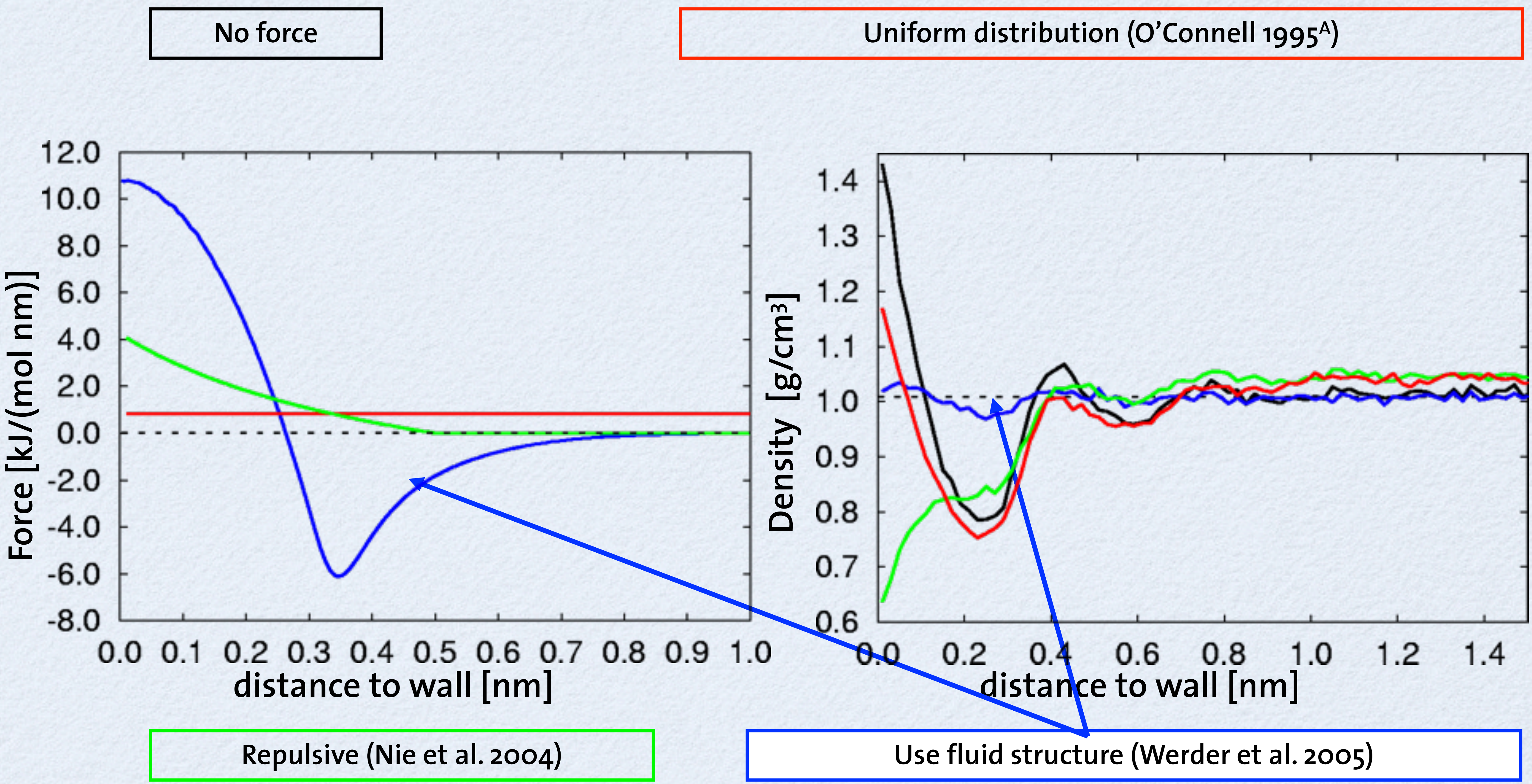

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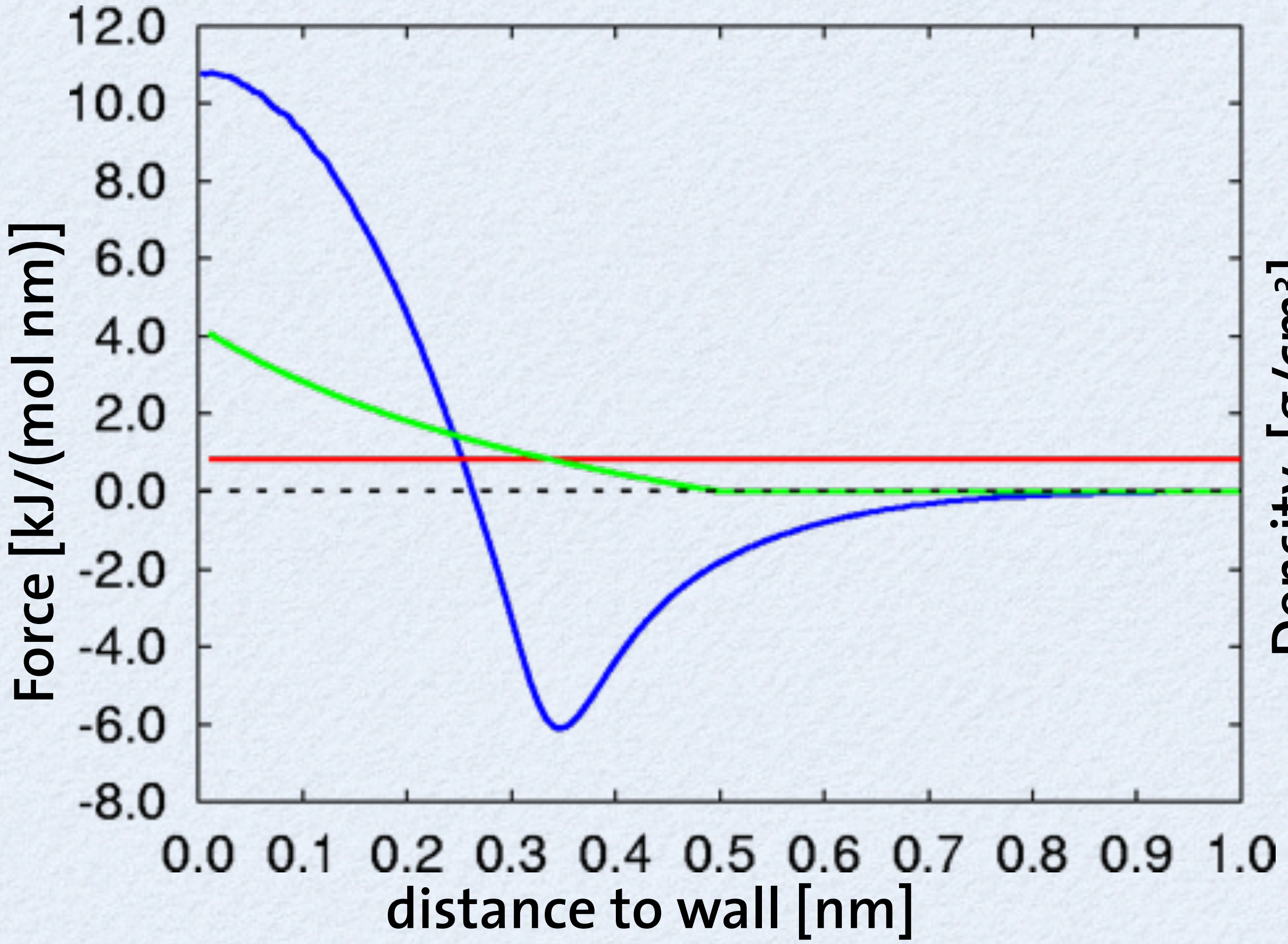

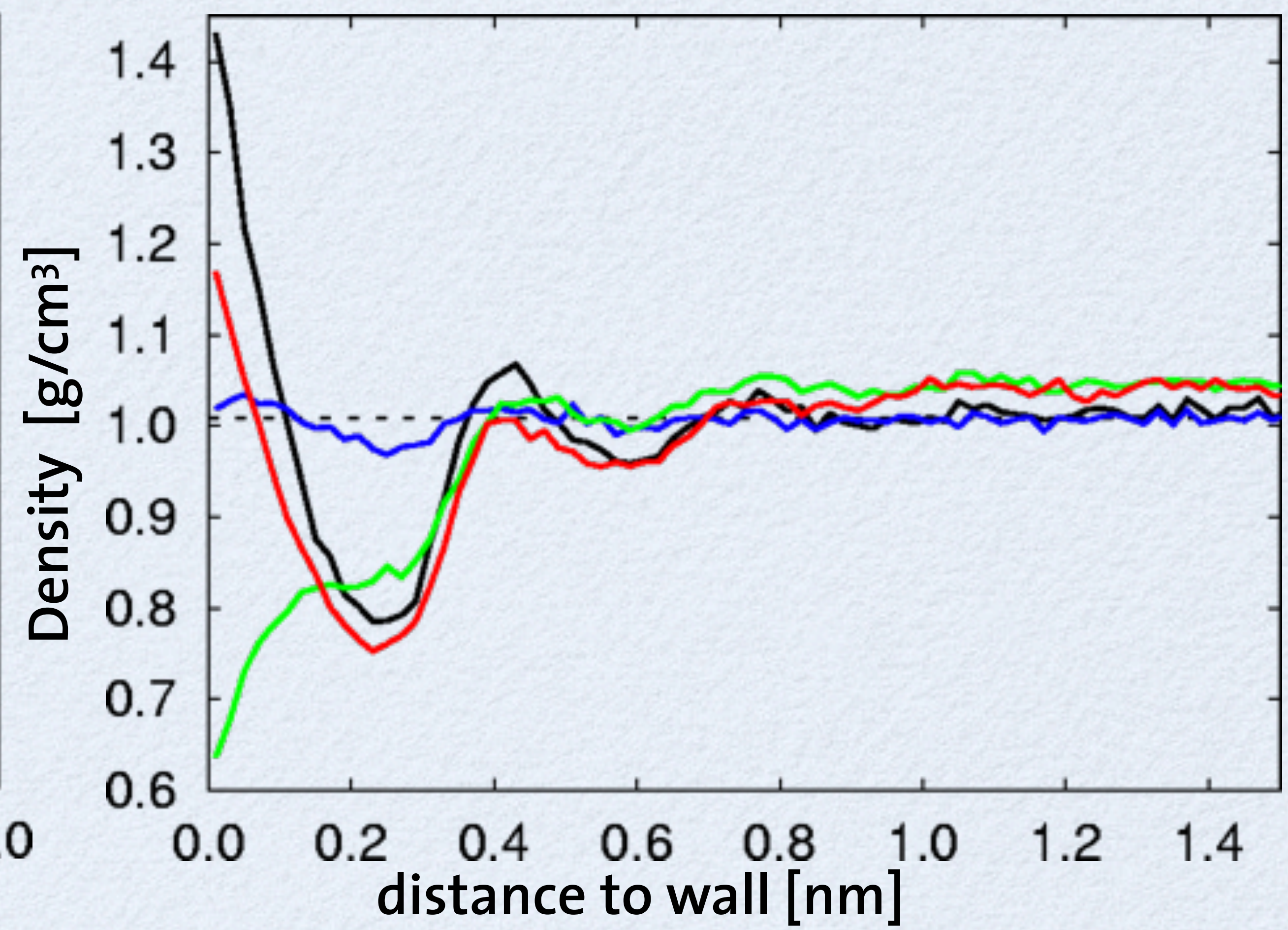

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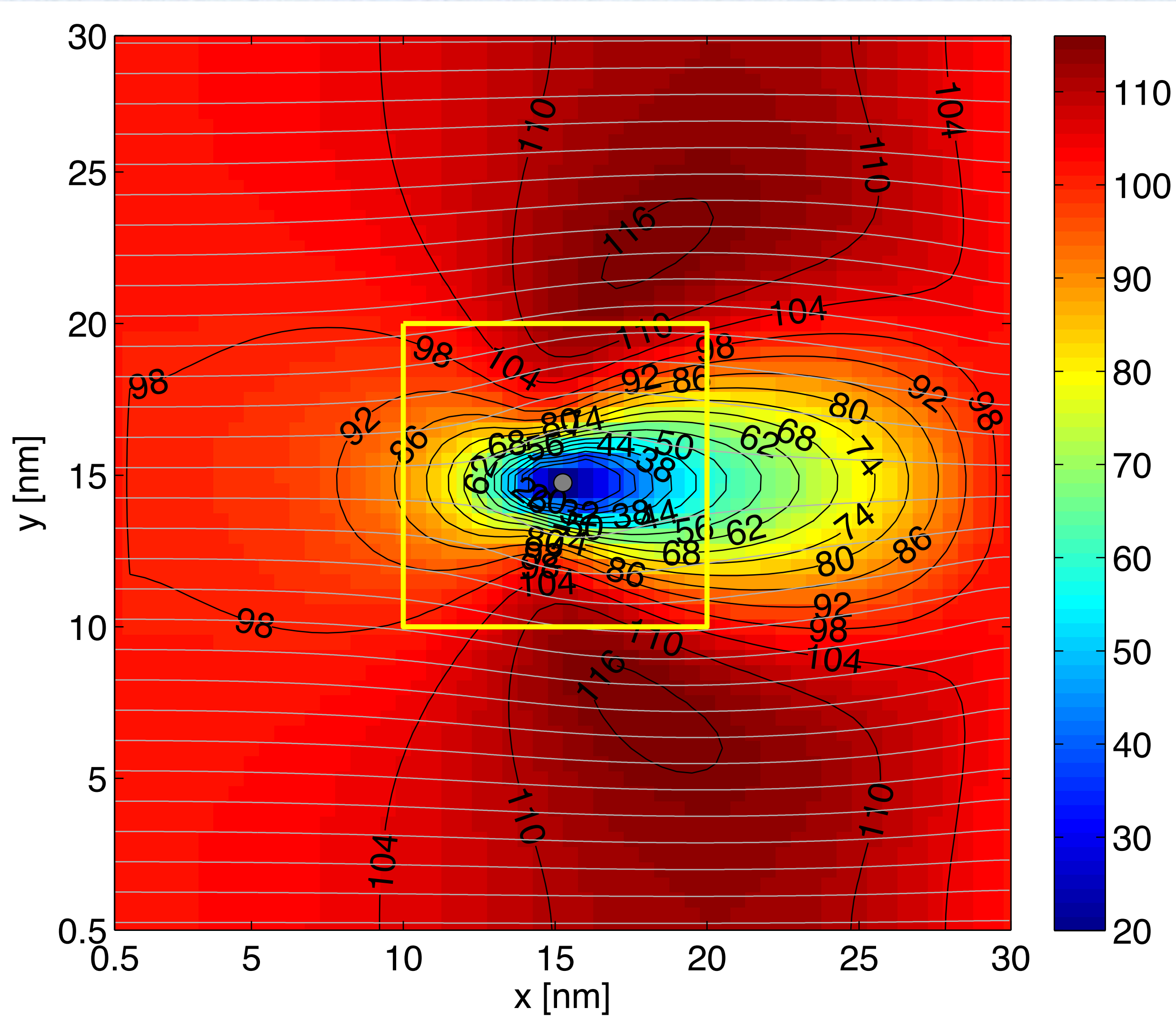
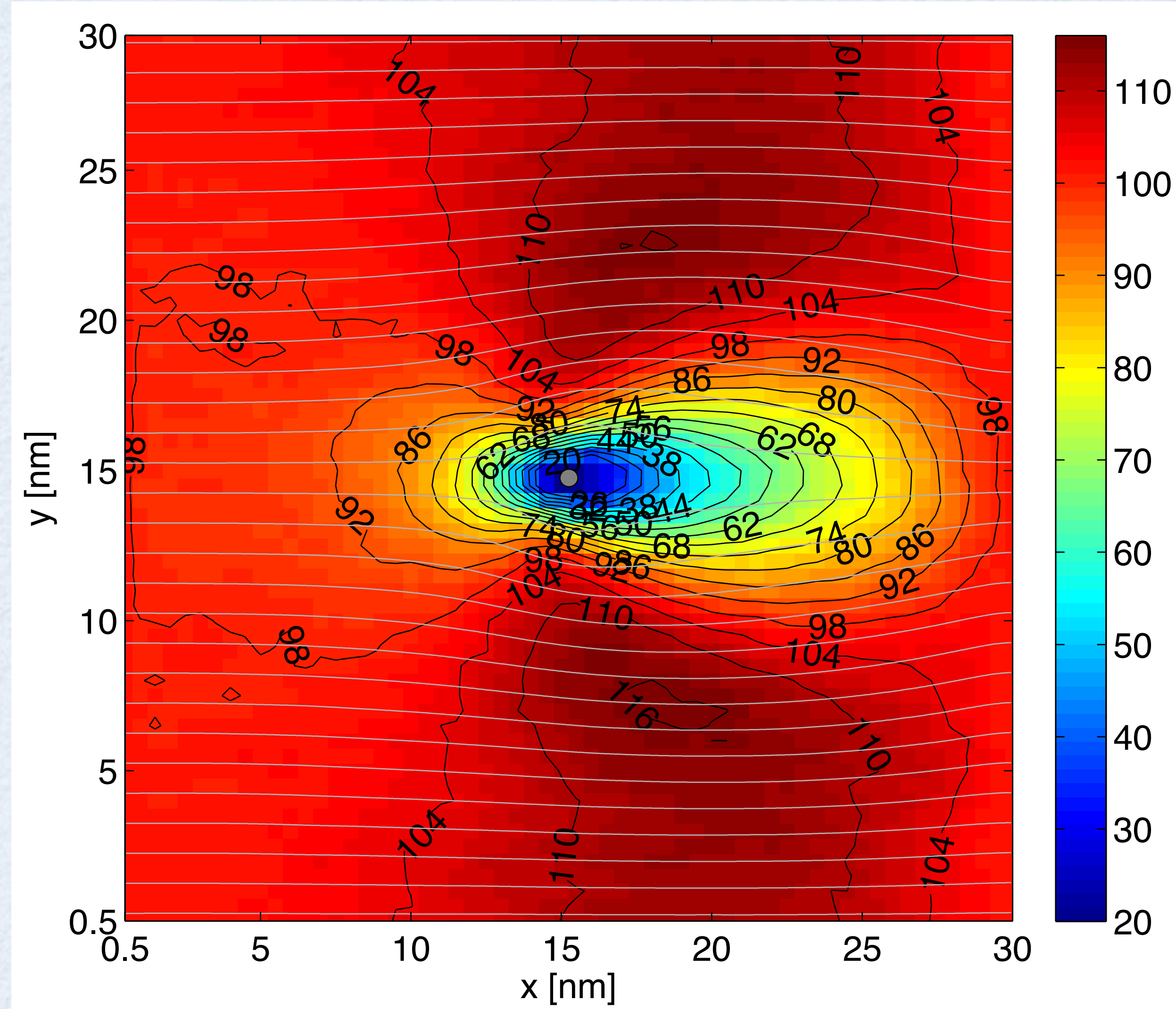
MD vs Hybrid scheme



Hybrid solution



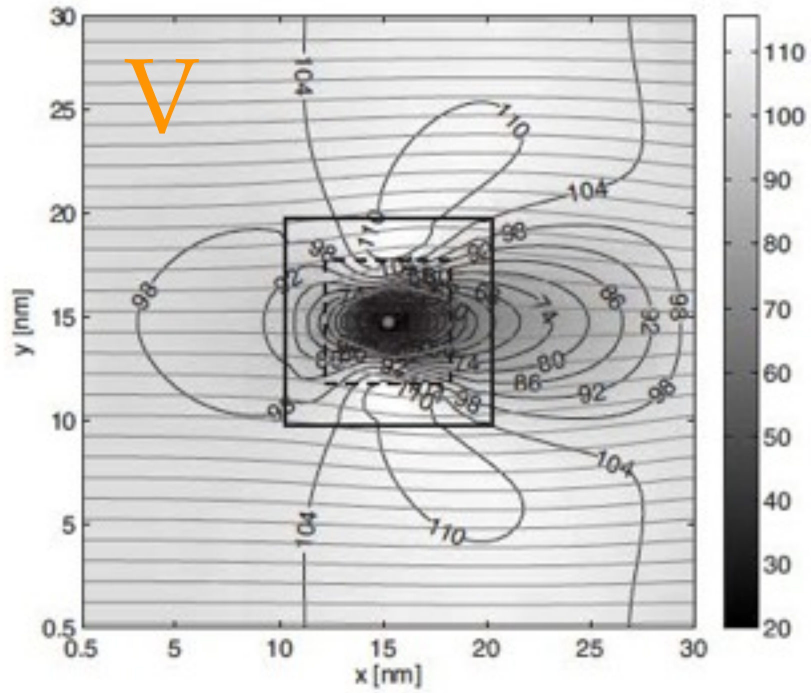
Reference MD solution

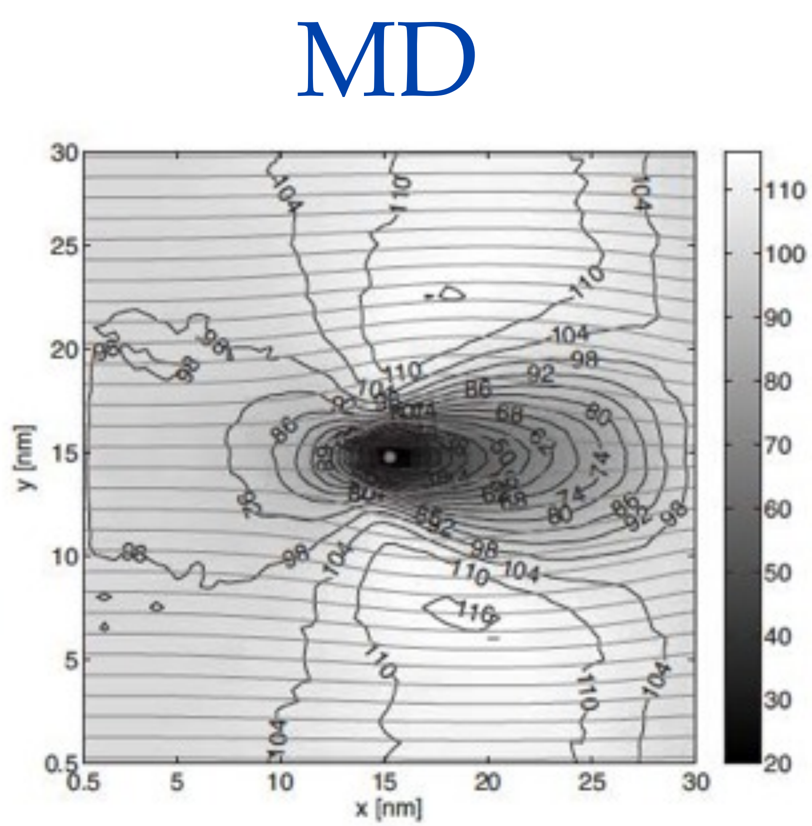
Relative Error ~ 1.3%

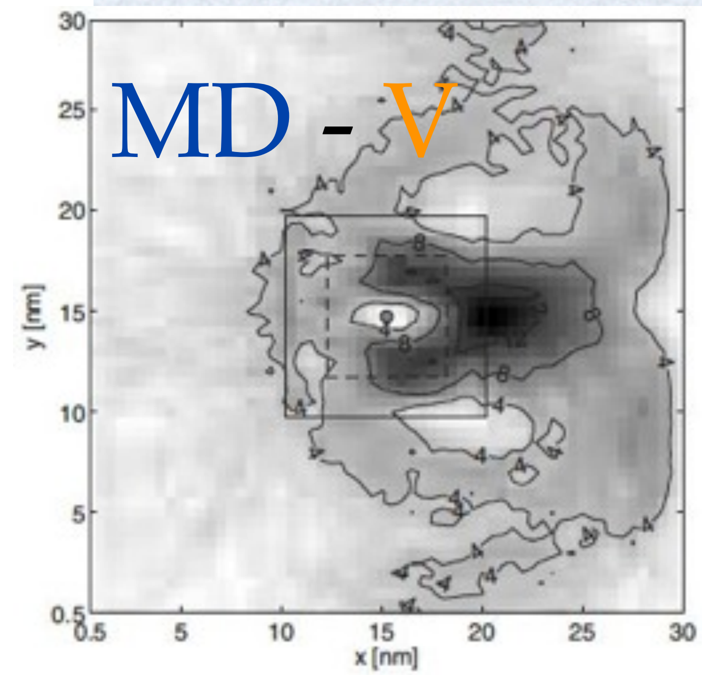
The hybrid scheme is ~ (L/R)3 times faster for a computational domain of size L and a MD subdomain of size R.**

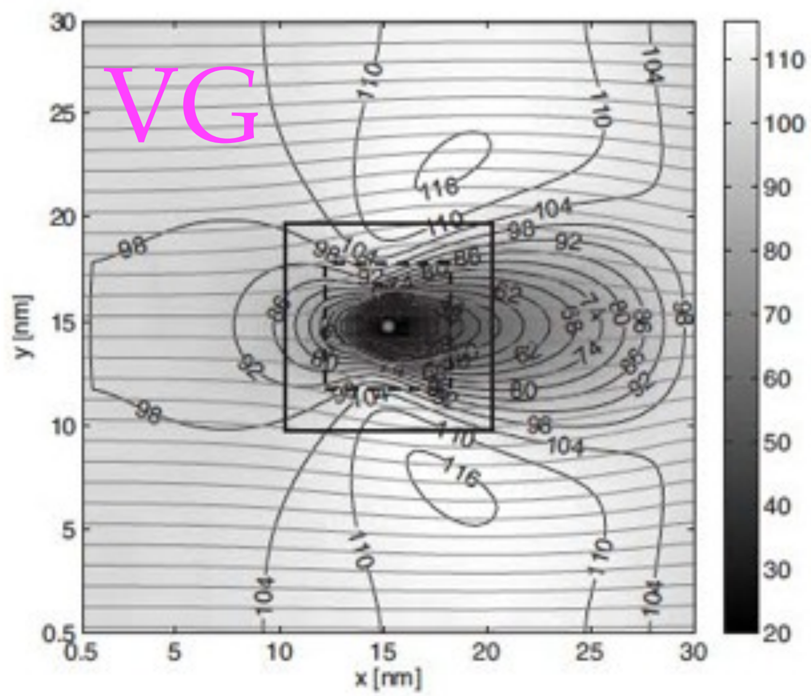
A. Dupuis, E.M. Kotsalis, and PK., Coupling lattice Boltzmann and molecular dynamics for dense fluids. Phys. Rev. E, 75: 046704, 2007

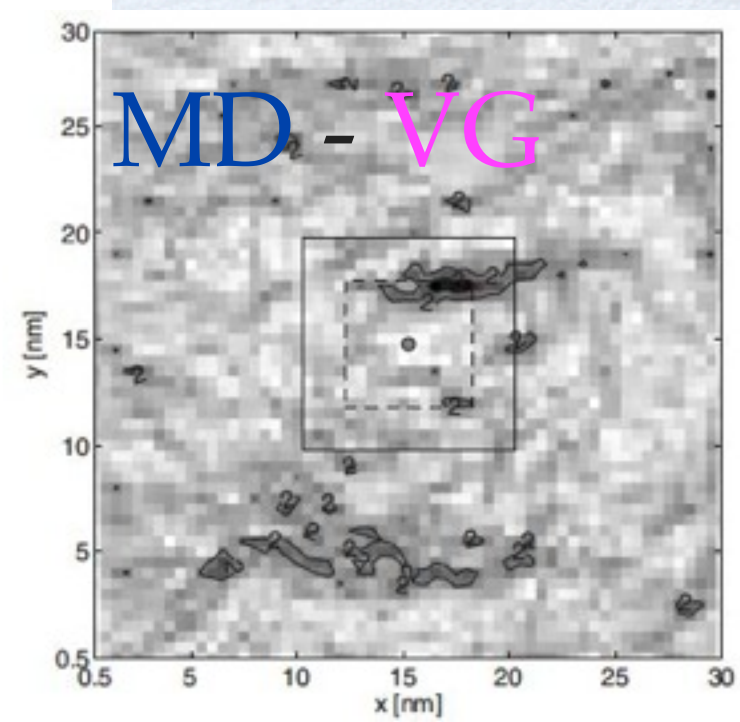
Errors for Different Couplings



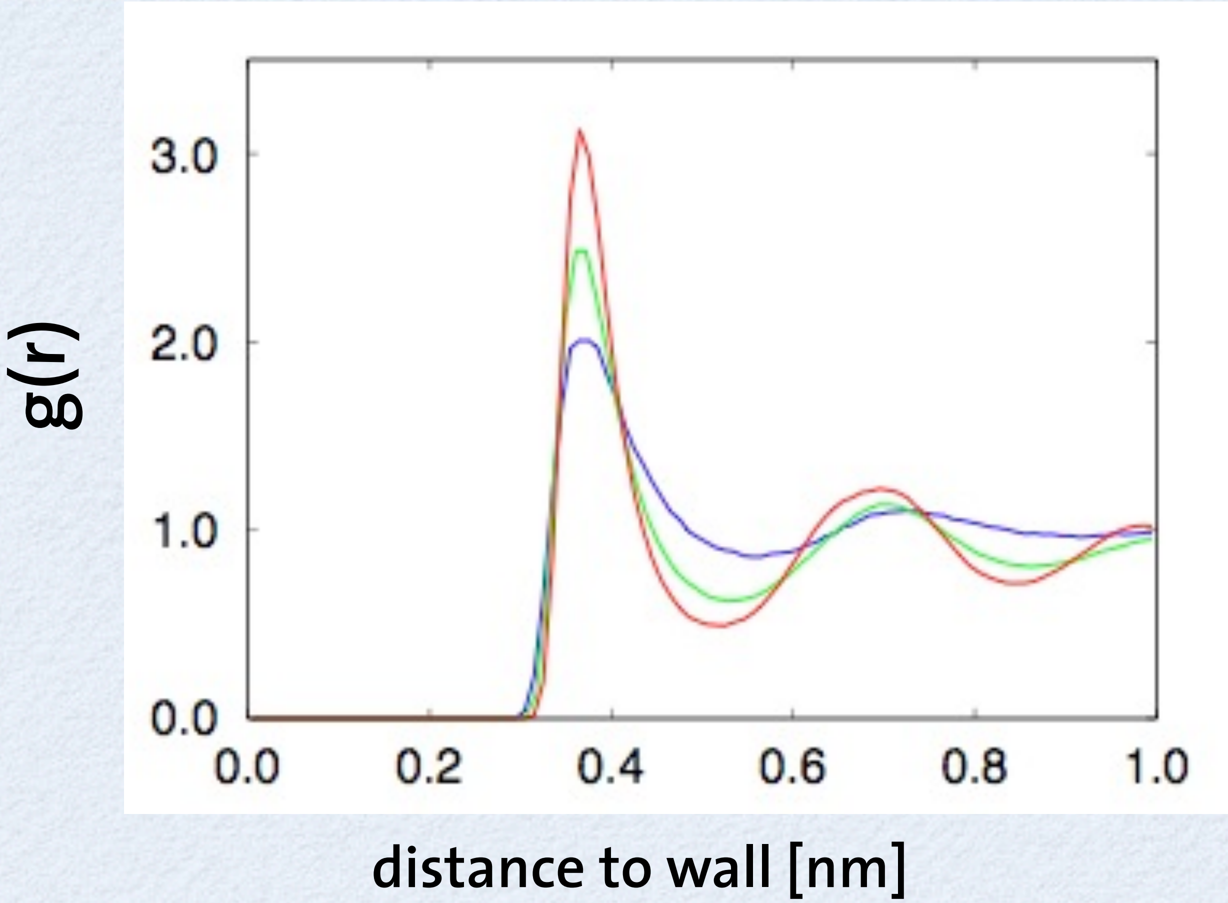


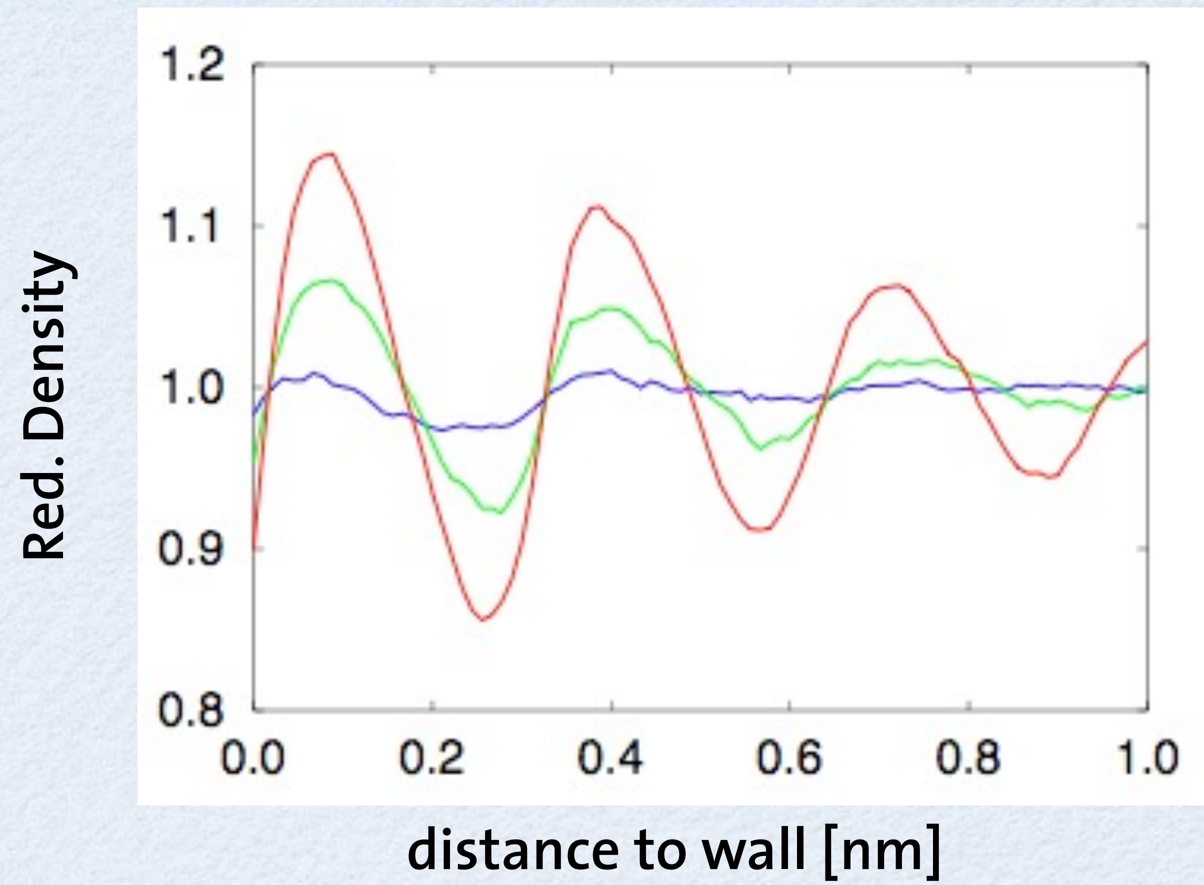






The problem with density variations





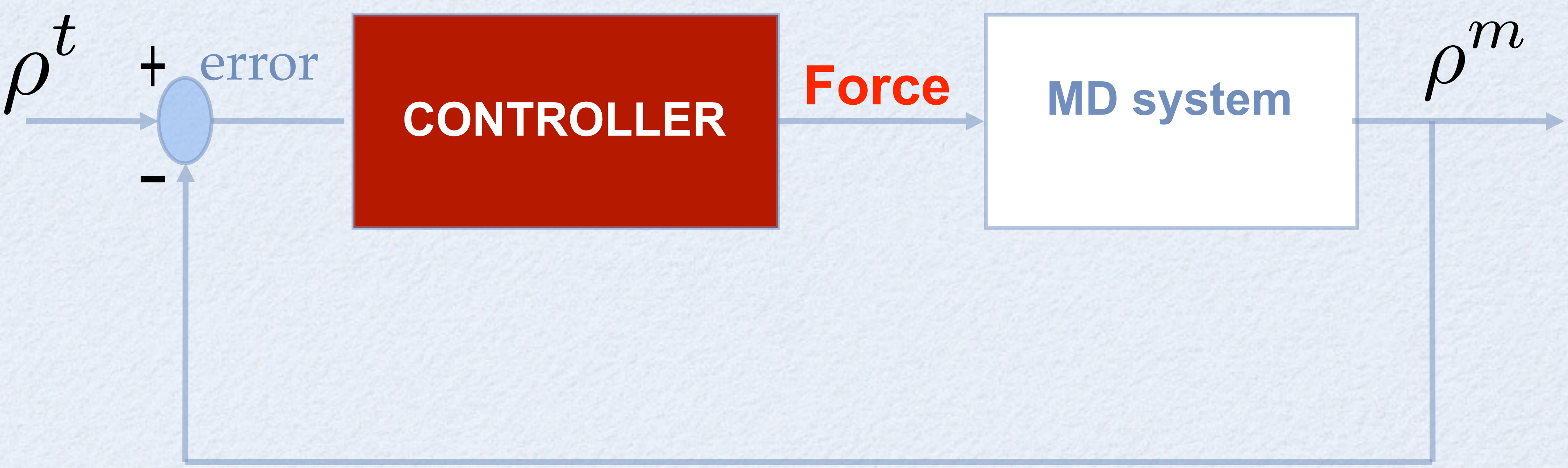
- (red) $T = 84K, \rho = 1.5 gcm^{-3}$
- (green) $T = 131K, \rho = 1.35 gcm^{-3}$
- (blue) $T = 215K, \rho = 1.0 gcm^{-3}$

- Density variations depend on liquid state
- **Amplitude** proportional to **structural correlations** in the liquid

a simple Control approach to Coupling

E.M. Kotsalis, J.H. Walther, and P. Koumoutsakos., Phys. Rev. E, 2007.

- Controlling of the external boundary force
- **measured density** ρ^m **=>** target density ρ^t

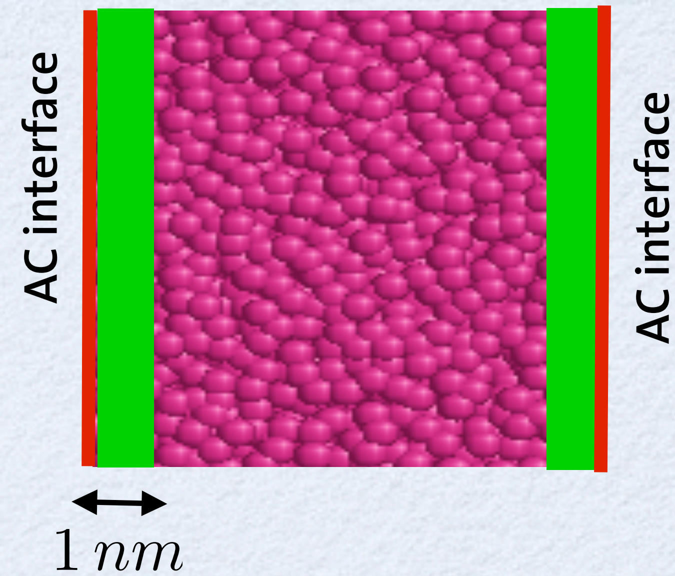


$$e(r) = \rho^t(r) - \rho^m(r)$$

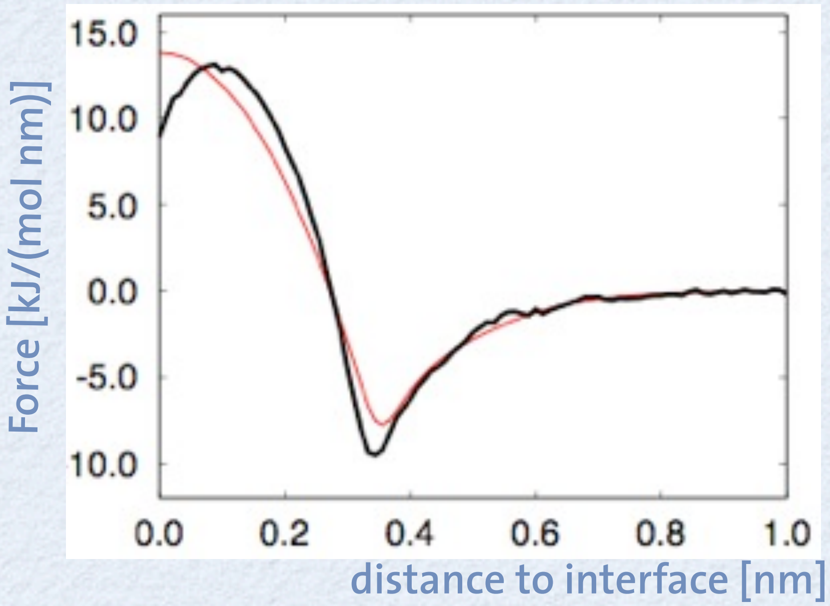
Force = $k\widetilde{\nabla e(r)}$

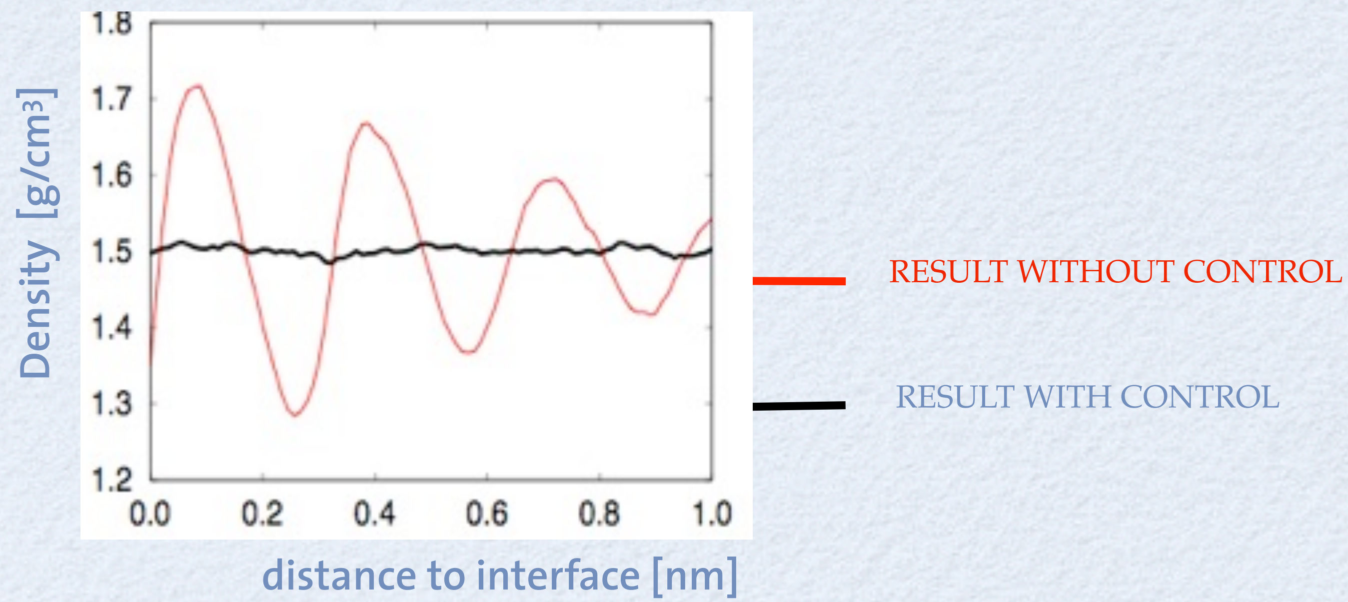
Results with Control Approach I

- at equilibrium (no flow)
- $T = 84K, \rho = 1.5gcm^{-3}$



AC interface = Elastic Boundary+External Force

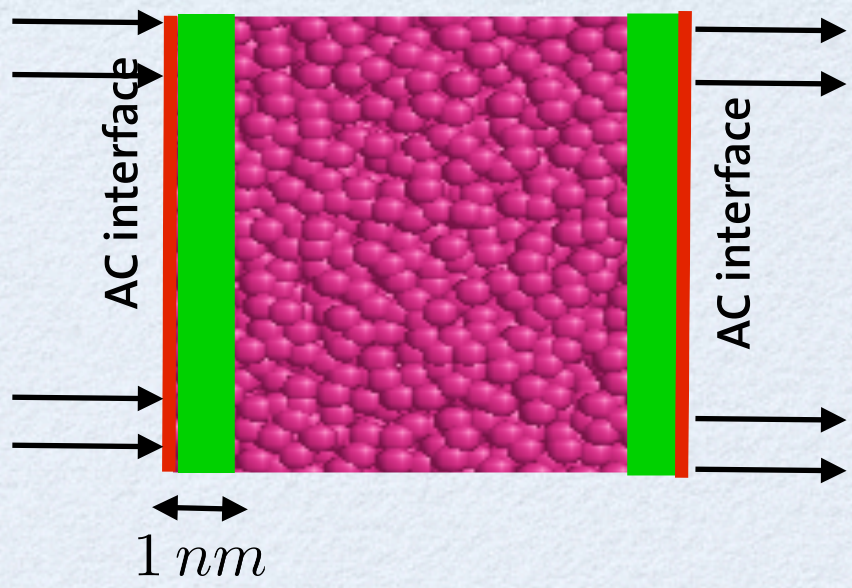




Controller deduces the boundary force

Results with Control Approach II

- uniform flow
- $T = 131K, \rho = 1.35gcm^{-3}$



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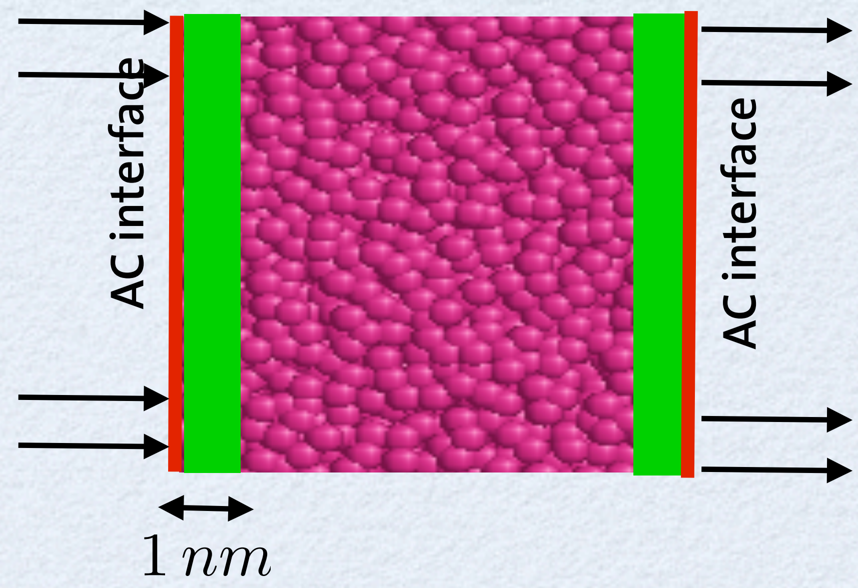
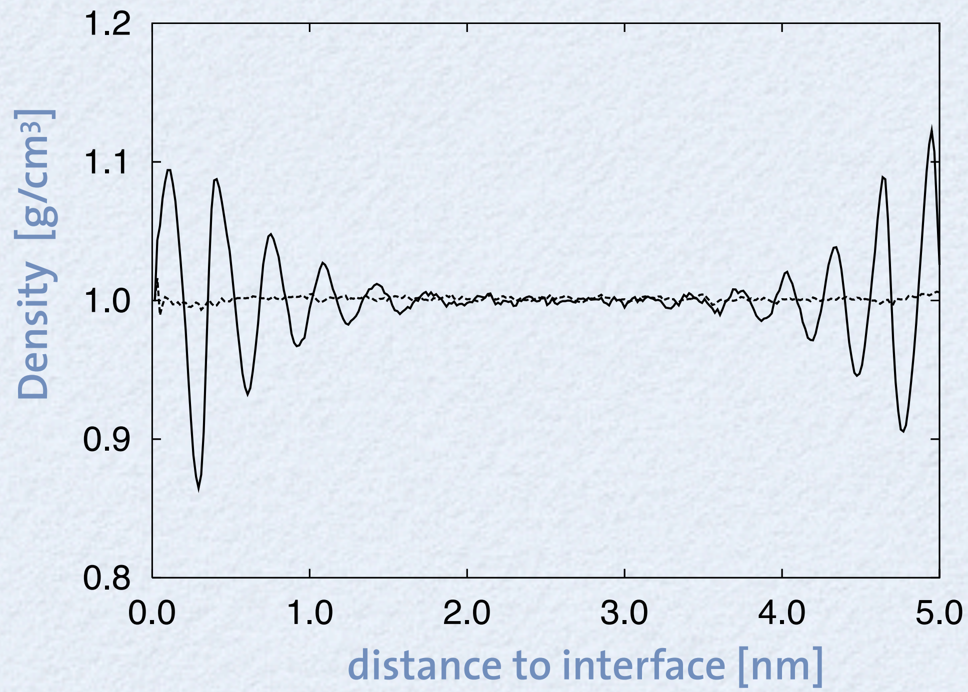
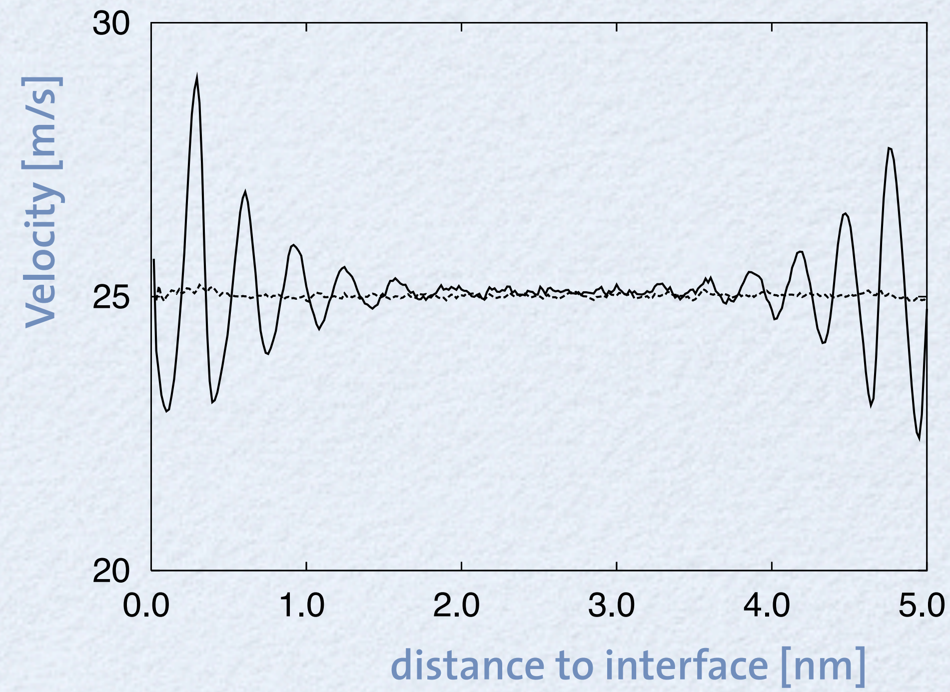


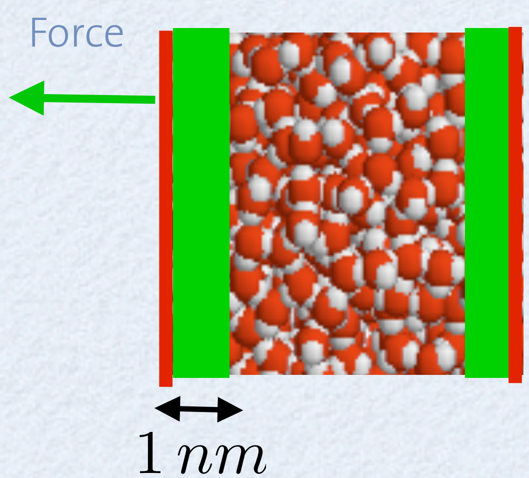




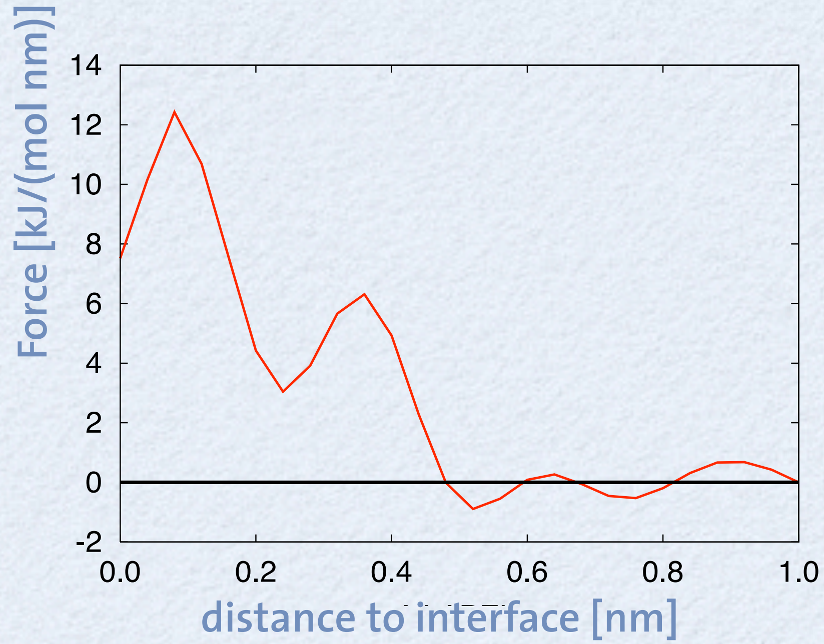
RESULT WITH CONTROL

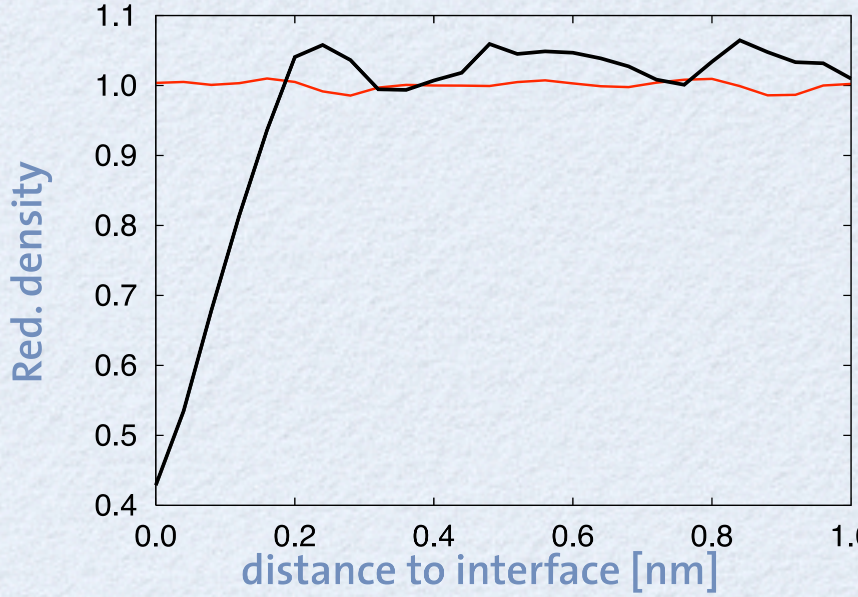
RESULT WITHOUT CONTROL

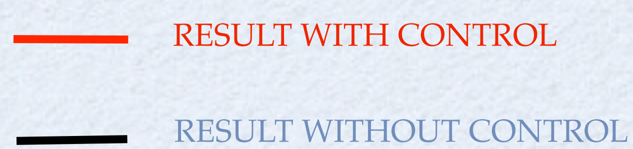
AC Interface for Water at Equilibrium



1D embedding







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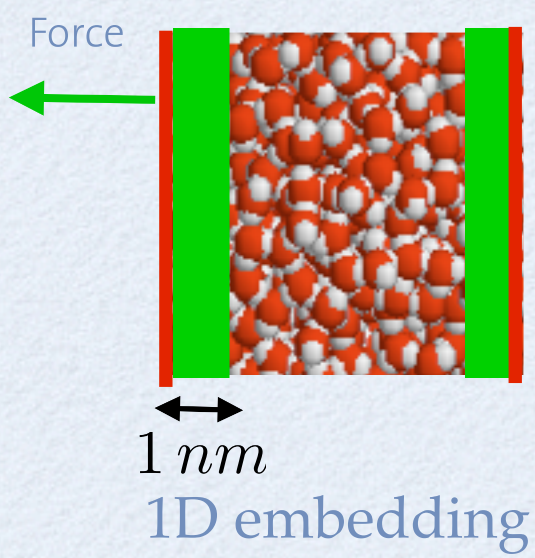
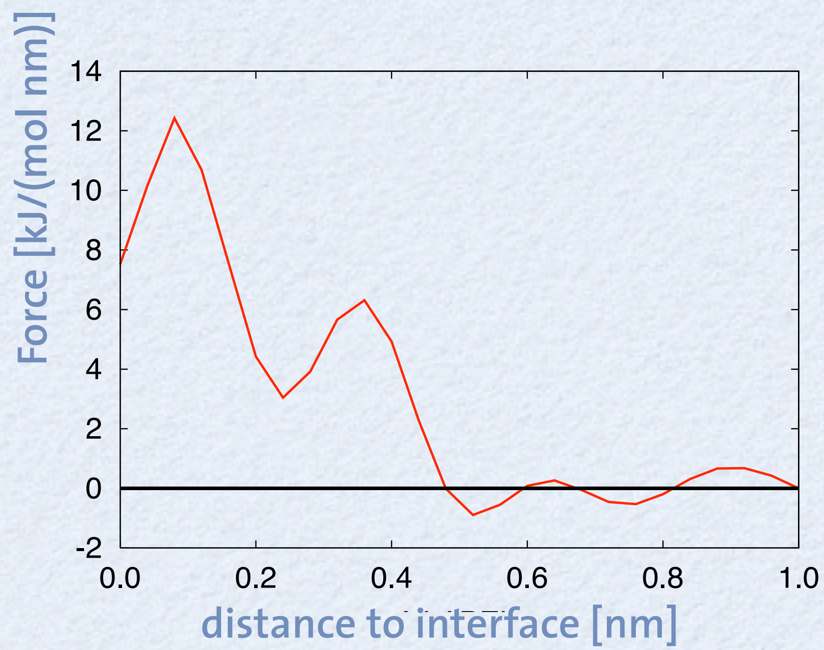
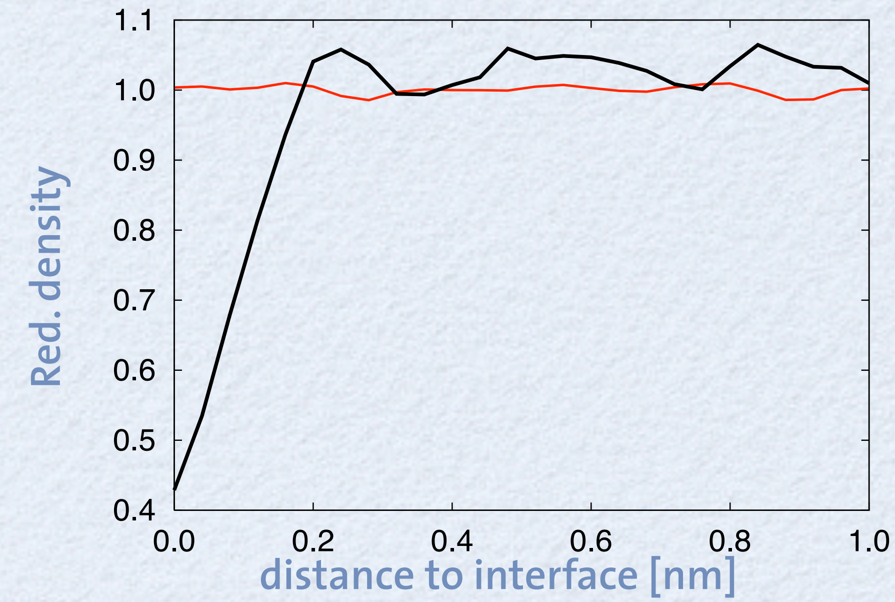
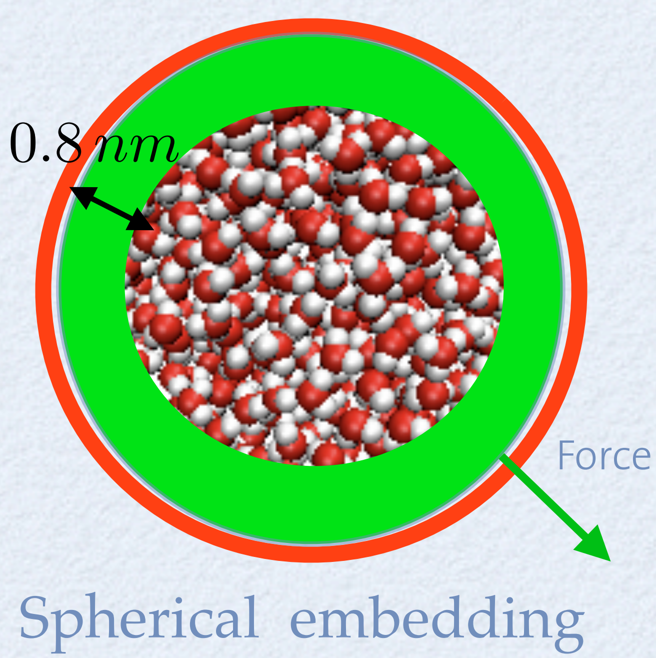


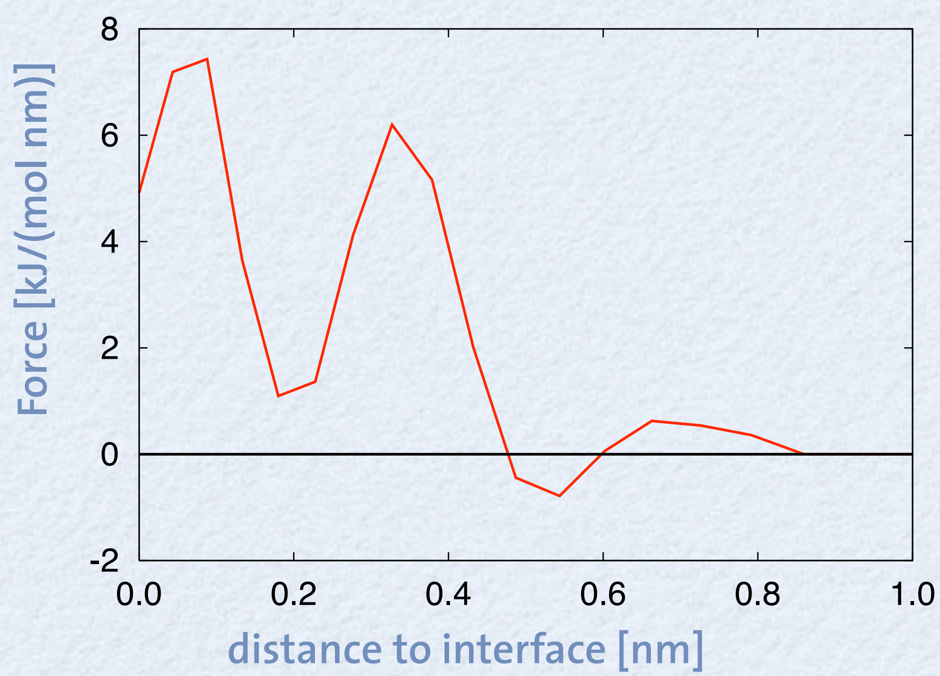


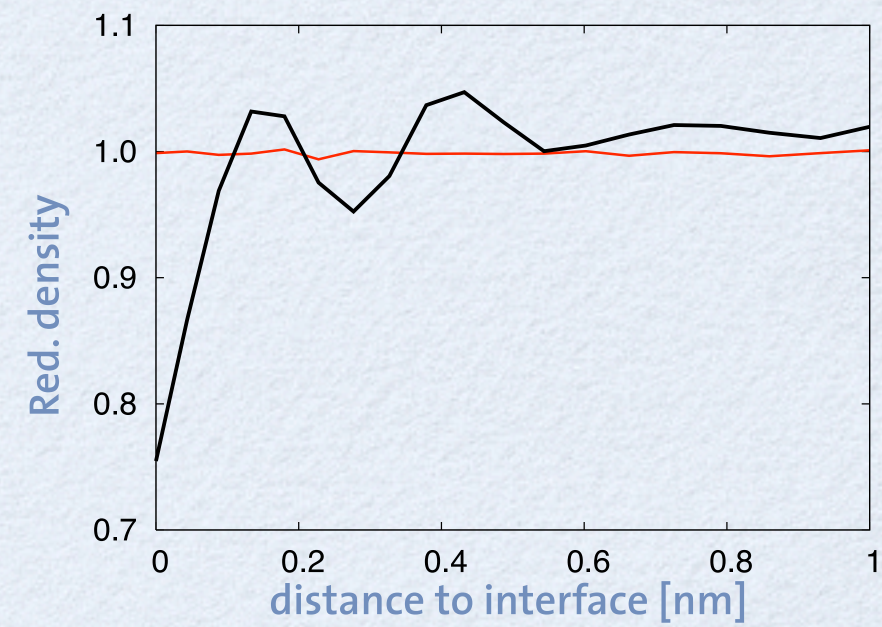


RESULT WITH CONTROL

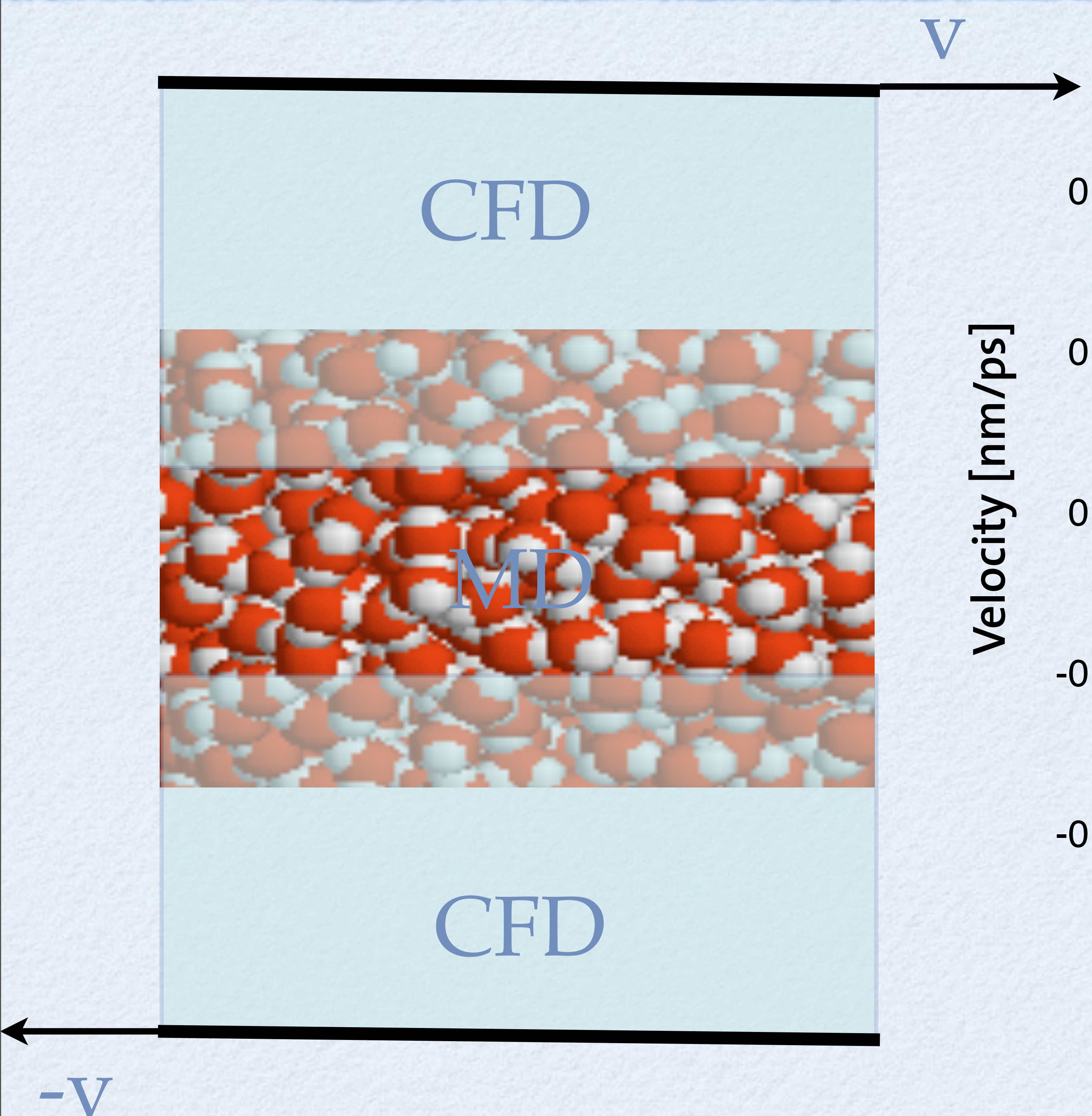
RESULT WITHOUT CONTROL

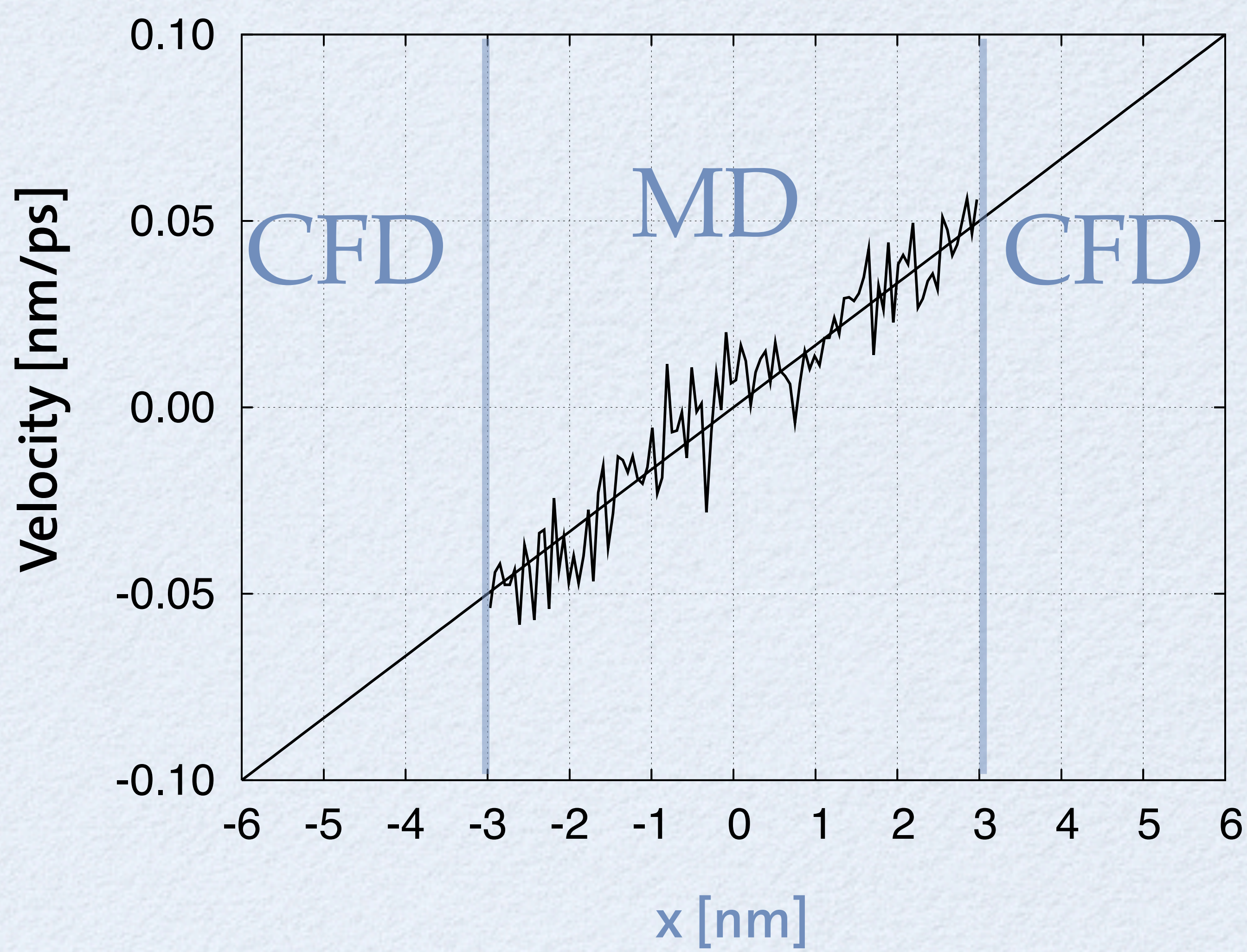






Water Couette Flow





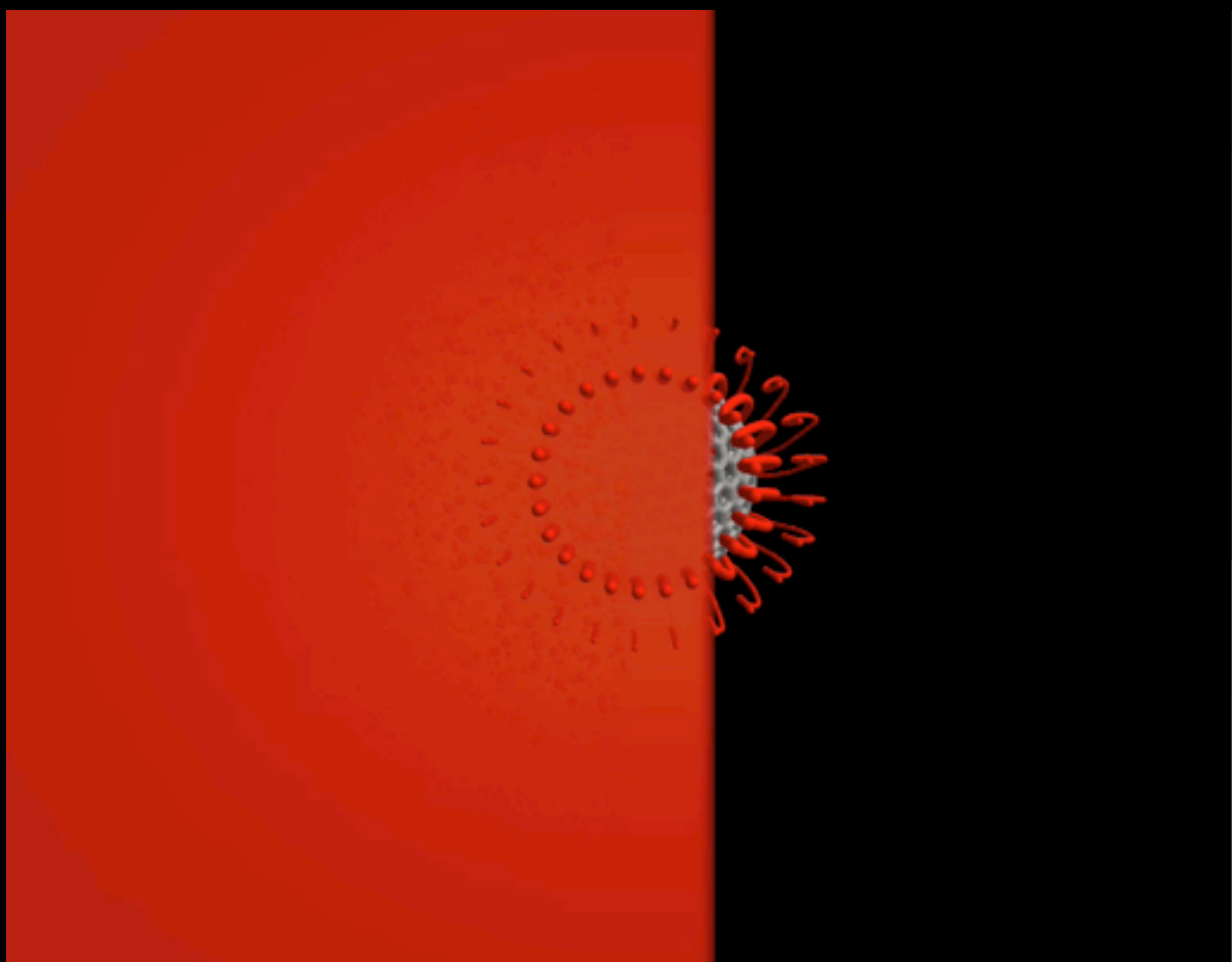
MULTISCALE METHODS

MULTISCALE METHODS + CORE CORE GPU CORE CORE GPU

MD - Lattice-Boltzmann

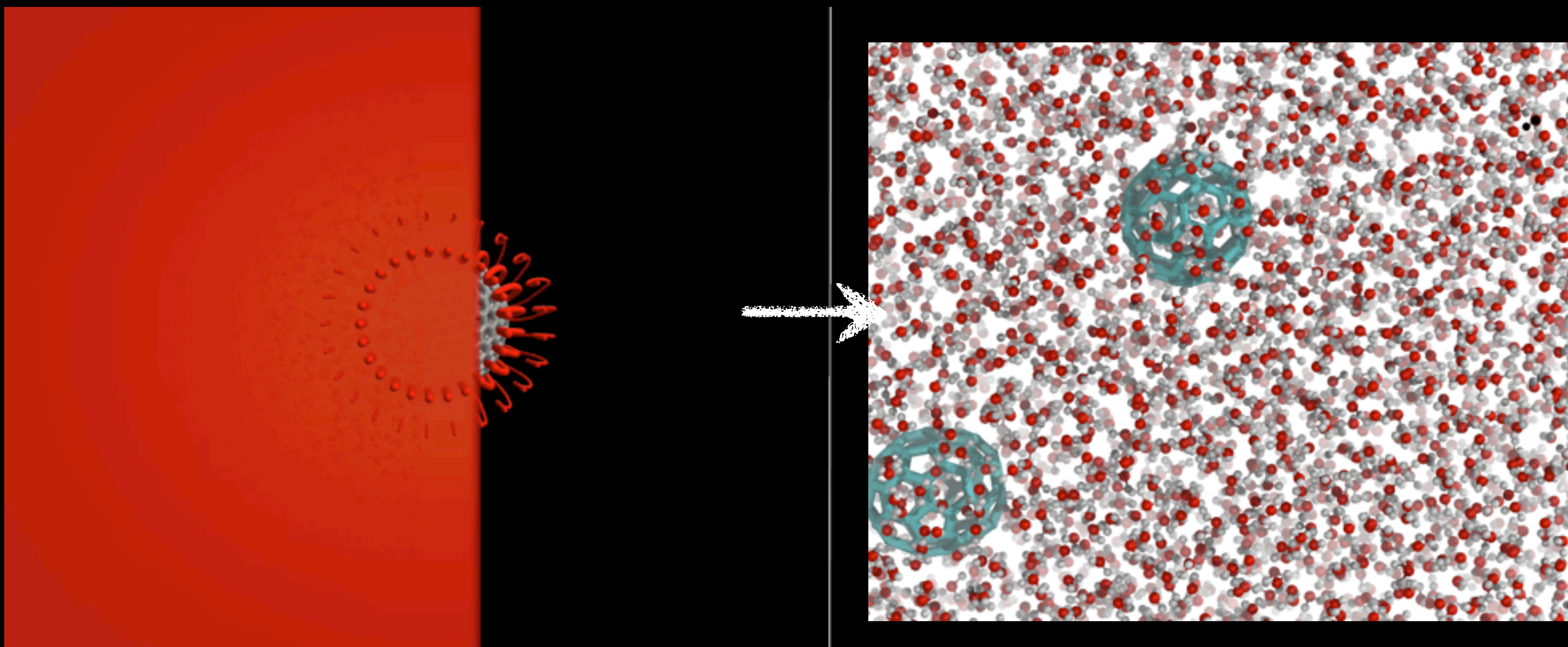
MULTISCALE METHODS + CORE CORE GPU CORE CORE GPU

MD - Lattice-Boltzmann

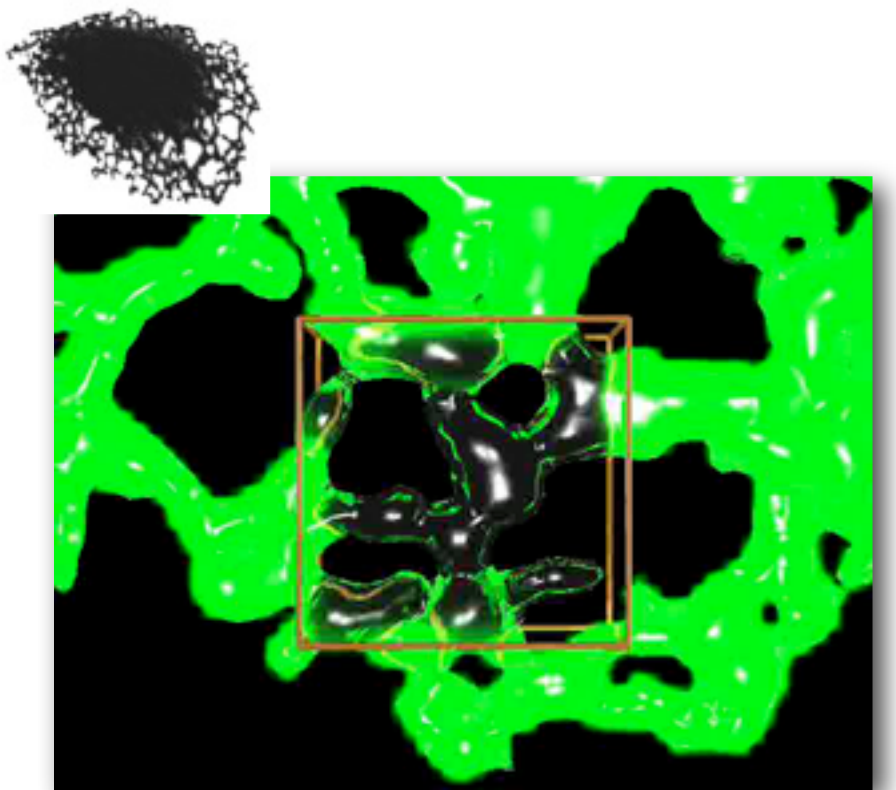


MULTISCALE METHODS + CORE CORE GPU CORE CORE GPU

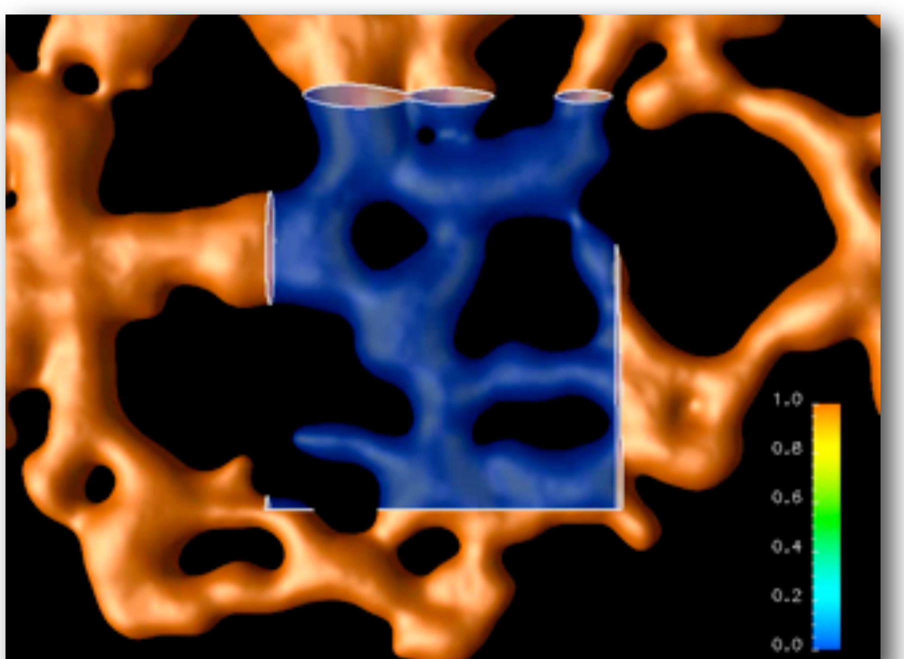
MD - Lattice-Boltzmann



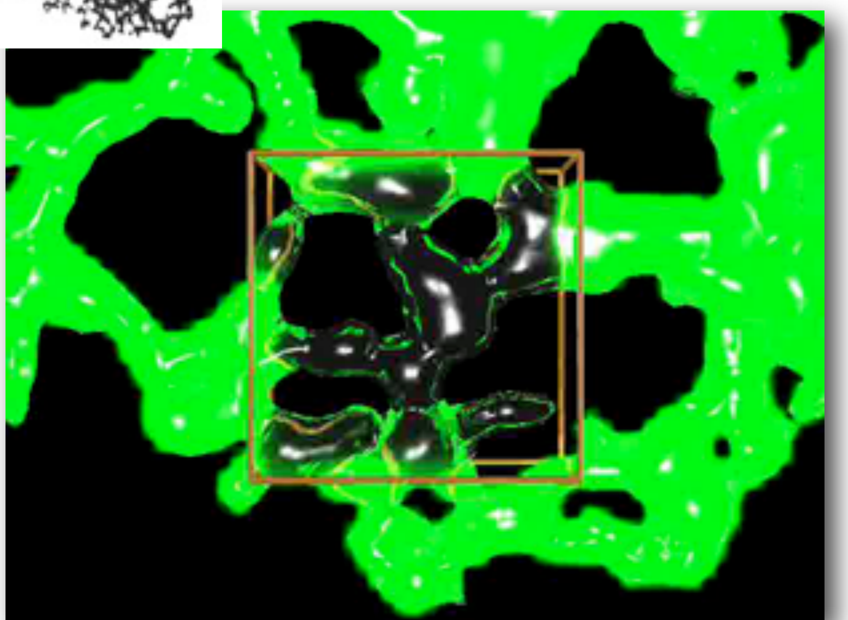
MULTIPHYSICS PARTICLE SIMULATIONS



Diffusion inside/ on Real Cells

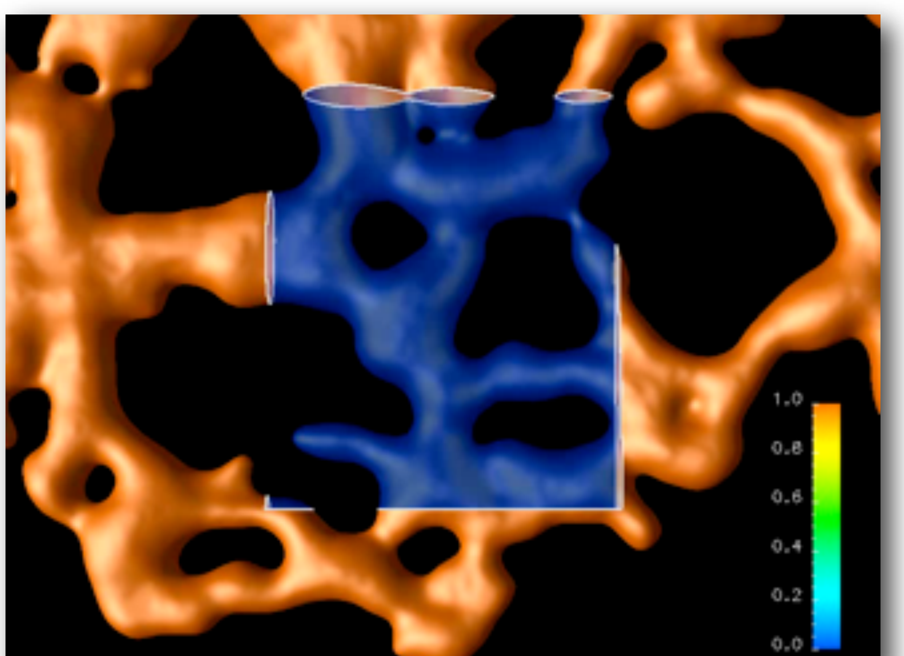


Particles for Biology @ CSE Lab

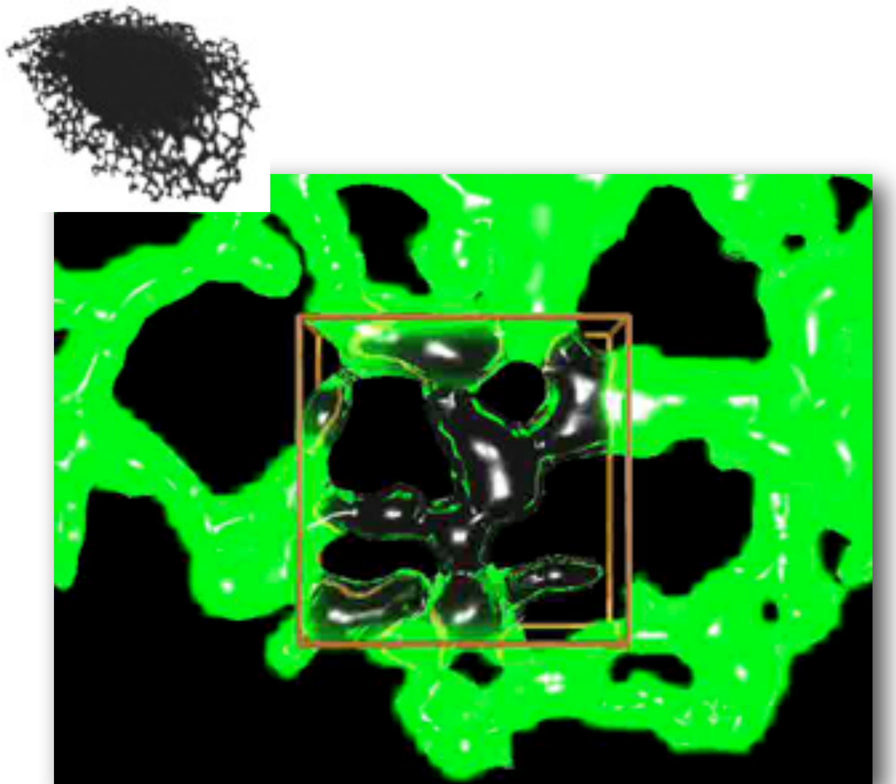


Diffusion inside/ on Real Cells

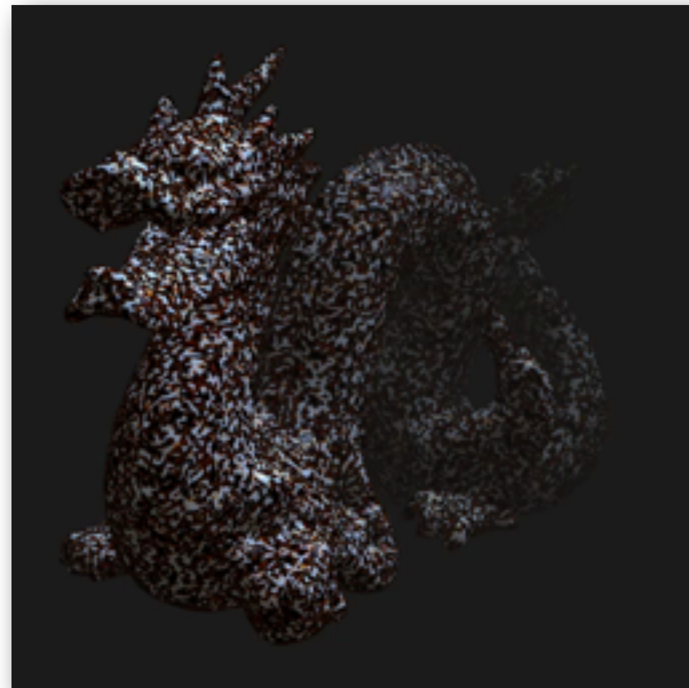
Mesenchymal Motion



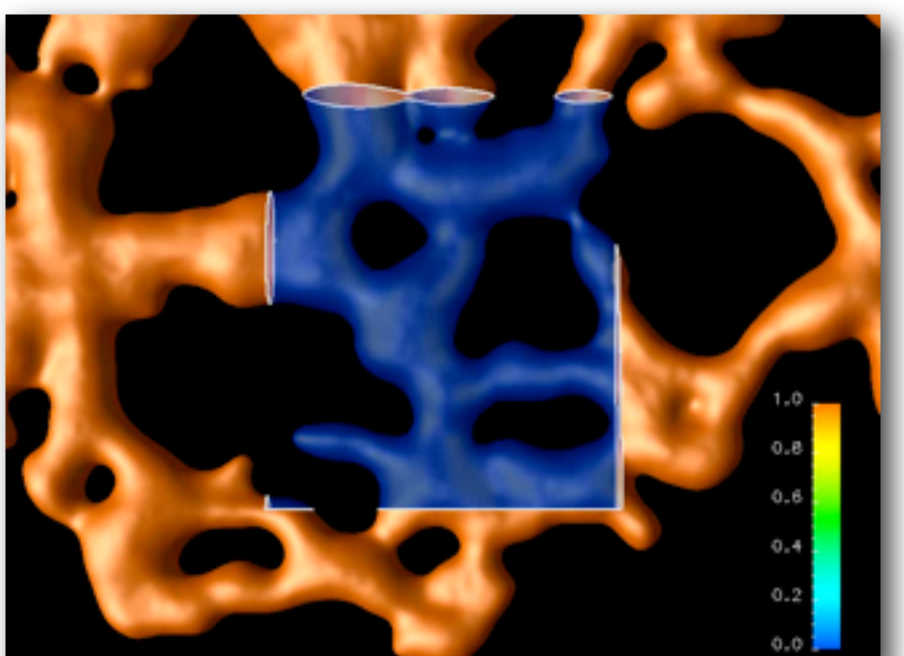
Particles for Biology @ CSE Lab



Growth and Form



Diffusion inside/ on Real Cells



Mesenchymal Motion

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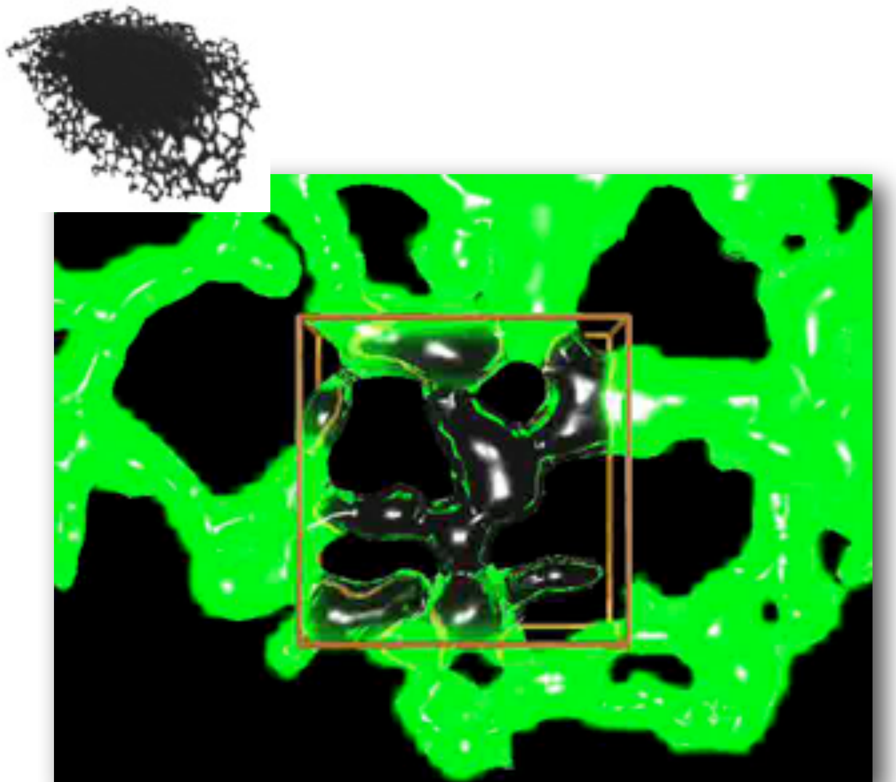

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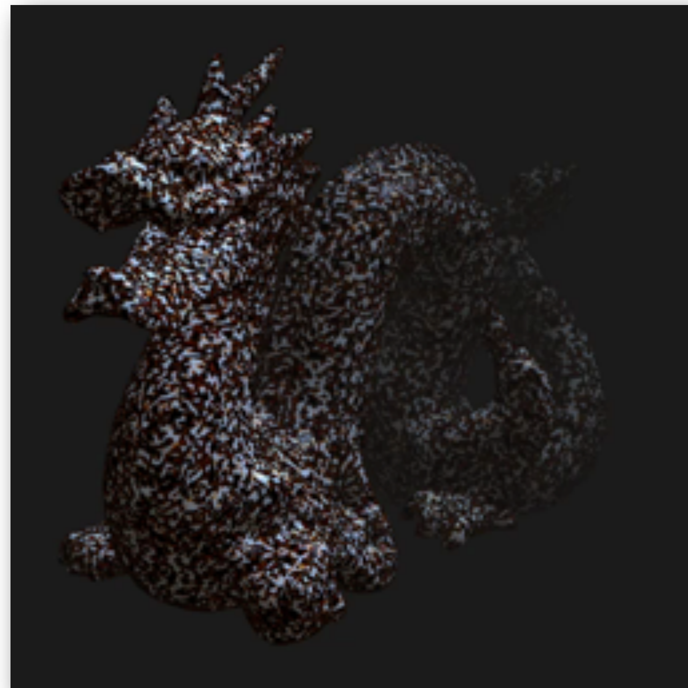
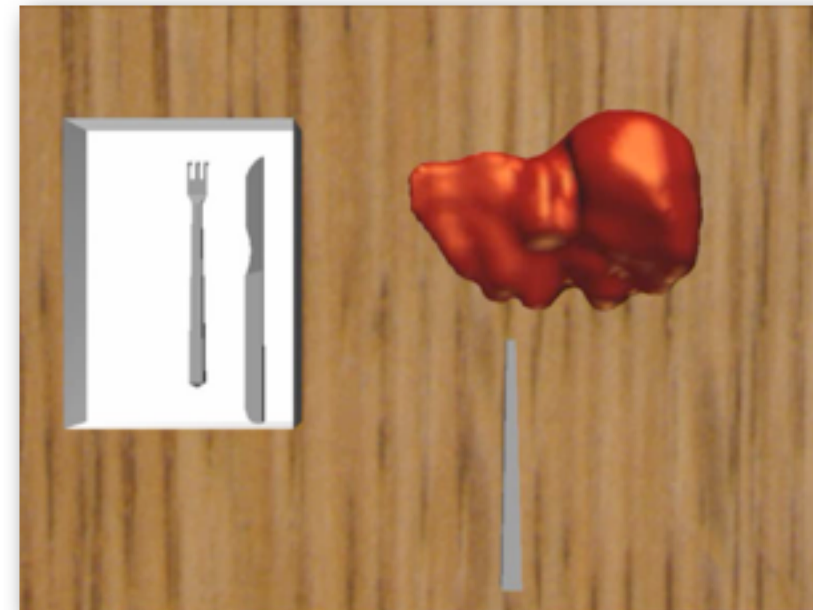


Virtual Surgery



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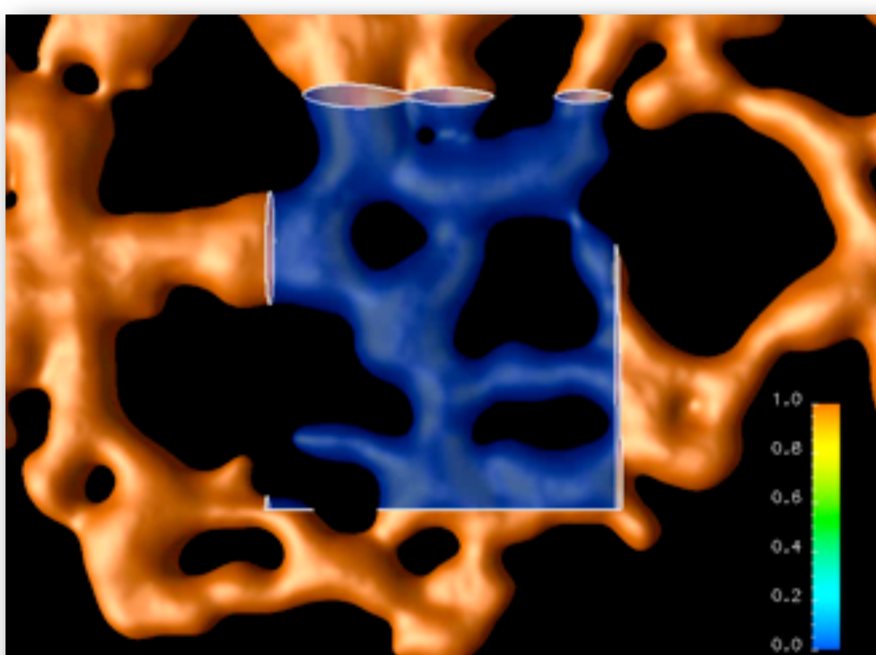
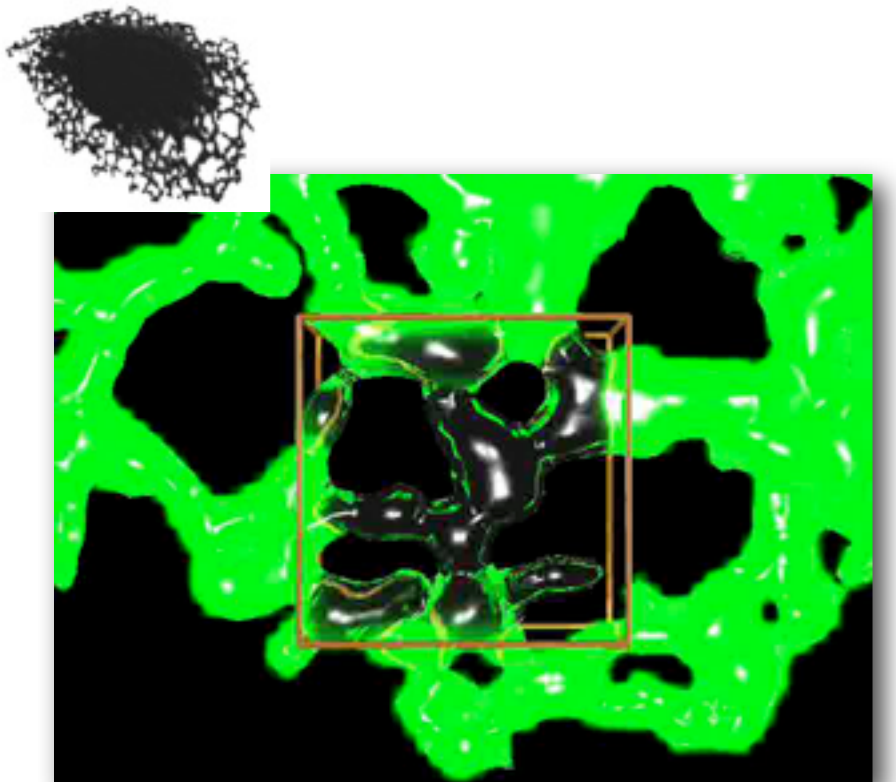


Mesenchymal Motion

Particles for Biology @ CSE Lab



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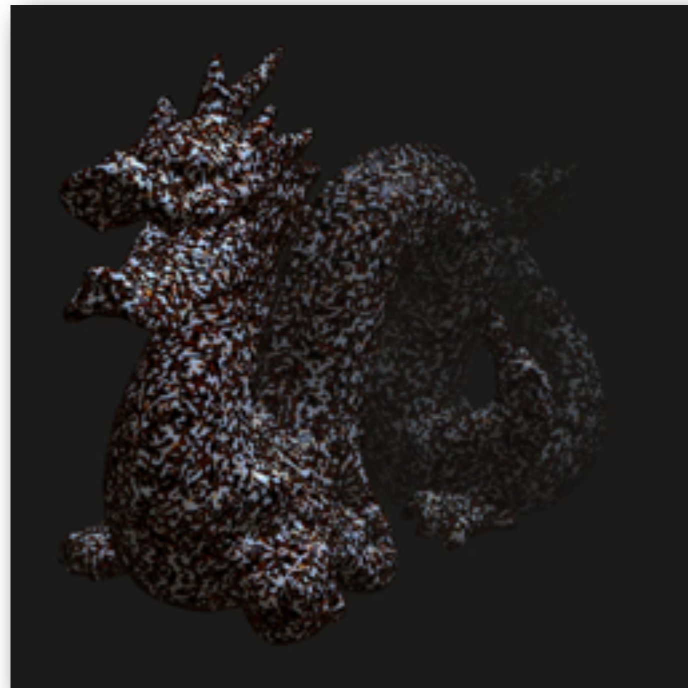

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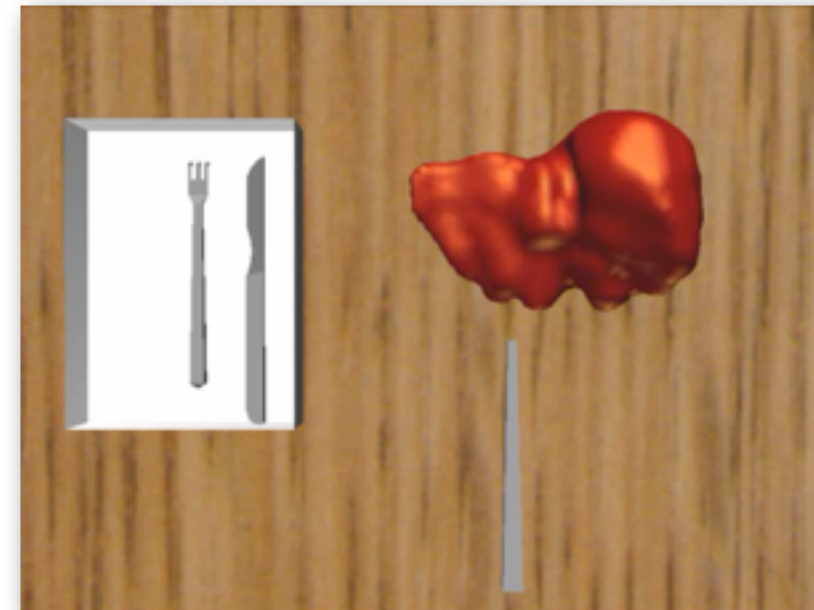

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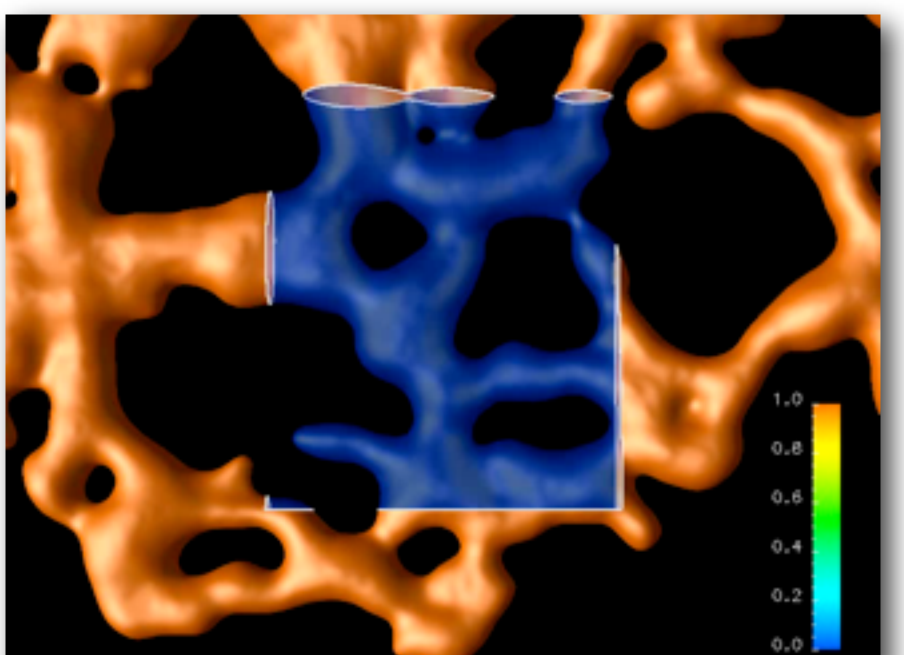
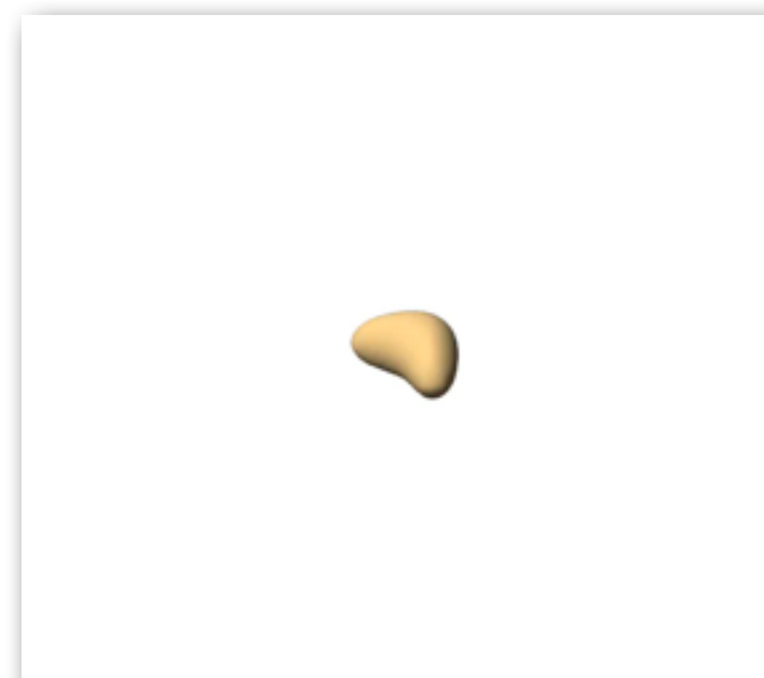
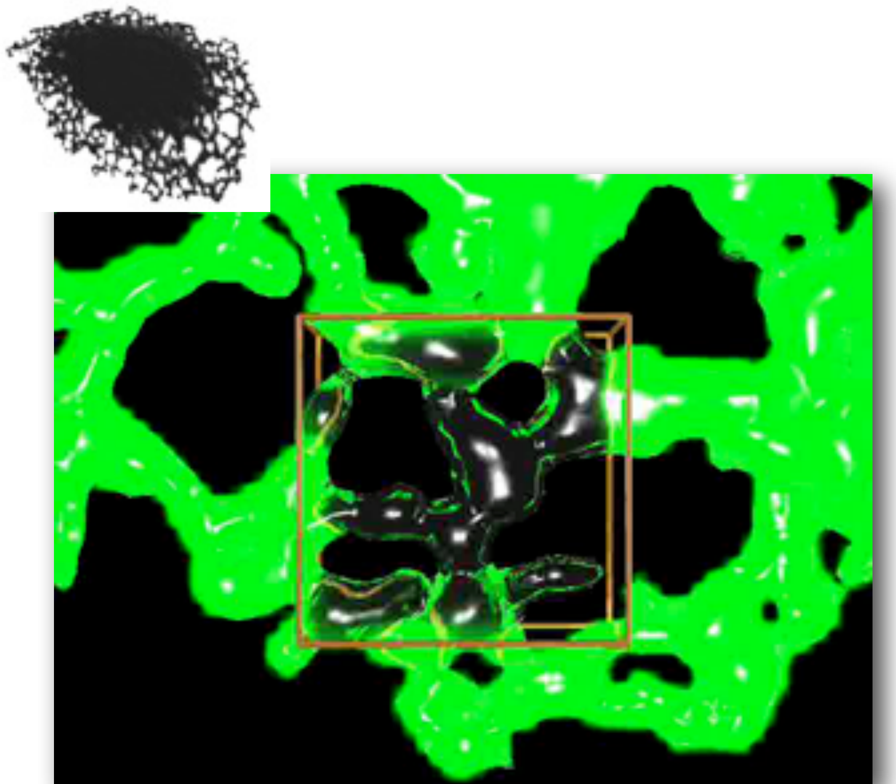


Mesenchymal Motion

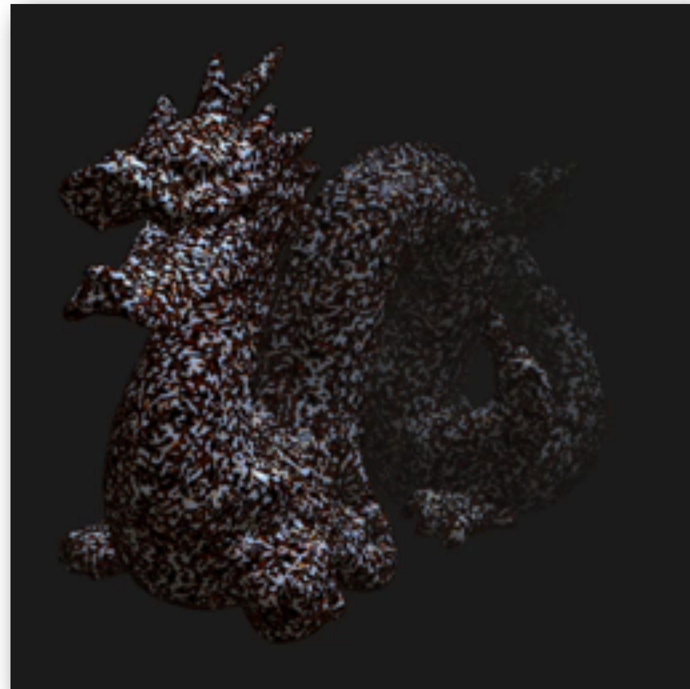
Cancer Modeling



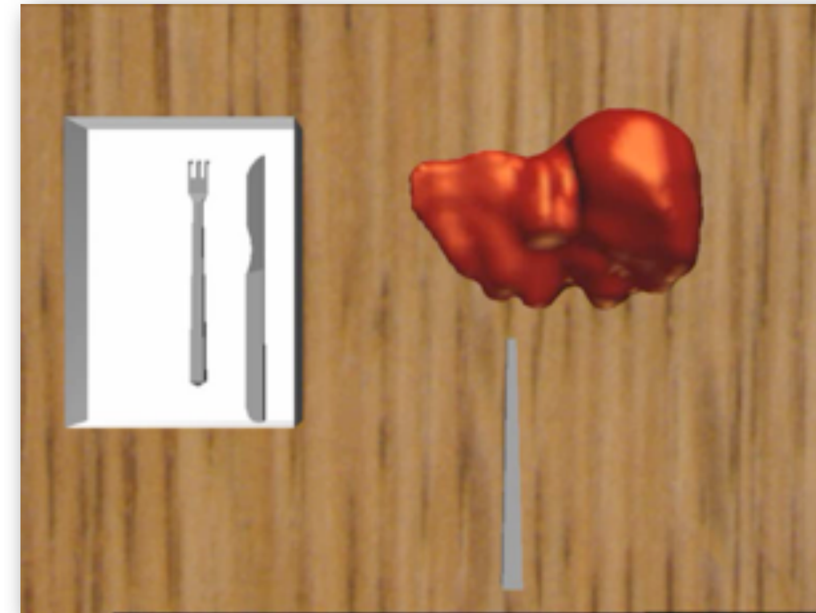
Particles for Biology @ CSE Lab



Growth and Form



Virtual Surgery



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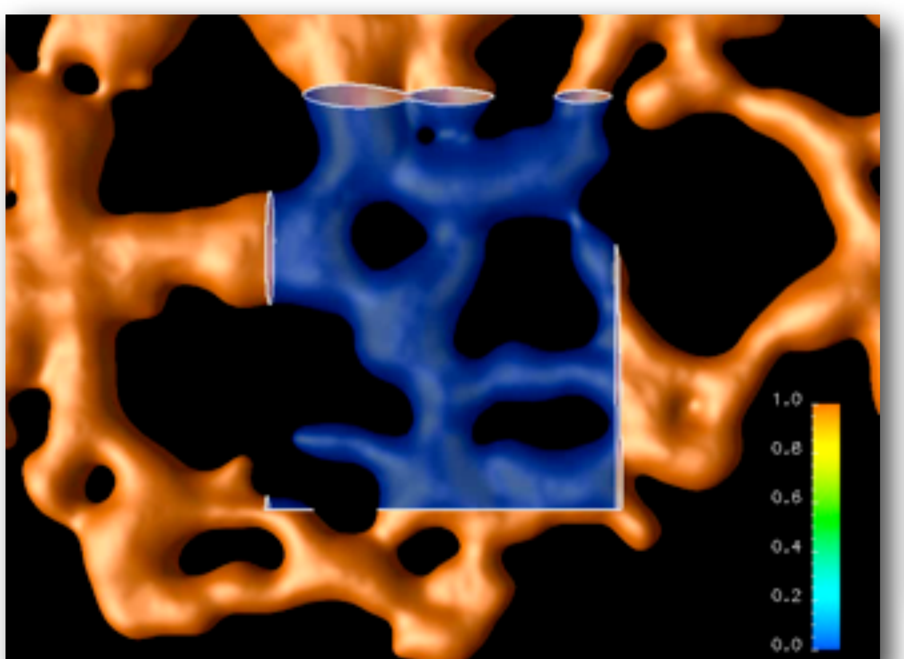

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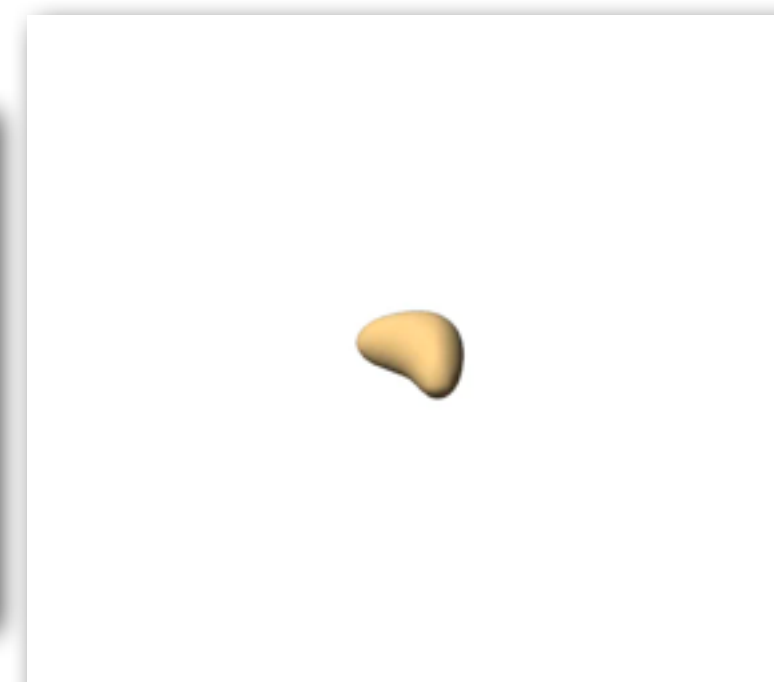


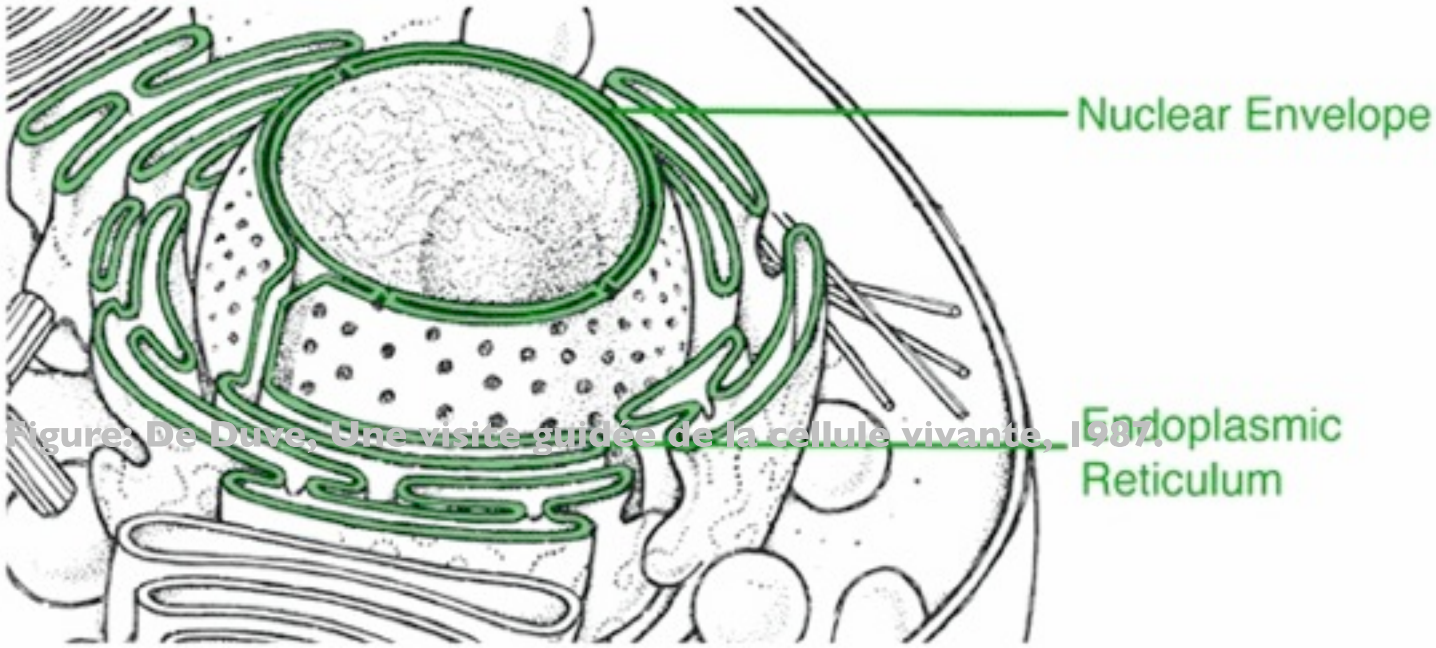


Figure: De Duve, Une visite guidée de la cellule vivante, 1987.

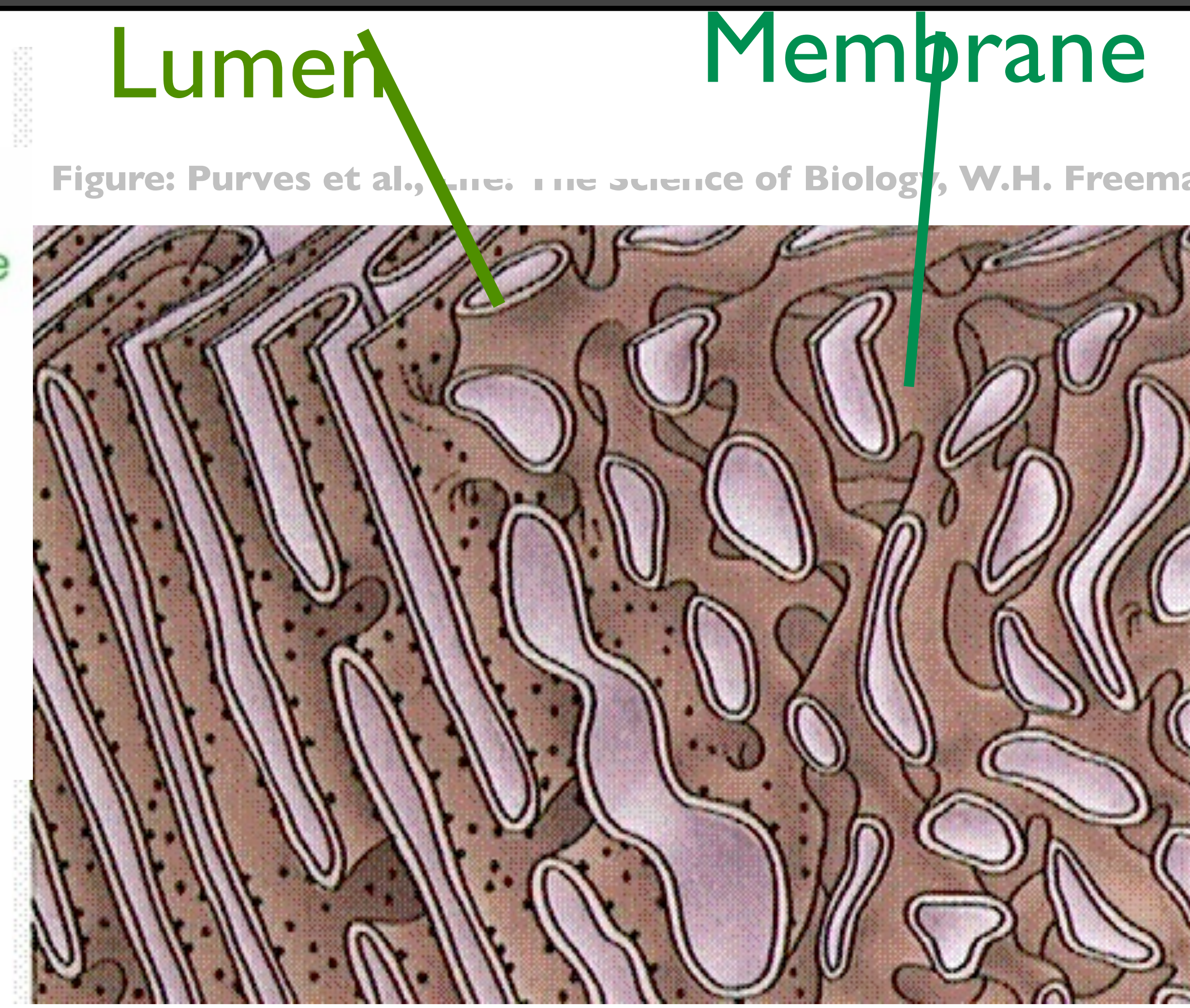
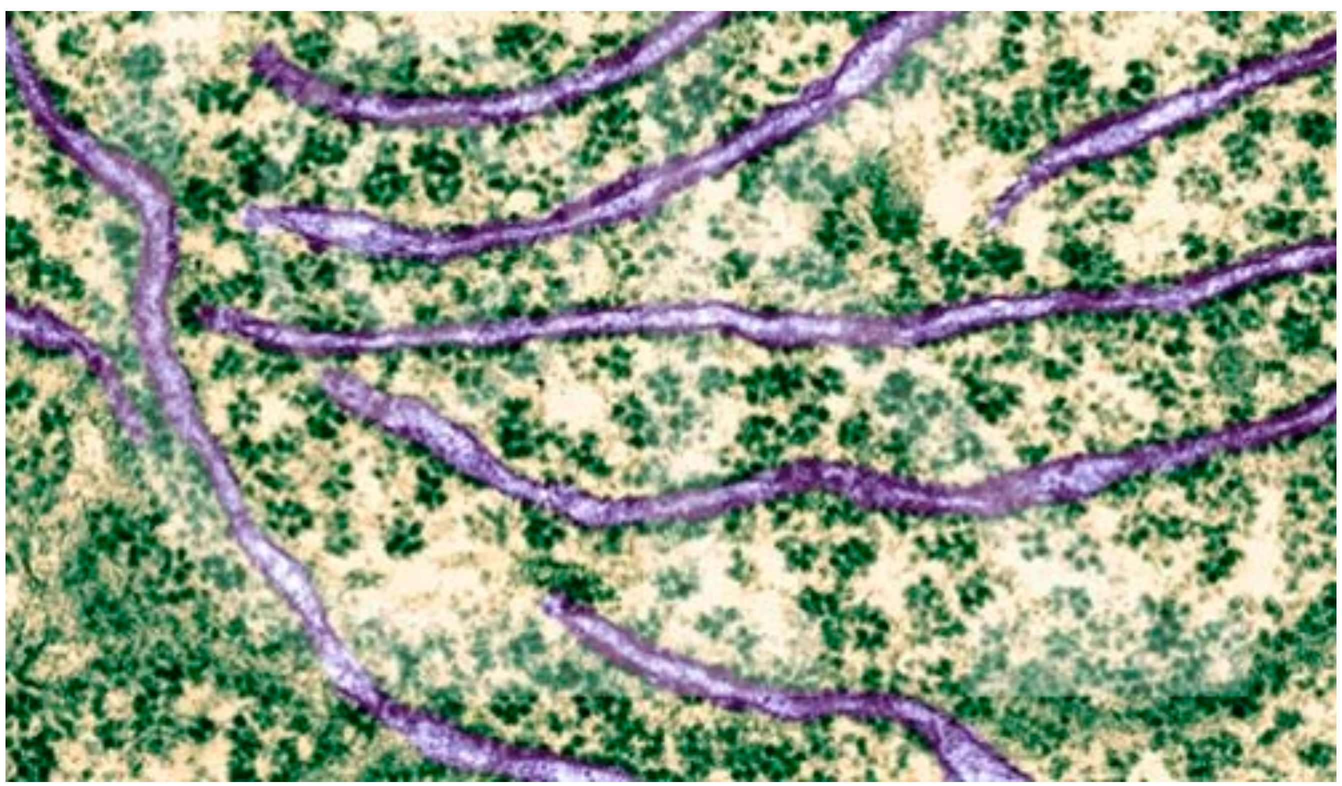


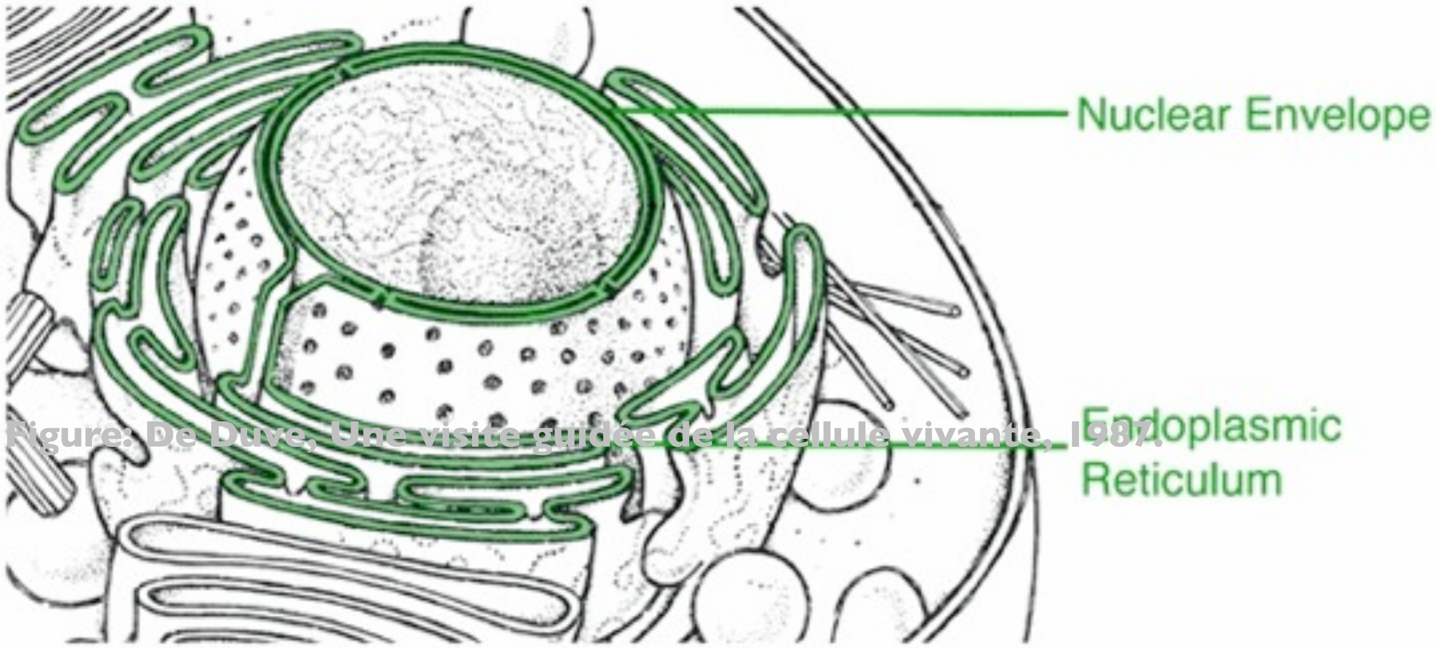
Figure: Purves et al., Life: The Science of Biology, W.H. Freeman.



The main biosynthetic organelle in Eukaryotes: Protein and lipid synthesis. Enclosed by a contiguous membrane

Figure: D. Kunkel, (c) www.DennisKunkel.com

COMPLEX GEOMETRIES : Diffusion in the ER



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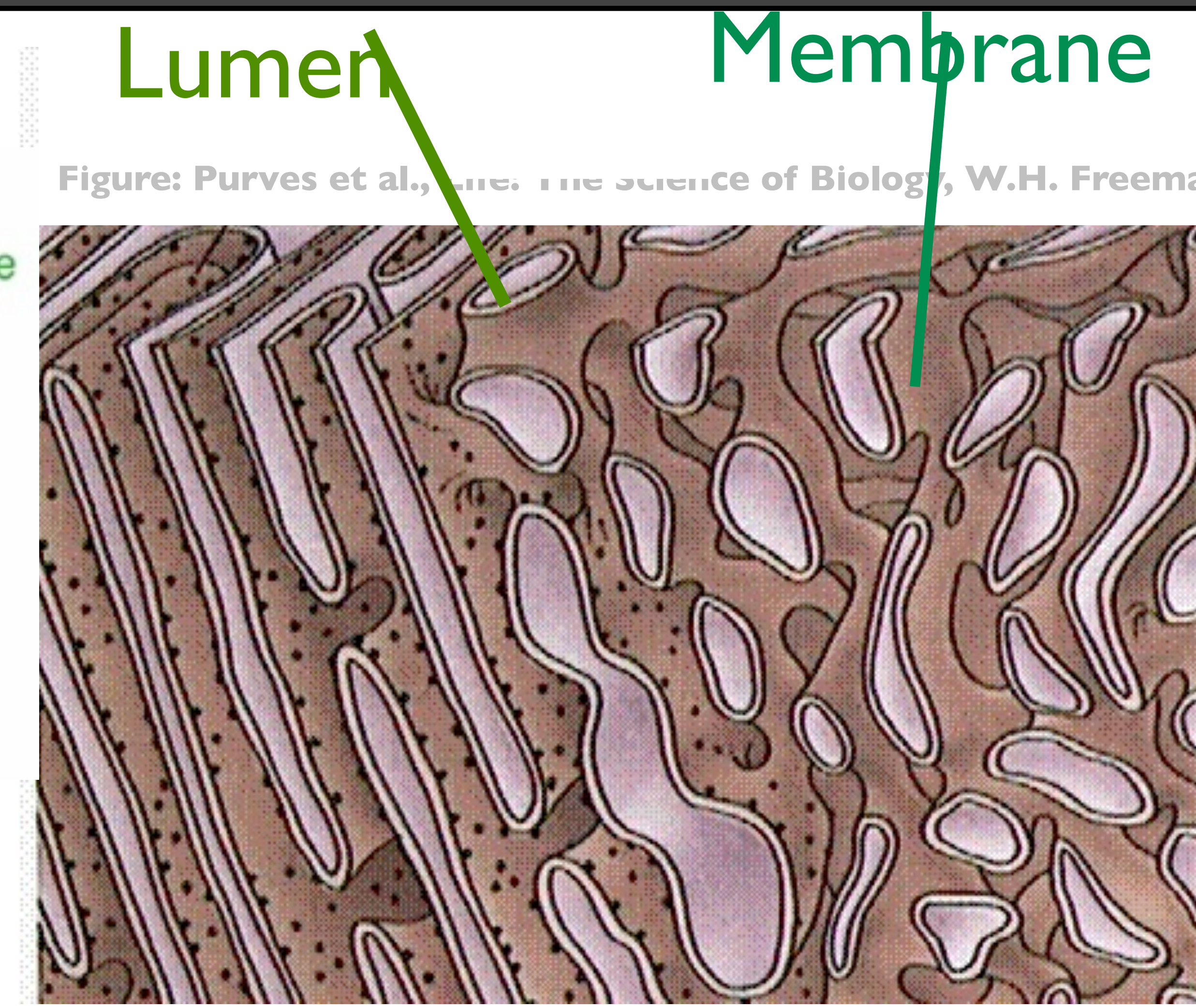


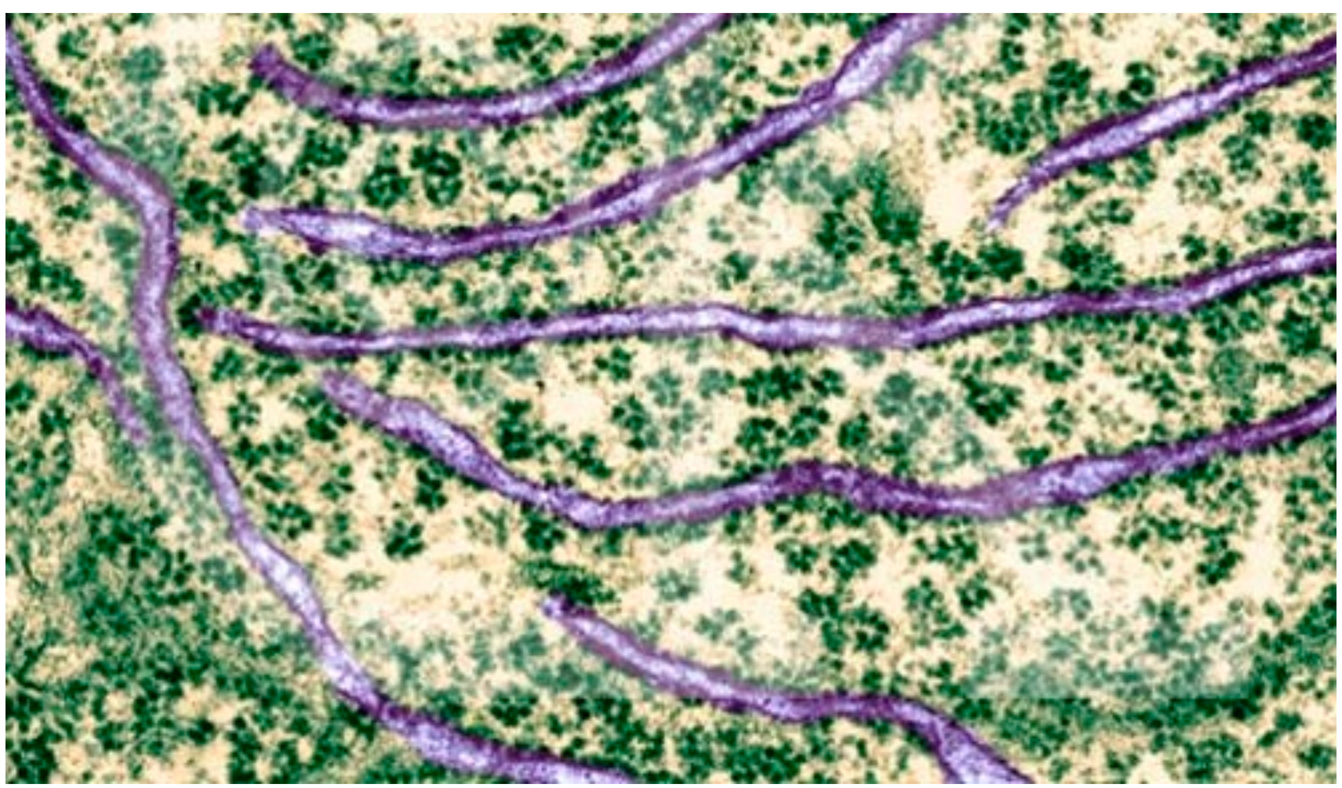


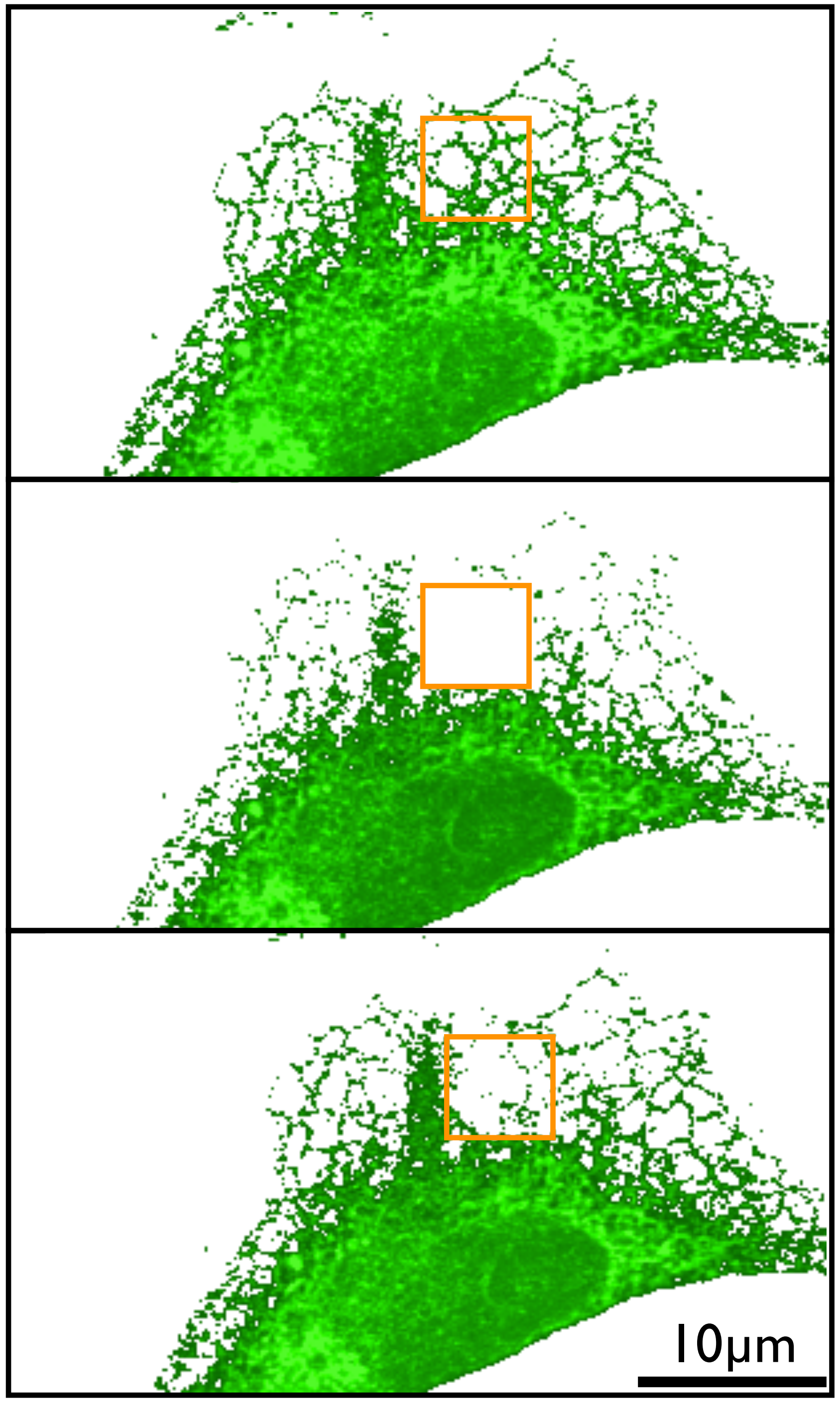
Figure: D. Kunkel, (c) www.DennisKunkel.com

The main biosynthetic organelle in Eukaryotes: Protein and lipid synthesis. Enclosed by a contiguous membrane

FRAP : Fluorescence Recovery After Photobleaching

- Tag protein fluorescently
- Laser Bleach **region of interest**
- Monitor influx of unbleached protein

$$D = ?$$



pre-bleach

t=0

t=2 min

Helenius group (ETHZ)

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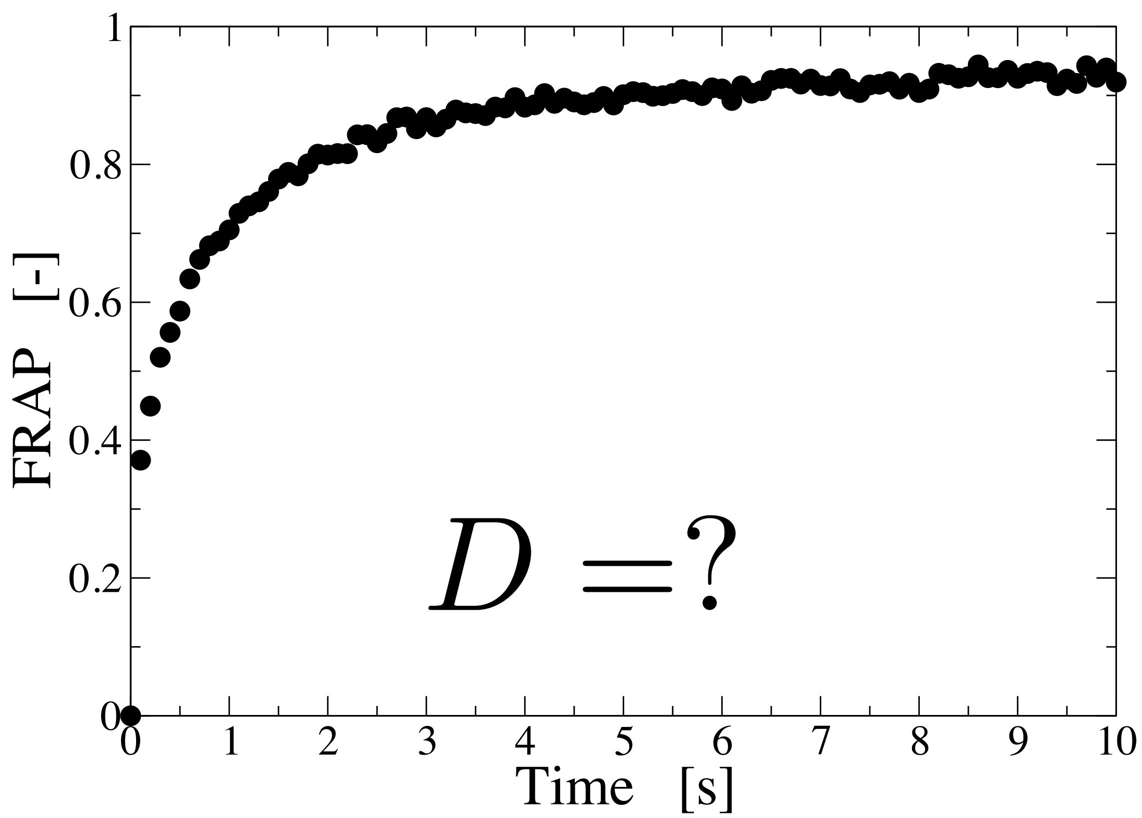

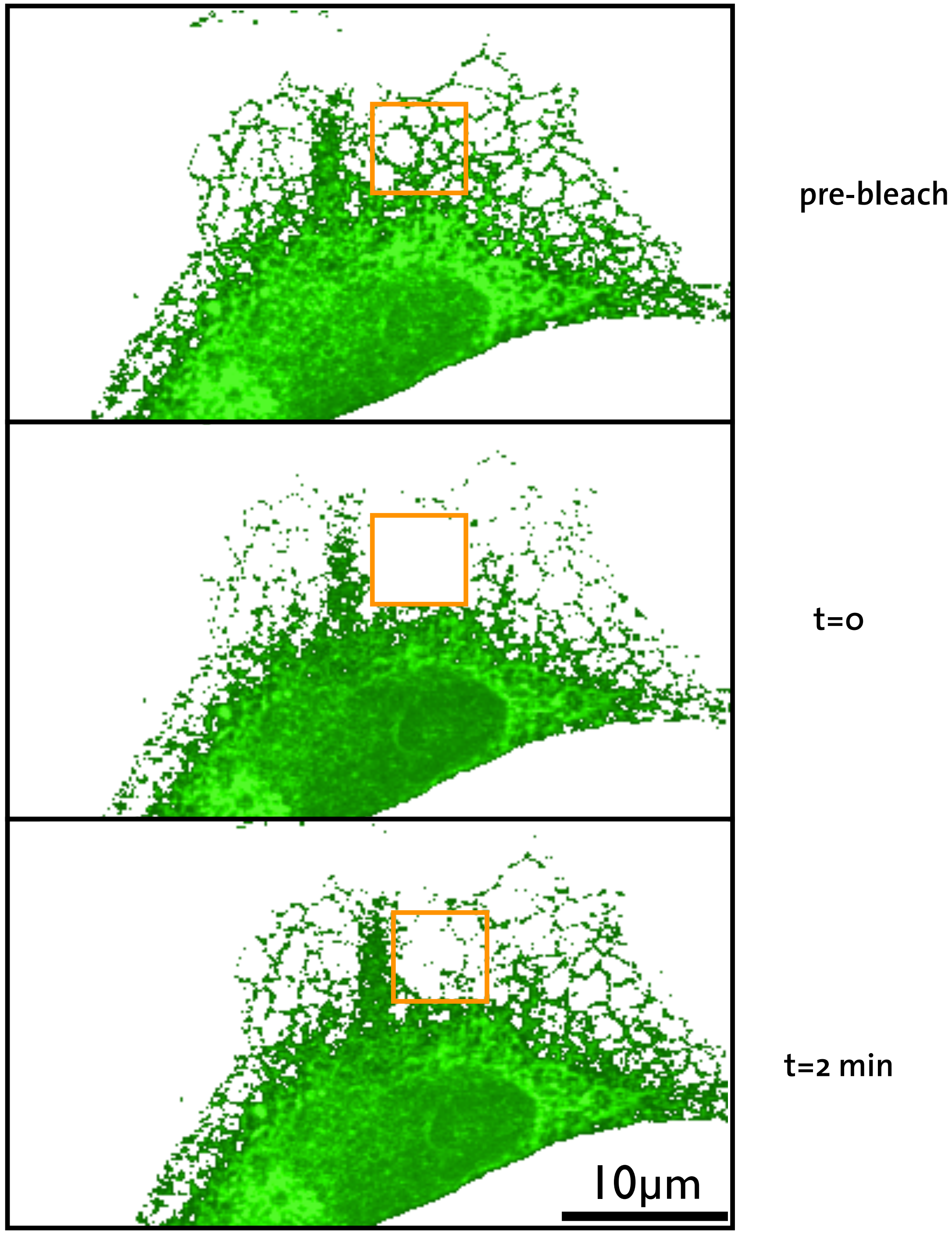

Helenius group (ETHZ)

Recall : Diffusion in CFD (relatively easy)

$$\frac{D\omega}{Dt} = \omega \cdot \nabla \mathbf{u} + \nu \nabla^2 \omega \qquad \frac{dx_p}{dt} = \mathbf{u}$$

Recall : Diffusion in CFD (relatively easy)

$$\frac{\partial u}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} = -\nabla P + \nu \nabla^2 \mathbf{u}$$

$$\frac{D\omega}{Dt} = \omega \cdot \nabla \mathbf{u} + \nu \nabla^2 \omega$$	$$\frac{dx_p}{dt} = \mathbf{u}$$

Recall : Diffusion in CFD (relatively easy)

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$\frac{D\omega}{Dt} = \omega \cdot \nabla \mathbf{u} + \nu \, \nabla^2 \omega$	$\frac{dx_p}{dt} = \mathbf{u}$

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$$\omega = \nabla \times \mathbf{u} \qquad \nabla^2 \mathbf{u} = -\nabla \times \omega$$

$\frac{D\omega}{Dt} = \omega \cdot \nabla \mathbf{u} + \nu \nabla^2 \omega$	$\frac{dx_p}{dt} = \mathbf{u}$

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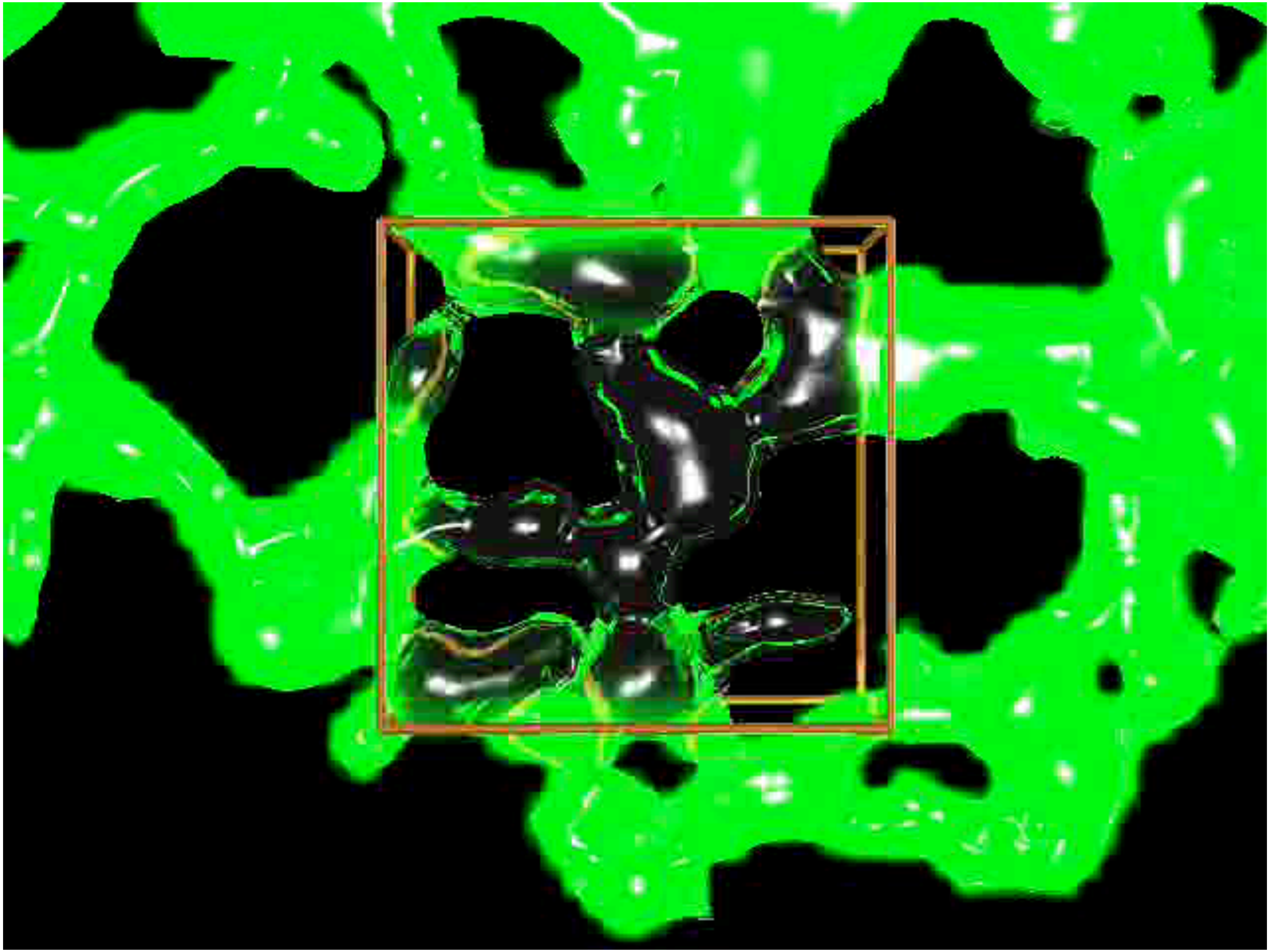
"Vorticity" becomes "Concentration"

Diffusion in the Endoplasmic Reticulum



Sbalzarini, Mezzacasa, Helenius, Koumoutsakos, Biophysical J., 2006

"...but, can you do this on a surface ?" - A. Helenius

on the surface

$$\frac{\partial u}{\partial t} = \nabla_{\mathcal{M}} \cdot (\boldsymbol{D} \nabla_{\mathcal{M}} u)$$

in the narrow band

$$\frac{\partial u}{\partial t} = \frac{J}{|\nabla \Phi|} \nabla(\Lambda \cdot \nabla u)$$

Projection operator

$$T = (1 - \frac{\nabla \Phi \times \nabla \Phi}{|\nabla \Phi|^2})|\nabla \Phi| \qquad \Lambda = T\, D$$

Bertalmio et al., J. Comp. Phys. 174:759. 2001.

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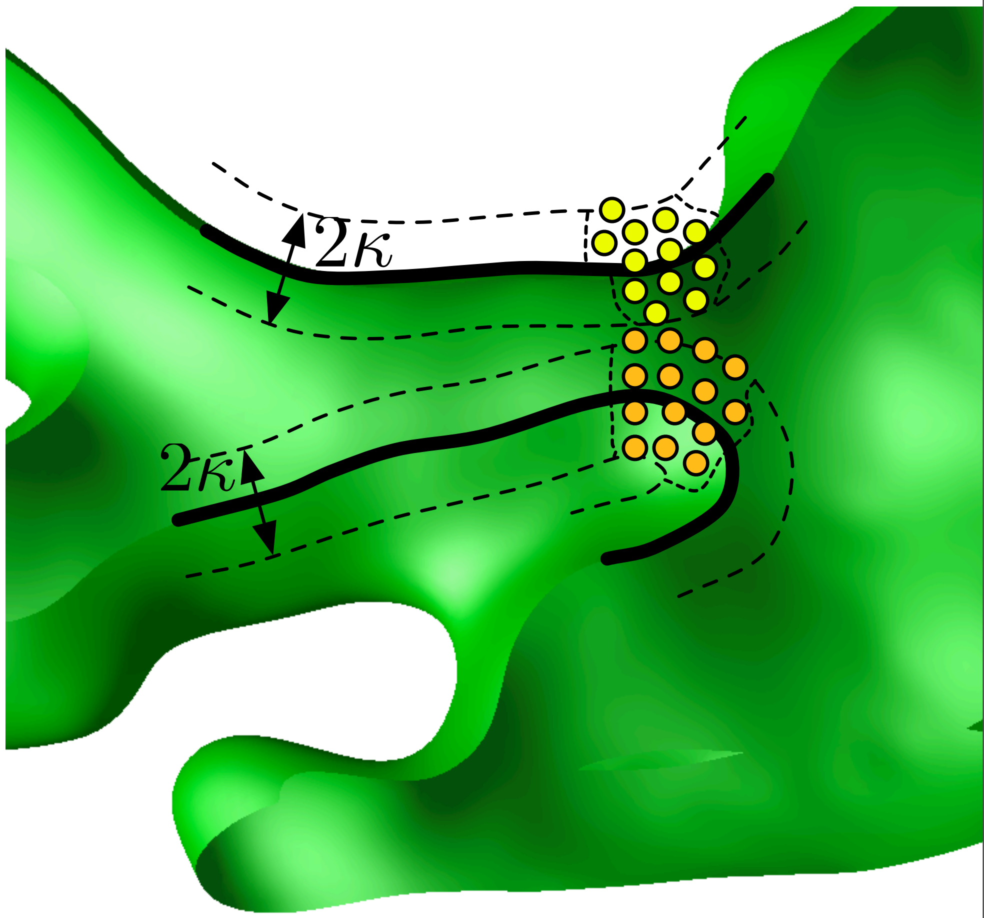
Multiresolution particles

- Particles in a band around the surface
- Surfaces have to be **at least one band thickness apart**



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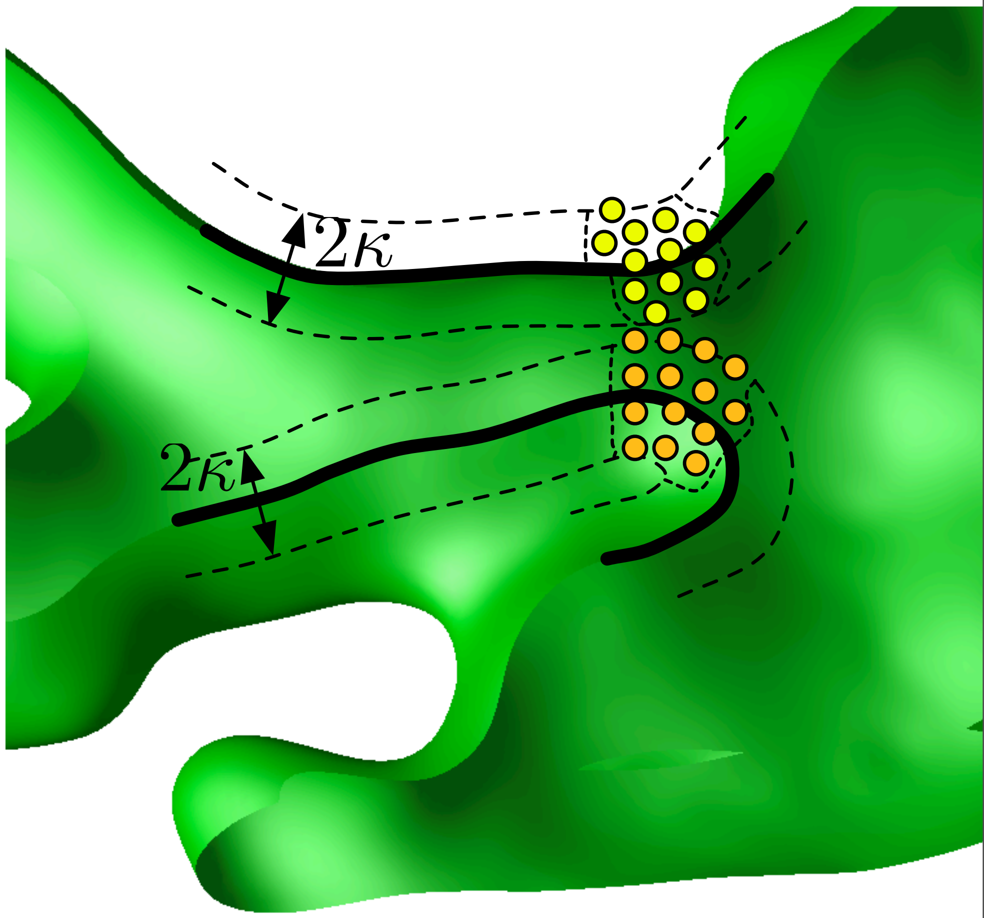

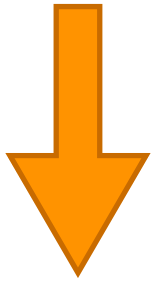

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- Particles in a band around the surface
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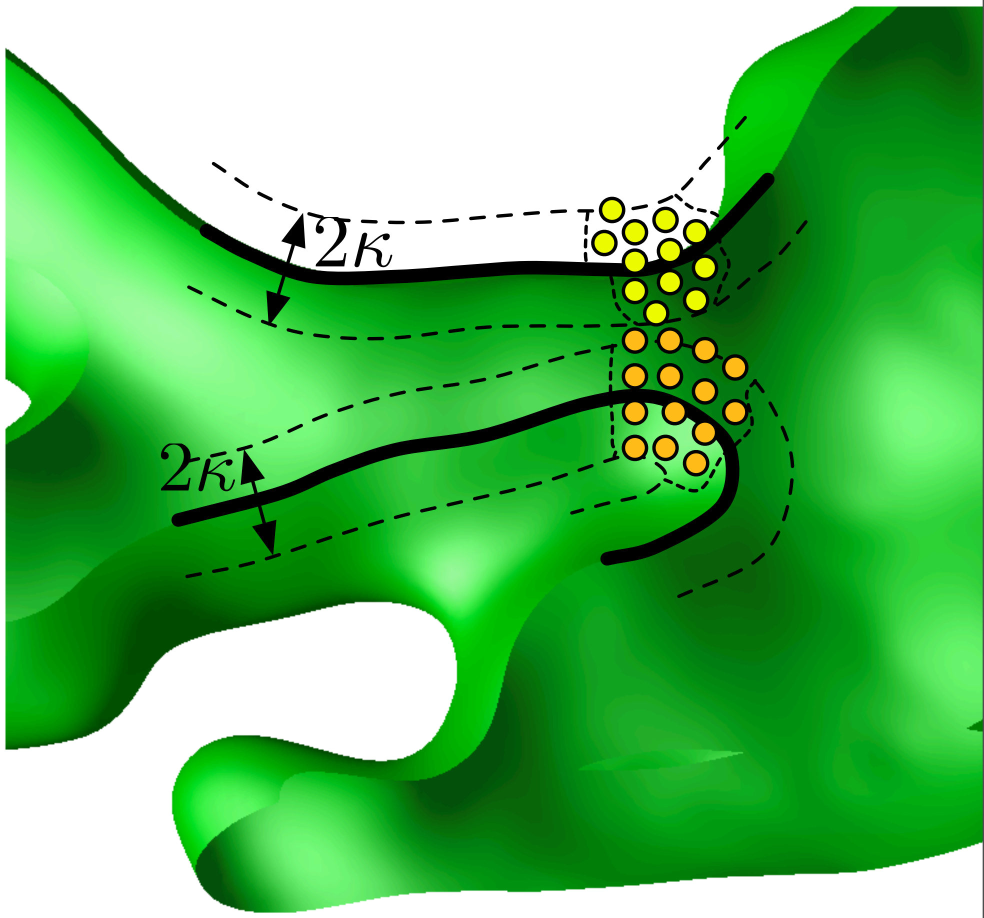


Use **adapted** particles around the surface to improve **resolution**

Multiresolution particles

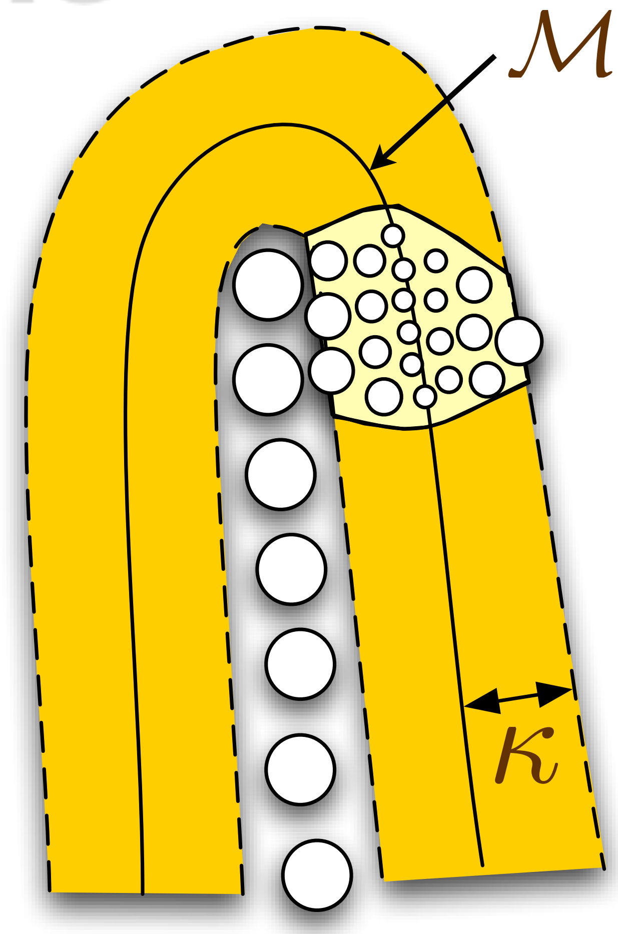
- Particles in a band around the surface
- Surfaces have to be **at least one band thickness apart**

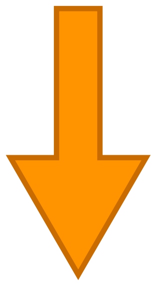
↓

Use adapted particles around the surface to improve resolution

Multiresolution particles

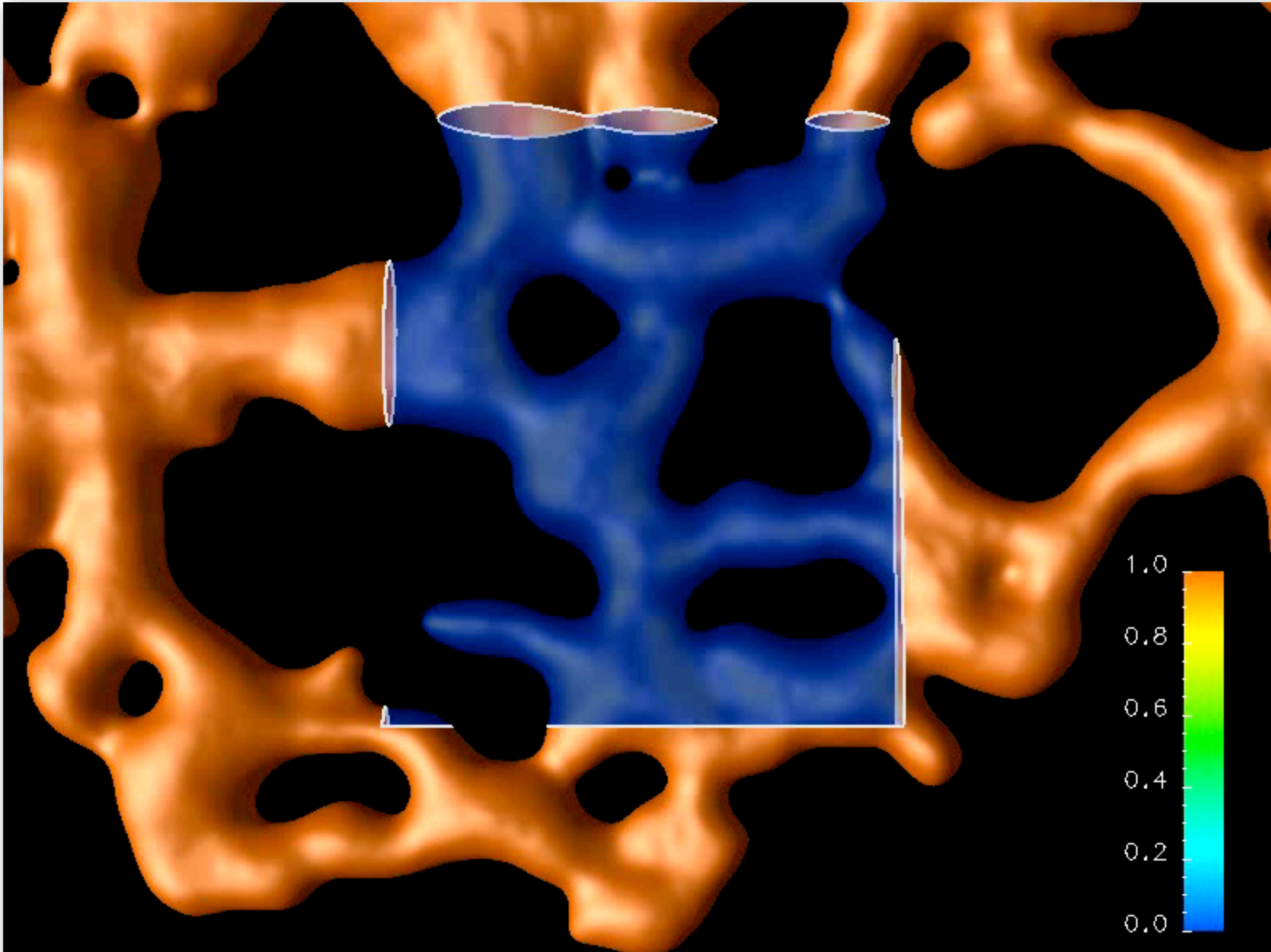
- Particles in a band around the surface
- Surfaces have to be **at least one band thickness apart**





Use **adapted** particles around the surface to improve **resolution**

Diffusion on reconstructed ER of VERO cells

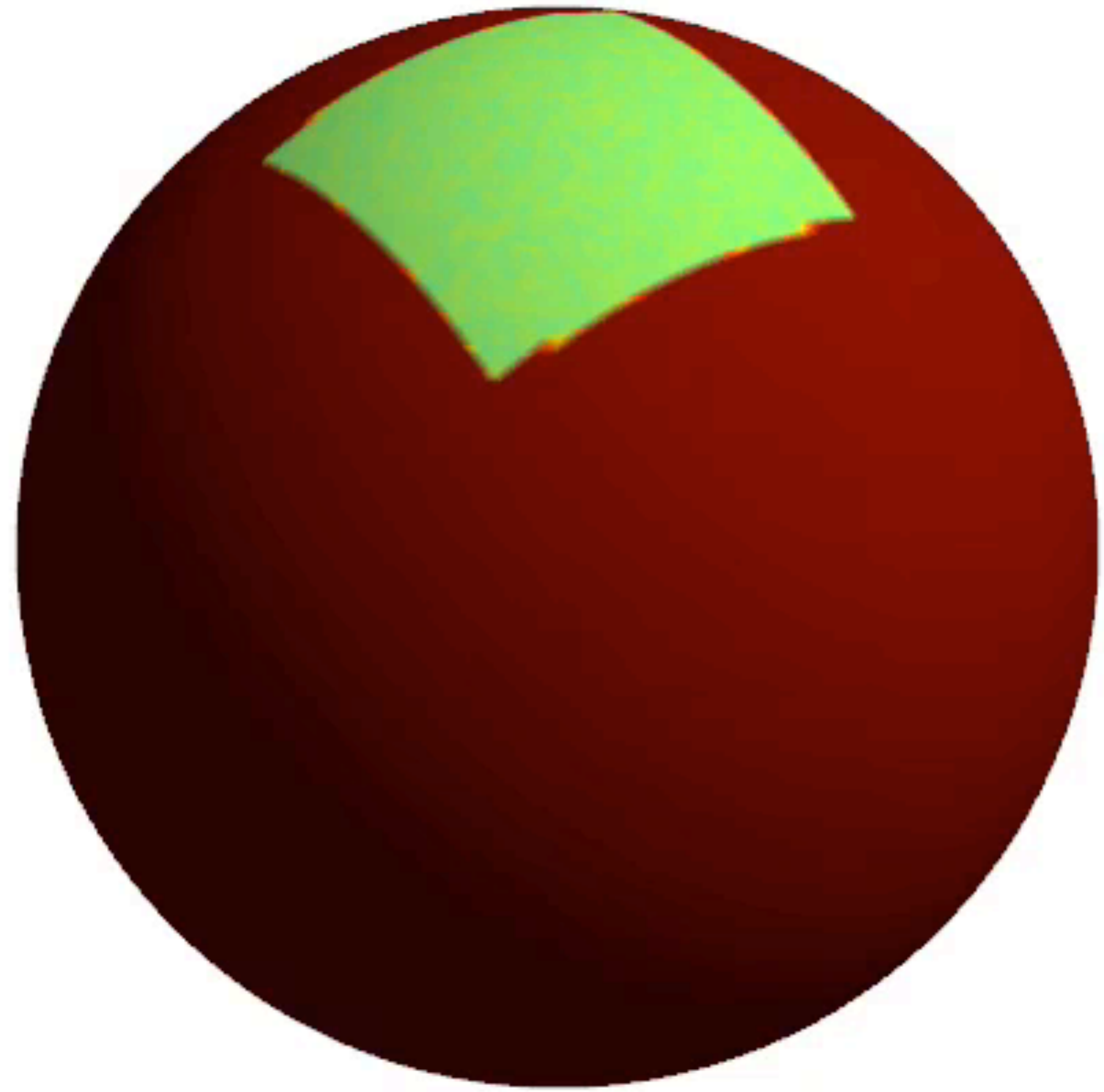


I. F. Sbalzarini, A. Hayer, A. Helenius, and P. Koumoutsakos. *Biophys. J.*, 2006.

Diffusion/Reaction on Surfaces

Gray Scott system

$$U + 2V \quad \rightarrow 3V,$$
$$V \quad \rightarrow P$$



Lagrangian particle level set method + reaction-diffusion on implicit surface

Diffusion/Reaction on Surfaces

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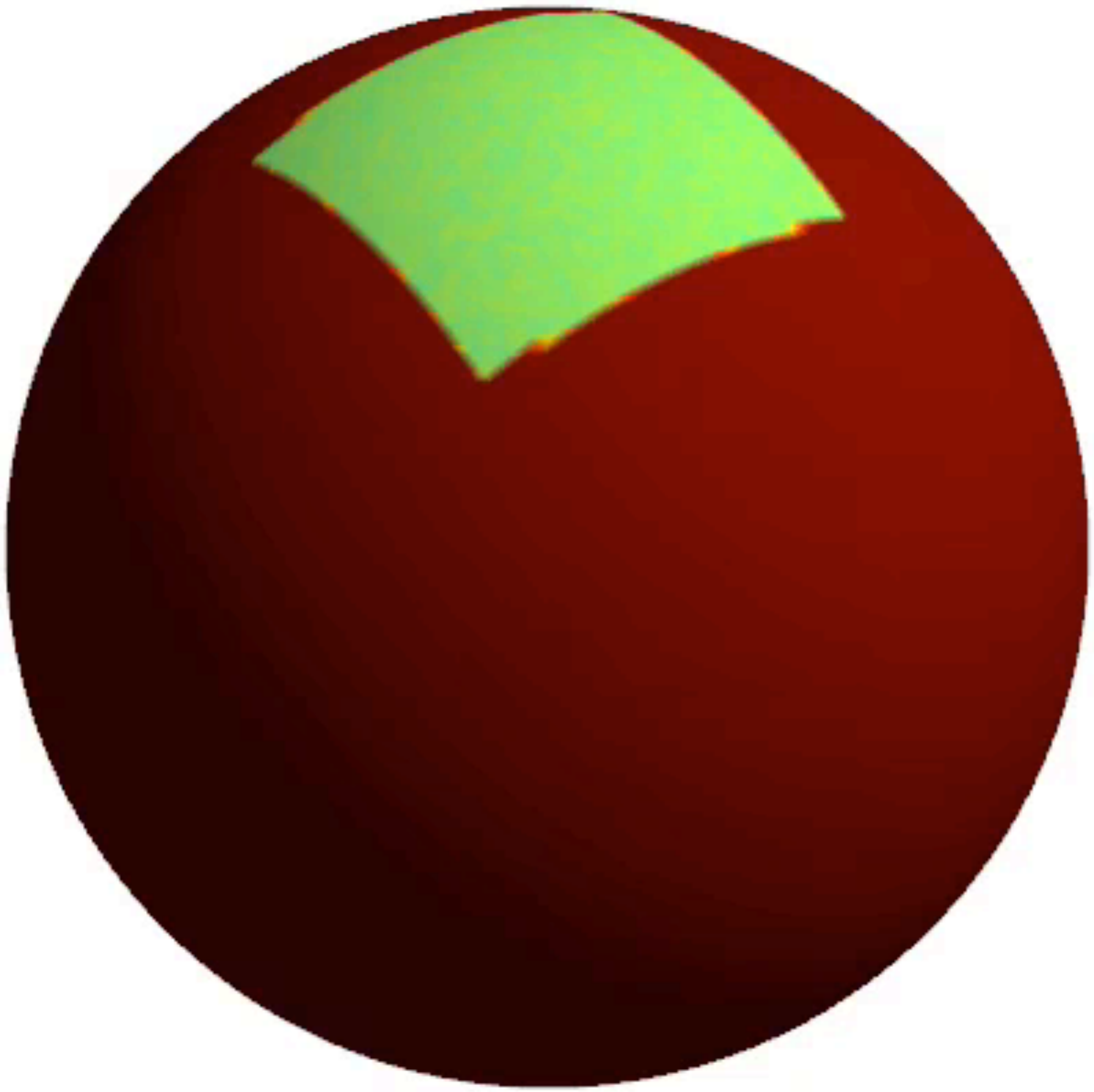
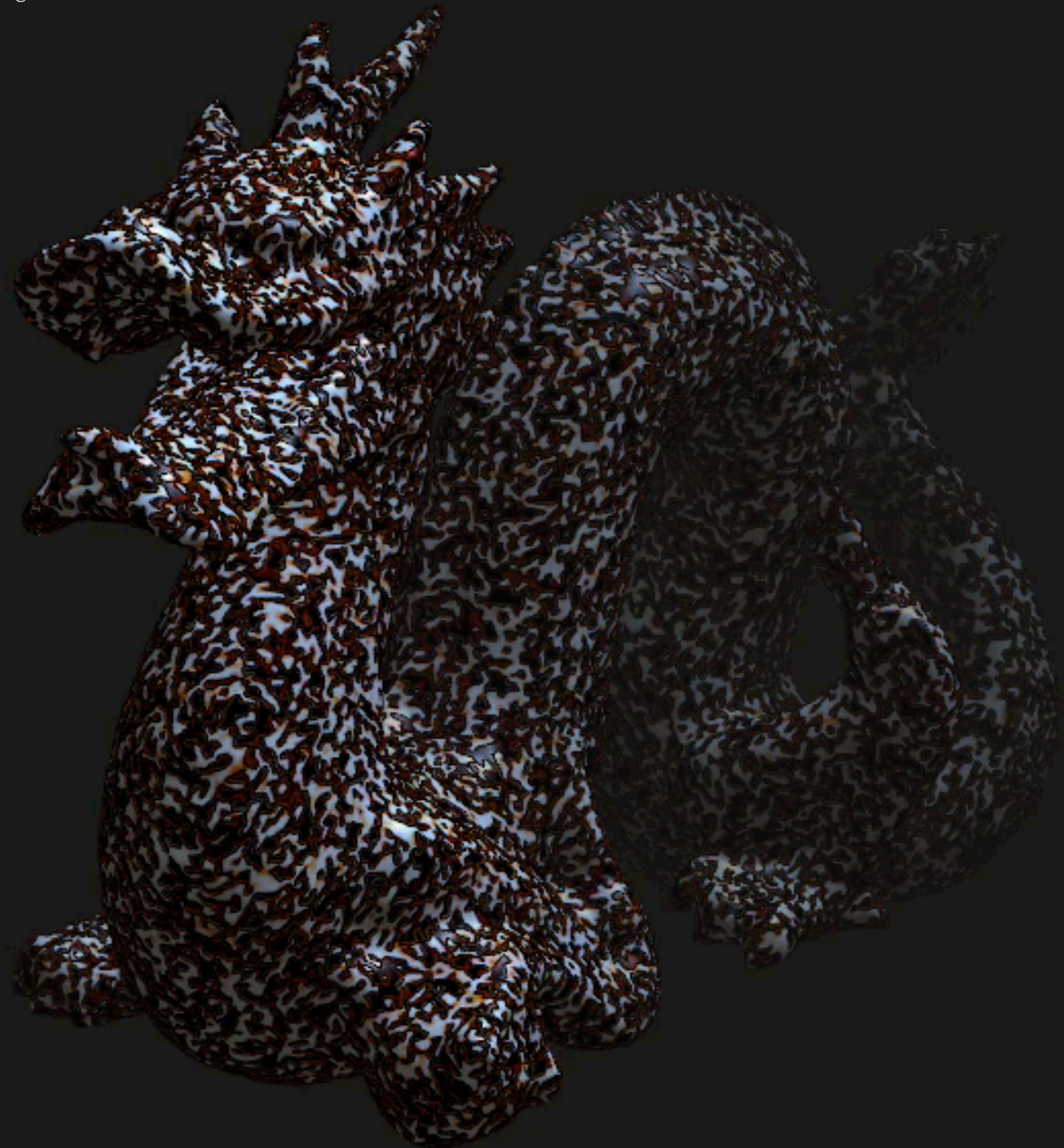


Lagrangian particle level set method + reaction-diffusion on implicit surface

M. Bergdorf, I. F, Sbalzarini, P. Koumoutsakos. *J. Comp. Phys., (submitted) 2008*

"Well, the stripes are easy, but what about the horse part " ? **Turing**

The Dragon : Grier-Meinhardt reaction kinetics



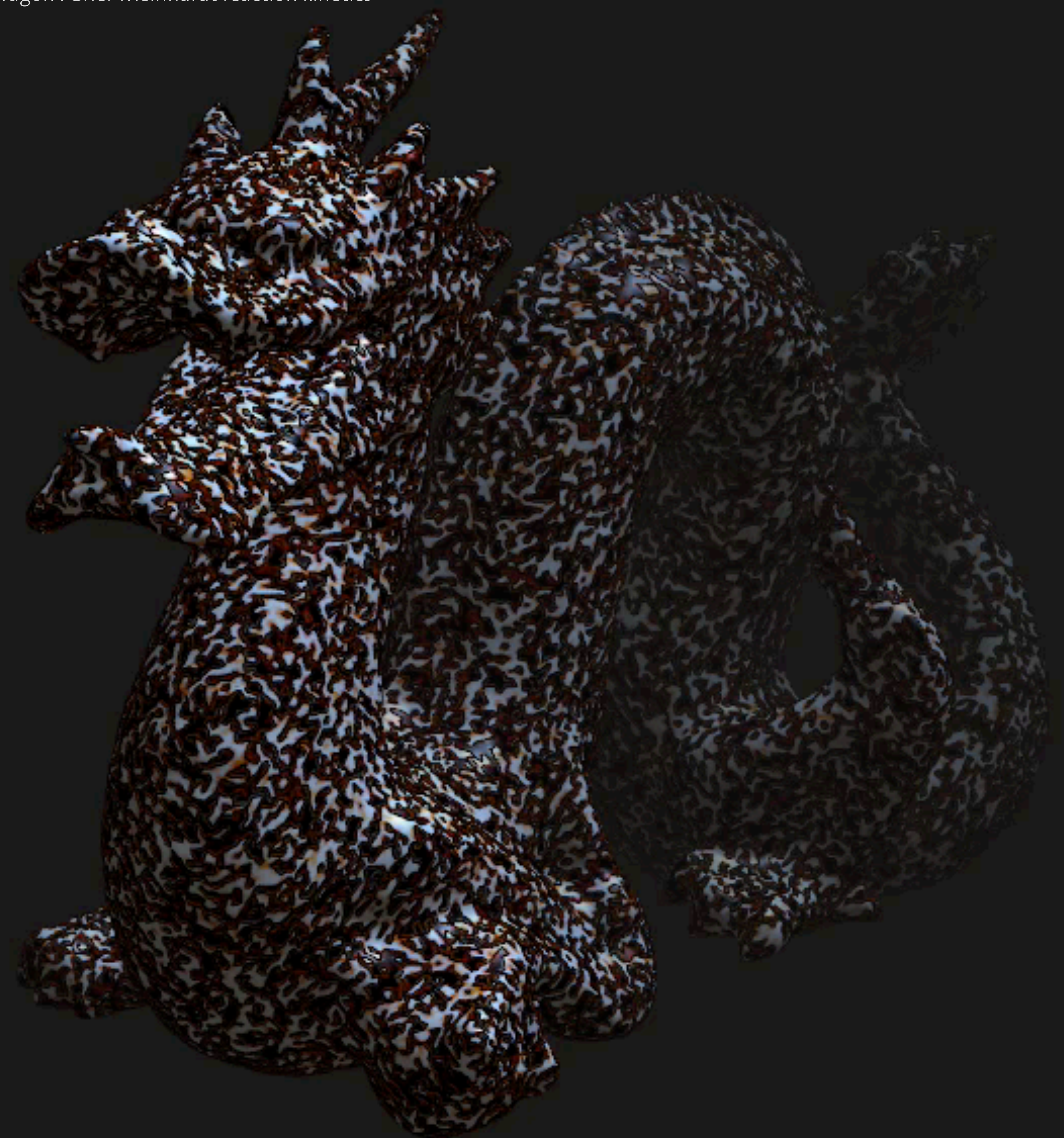
"Well, the stripes are easy, but what about the horse part " ? **Turing**

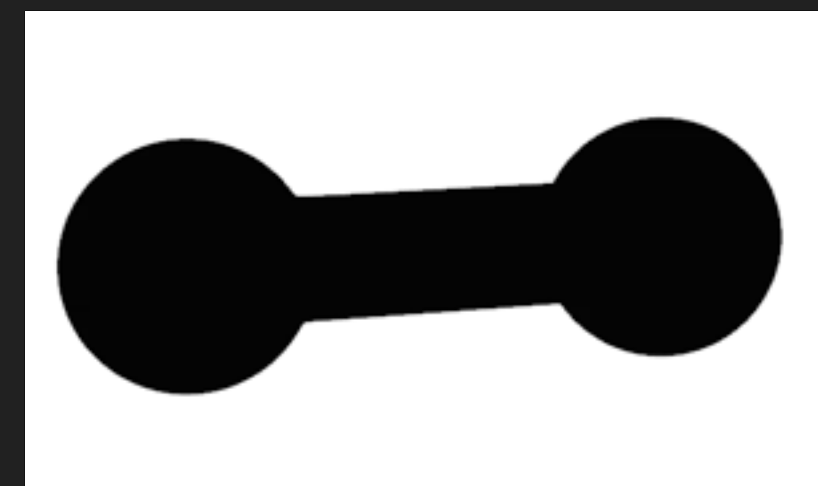
The Dragon : Grier-Meinhardt reaction kinetics

"Well, the stripes are easy, but what about the horse part " ? **Turing**

GROWTH : Reaction-Diffusion on Deforming Geometries

The Dragon : Grier-Meinhardt reaction kinetics

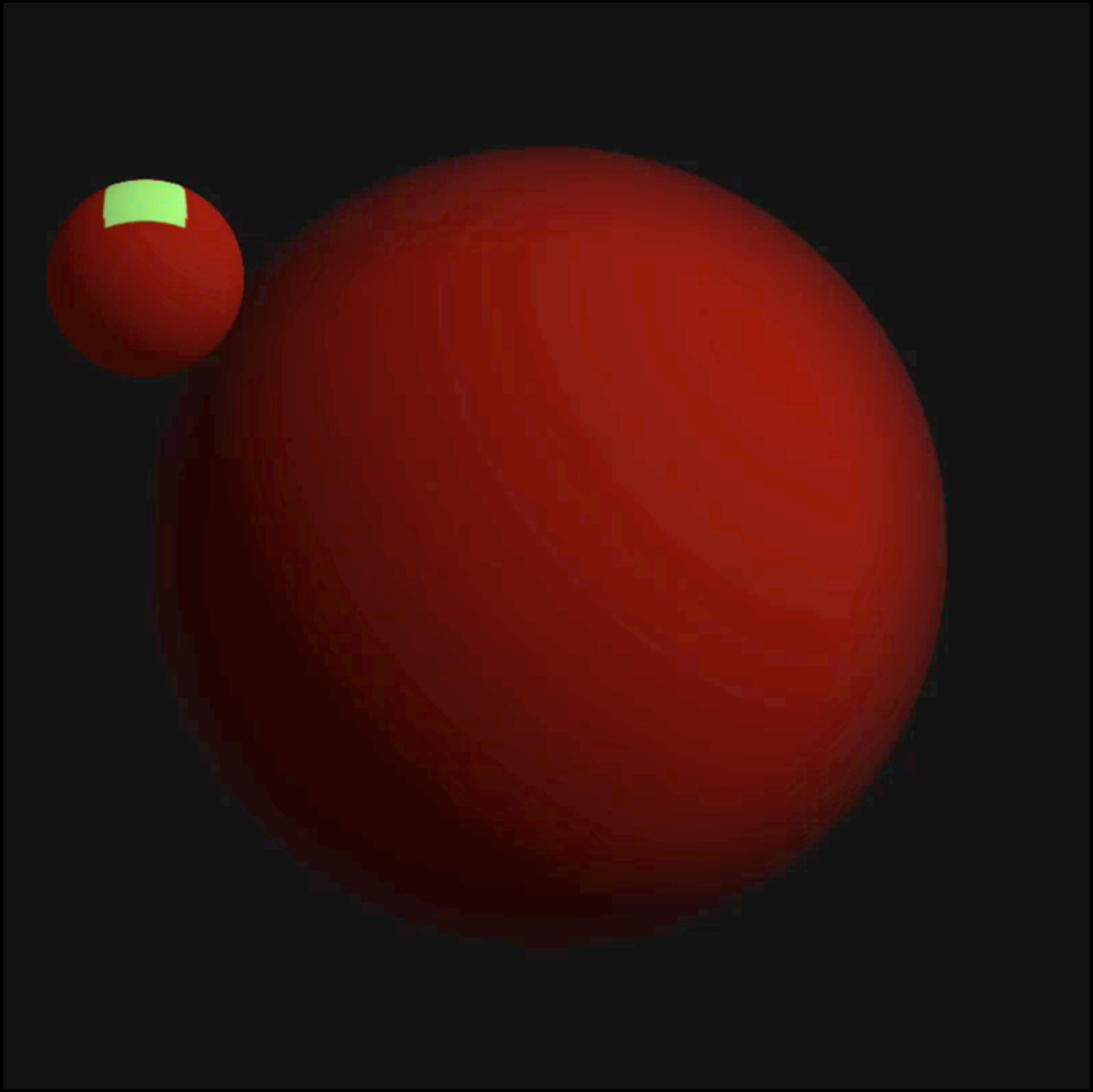




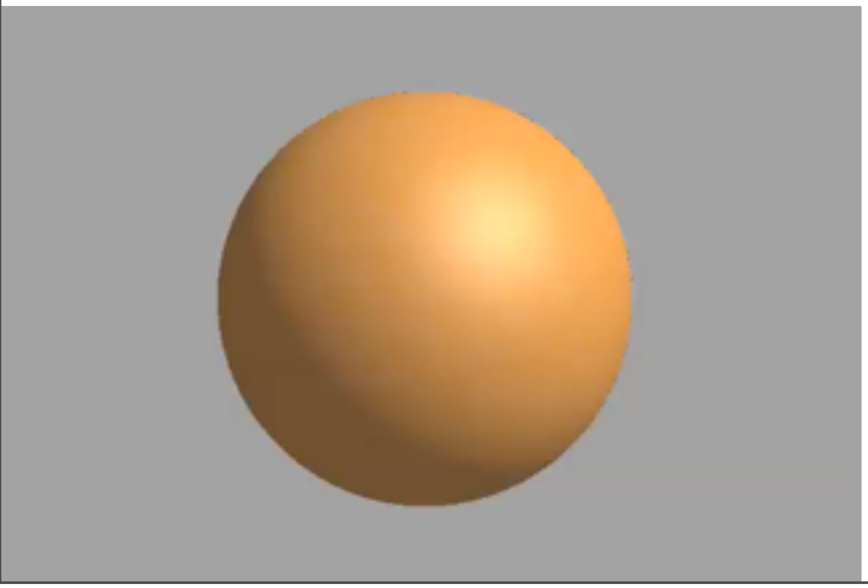
"Well, the stripes are easy, but what about the horse part " ? **Turing**

GROWTH : Reaction-Diffusion on Deforming Geometries

Diffusion/Reaction + Growth on Surfaces



Diffusion/Reaction + Growth Surfaces



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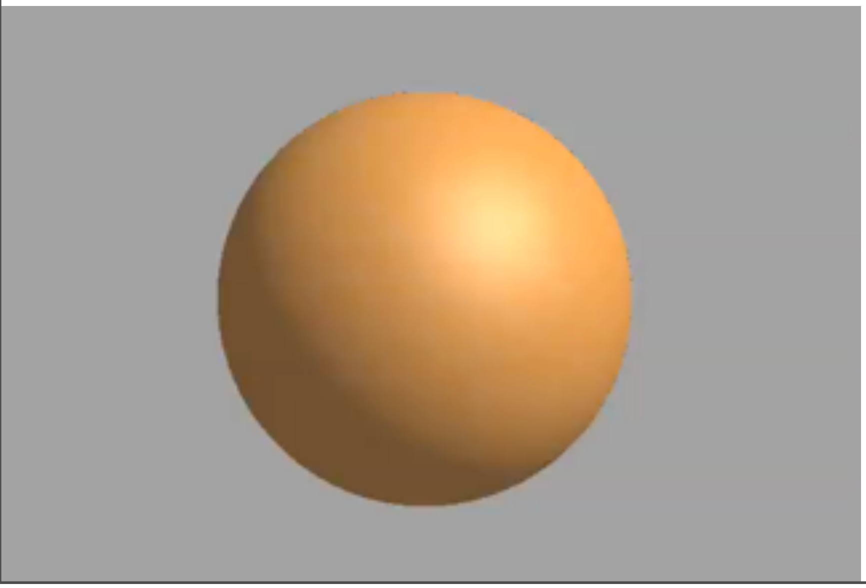
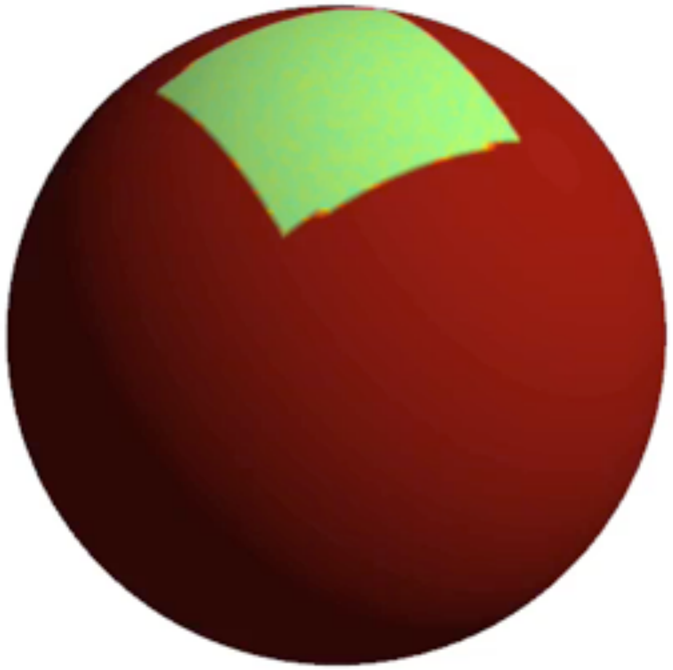
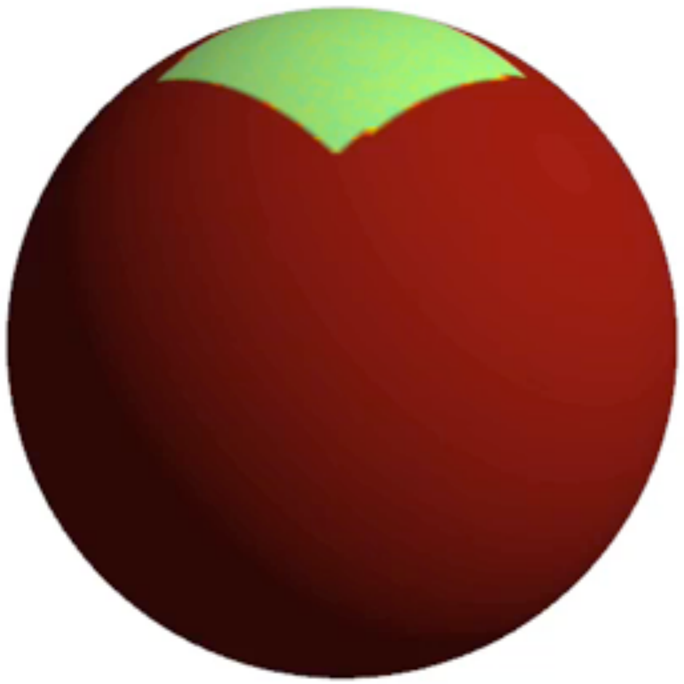
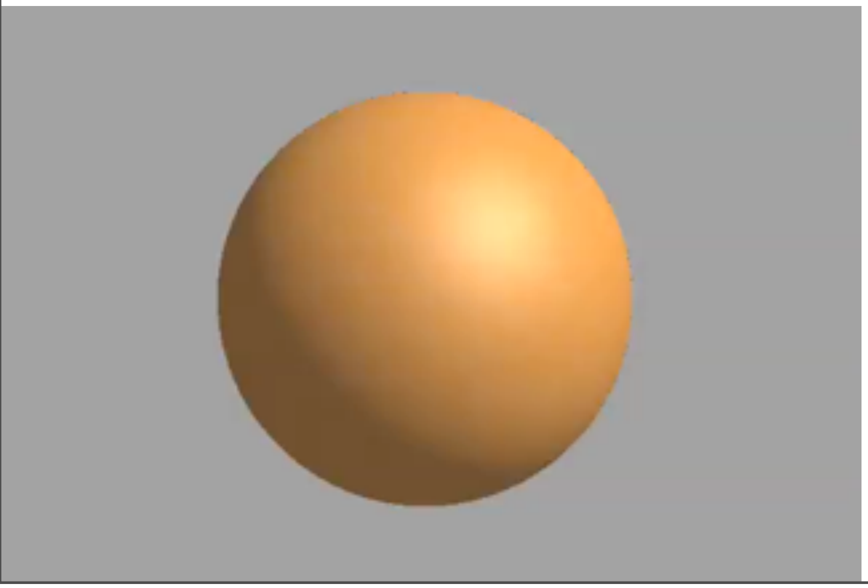
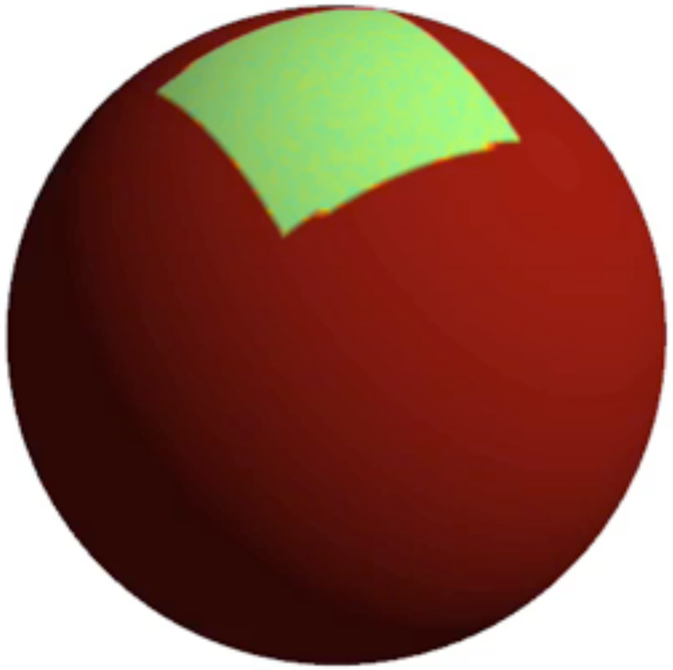




Diffusion/Reaction + Growth Surfaces







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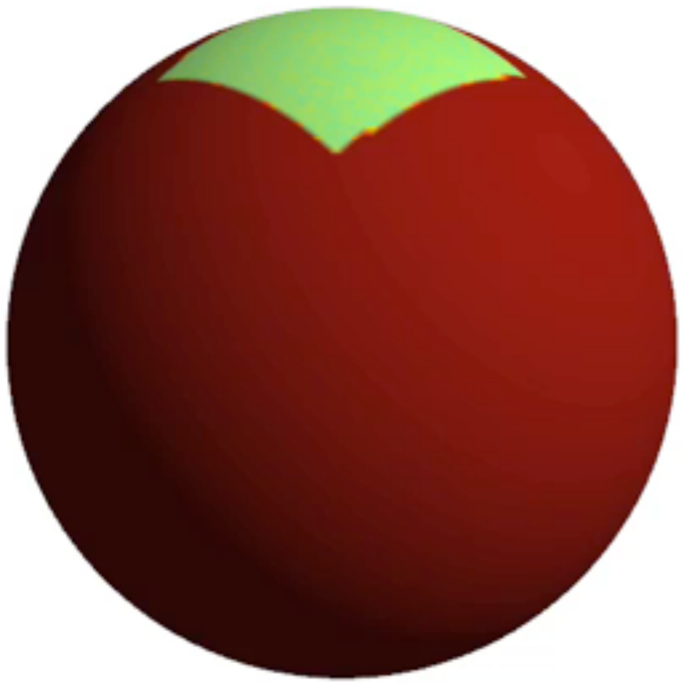
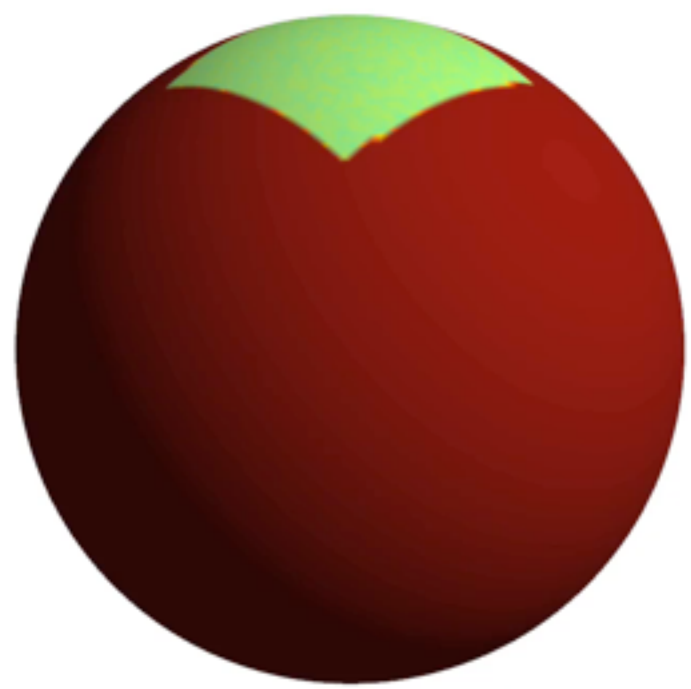
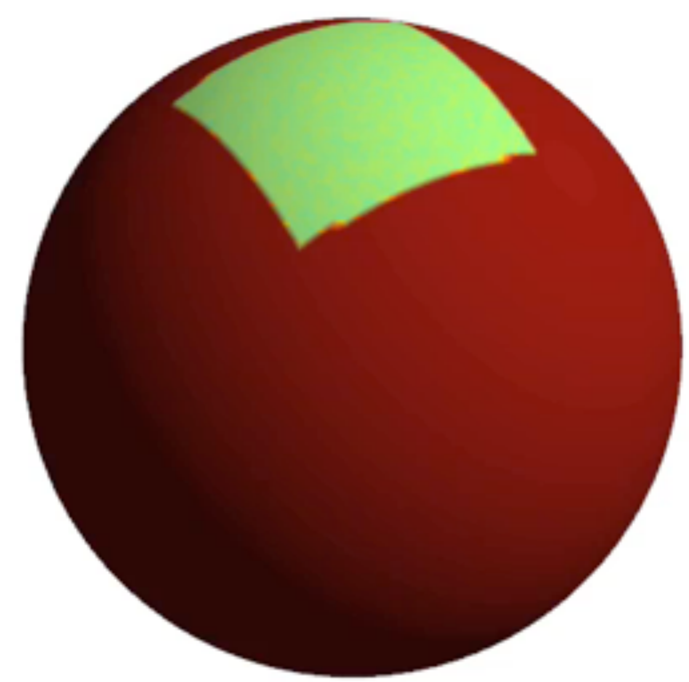
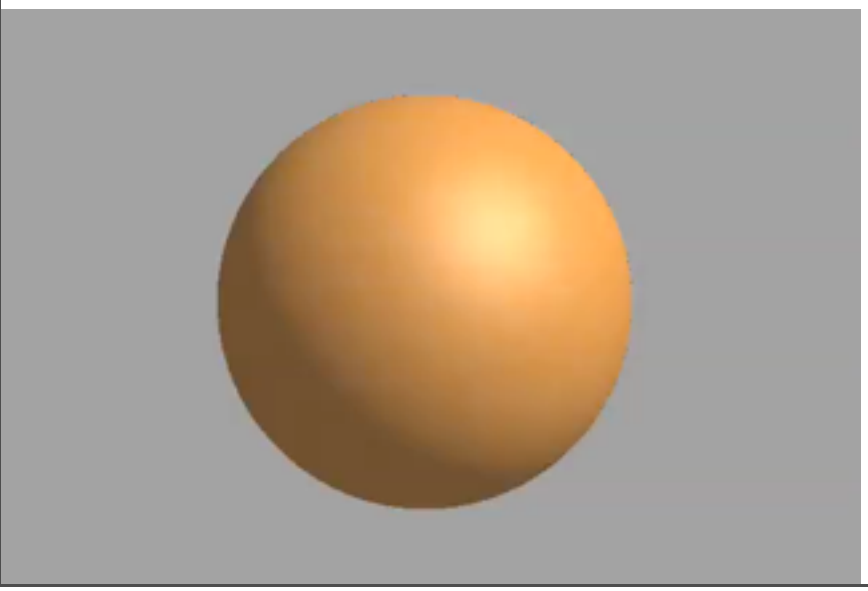
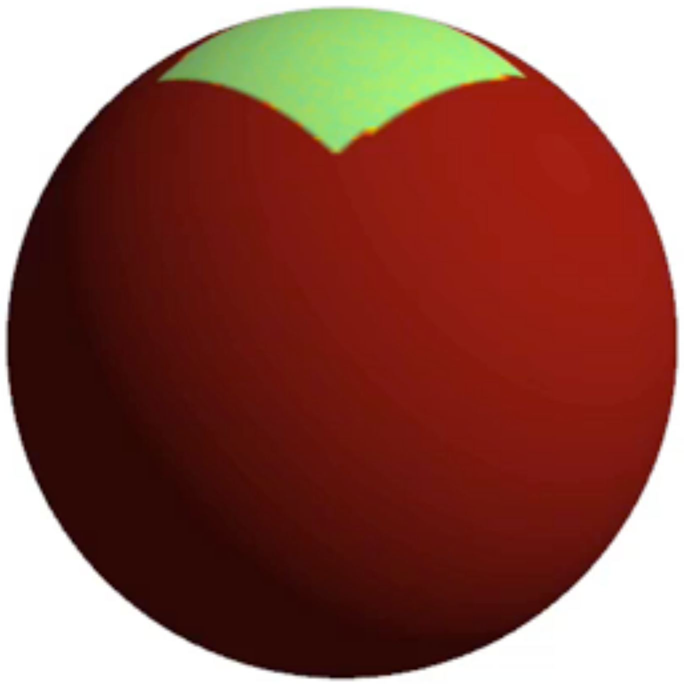


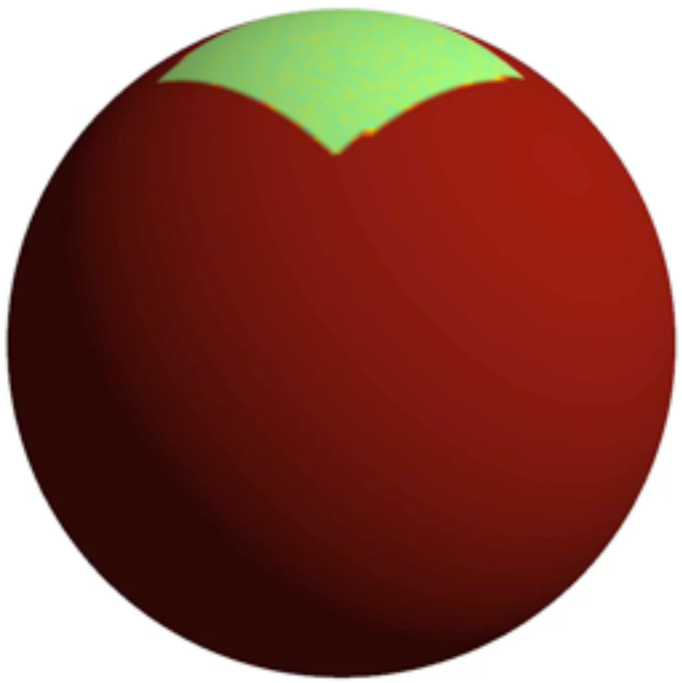


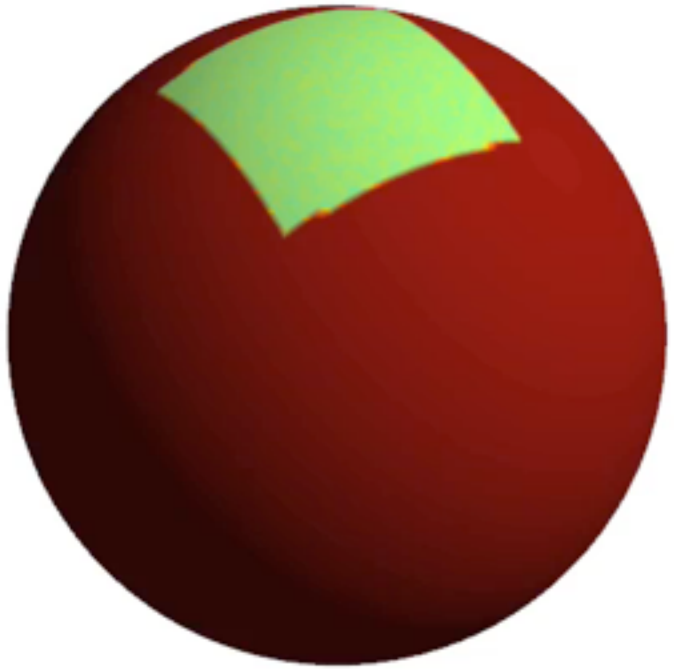


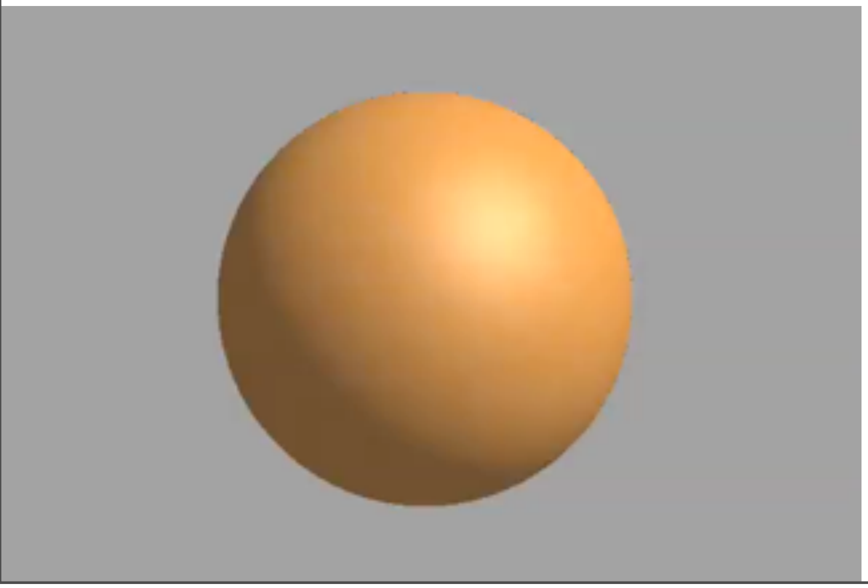


Diffusion/Reaction + Growth Surfaces





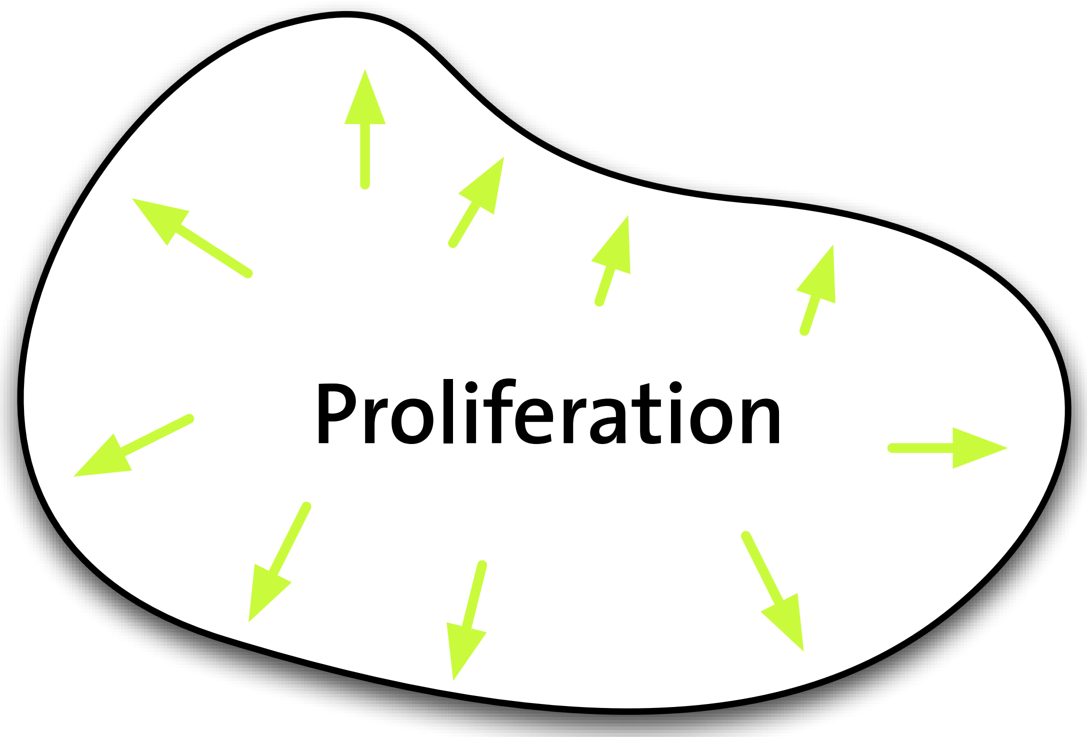




Reaction-diffusion coupled with growth

APPLICATION : Solid tumor model

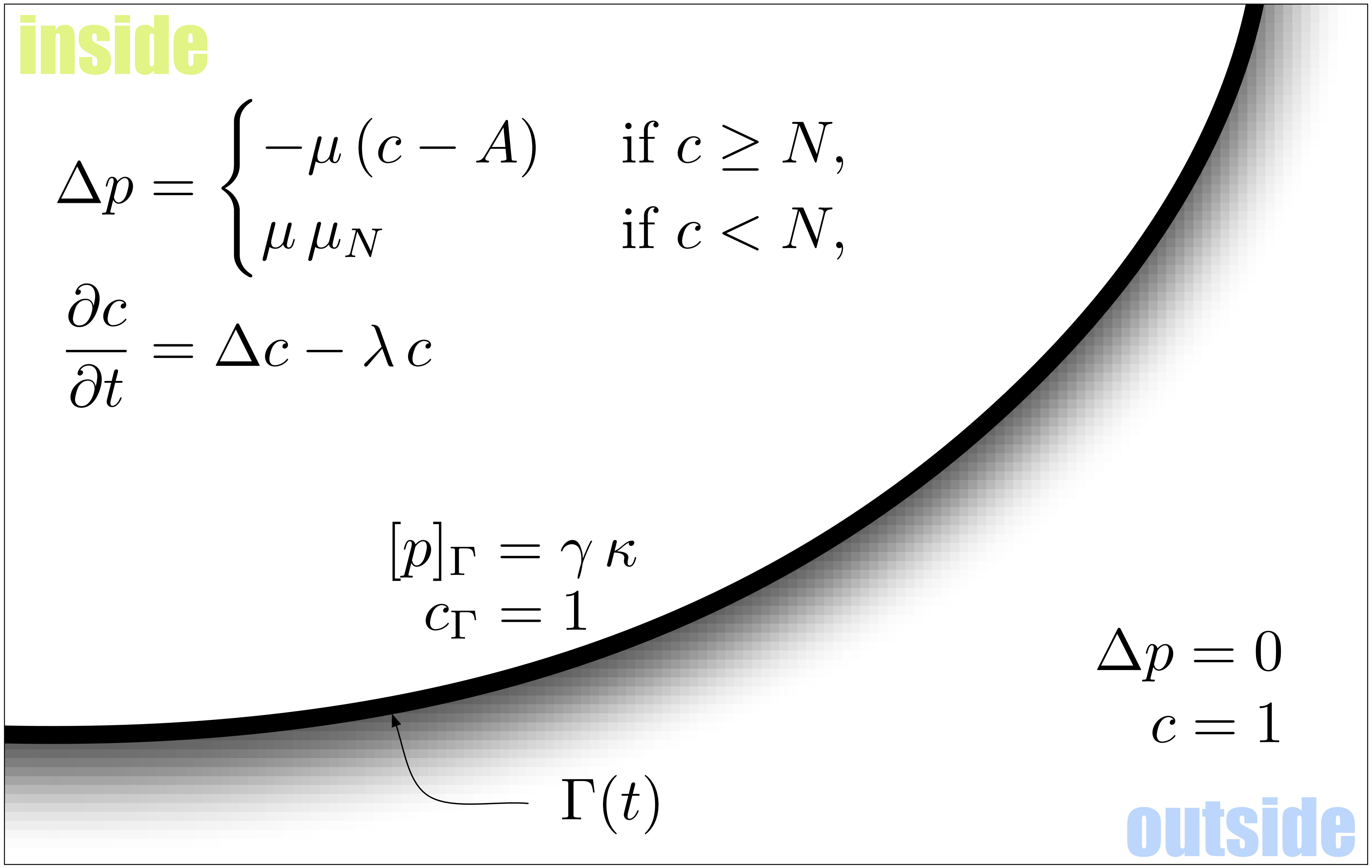
- Tissue incompressible
- Porous medium
- Sharp interface



Proliferation => Pressure => Velocity
i.e. proliferation has **global** effect

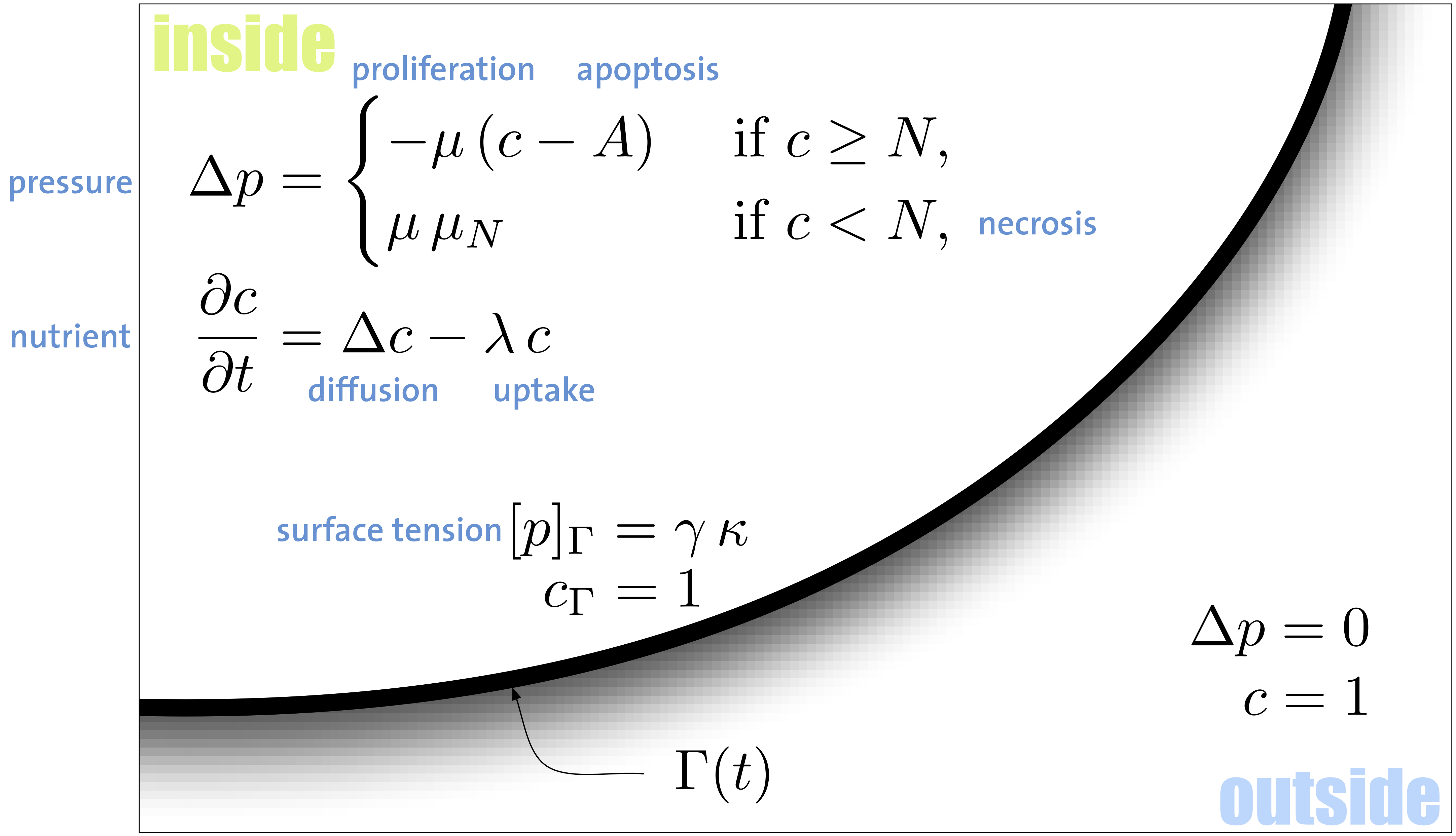
$$-\nabla \cdot \boldsymbol{u} = S \qquad \textbf{mass conservation}$$
$$\boldsymbol{u} = -\nabla p \qquad \textbf{Darcy's Law}$$

Solid tumor model



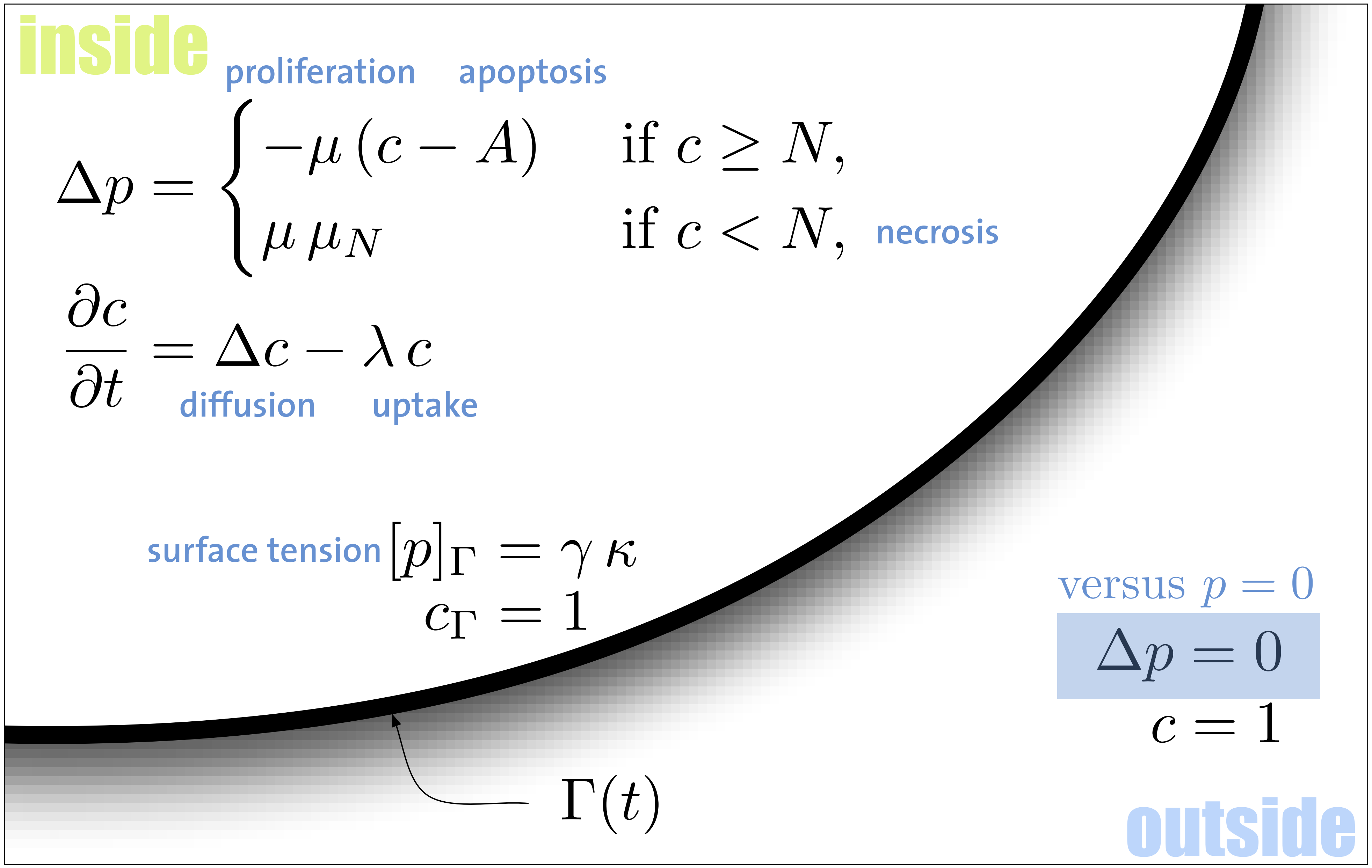
Cristini, Lowengrub, Nie, Friedman

Solid tumor model



Cristini, Lowengrub, Nie, Friedman

Solid tumor model



proliferation apoptosis

pressure
$$\Delta p = \begin{cases} -\mu\,(c - A) & \text{if } c \geq N, \\ \mu\,\mu_N & \text{if } c < N, \end{cases}$$
necrosis

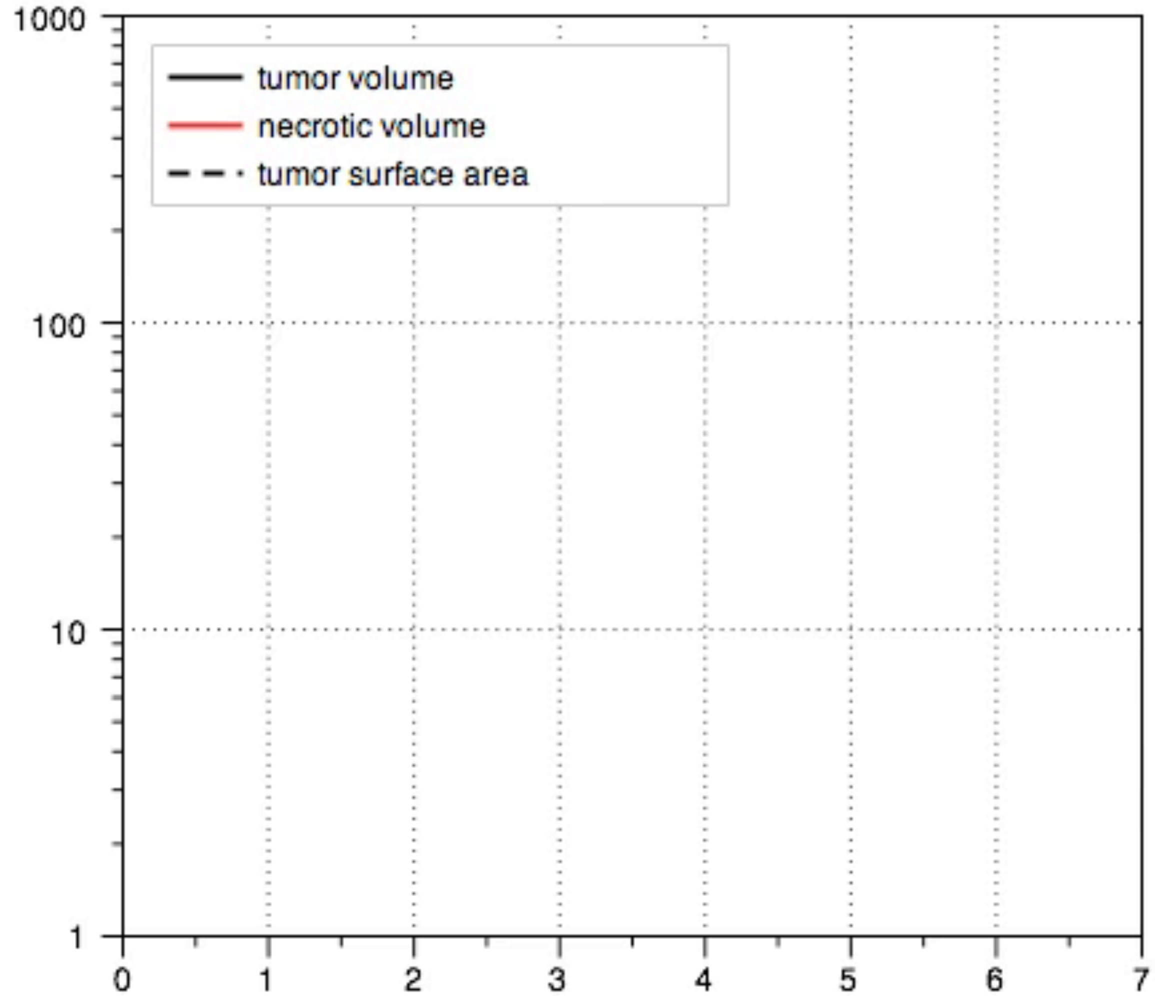
nutrient
$$\frac{\partial c}{\partial t} = \Delta c - \lambda\, c$$
diffusion uptake

surface tension
$$[p]_\Gamma = \gamma\,\kappa$$
$$c_\Gamma = 1$$

versus $p = 0$
$$\Delta p = 0$$
$$c = 1$$

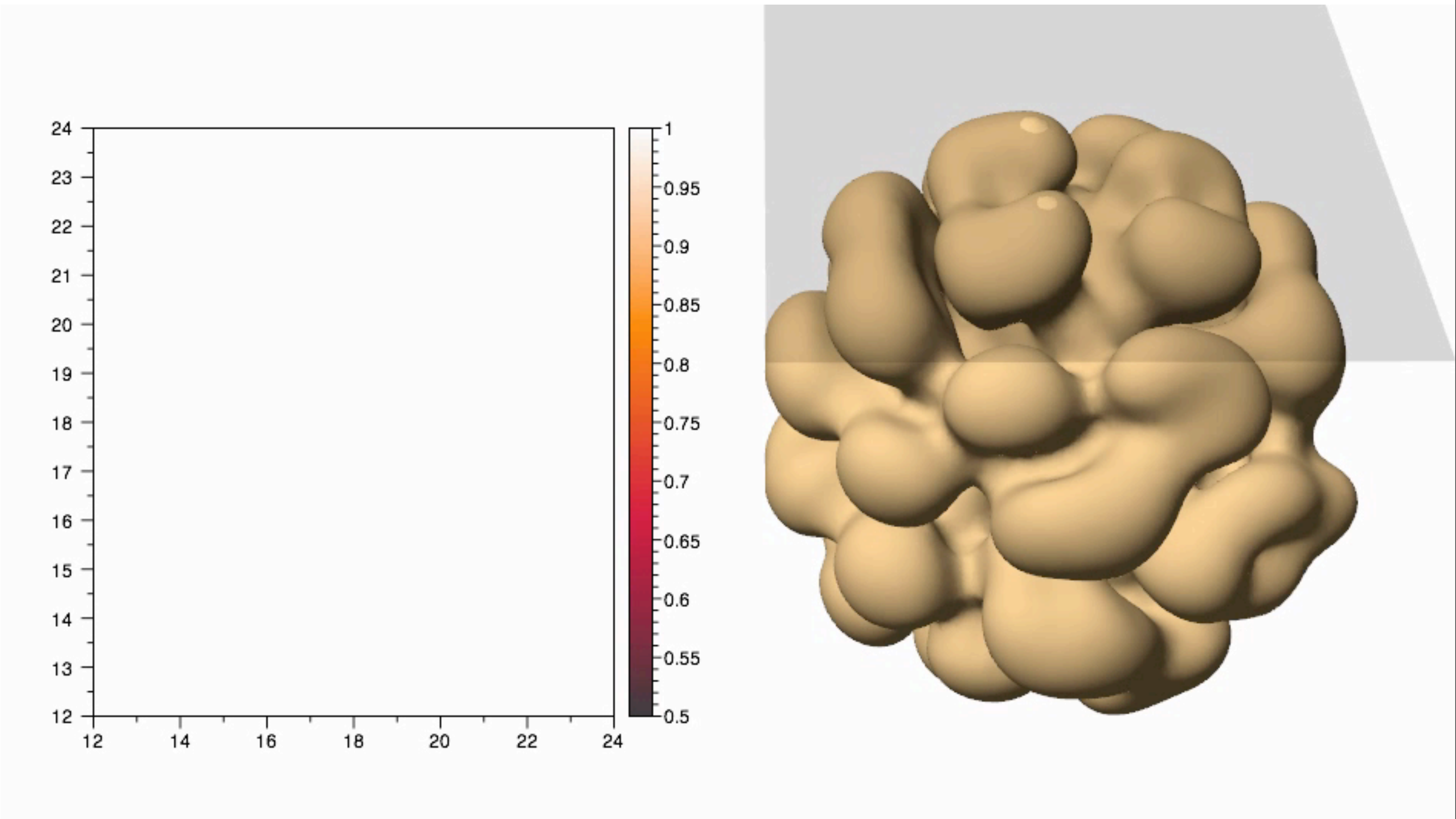
Cristini, Lowengrub, Nie, Friedman

Solid tumor model with necrosis



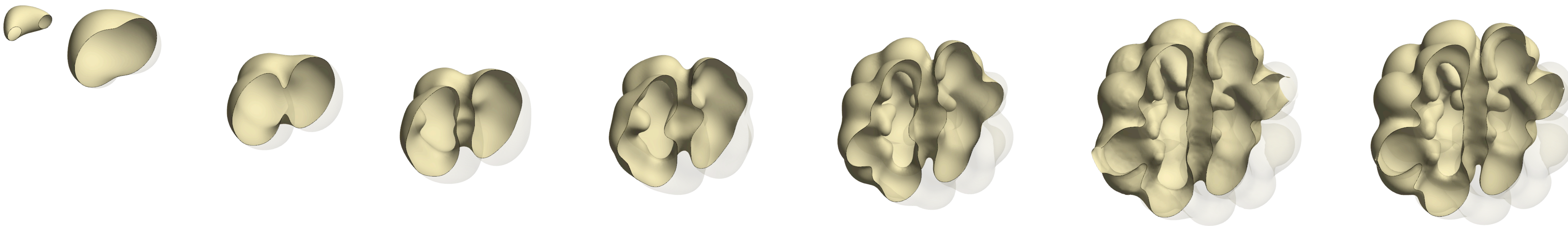
$\gamma = 1 \quad N = \frac{1}{2} \quad \lambda = 1 \quad \mu = 20 \quad \mu_G = 1 \quad \mu_N = 1$

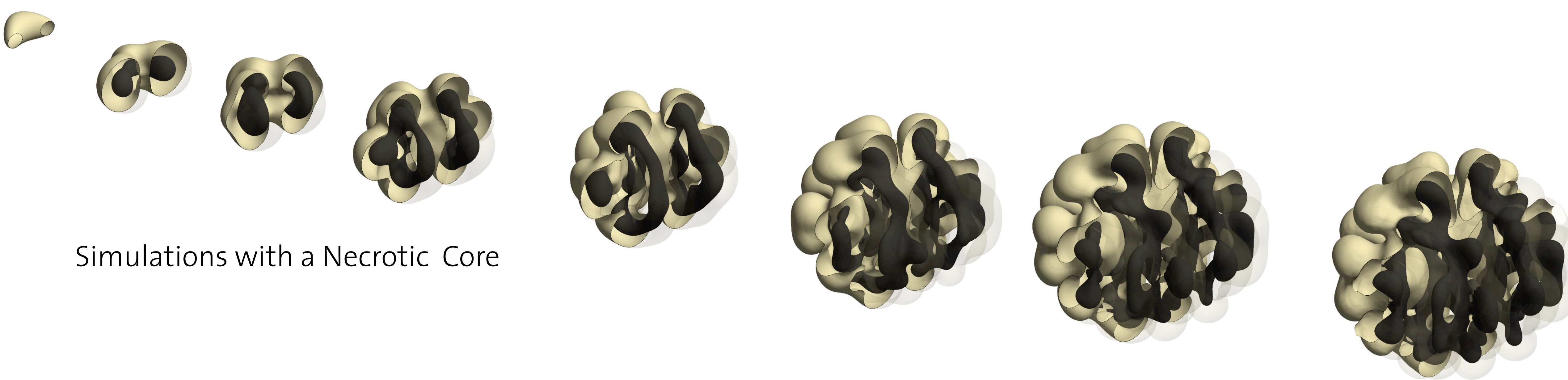
Solid tumor model with necrosis



$\gamma = 1 \quad N = \frac{1}{2} \quad \lambda = 1 \quad \mu = 20 \quad \mu_G = 1 \quad \mu_N = 1$

Tumor Growth :

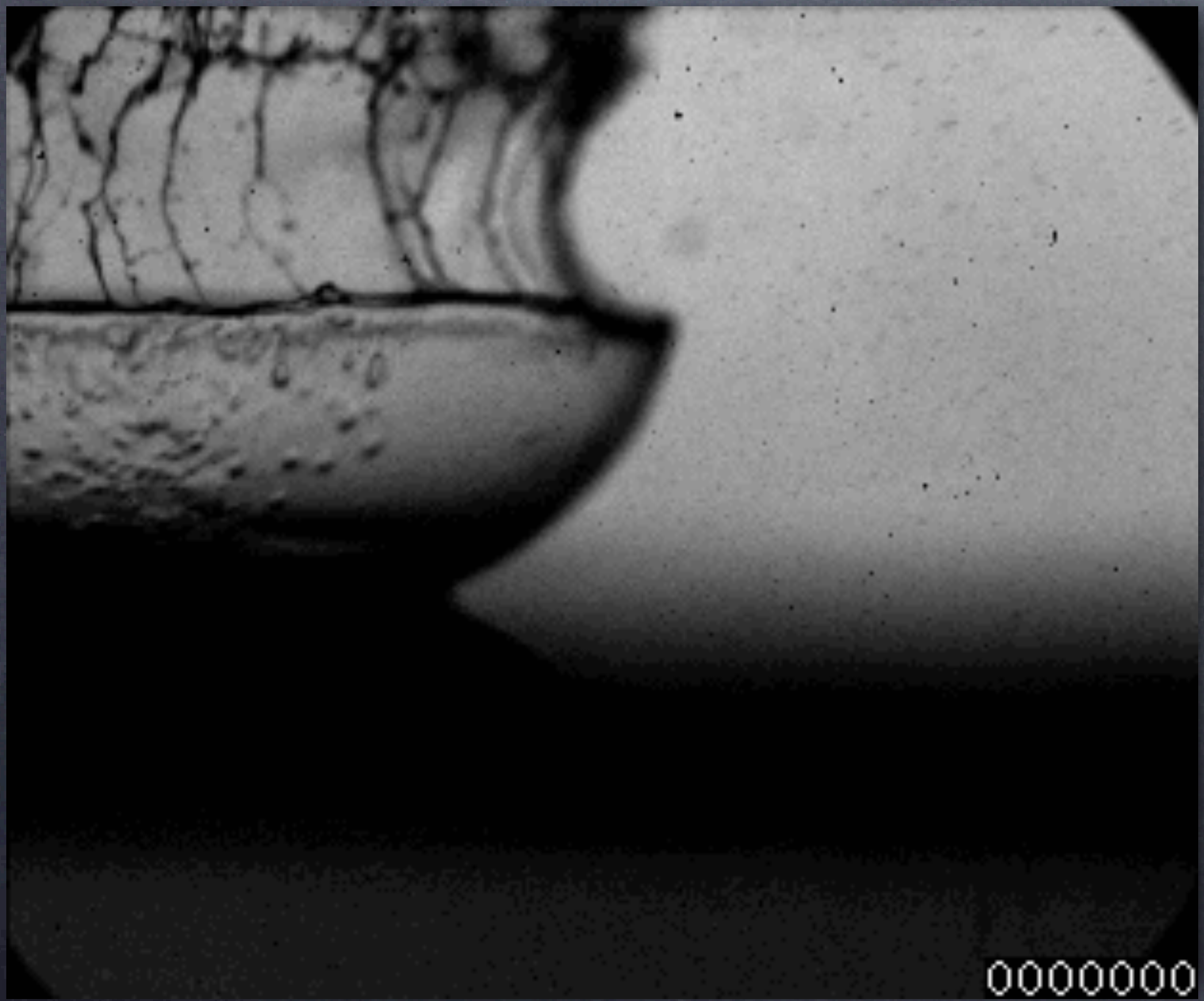




Simulations with a Necrotic Core

$\tilde{c} = 0.5$ $\mu = 20$ $N = 0.5$ $G_\nu = 1.0$ $\gamma = 1.0$

COMPUTATION : Exploring Possibilities (and bridging disciplines)



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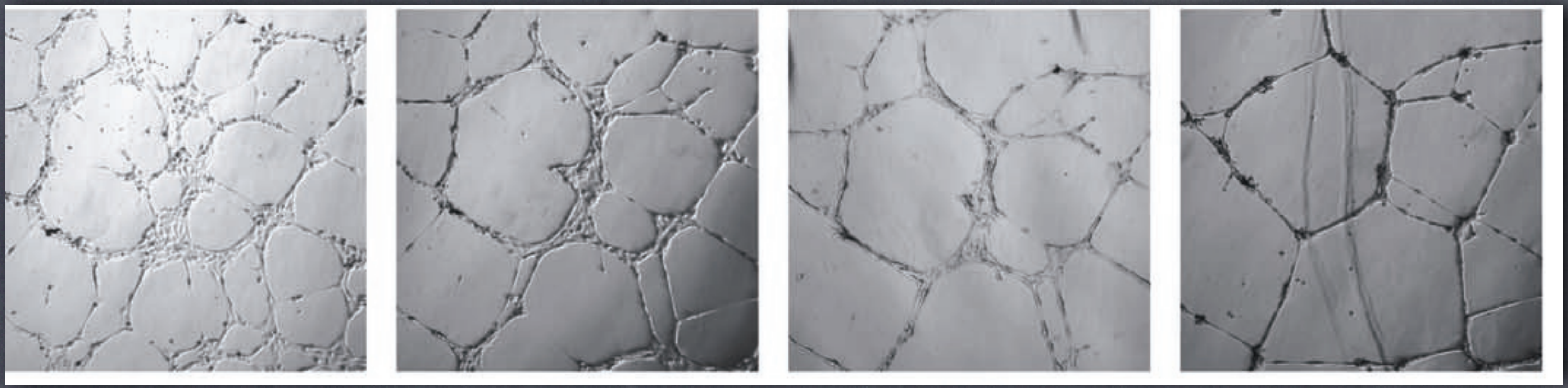

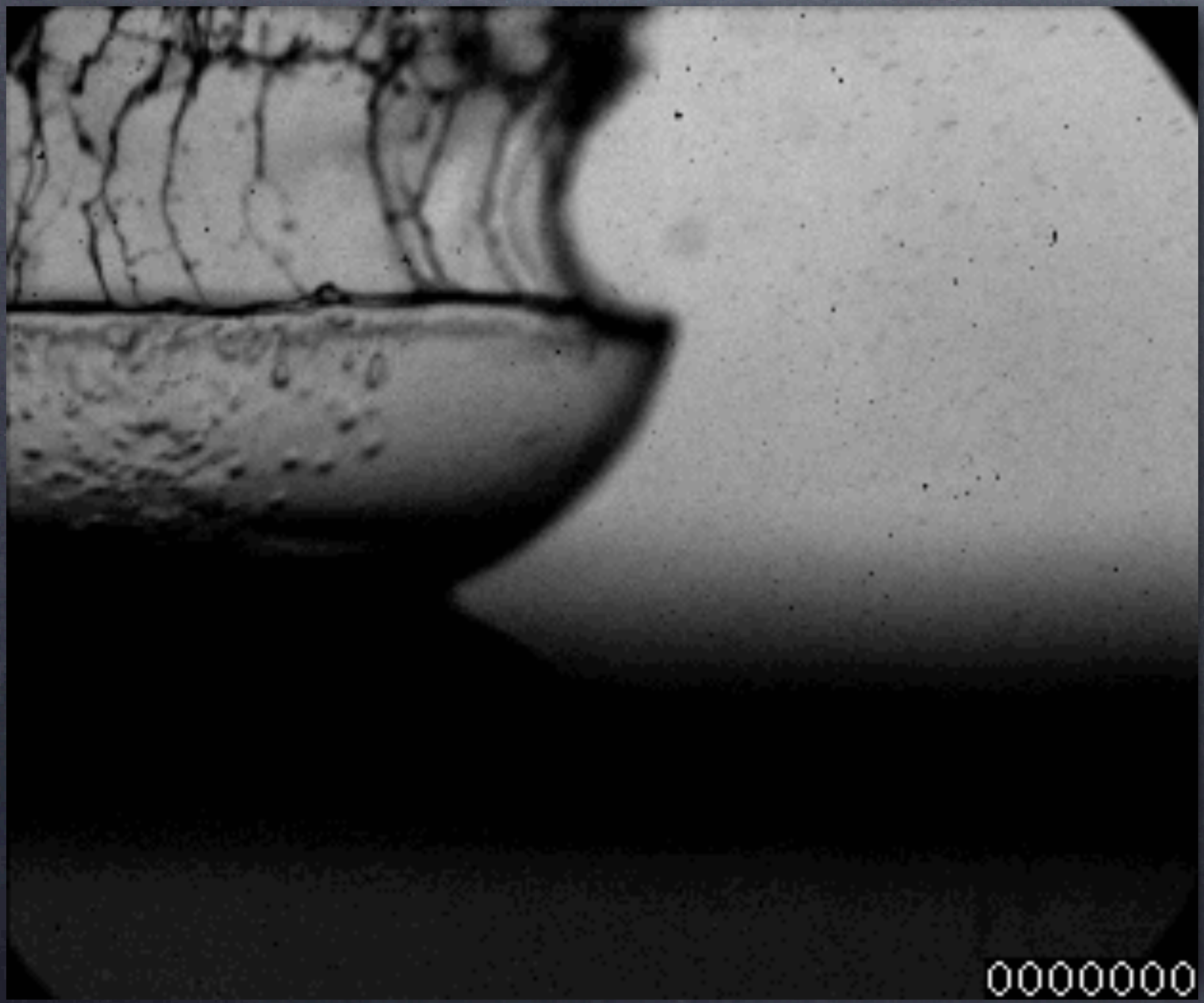

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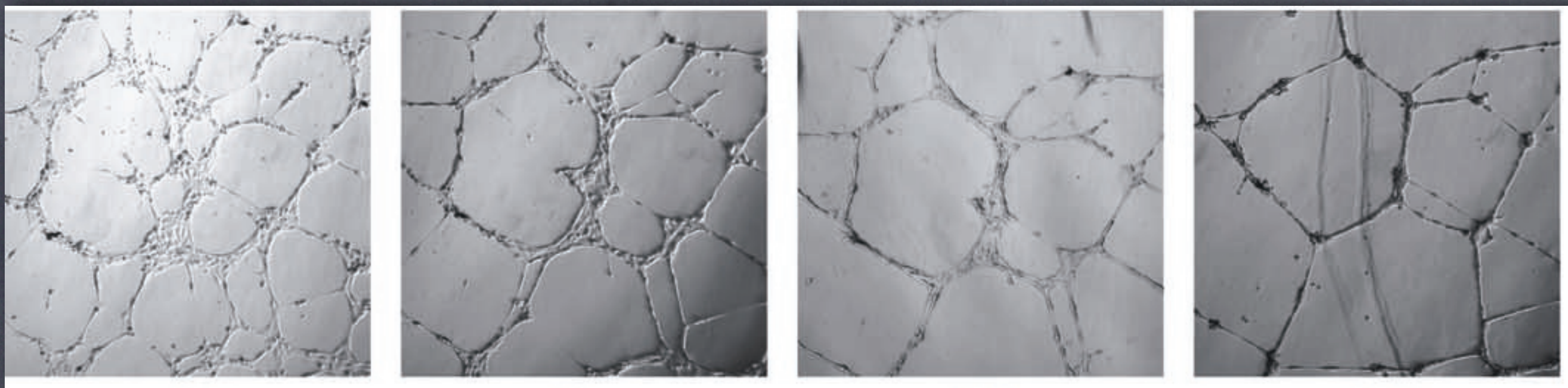

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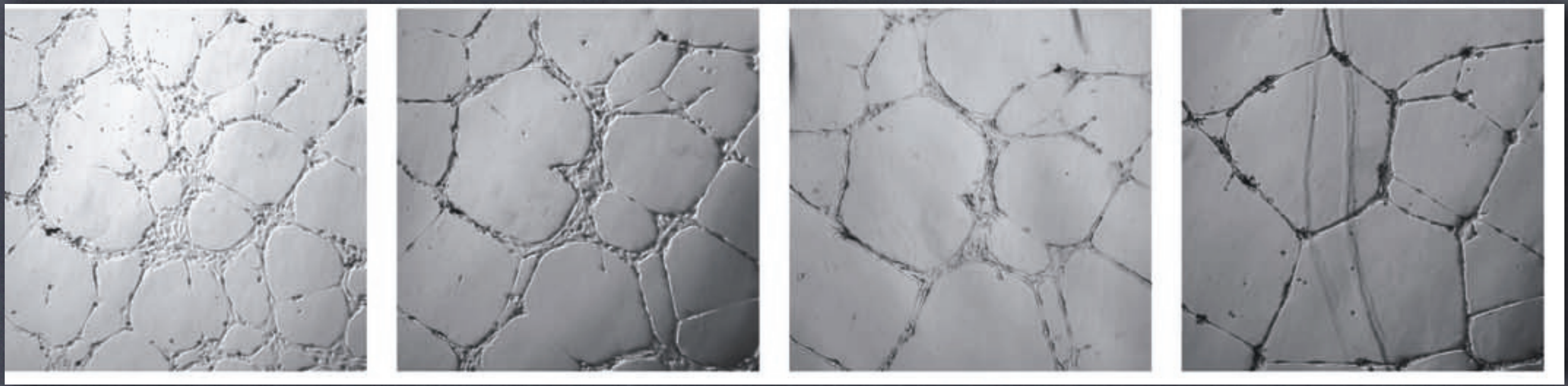
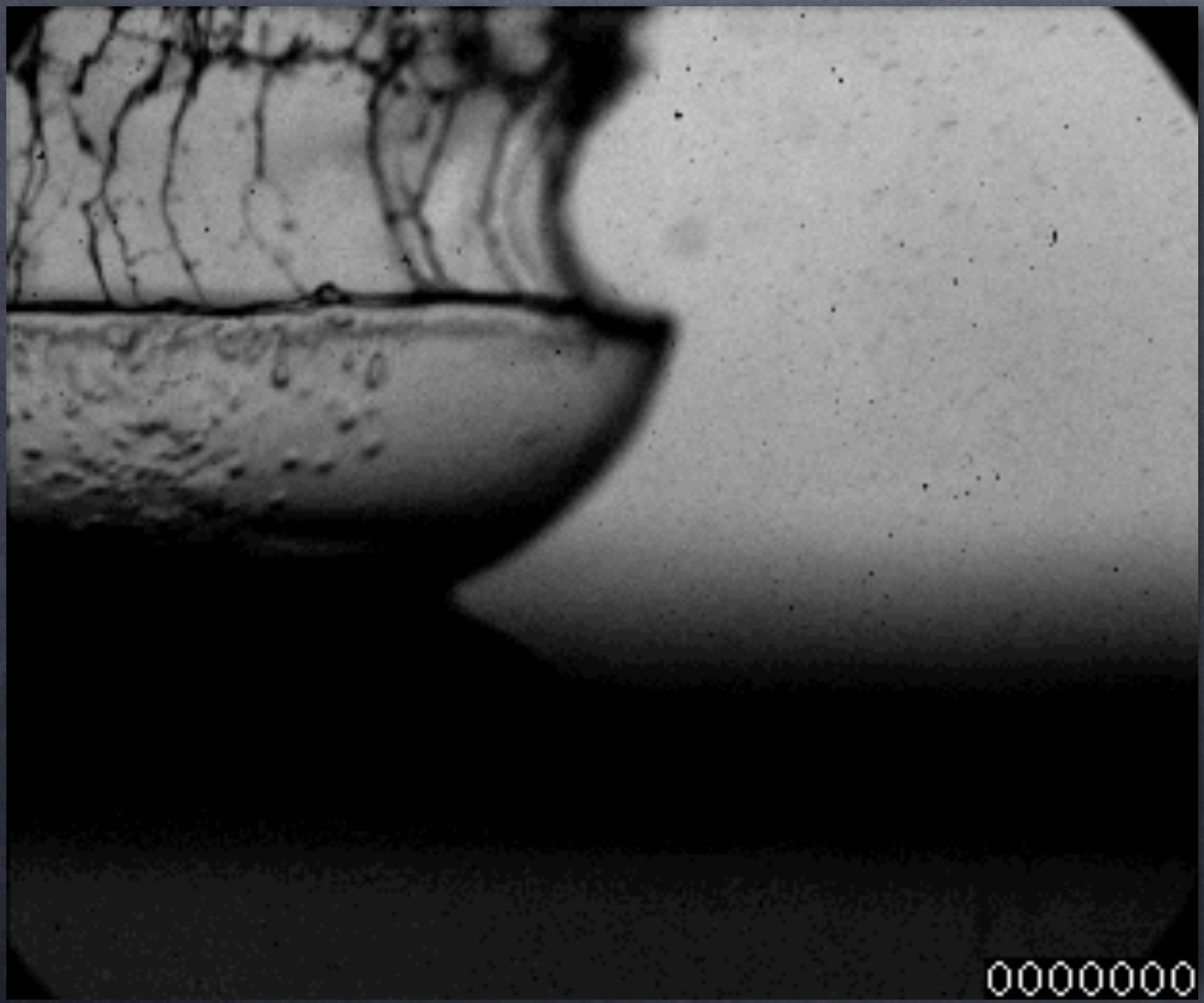




CROWN DROPLET BREAKUP

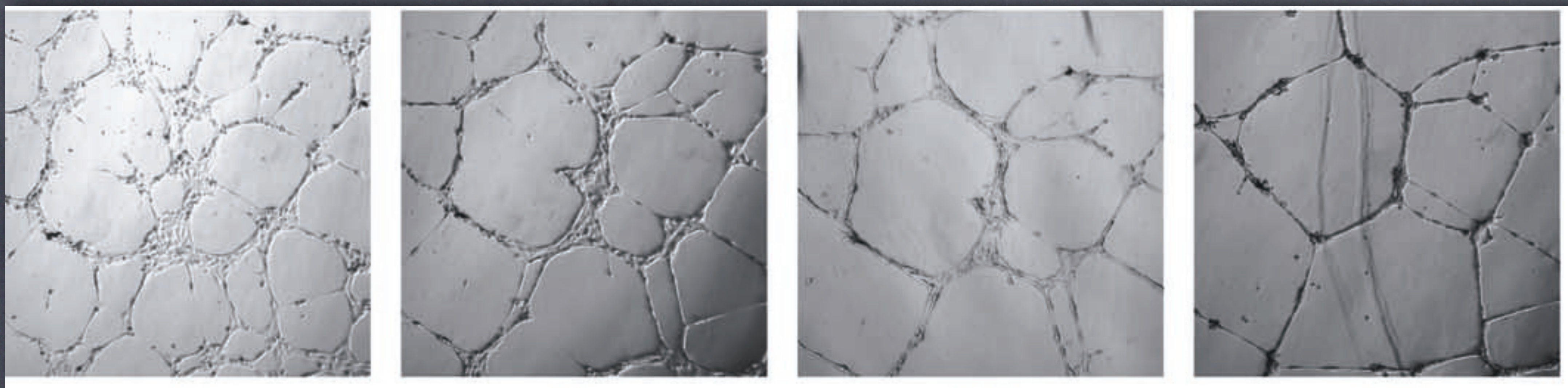
marangoni instability of a drop impact onto an ethanol sheet

[2] S. T. Thoroddsen, T. G. Etoh, and K. Takehara. Crown breakup by marangoni instability. *J. Fluid Mech.*, 557(-1):63–72, 2006.

COMPUTATION : Exploring Possibilities (and bridging disciplines)

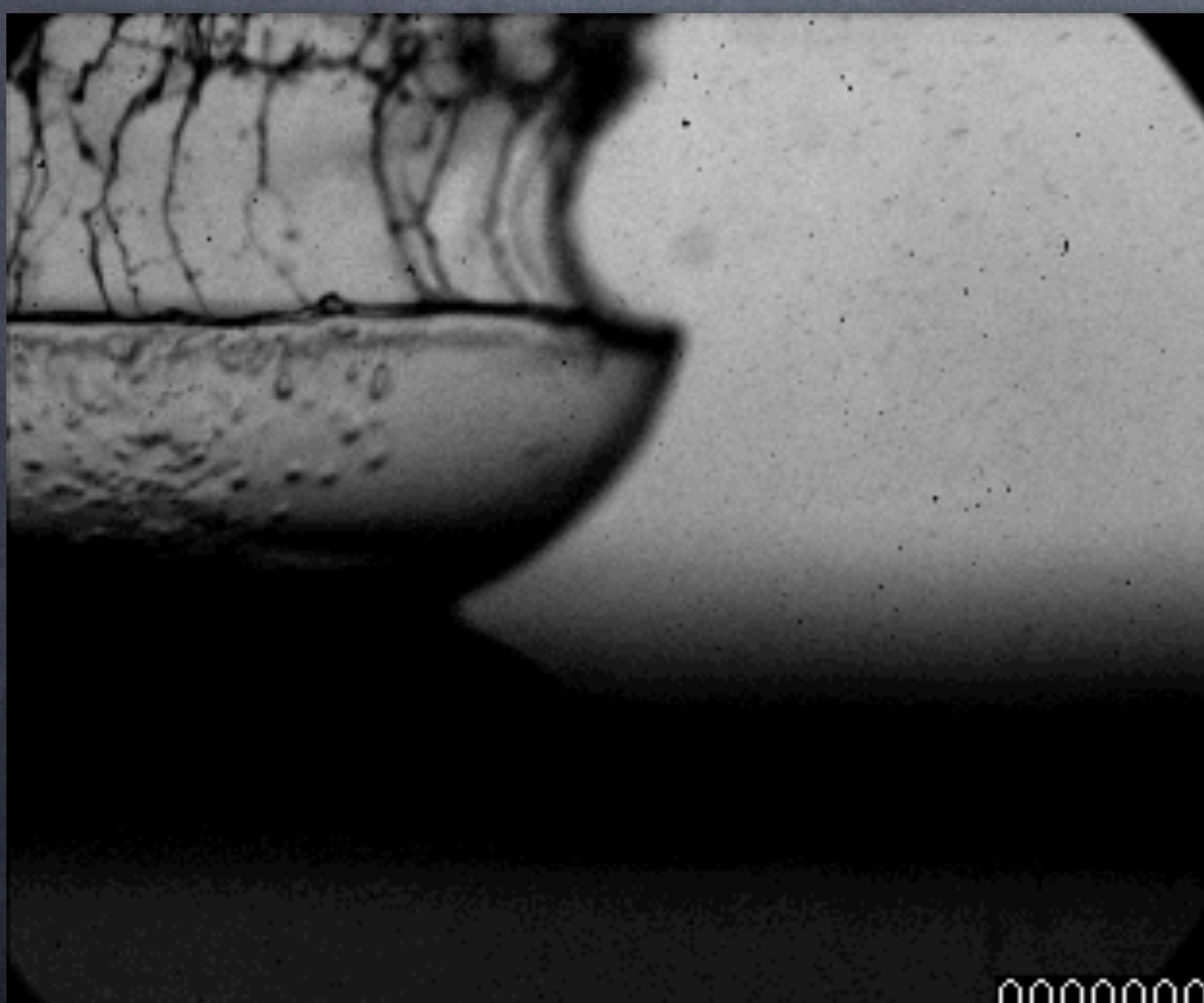
VASCULOGENESIS

blood vessel formation in embryonic development



4h 9h 12h 24h

[1] R. M. H. Merks, S. V. Brodsky, M. S. Goligorksy, S. A. Newman, and J. A. Glazier. Cell elongation is key to in silico replication of in vitro vasculogenesis and subsequent remodeling. *Developmental Biology*, 289(1):44–54, 2006.



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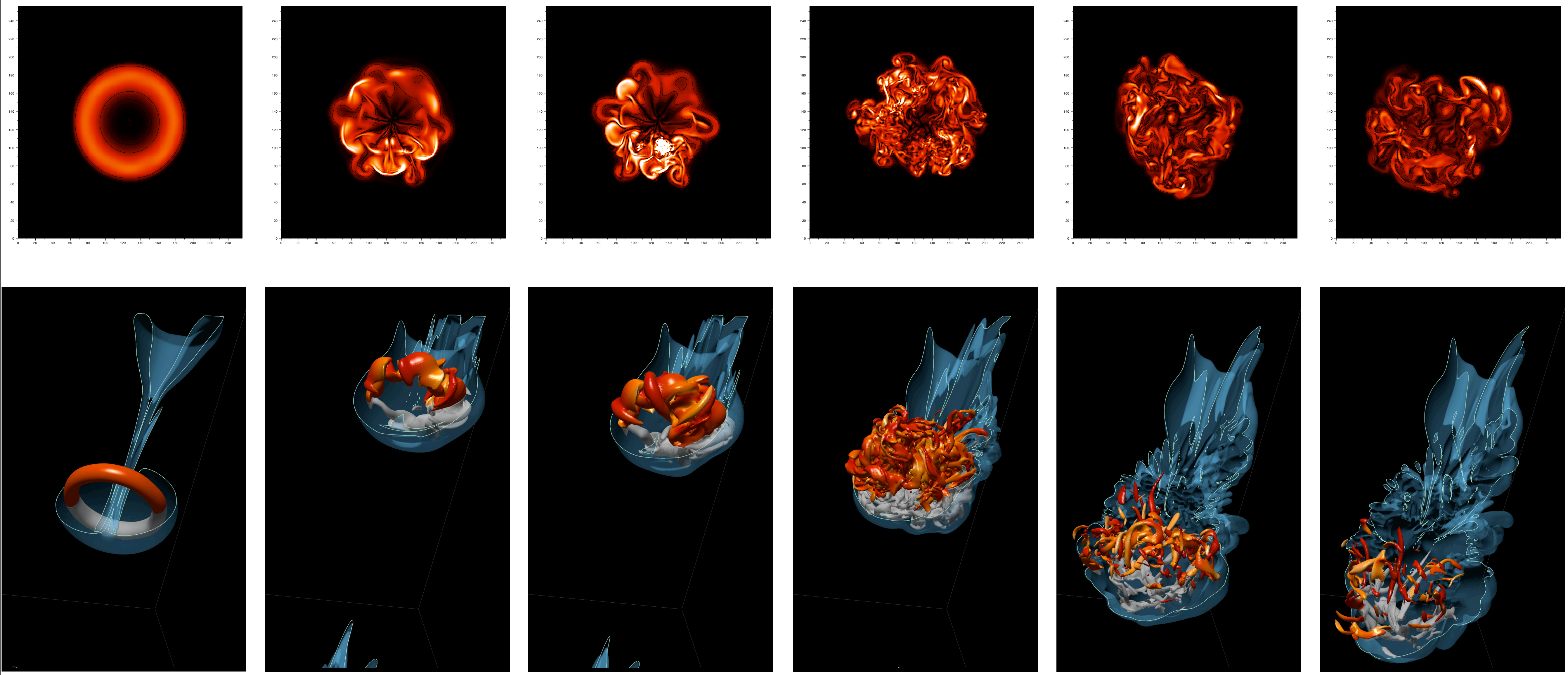
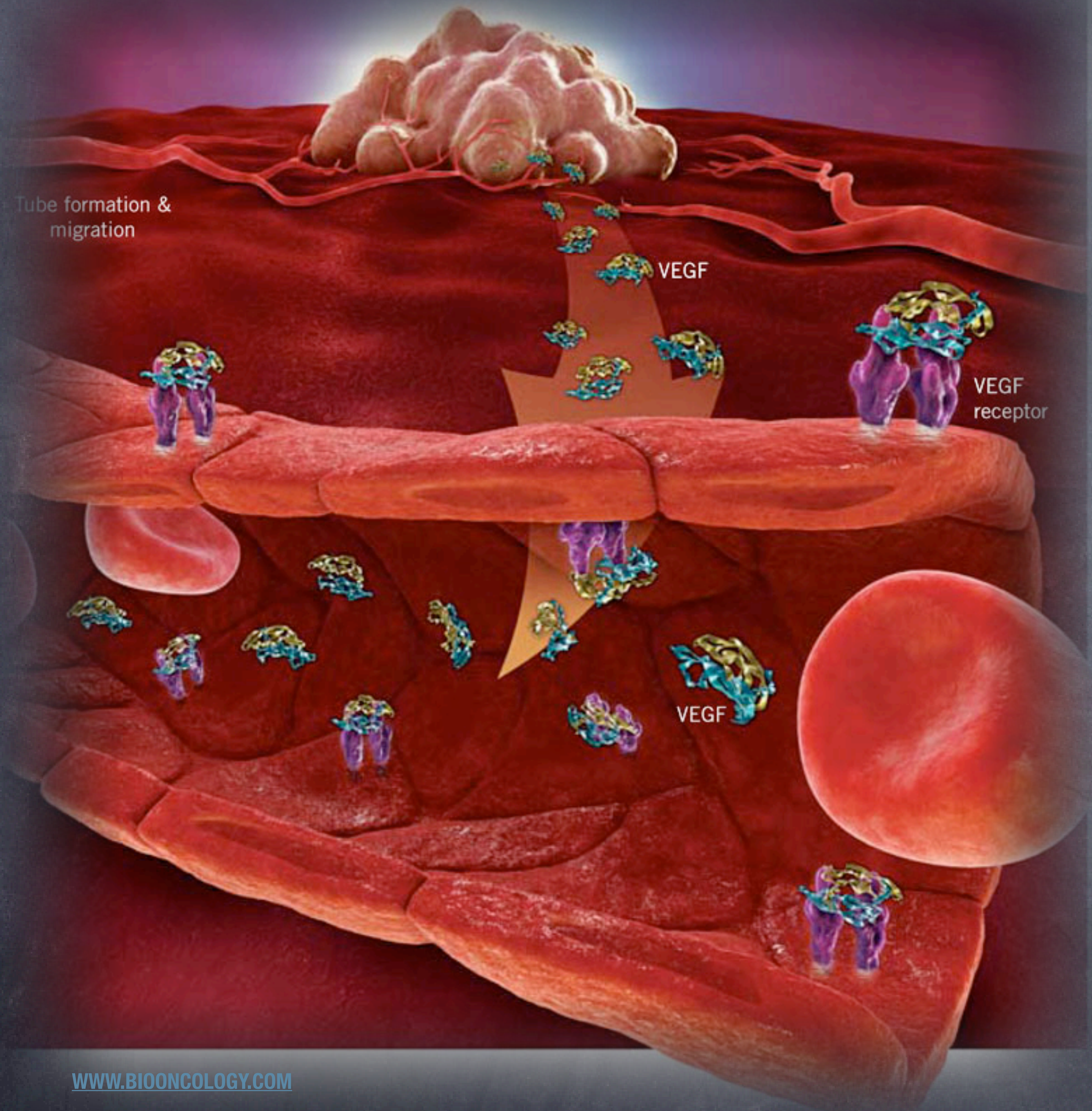
COMPUTATION : Exploring Possibilities (and bridging disciplines)

Vortex Rin gs : Re = 3000





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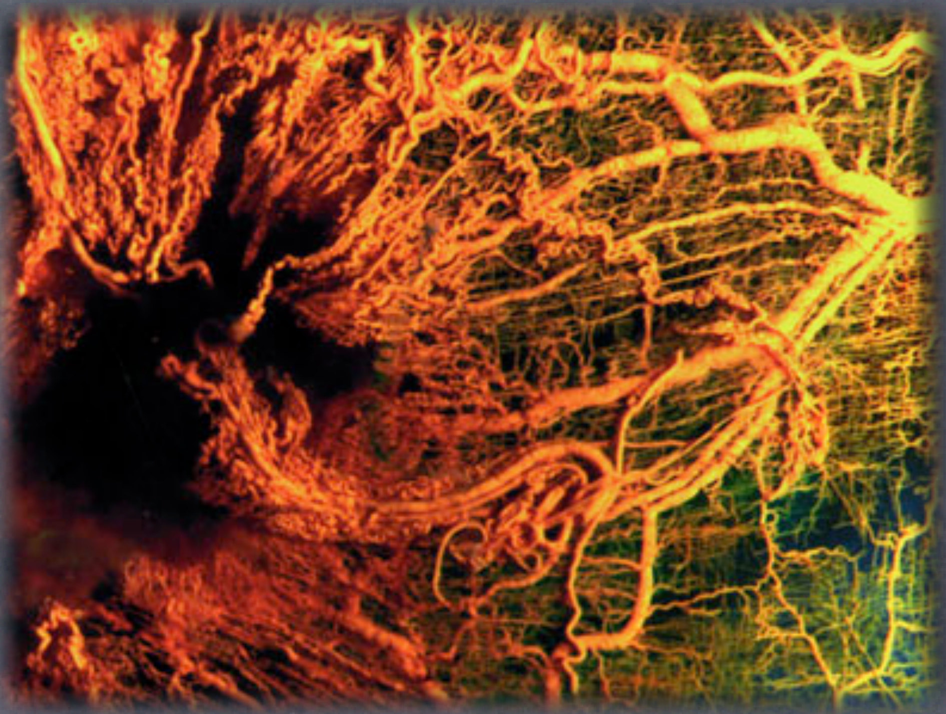
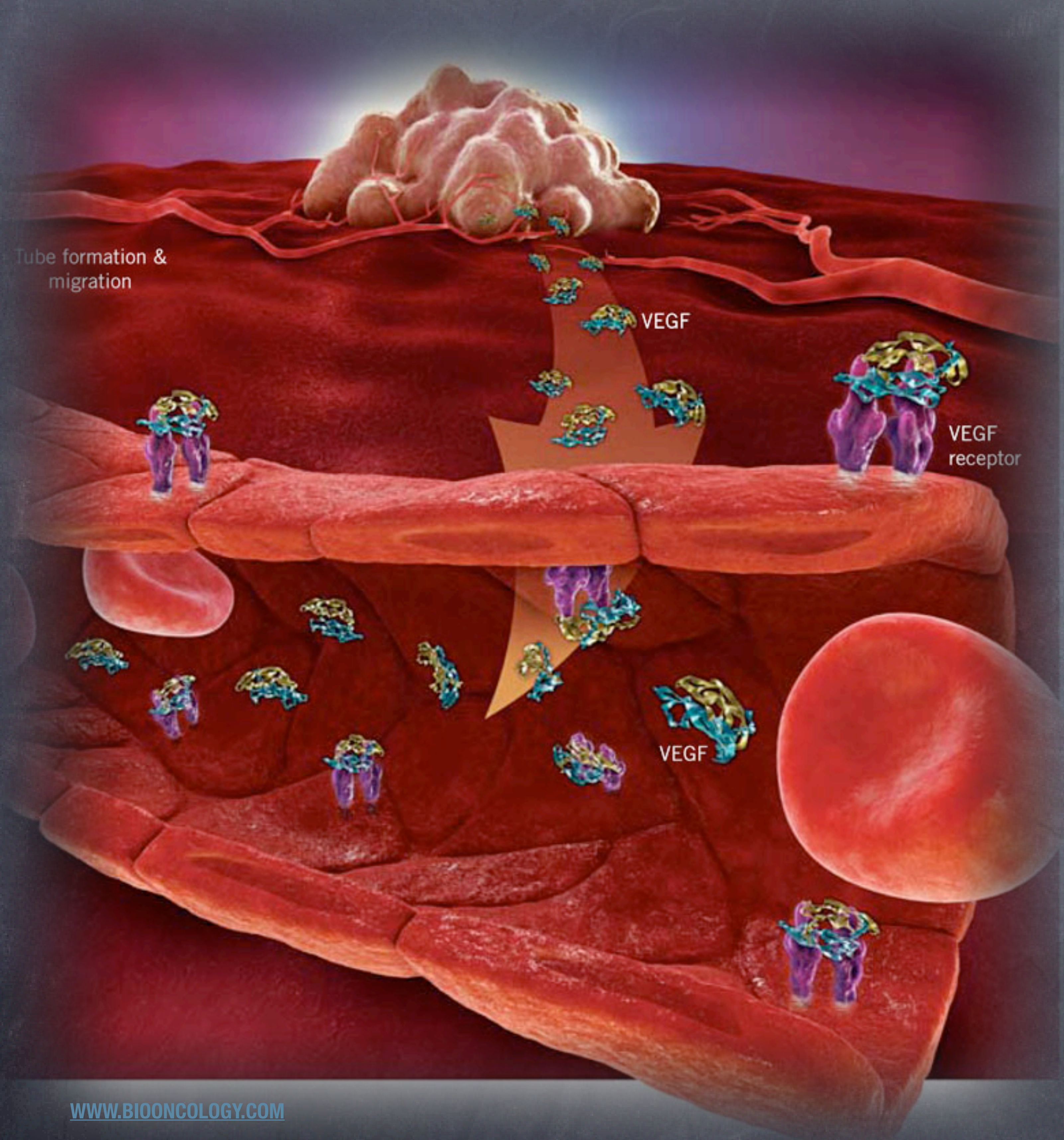


CRANIAL VESSEL ANGIOGENESIS IN ZEBRAFISH

HTTP://ZFISH.NICHD.NIH.GOV/ZFATLAS/FLI-GFP/FLI_MOVIES.HTML

The Fluid Mechanics of Cancer : **Angiogenesis**



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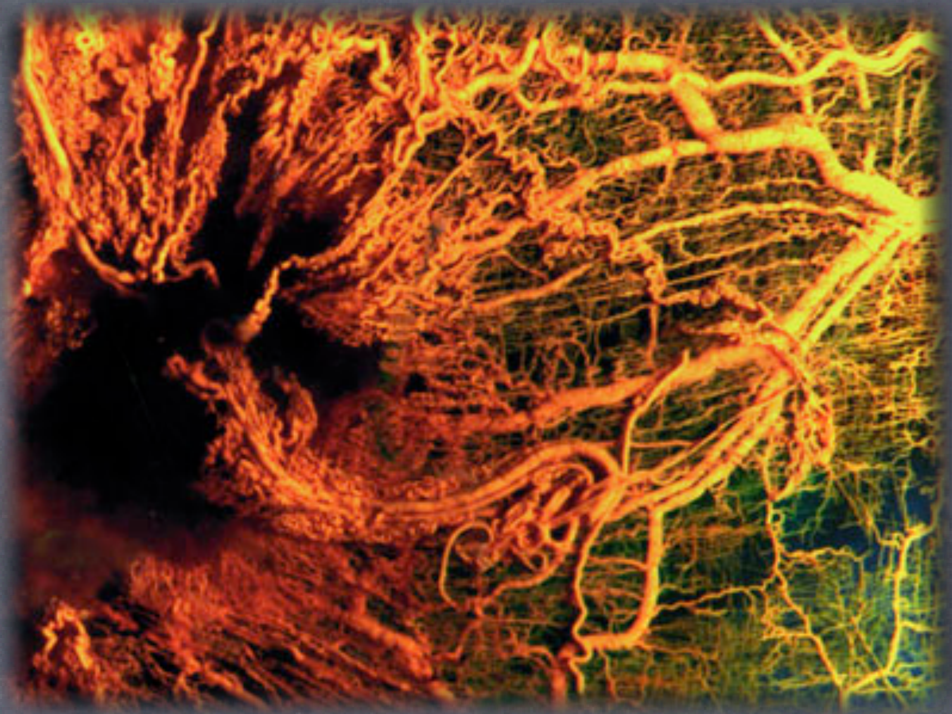

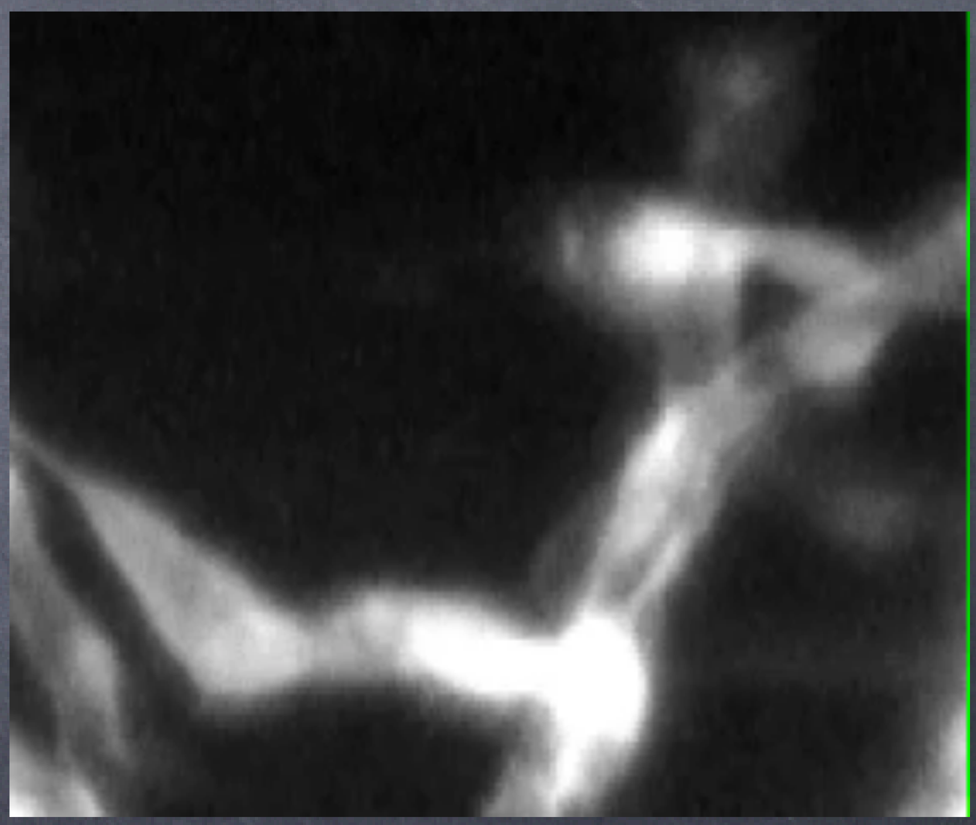

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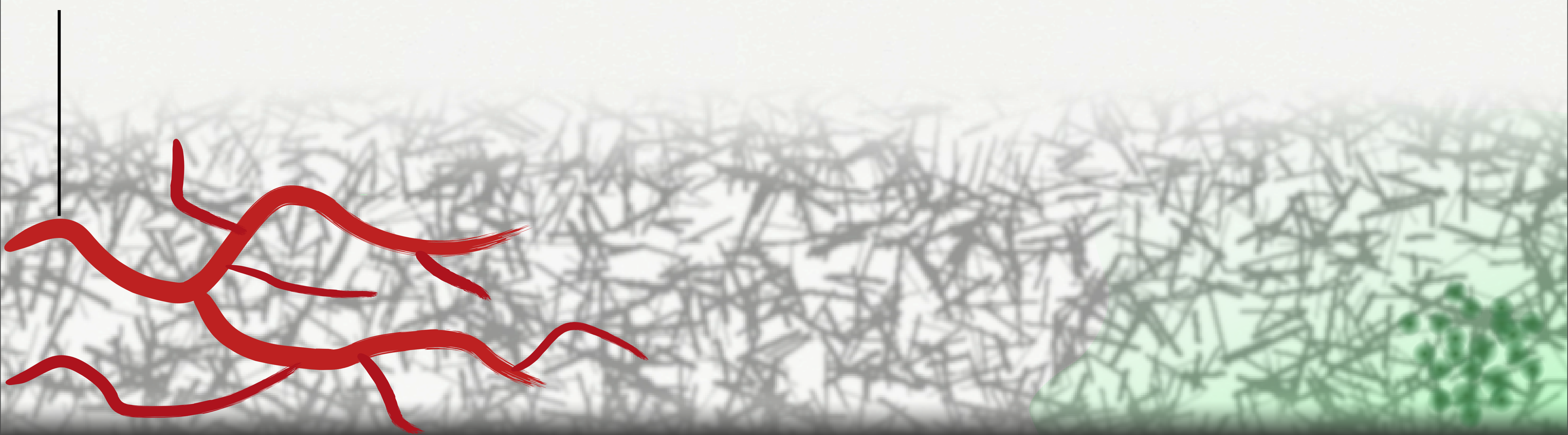
The Fluid Mechanics of Cancer : Angiogenesis

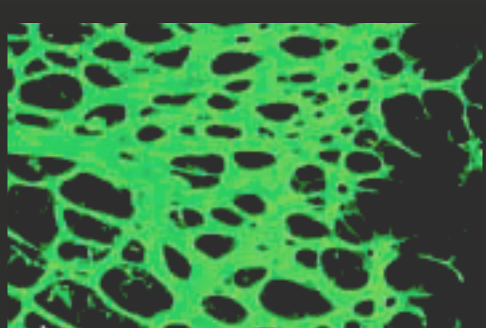
Multiscale modeling of Angiogenesis

[1] H. GERHARDT, M. GOLDING, M.FRUTTIGER, C. RUHRBERG, A. LUNDKVIST A. ABRAMSSON, M. JELTSCH C. MICHELL, . ALITALO, D. SHIMA AND C. BETSHOLTZ, VEGF GUIDES ANGIOGENIC SPROUTING UTILIZING ENDOTHELIAL TIP CELL FILOPODIA, J. CELL. BIOL., 2003

Multiscale modeling of Angiogenesis

Vasculature





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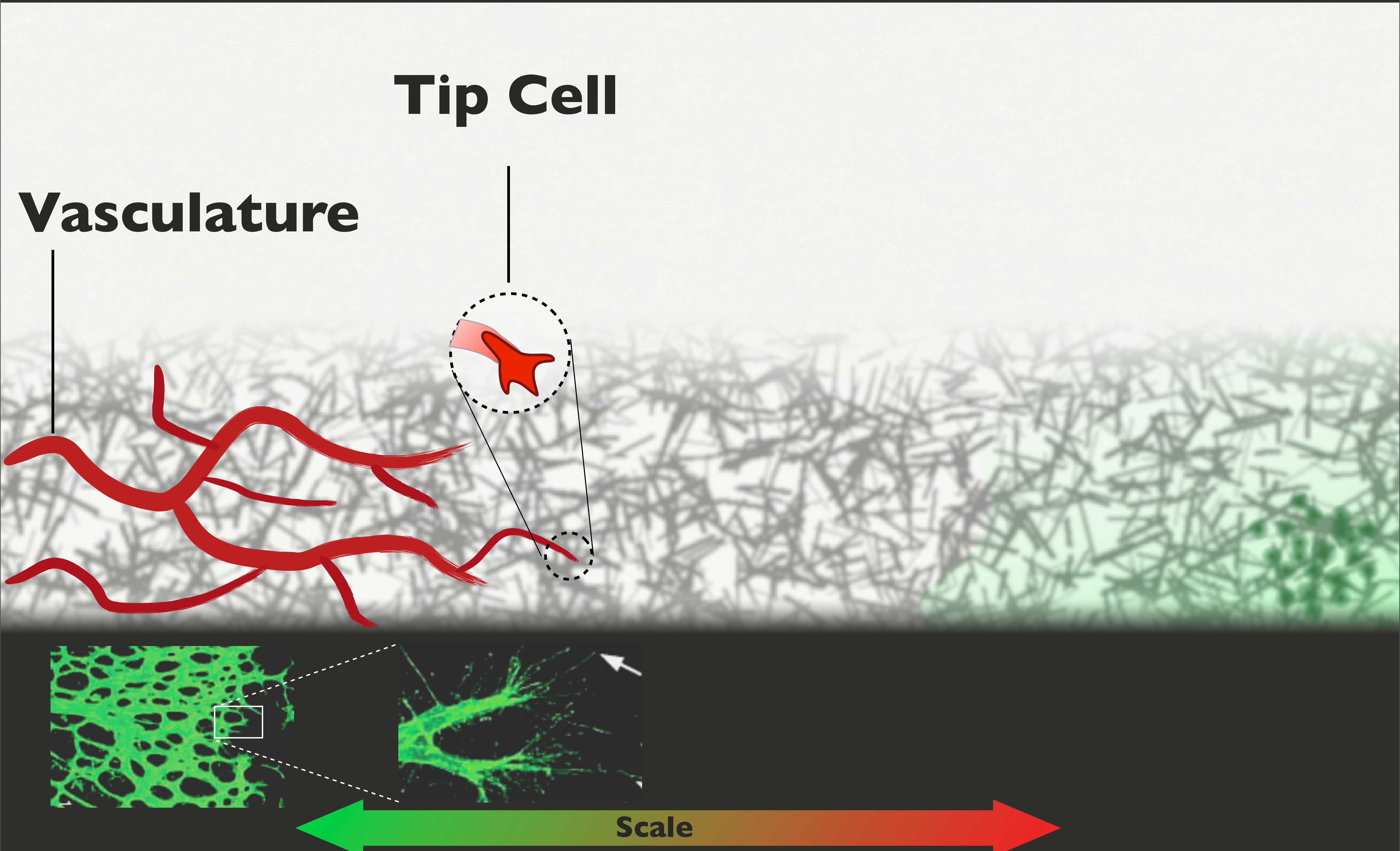

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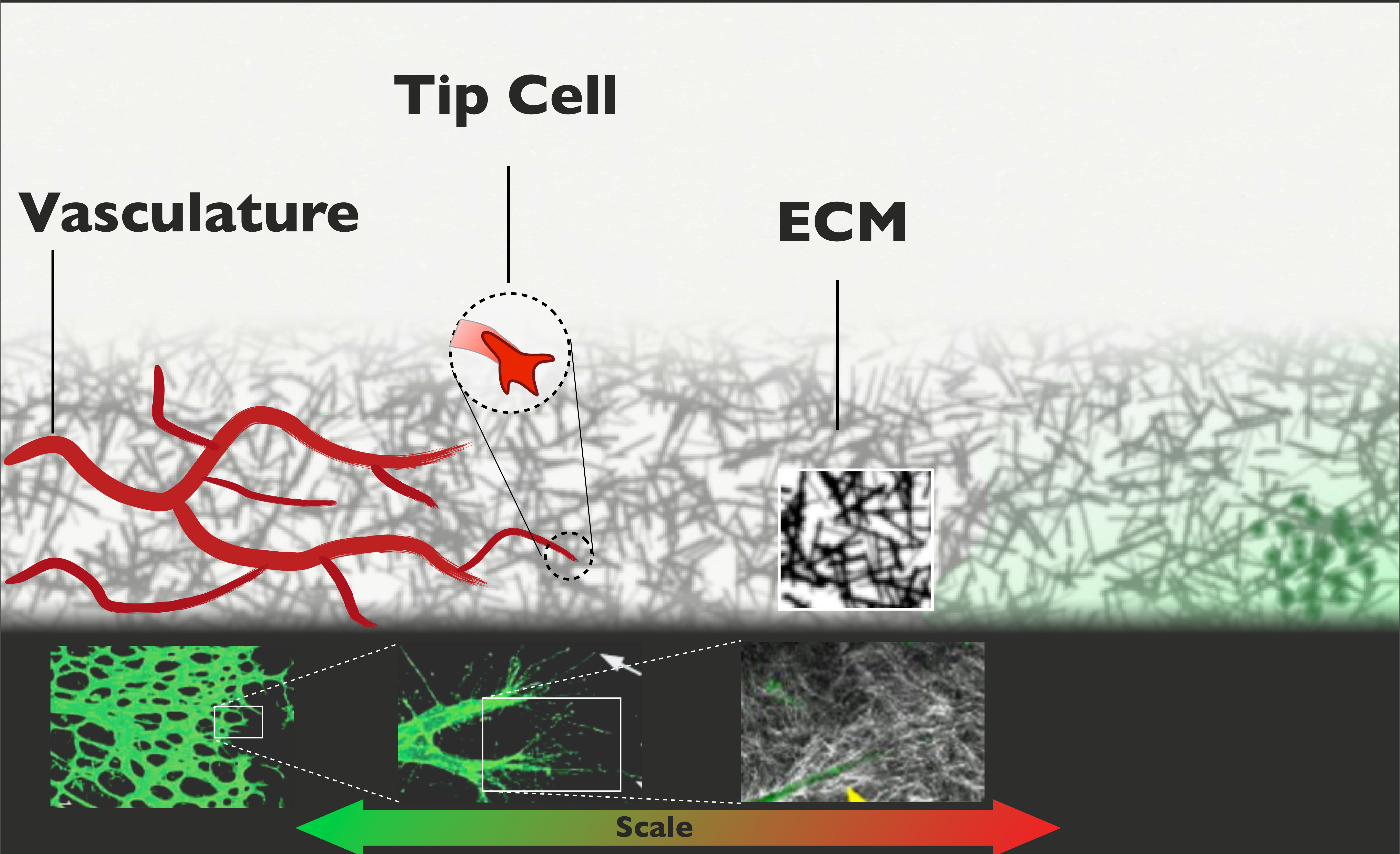

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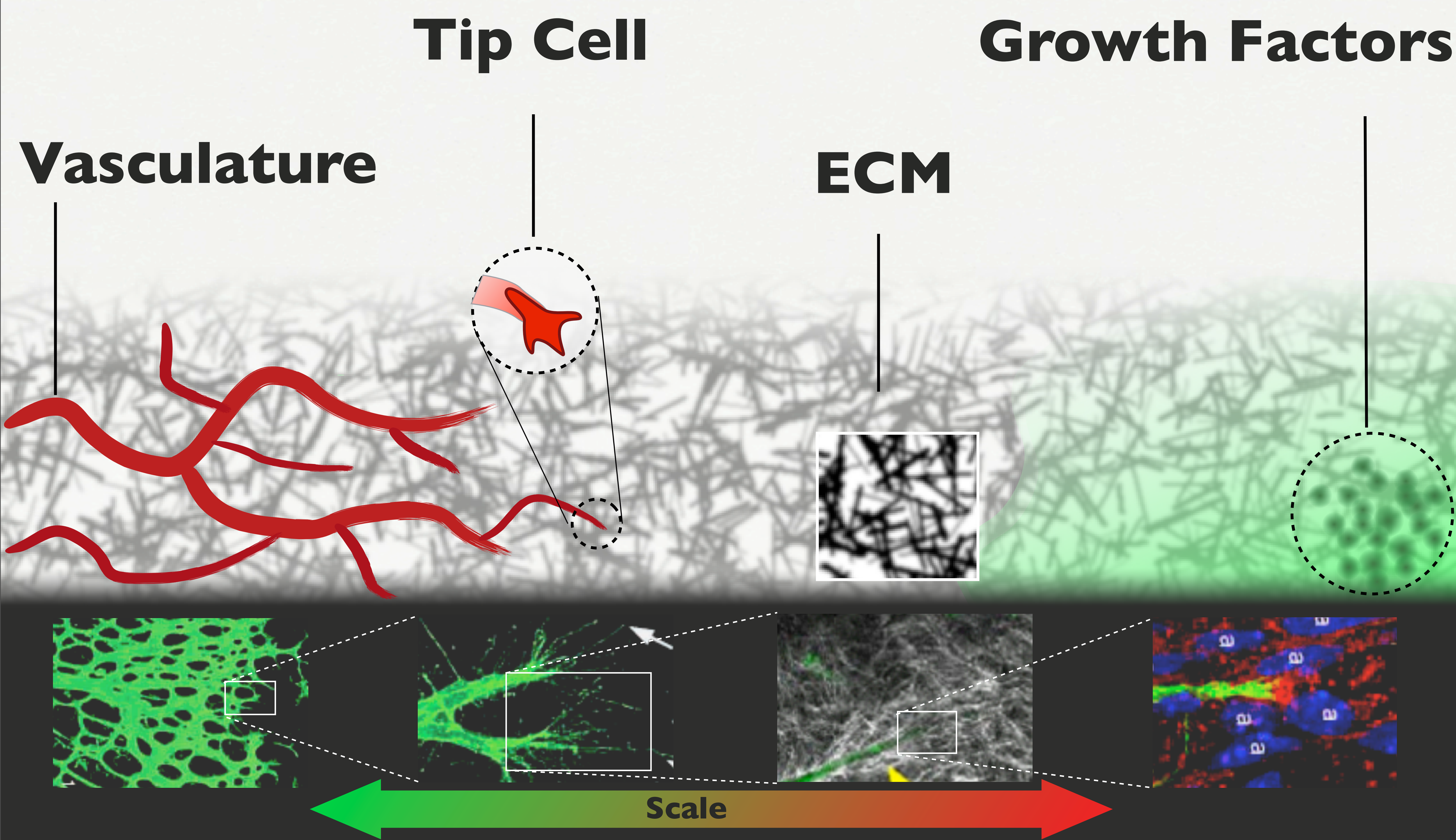

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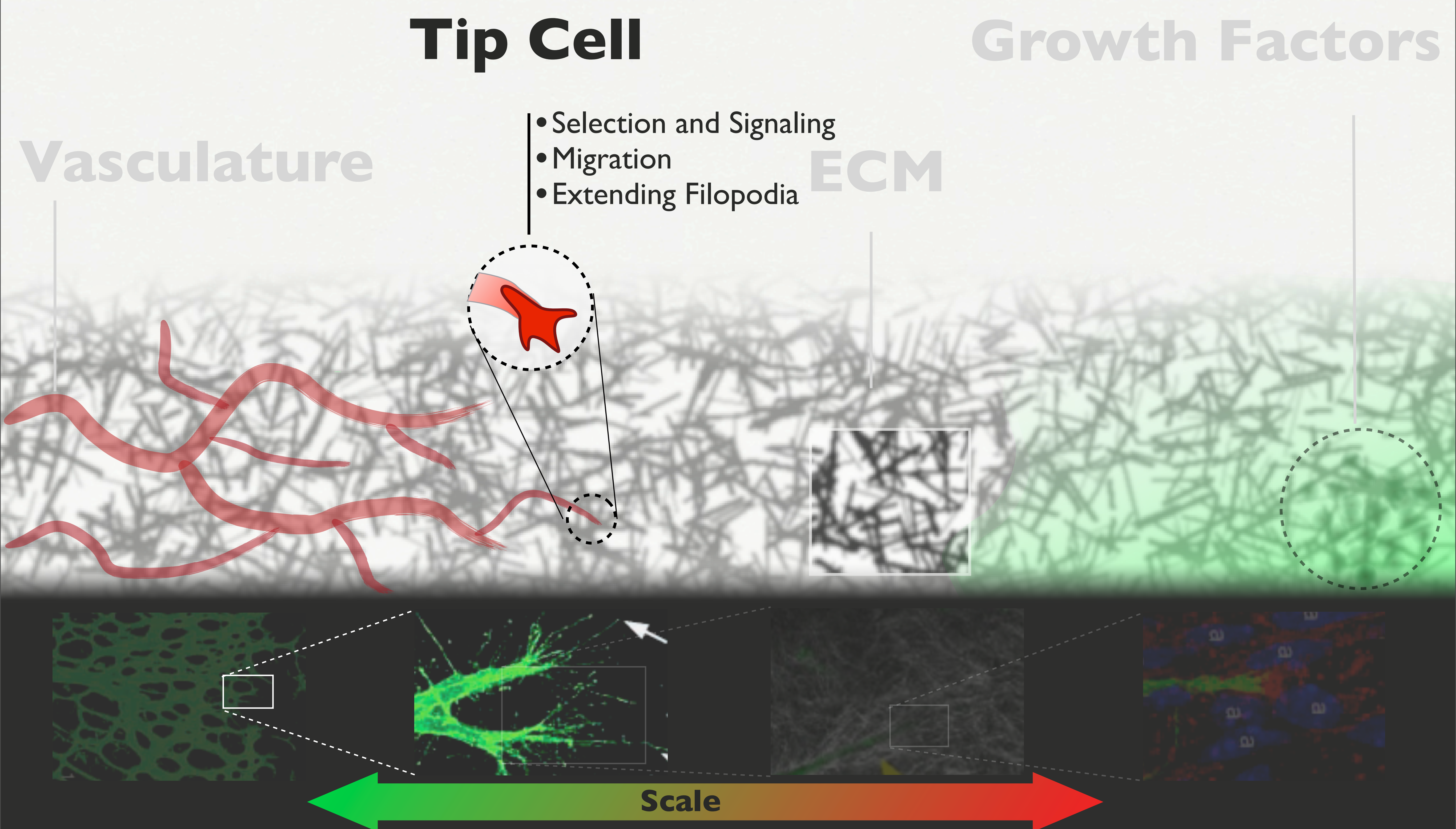

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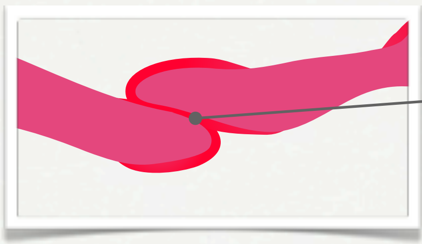
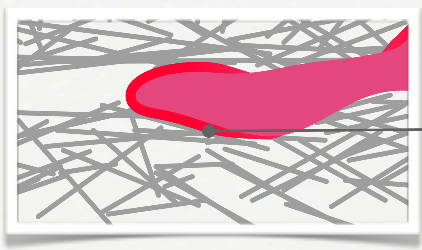
Elements of Cellular Dynamics



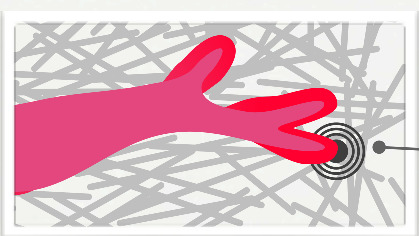
cells stick to cells

transmembrane CAMs: cadherin, ICAM-1, ...
formation of **clusters**, cords



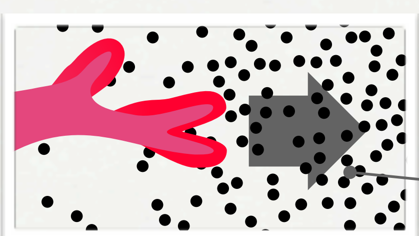
cells guided by the extracellular matrix

transmembrane CAMs: integrins,...
facilitates **migration**



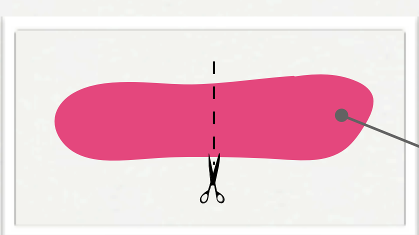
cells secrete proteinases

Matrix metalloproteinases: degrade matrix,
free matrix-bound growth factors



cells sense chemical gradients

gradients of "chemoattractant" serve as migratory cues

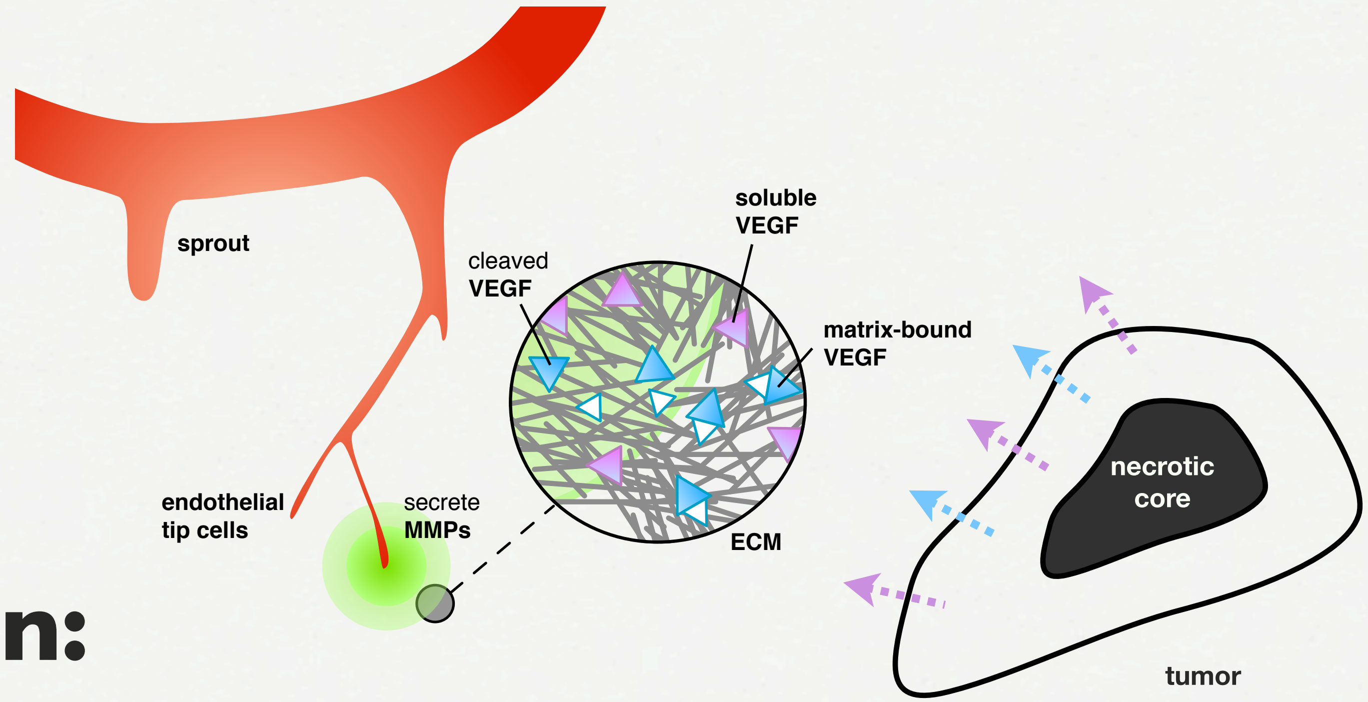


cells proliferate

Tip Cell Migration - Chemotaxis

Tip Cell Migration:

$$\frac{\boldsymbol{x}_p}{\partial t} = \boldsymbol{u}_p, \quad \frac{\boldsymbol{u}_p}{\partial t} = \boldsymbol{a}_p - \lambda \boldsymbol{u}_p$$



VEGF Reaction-Diffusion:

$$\frac{\partial[\mathrm{dV}]}{\partial t} = k_V \nabla^2[\mathrm{dV}] + \gamma_V[\mathrm{T}][\mathrm{V}] + \alpha_V[\mathrm{bV}] - d_V[\mathrm{dV}]$$
$$-\beta_V[\mathrm{dV}]\left([\mathrm{ECM}] - [\mathrm{bV}]\right) - \upsilon_V[\mathrm{dV}][\mathrm{EC}].$$

Concentrations:

$[\mathrm{bV}]$ - bound VEGF
$[\mathrm{dV}]$ - soluble VEGF
$[\mathrm{V}]$ - total VEGF

Densities:

$[\mathrm{T}]$ - Tumor Cells
$[\mathrm{ECM}]$ - ECM
$[\mathrm{EC}]$ - Endothelial Cells

$\boldsymbol{x}_p$ - Particle location
$\boldsymbol{a}_p$ - Migration acceleration
$\boldsymbol{u}_p$ - Migration velocity
λ - Drag coefficient

[2] MILDE F, BERGDORF M. KOUMOUTSAKOS P., A HYBRID MODEL FOR 3D SIMULATION OF SPROUTING ANGIOGENESIS, BIOPHYSICAL J., 2008

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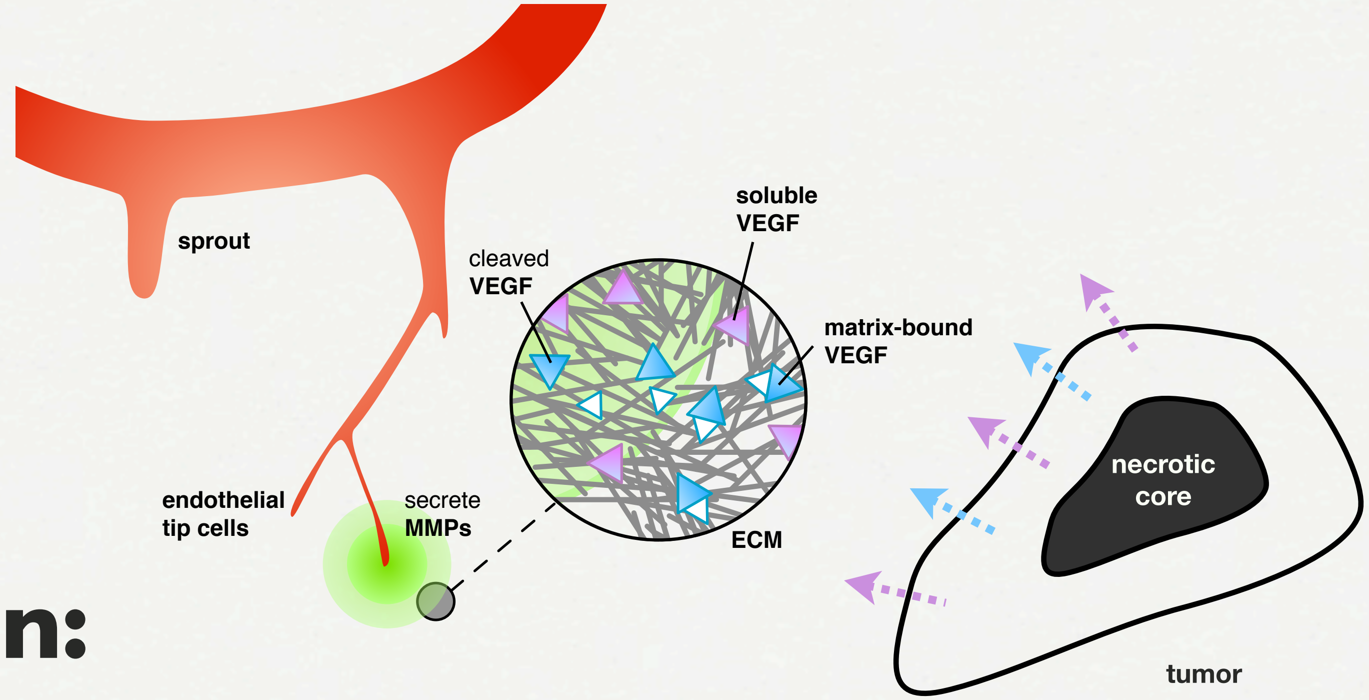

VEGF Reaction-Diffusion:

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$$-\beta_V [\mathrm{dV}] ([\mathrm{ECM}] - [\mathrm{bV}]) - \upsilon_V [\mathrm{dV}][\mathrm{EC}].$$

Diffusion

Concentrations:

[bV] - bound VEGF
[dV] - soluble VEGF
[V] - total VEGF

Densities:

[T] - Tumor Cells
[ECM] - ECM
[EC] - Endothelial Cells

$\boldsymbol{x}_p$ - Particle location
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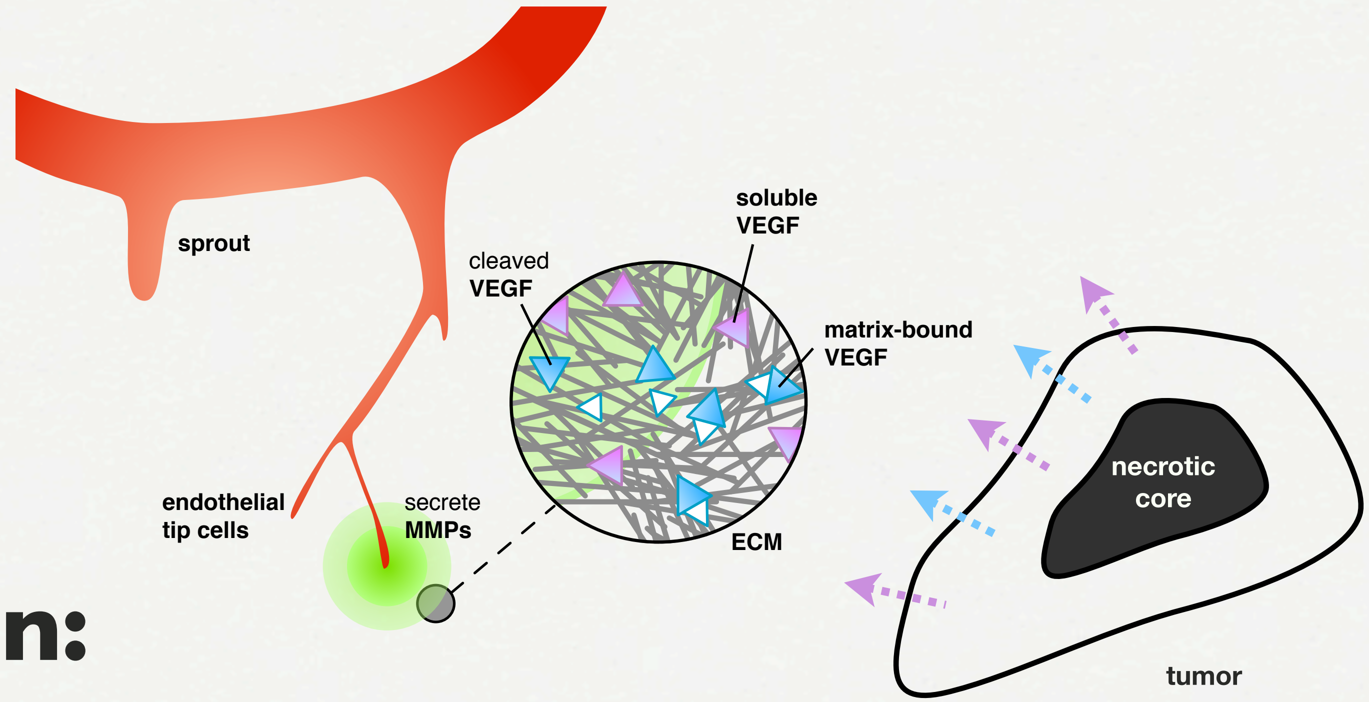

VEGF Reaction-Diffusion:

$$\frac{\partial[\mathrm{dV}]}{\partial t} = k_V \nabla^2 [\mathrm{dV}] + \gamma_V [\mathrm{T}][\mathrm{V}] + \alpha_V [\mathrm{bV}] - d_V [\mathrm{dV}]$$
$$-\beta_V [\mathrm{dV}] \left([\mathrm{ECM}] - [\mathrm{bV}]\right) - \upsilon_V [\mathrm{dV}][\mathrm{EC}].$$

Tumor Secretion

Concentrations:

$[\mathrm{bV}]$ - bound VEGF
$[\mathrm{dV}]$ - soluble VEGF
$[\mathrm{V}]$ - total VEGF

Densities:

$[\mathrm{T}]$ - Tumor Cells
$[\mathrm{ECM}]$ - ECM
$[\mathrm{EC}]$ - Endothelial Cells

$\boldsymbol{x}_p$ - Particle location
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[2] MILDE F, BERGDORF M. KOUMOUTSAKOS P., A HYBRID MODEL FOR 3D SIMULATION OF SPROUTING ANGIOGENESIS, BIOPHYSICAL J., 2008

Tip Cell Migration - Chemotaxis

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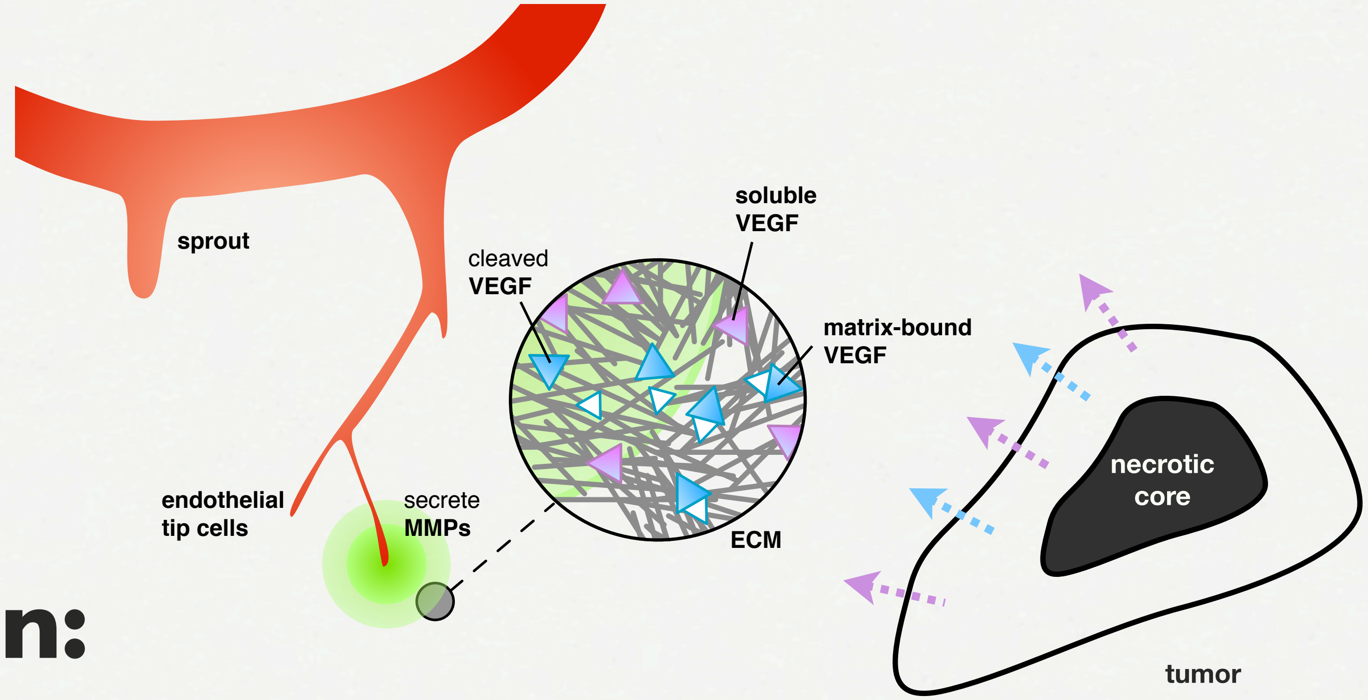

VEGF Reaction-Diffusion:

$$\frac{\partial[\mathrm{dV}]}{\partial t} = k_V \nabla^2[\mathrm{dV}] + \gamma_V[\mathrm{T}][\mathrm{V}] + \alpha_V[\mathrm{bV}] - d_V[\mathrm{dV}] - \beta_V[\mathrm{dV}]([\mathrm{ECM}] - [\mathrm{bV}]) - \upsilon_V[\mathrm{dV}][\mathrm{EC}].$$

ECM Unbinding

Concentrations:

$[\mathrm{bV}]$ - bound VEGF

$[\mathrm{dV}]$ - soluble VEGF

$[\mathrm{V}]$ - total VEGF

Densities:

$[\mathrm{T}]$ - Tumor Cells

$[\mathrm{ECM}]$ - ECM

$[\mathrm{EC}]$ - Endothelial Cells

$\boldsymbol{x}_p$ - Particle location

$\boldsymbol{a}_p$ - Migration acceleration

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[2] MILDE F, BERGDORF M. KOUMOUTSAKOS P., A HYBRID MODEL FOR 3D SIMULATION OF SPROUTING ANGIOGENESIS, BIOPHYSICAL J., 2008

Tip Cell Migration - Chemotaxis

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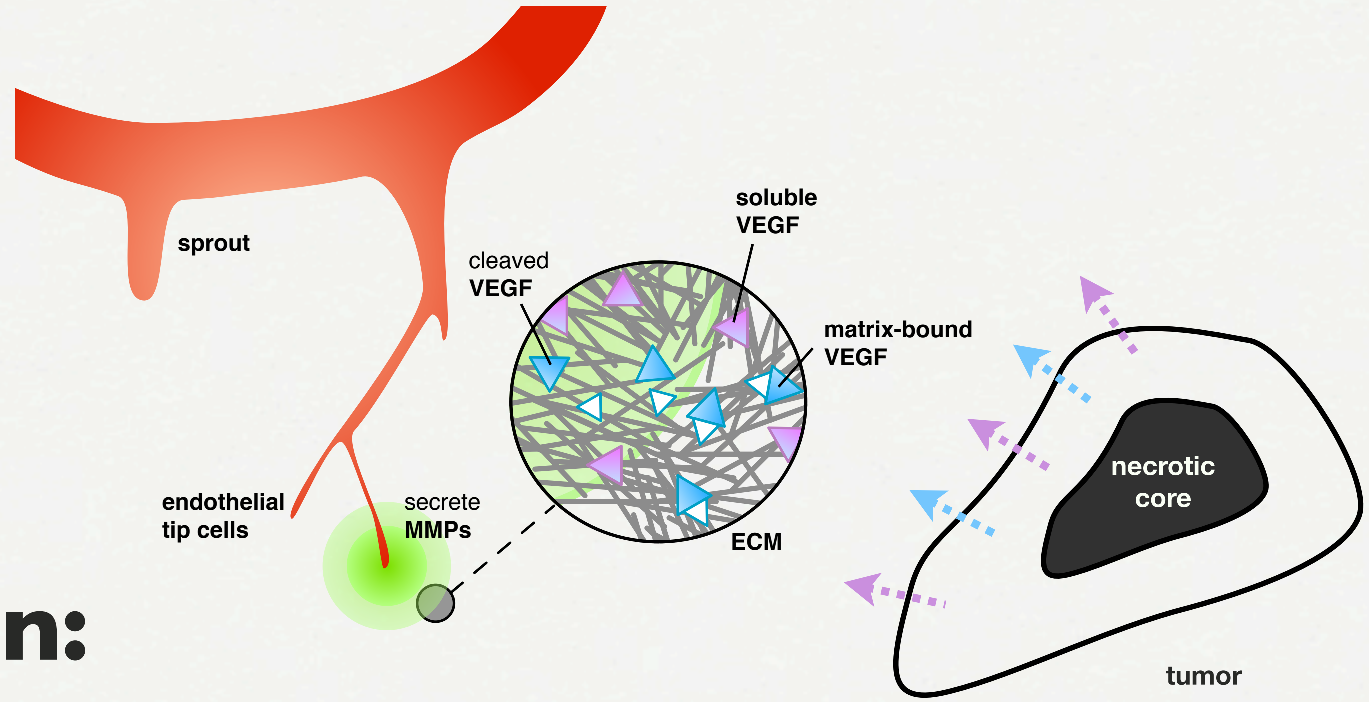

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$$- \beta_V[\mathrm{dV}]([\mathrm{ECM}] - [\mathrm{bV}]) - \upsilon_V[\mathrm{dV}][\mathrm{EC}].$$

Degradation

Concentrations:

- $[\mathrm{bV}]$ - bound VEGF
- $[\mathrm{dV}]$ - soluble VEGF
- $[\mathrm{V}]$ - total VEGF

Densities:

- $[\mathrm{T}]$ - Tumor Cells
- $[\mathrm{ECM}]$ - ECM
- $[\mathrm{EC}]$ - Endothelial Cells

- $\boldsymbol{x}_p$ - Particle location
- $\boldsymbol{a}_p$ - Migration acceleration
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- λ - Drag coefficient

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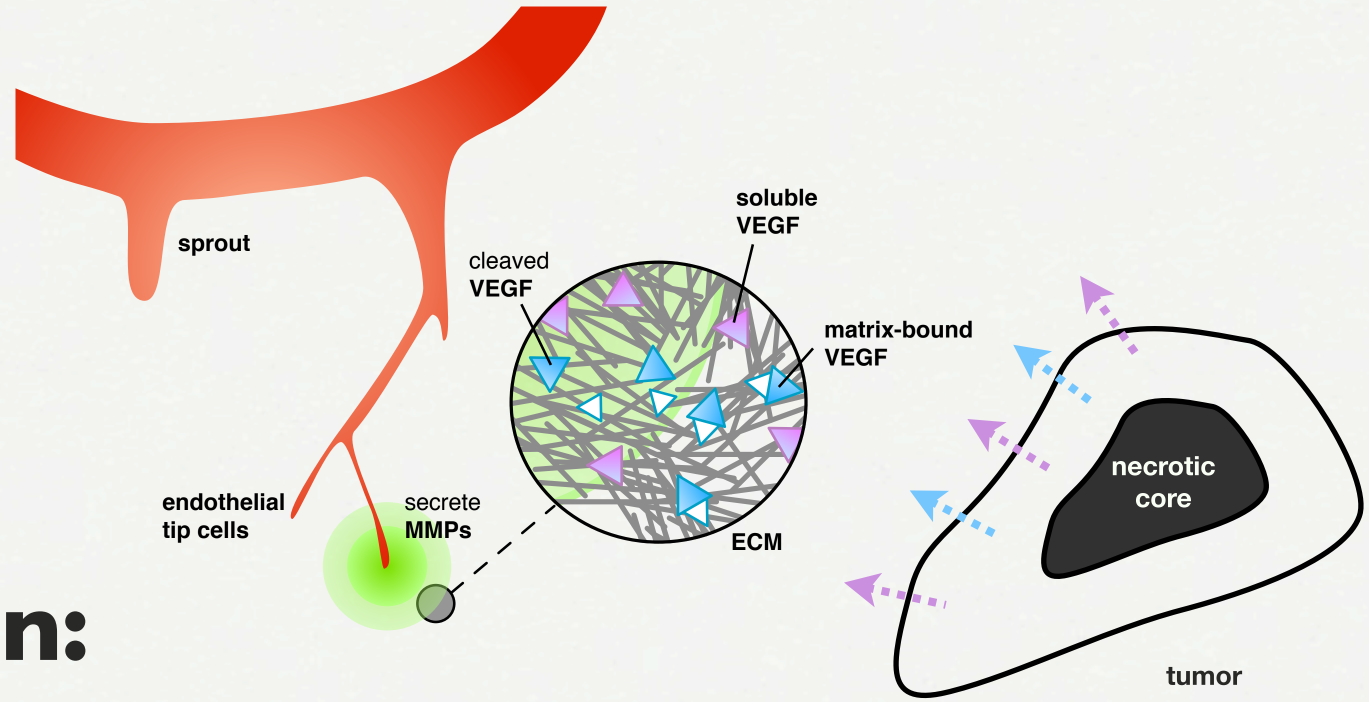

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$$-\beta_V[\mathrm{dV}]\left([\mathrm{ECM}] - [\mathrm{bV}]\right) - \upsilon_V[\mathrm{dV}][\mathrm{EC}].$$

ECM Binding

Concentrations:

$[\mathrm{bV}]$ - bound VEGF
$[\mathrm{dV}]$ - soluble VEGF
$[\mathrm{V}]$ - total VEGF

Densities:

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$[\mathrm{ECM}]$ - ECM
$[\mathrm{EC}]$ - Endothelial Cells

$\boldsymbol{x}_p$ - Particle location
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λ - Drag coefficient

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Tip Cell Migration - Chemotaxis

Tip Cell Migration:

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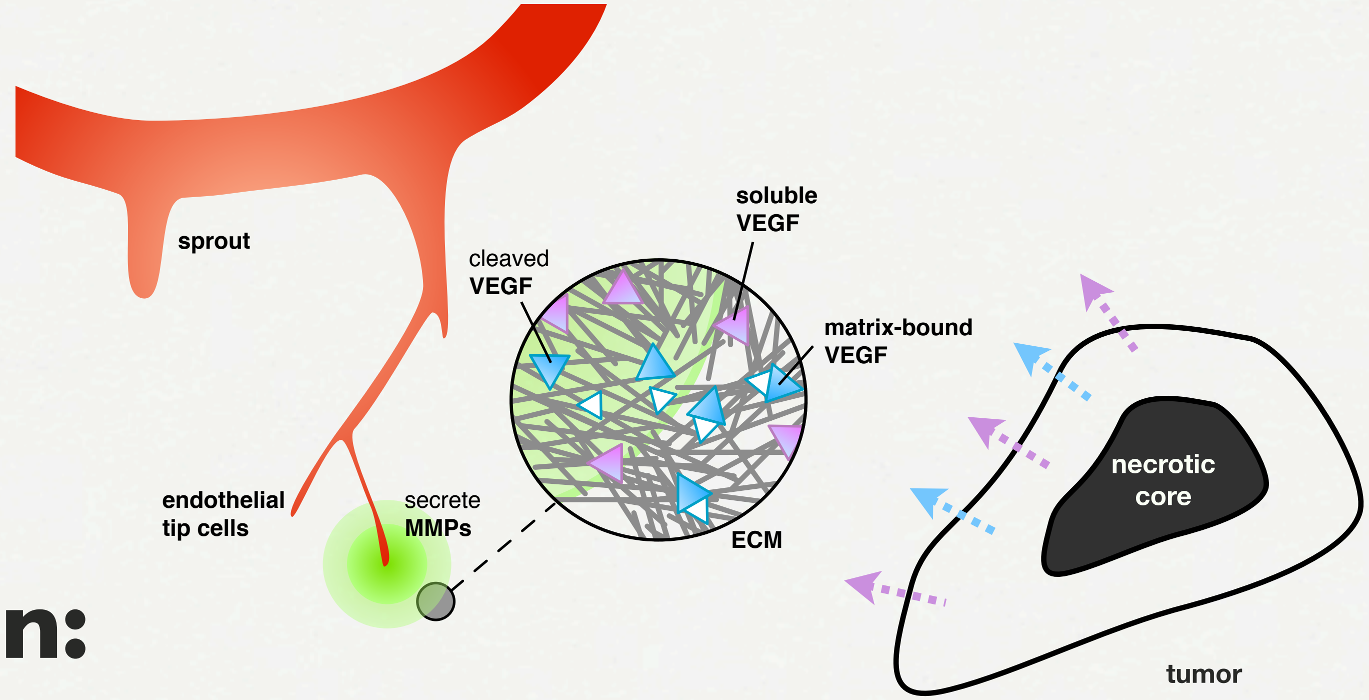

VEGF Reaction-Diffusion:

$$\frac{\partial[\mathrm{dV}]}{\partial t} = k_V \nabla^2[\mathrm{dV}] + \gamma_V[\mathrm{T}][\mathrm{V}] + \alpha_V[\mathrm{bV}] - d_V[\mathrm{dV}]$$
$$-\beta_V[\mathrm{dV}]([\mathrm{ECM}] - [\mathrm{bV}]) - \upsilon_V[\mathrm{dV}][\mathrm{EC}].$$

EC Uptake

Concentrations:

$[\mathrm{bV}]$ - bound VEGF
$[\mathrm{dV}]$ - soluble VEGF
$[\mathrm{V}]$ - total VEGF

Densities:

$[\mathrm{T}]$ - Tumor Cells
$[\mathrm{ECM}]$ - ECM
$[\mathrm{EC}]$ - Endothelial Cells

$\boldsymbol{x}_p$ - Particle location
$\boldsymbol{a}_p$ - Migration acceleration
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Tip Cell Migration - Chemotaxis

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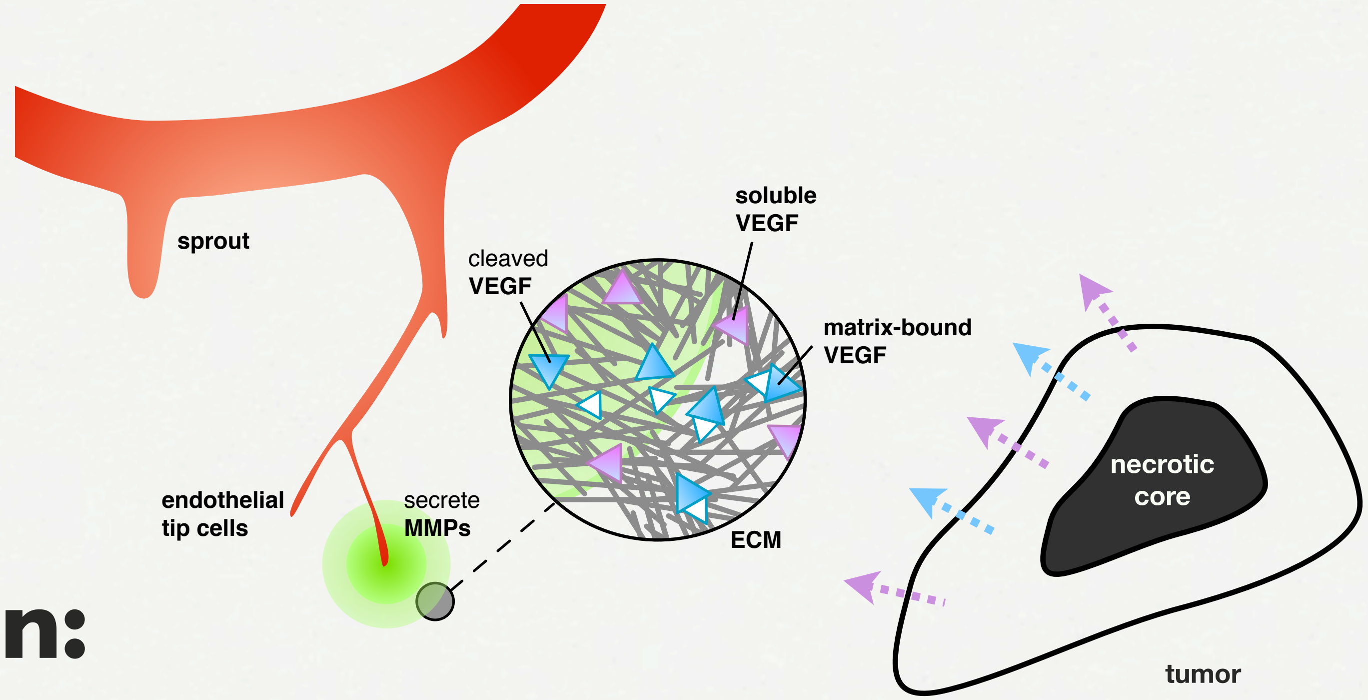

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Parameters

Concentrations:

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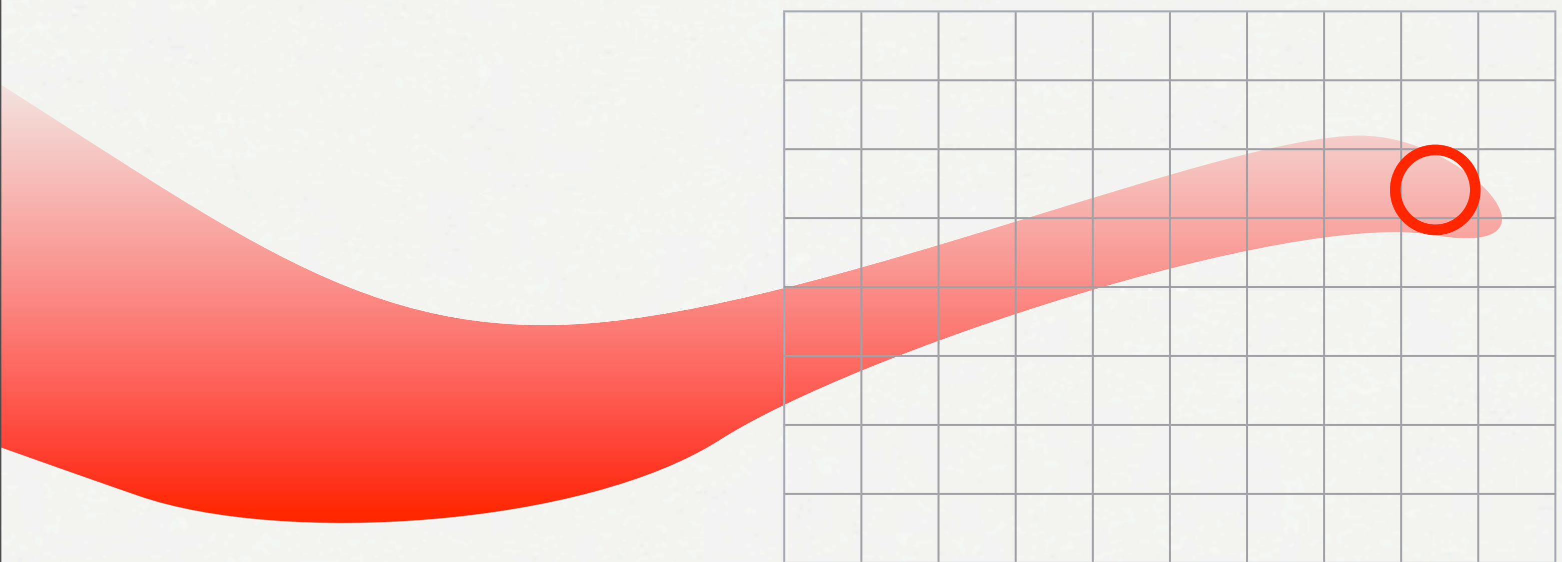
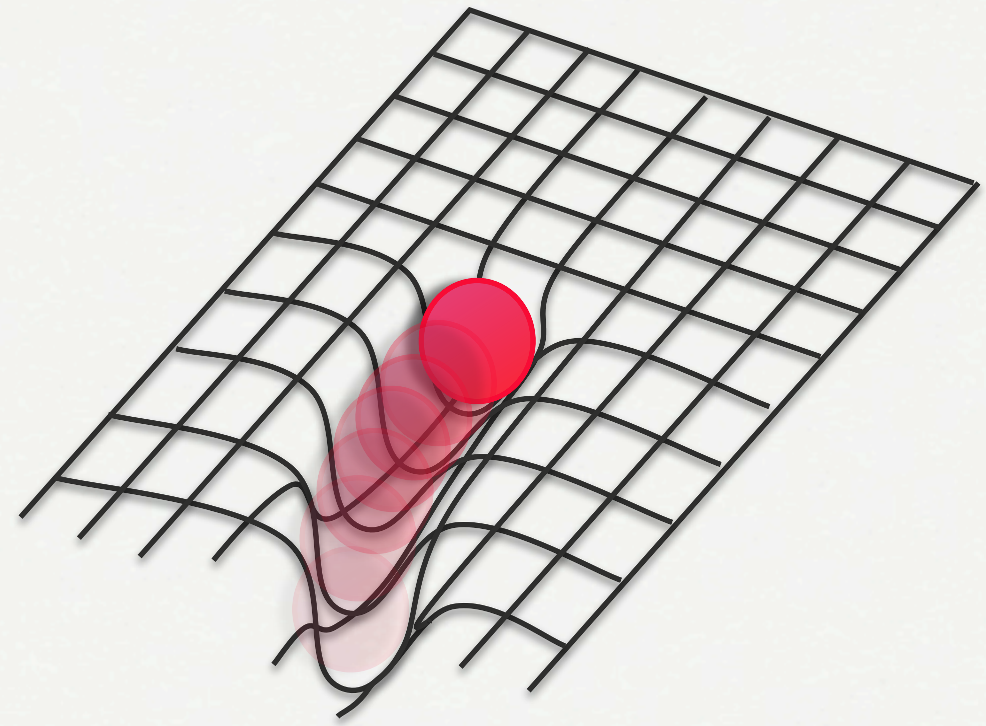
Endothelial Cell Representation



Tip Cell “deposes” endothelial cells



Hybrid representation of ECs:

Tip cell particles Q_p:

- Discrete particle representation
- Particle location: $\boldsymbol{x}_p$
- Migration acceleration: $\boldsymbol{u}_p$
- Drag coefficient: λ

$$\frac{\boldsymbol{x}_p}{\partial t} = \boldsymbol{u}_p, \quad \frac{\boldsymbol{u}_p}{\partial t} = \boldsymbol{a}_p - \lambda \boldsymbol{u}_p$$

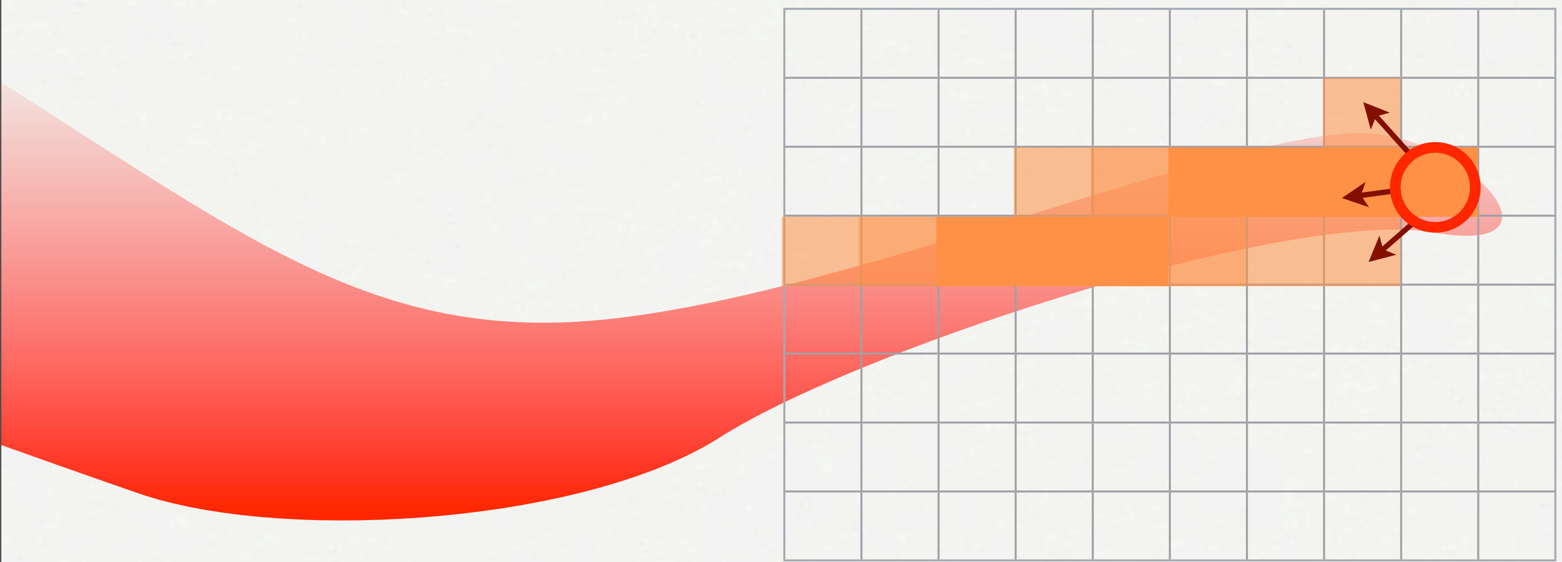
Stalk cell density ρ:

- Continuum vessel representation
- Tip and stalk communicate through Particle-Mesh, Mesh-Particle interpolations

$$\rho_{\boldsymbol{i}}^{n+1} = max\left(\rho_{\boldsymbol{i}}^{n}, \sum_p B(\boldsymbol{i}\,h - \boldsymbol{x}_p)\,Q_p\right)$$

$$Q_p = \sum_{\boldsymbol{i}} h^3 q_{\boldsymbol{i}} M_4'\left(\boldsymbol{x}_p - \boldsymbol{i}h\right)$$

Endothelial Cell Representation



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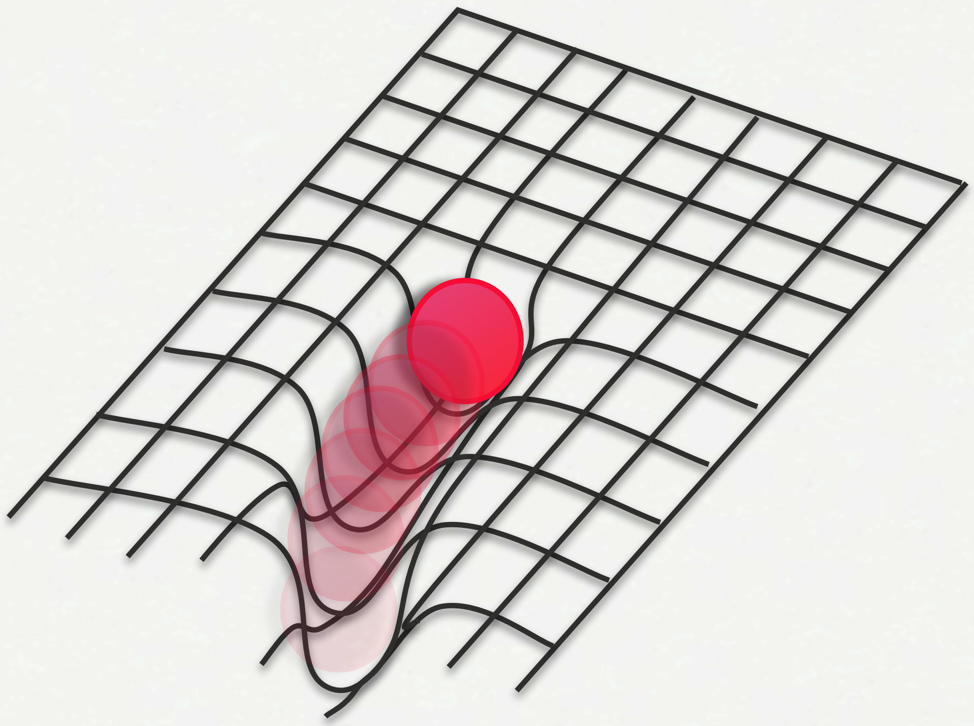

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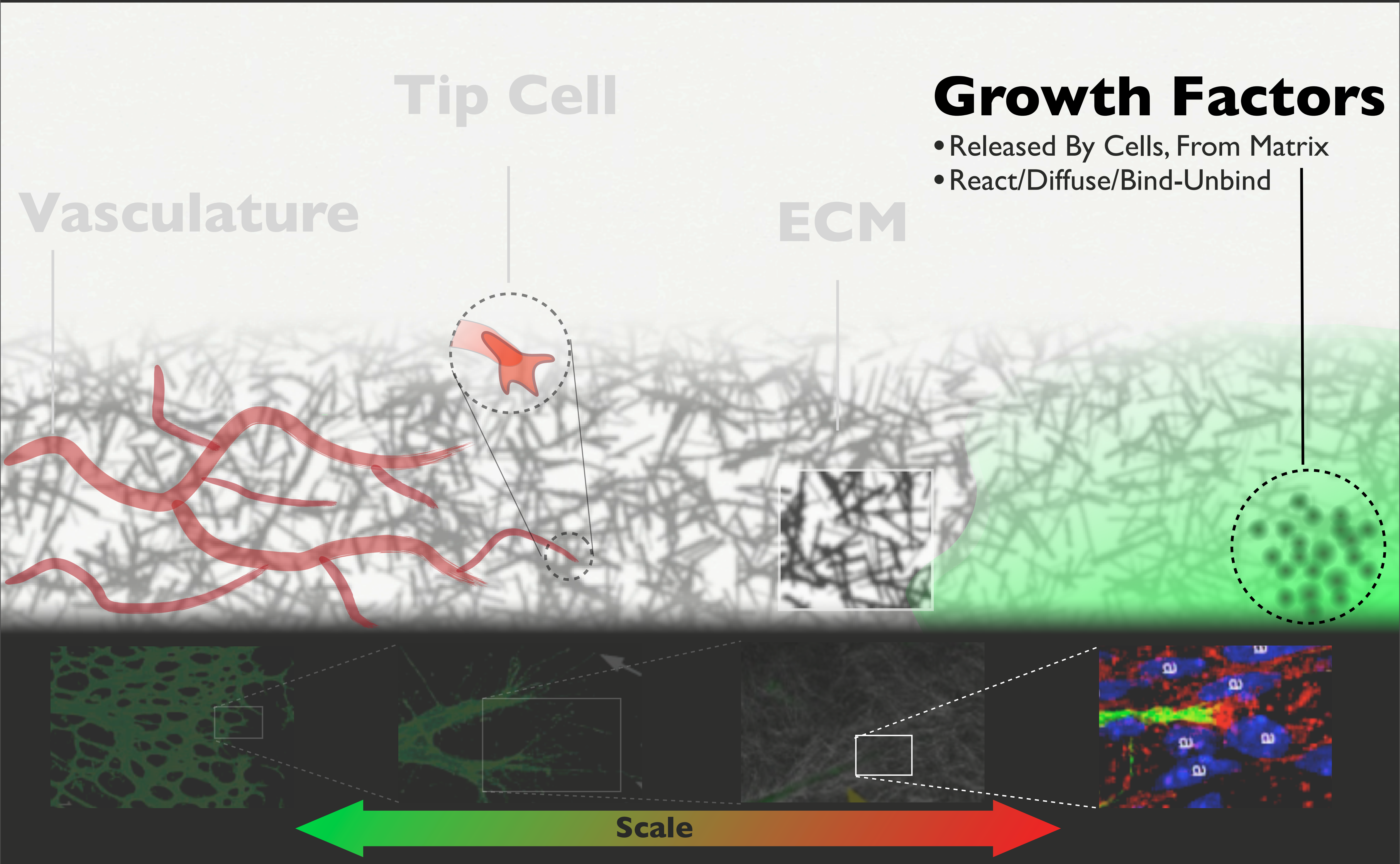
Vascular Endothelial Growth Factors



[1] H. GERHARDT, M. GOLDING, M.FRUTTIGER, C. RUHRBERG, A. LUNDKVIST A. ABRAMSSON, M. JELTSCH C. MICHELL, .ALITALO, D. SHIMA AND C. BETSHOLTZ, VEGF GUIDES ANGIOGENIC SPROUTING UTILIZING ENDOTHELIAL TIP CELL FILOPODIA, J. CELL. BIOL., 2003

Model equations

living tumor cells

$$
\begin{cases}
\frac{\partial u_T}{\partial t} = \omega_T \nabla \cdot (u_T \nabla u) & \text{convection} \\
\quad + u_T u_N H(u_N - \tilde{u}_N u_T) & \text{proliferation} \\
\quad \text{death } - \delta_T H(\bar{u}_N u_T - u_N)\, u_T & \text{in } \Omega, \\
u_T = \bar{u} - u_D - u_C - \hat{u}_C & \text{on } \delta\Omega.
\end{cases}
$$

TAF

$$
\begin{cases}
\frac{\partial u_A}{\partial t} = k_A \nabla^2 u_A & \text{diffusion} \\
\quad + \gamma_A u_T H(\hat{u}_N u_T - u_N) & \text{secretion by hypoxic tumor cells} \\
\quad - \upsilon_A u_C u_A & \text{uptake by EC} \\
\quad \text{decay } - \delta_A u_A & \text{in } D, \\
u_A = 0 & \text{on } \delta D.
\end{cases}
$$

nutrient

$$
\begin{cases}
\frac{\partial u_N}{\partial t} = \upsilon_N \nabla \cdot \left[(k_E + k_N (u_C + \hat{u}_C)) \nabla u_N \right] & \text{diffusion} \\
\quad - \upsilon_N u_T u_N \text{ consumption} & \text{in } \Omega, \\
u_N = \epsilon + \beta (u_C + \hat{u}_C) & \text{on } \delta\Omega.
\end{cases}
$$

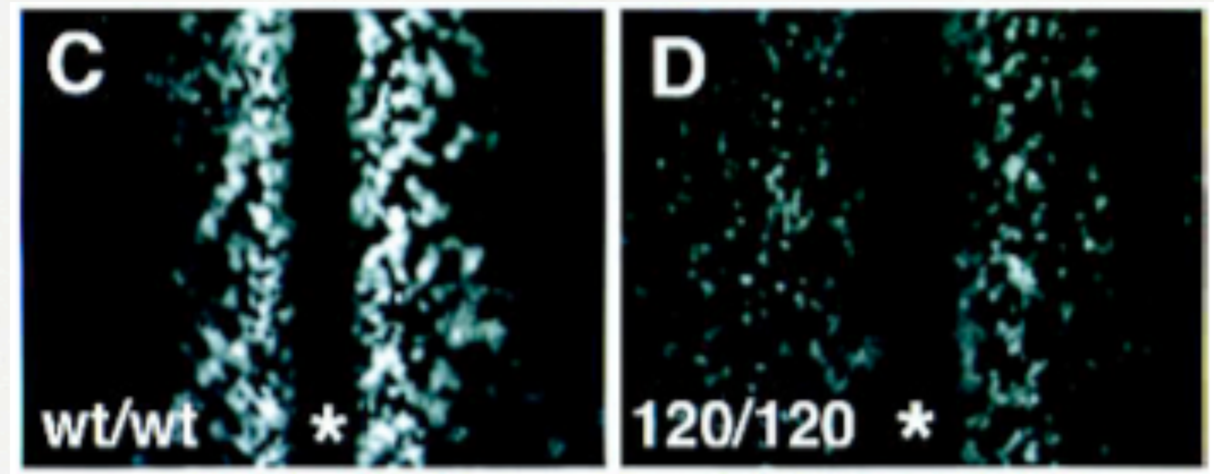
endothelial cells

$$
\begin{cases}
\frac{\partial u_C}{\partial t} = k_C \nabla^2 u_C & \text{diffusion} \\
\quad + \gamma_C u_A (\bar{u}_C - u_C - u_T - u_D)_+ (u_C + \hat{u}_C) & \text{proliferation} \\
\quad - \delta_C u_C \text{ death} & \text{in } \Omega \\
\frac{\partial u_C}{\partial t} = k_C \nabla^2 u_C & \text{diffusion} \\
\quad \text{chemotaxis } - \omega_{CA} \nabla \cdot (u_C \nabla u_A) - \omega_{CF} \nabla \cdot (u_C \nabla u_F) & \text{haptotaxis} \\
\quad + \gamma_C u_A (\bar{u}_C - u_C)_+ (u_C + \hat{u}_C) & \text{proliferation} \\
\quad - \delta_C u_C \text{ death} & \text{outside } \Omega, \\
u_C = 0 & \text{on } \delta D.
\end{cases}
$$

Matrix-bound VEGF (bVEGF) - Assumptions

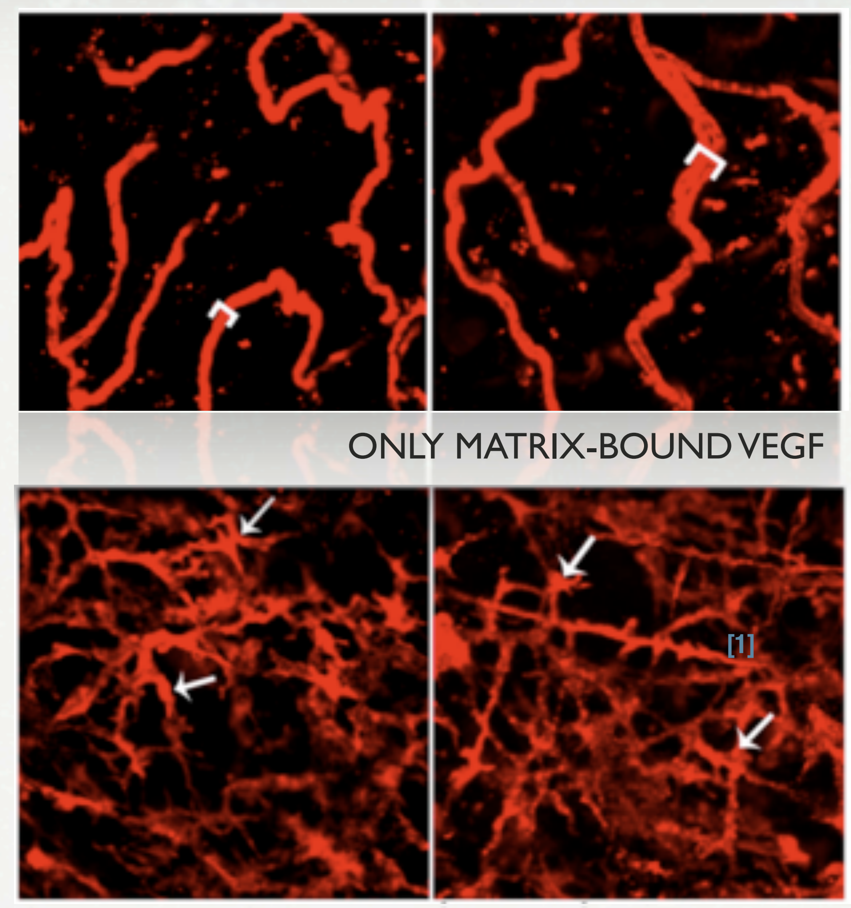
- Some VEGF isoforms express heparin-binding sites binding to domains in the ECM
- Local gradients of matrix bound VEGF influence sprout morphology
- Matrix bound VEGF is cleaved by Matrix Metalloproteinases (MMPs) released at endothelial sprout tips

MATRIX BOUND VEGF



WILD TYPE

BLOOD VESSELS

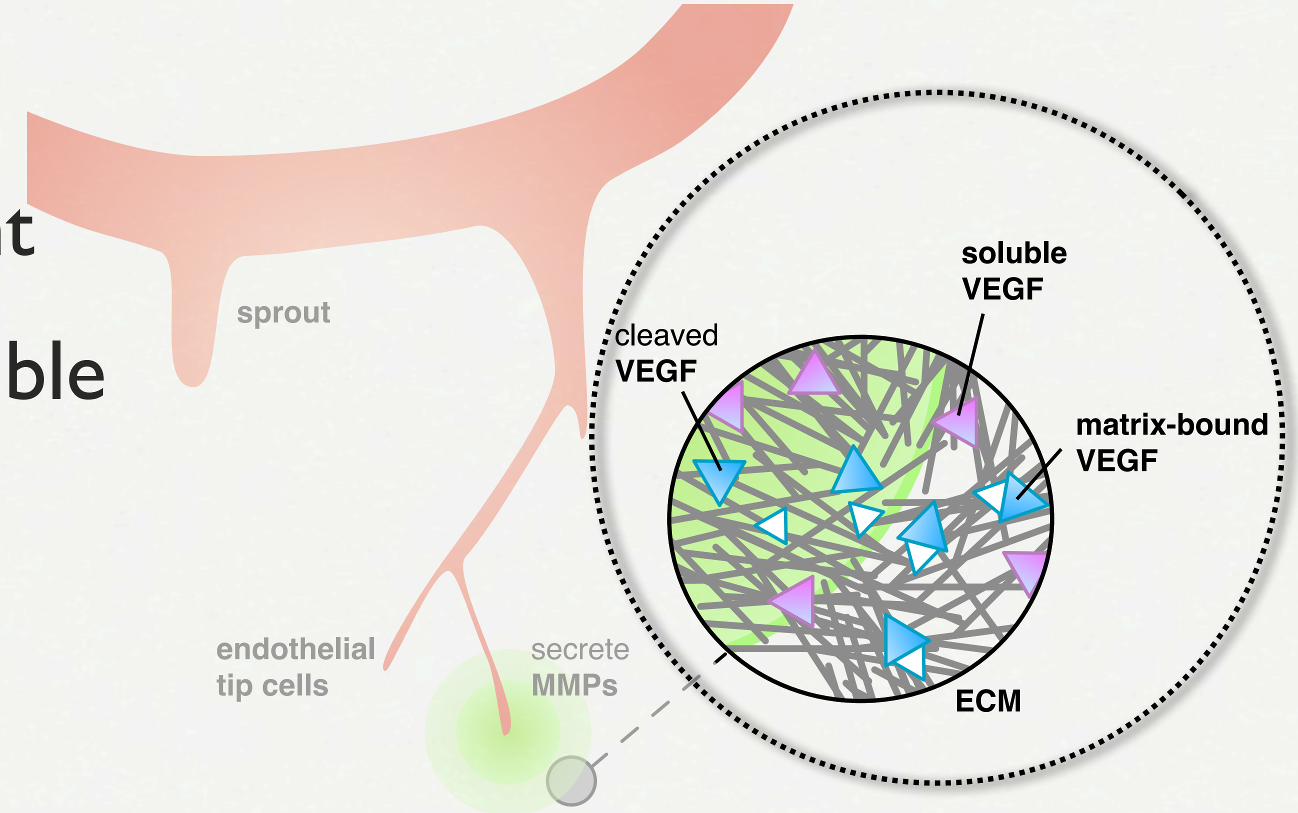


ONLY MATRIX-BOUND VEGF

[7] C. RUHRBERG, H. GERHARDT, M. GOLDING, R. WATSON, S. IOANNIDOU, H. FUJISAWA, C. BETSHOLTZ AND D. T. SHIMA. SPATIALLY RESTRICTED PATTERNING CUES PROVIDED BY HEPARIN-BINDING VEGF-A CONTROL BLOOD VESSEL BRANCHING MORPHOGENESIS. GENES DEV., 16(20):2684-2698, 2002.
[8] S. LEE, S. M. JILAI, G. V. NIKOLOVA, D. CARPIZO, AND M. L. IRUELA-ARISPE. PROCESSING OF VEGF-A BY MATRIX METALLOPROTEINASES REGULATES BIOAVAILABILITY AND VASCULAR PATTERNING IN TUMORS. J. CELL BIOL., V42(3):195-238, 2001

Matrix-bound VEGF - Modeling

- Initially distributed in pockets
- establishes local chemotactic gradient
- cleaved VEGF (cVEGF) becomes soluble



  - bVEGF is cleaved by MMPs
  - Uptake of cVEGF by ECs ρ
  - cVEGF diffuses through ECM
  - cVEGF is subject to natural decay

$$\frac{\partial[\mathrm{bVEGF}]}{\partial t} = -C\left([\mathrm{bVEGF}],[\mathrm{MMP}]\right) - U\left([\mathrm{bVEGF}],\rho\right)$$

$$C\left([\mathrm{bVEGF}],[\mathrm{MMP}]\right) = min\left([\mathrm{bVEGF}], \upsilon_{bV}[\mathrm{MMP}][\mathrm{bVEGF}]\right)$$

$$\frac{\partial[\mathrm{cVEGF}]}{\partial t} = k_V\nabla^2[\mathrm{cVEGF}] + C\left([\mathrm{bVEGF}],[\mathrm{MMP}]\right) - U\left([\mathrm{cVEGF}],\rho\right) - \delta_V[\mathrm{cVEGF}]$$

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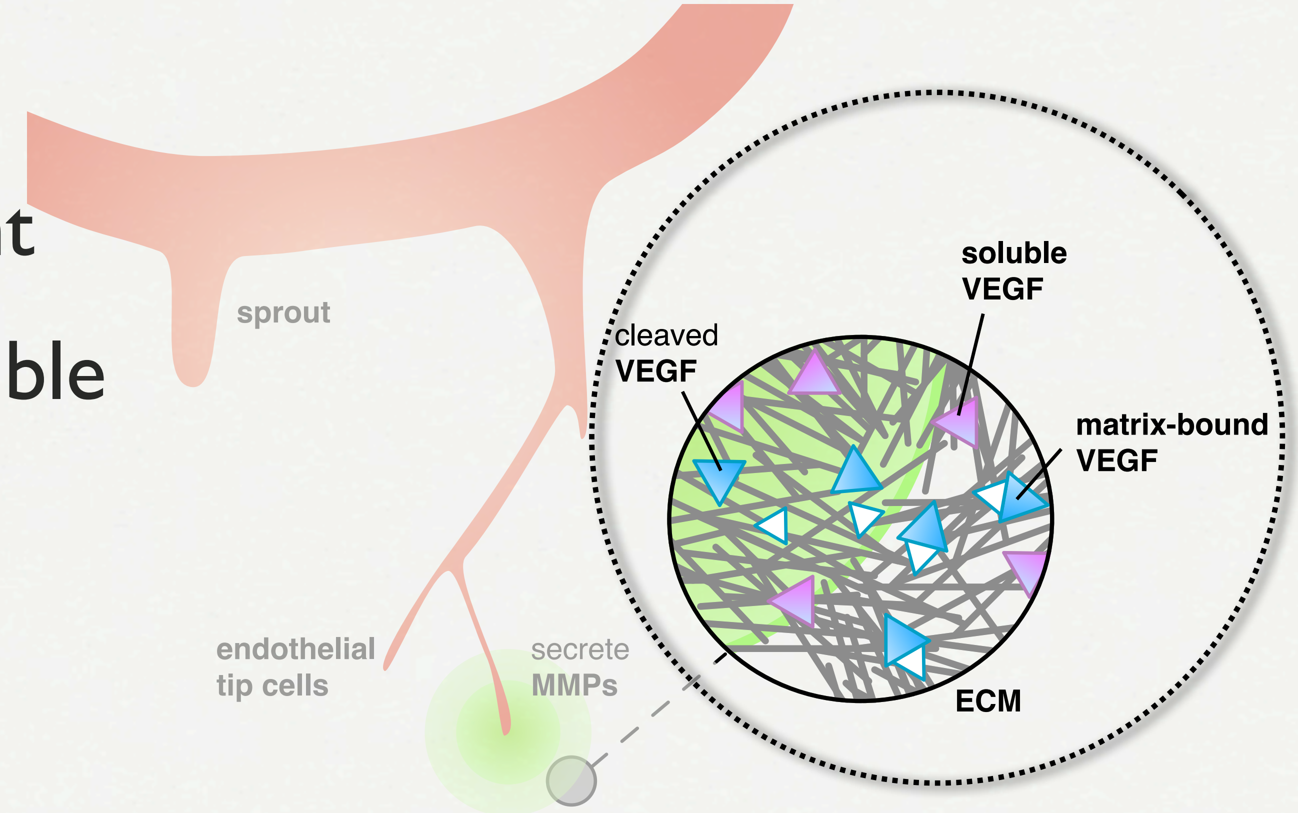

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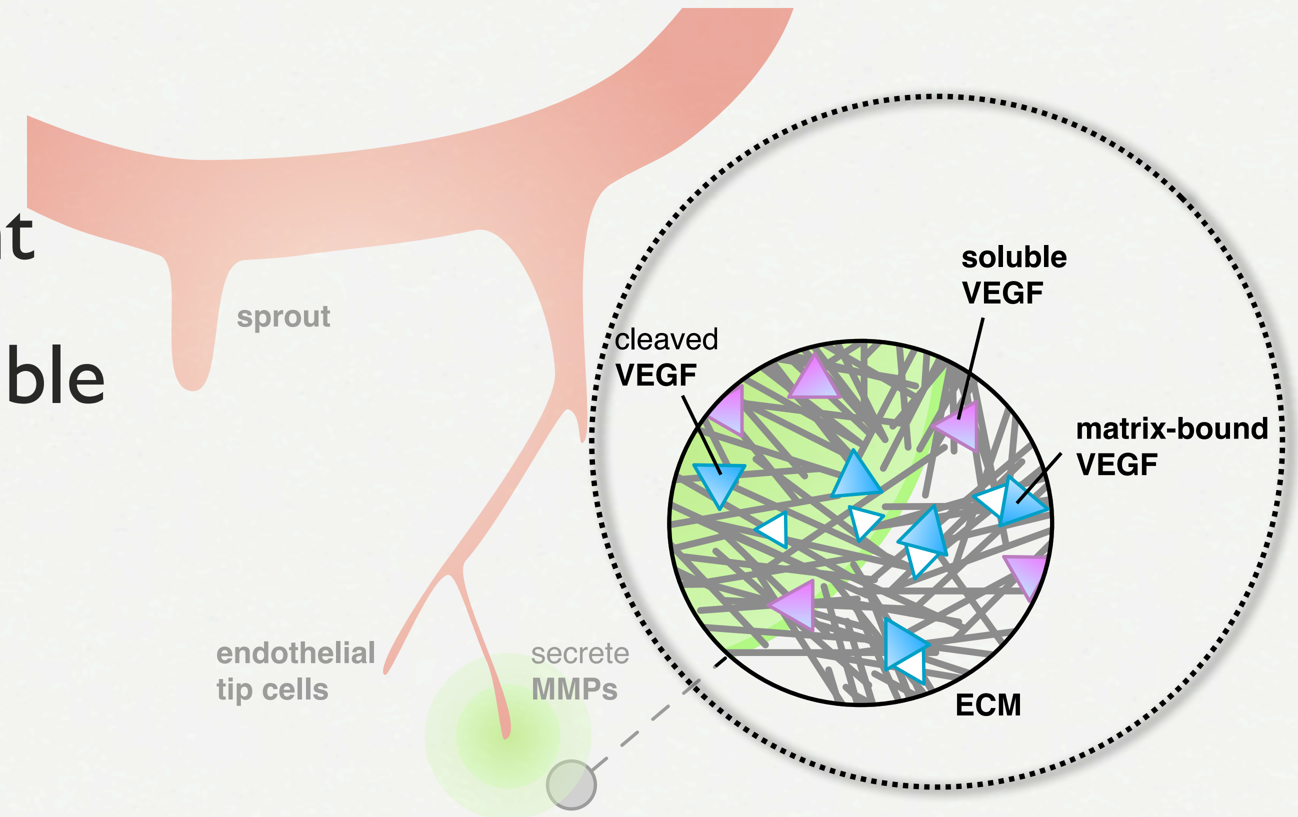

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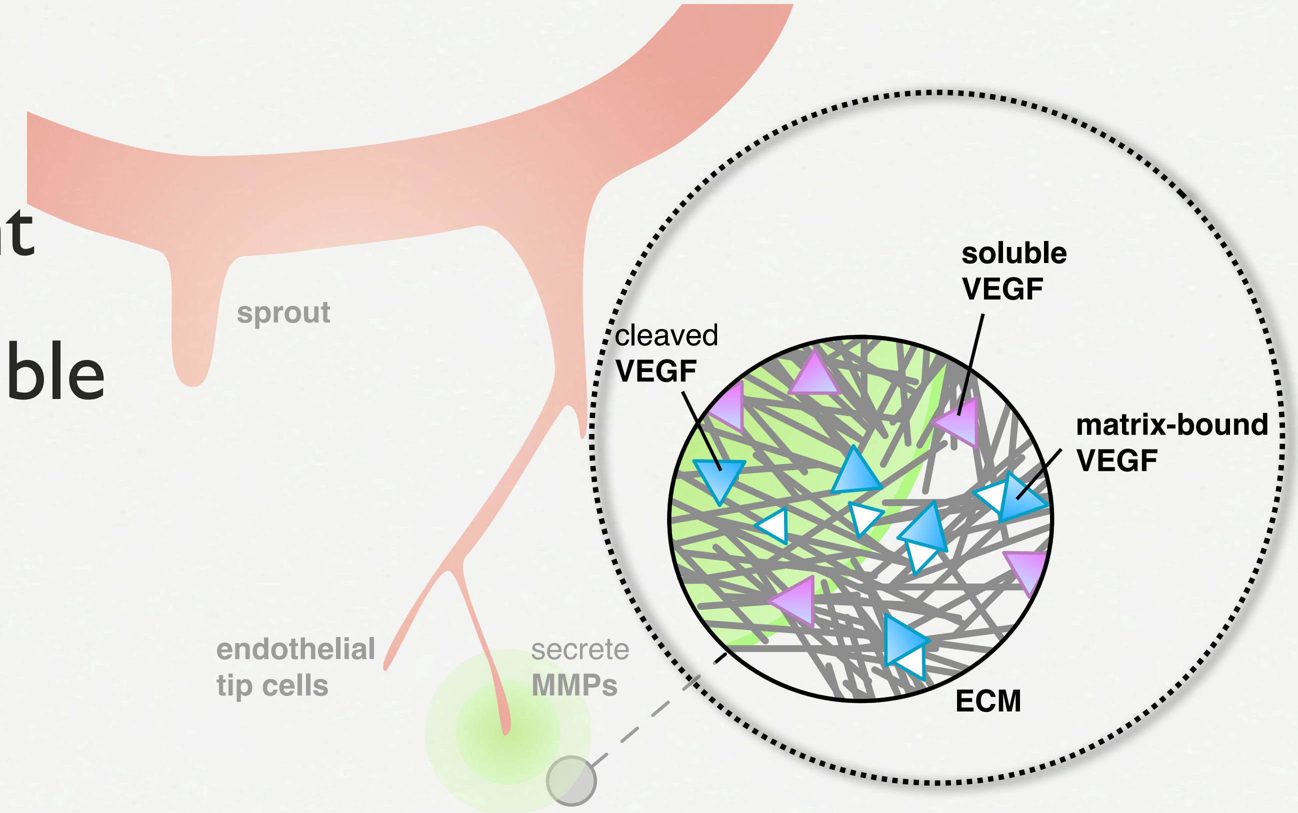

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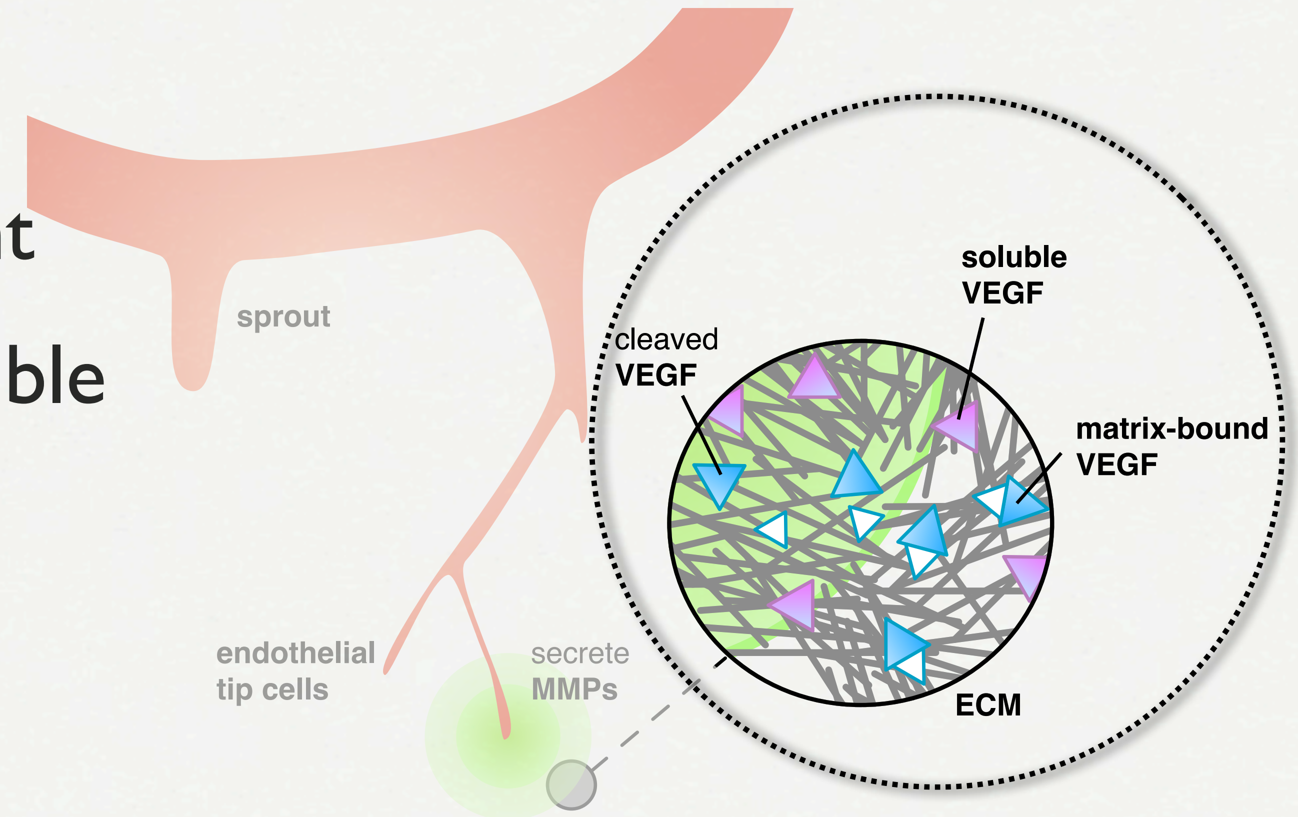
- establishes local chemotactic gradient
- cleaved VEGF (cVEGF) becomes soluble



  - bVEGF is cleaved by MMPs
  - Uptake of cVEGF by ECs ρ
  - cVEGF diffuses through ECM
  - cVEGF is subject to natural decay

$$\frac{\partial[\text{bVEGF}]}{\partial t} = -C\left([\text{bVEGF}],[\text{MMP}]\right) - U\left([\text{bVEGF}],\rho\right)$$

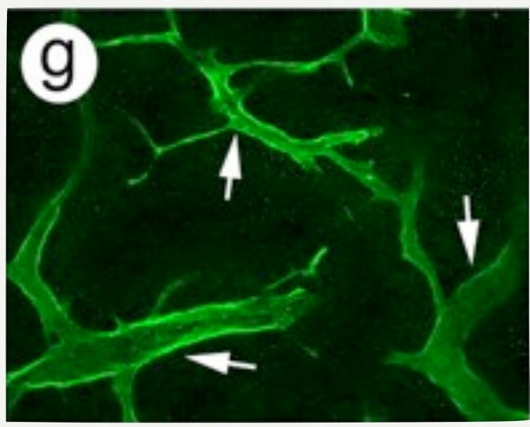
$$C\left([\text{bVEGF}],[\text{MMP}]\right) = min\left([\text{bVEGF}], v_{bV}[\text{MMP}][\text{bVEGF}]\right)$$

$$\frac{\partial[\text{cVEGF}]}{\partial t} = k_V \nabla^2[\text{cVEGF}] + C\left([\text{bVEGF}],[\text{MMP}]\right) - U\left([\text{cVEGF}],\rho\right) - \delta_V[\text{cVEGF}]$$

Angiogenesis: Post-dicting Experiments

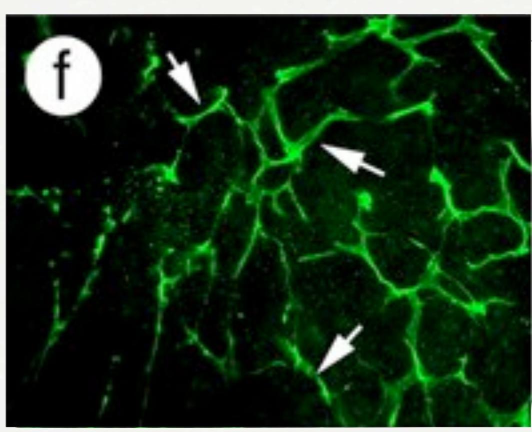
Matrix-bound VEGF leads to increased branching.
vessel branching ↔ capillary function

BLOOD VESSEL FORMATION IN A MOUSE MODEL



ONLY SOLUBLE VEGF
> THICKER VESSELS

ONLY SOLUBLE VEGF



SOLUBLE + MATRIX-BOUND VEGF
> INCREASED BRANCHING

SOLUBLE & MATRIX-BOUND VEGF

RADIAL SOLUBLE VEGF GRADIENT AND
LOCALIZED MATRIX-BOUND VEGF

[1] S. Lee, S. M. Jilani, G. V. Nikolova, D. Carpizo, and M. L. Iruela-Arispe. Processing of VEGF-A by matrix metalloproteinases regulates bioavailability and vascular patterning in tumors. *J. Cell Biol.*, 169(4):681–691, 2005.

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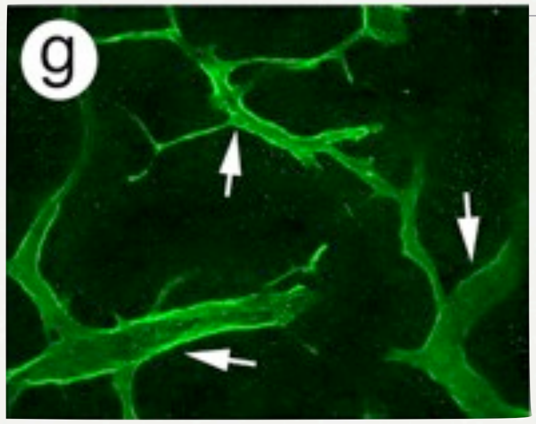

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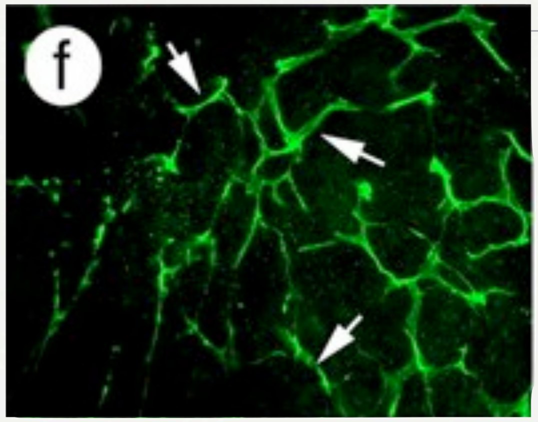

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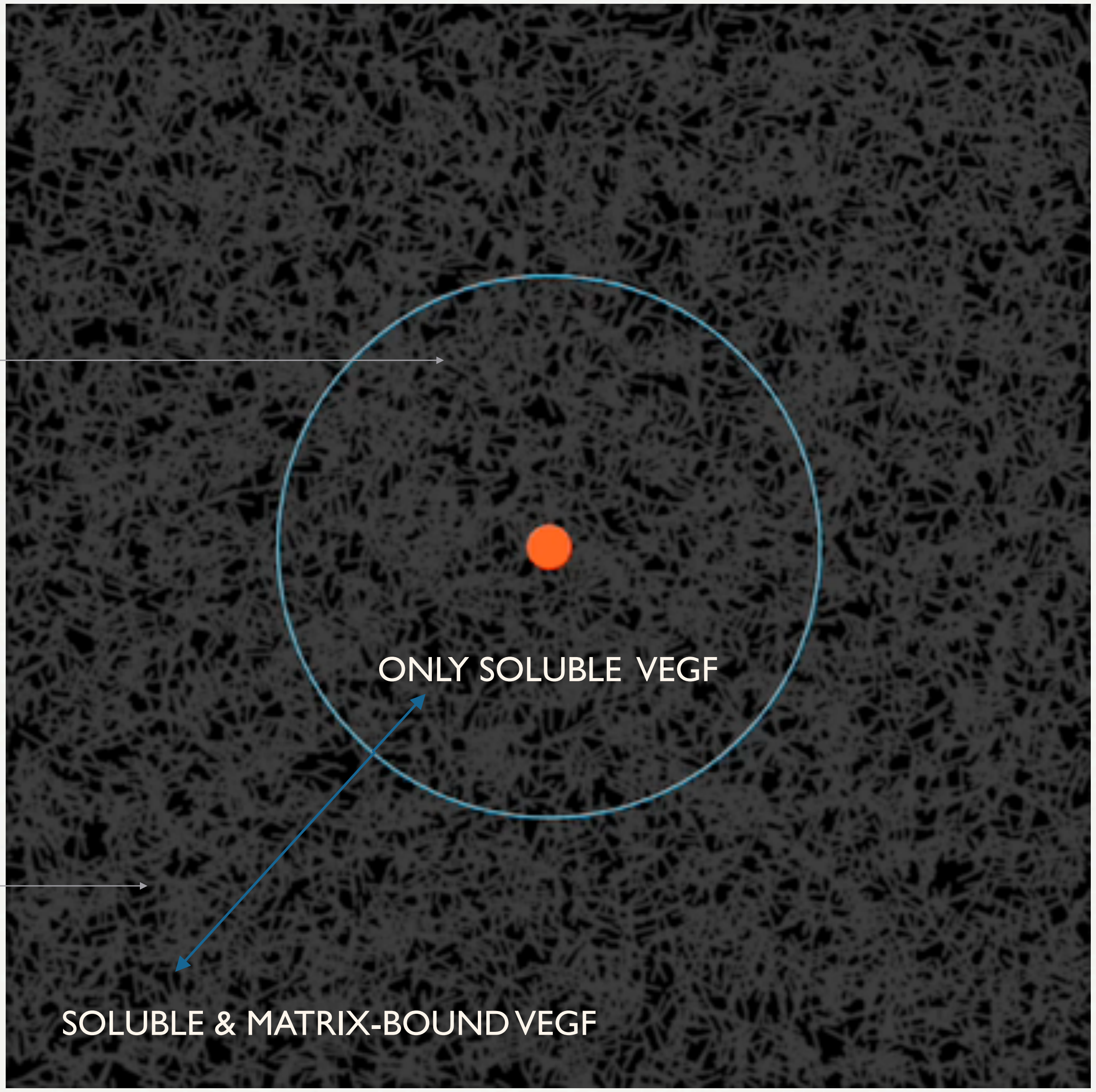

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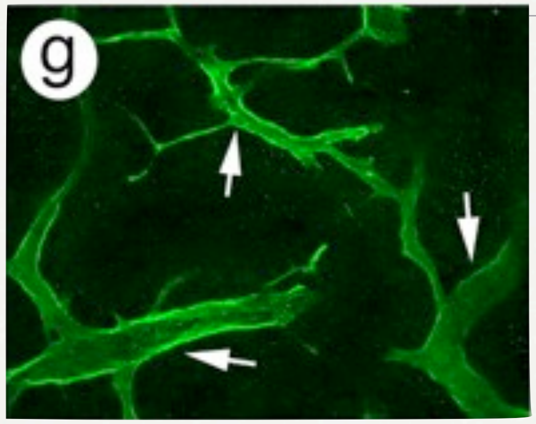

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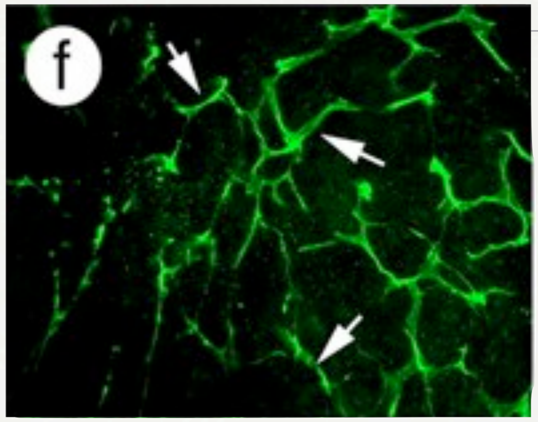

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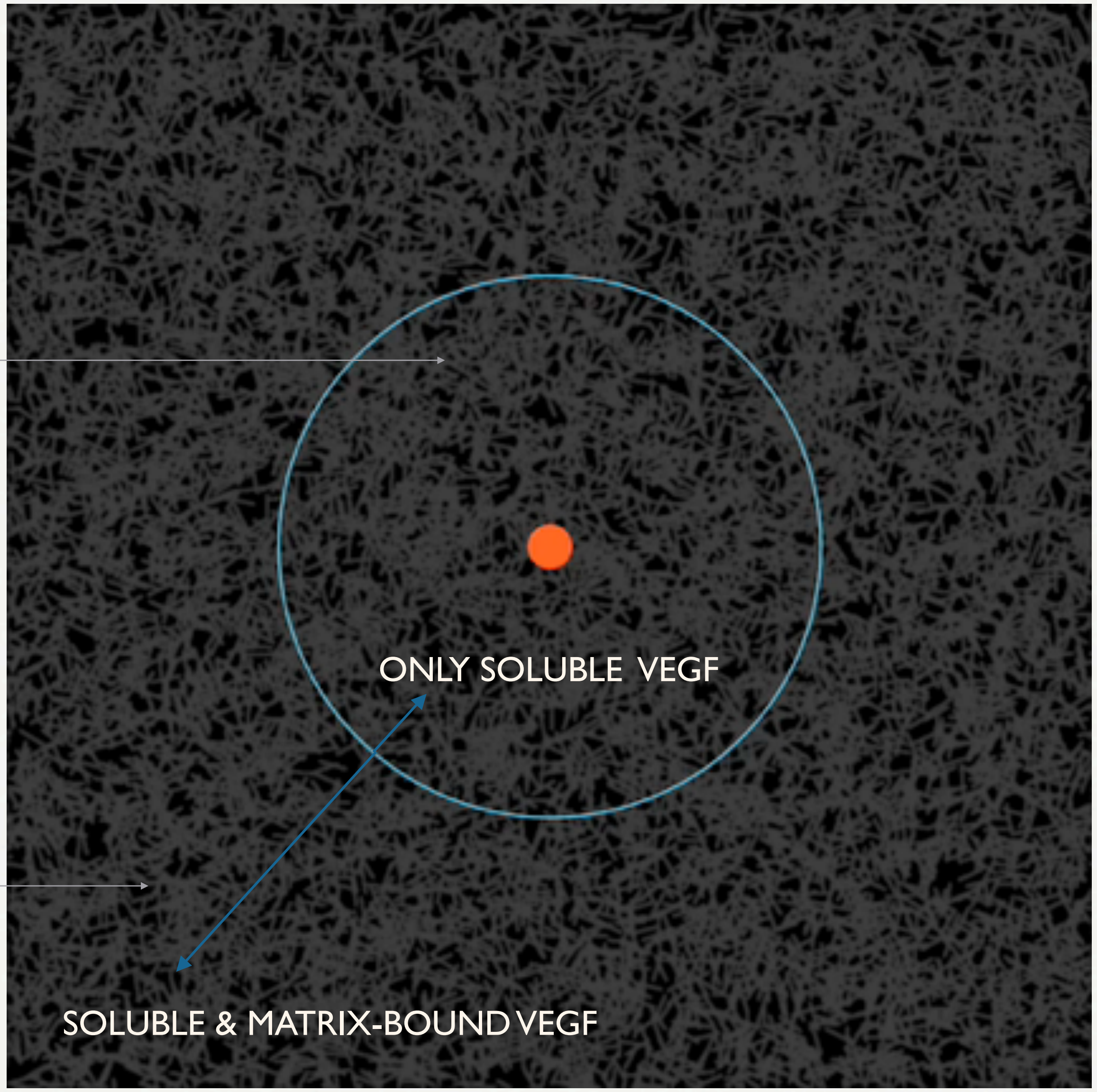

RADIAL SOLUBLE VEGF GRADIENT AND LOCALIZED MATRIX-BOUND VEGF

new: branching is an output of the simulation

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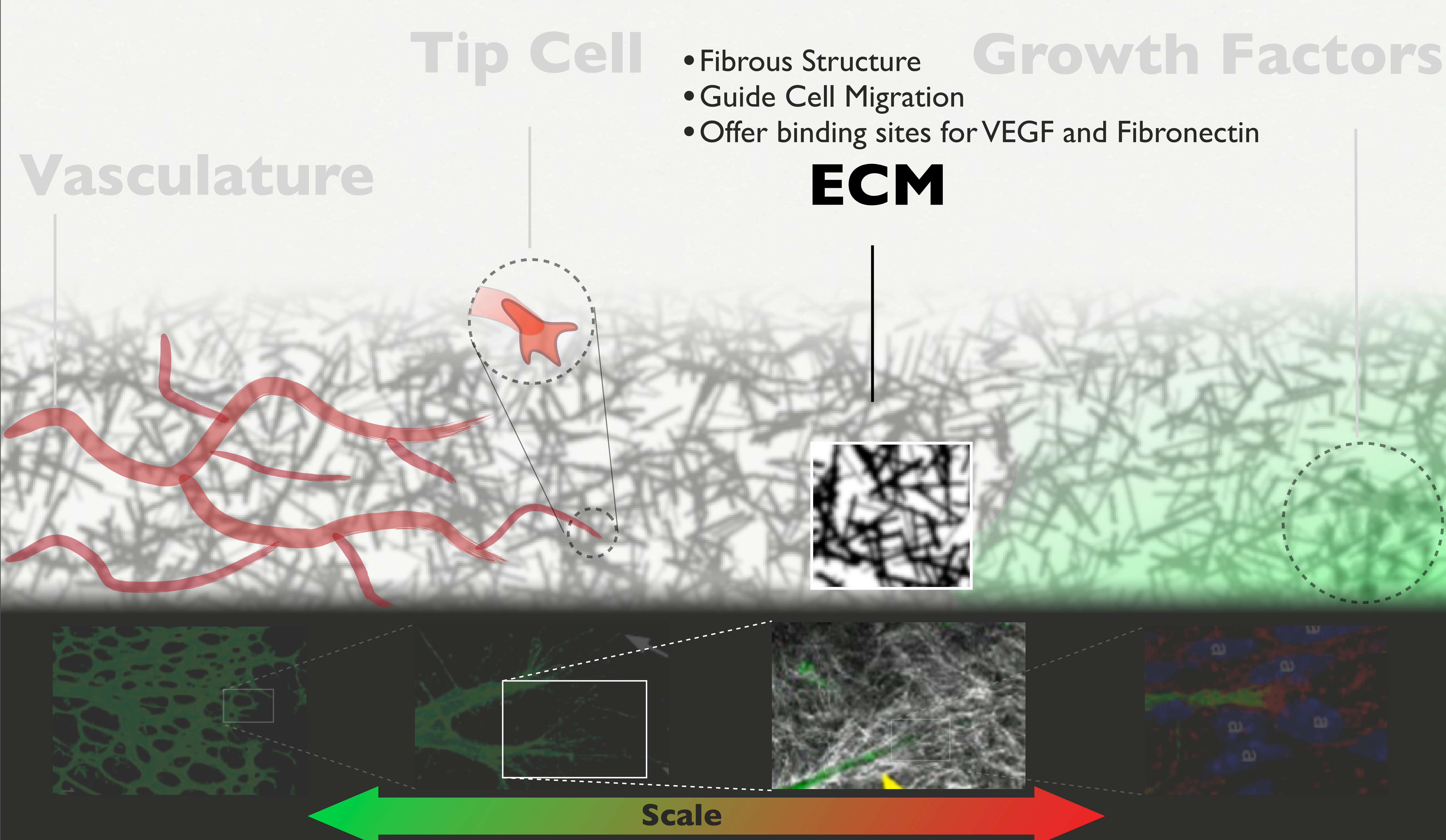
The Extra-Cellular Matrix



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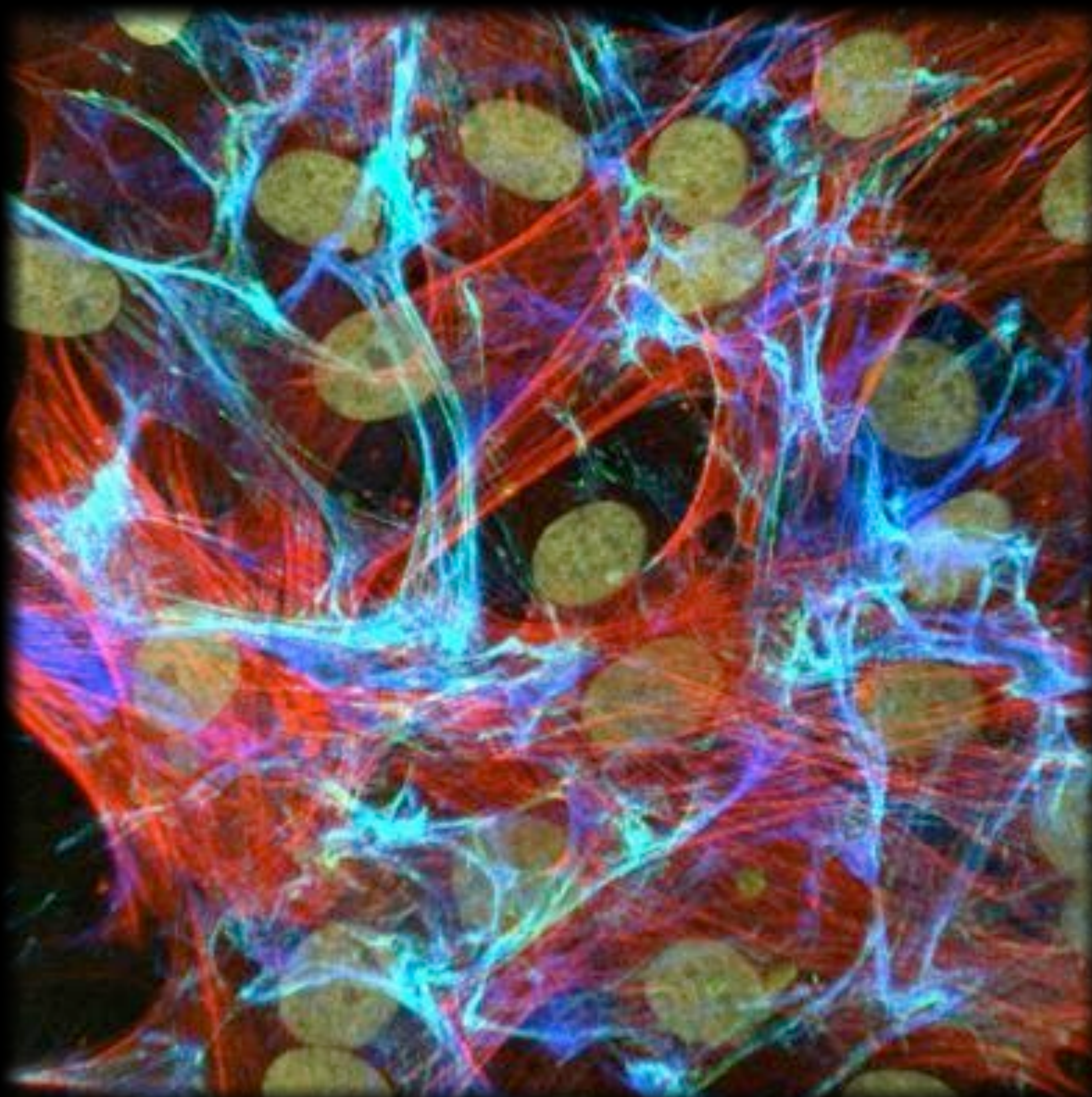
The Extra-Cellular Matrix and Matrix bound Growth Factors

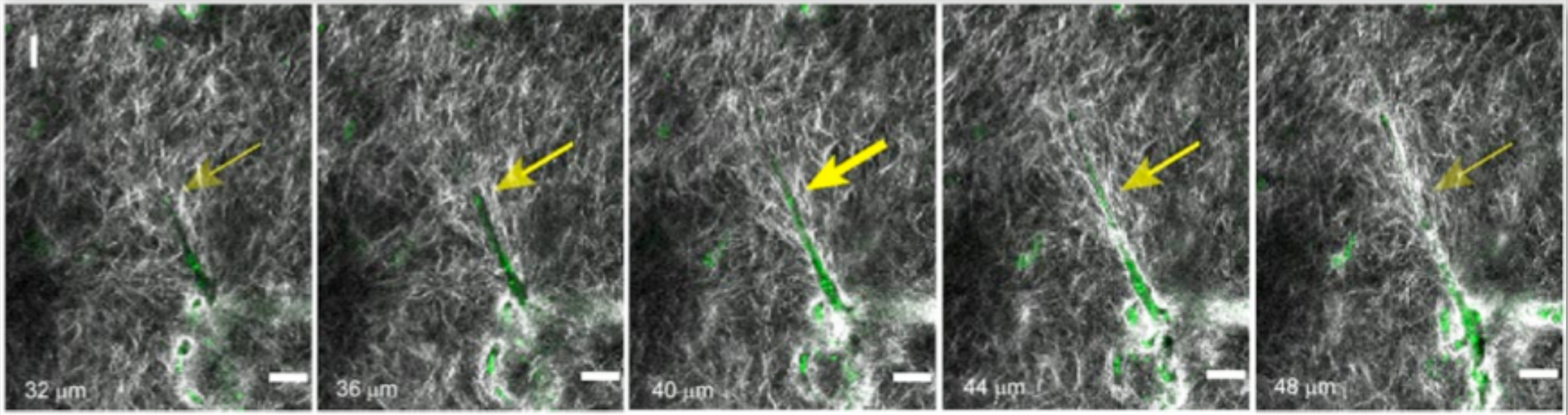


Contractile fibroblasts secrete and organize extracellular matrix fibers (blue) that are loaded with growth factor complexes (green), resulting in a turquoise overlay color. The contractile fibers inside the cells are visualized by detecting a smooth muscle protein (red). The cells' nuclei are visualized in yellow. (Photo Credit: EPFL/LCB)

Extra-Cellular Matrix: Model

- Fibrous structures in ECM provide a guiding structure for migrating endothelial cells
- ECM fibers are subject of remodeling by migrating EC's
- The ECM expresses binding sites for various growth factors and integrins

in vitro model I: series of image slices illustrate the collagen fibril rearrangement around an early sprout in the axial dimension. The emboldened arrow signifies the center of the sprout.



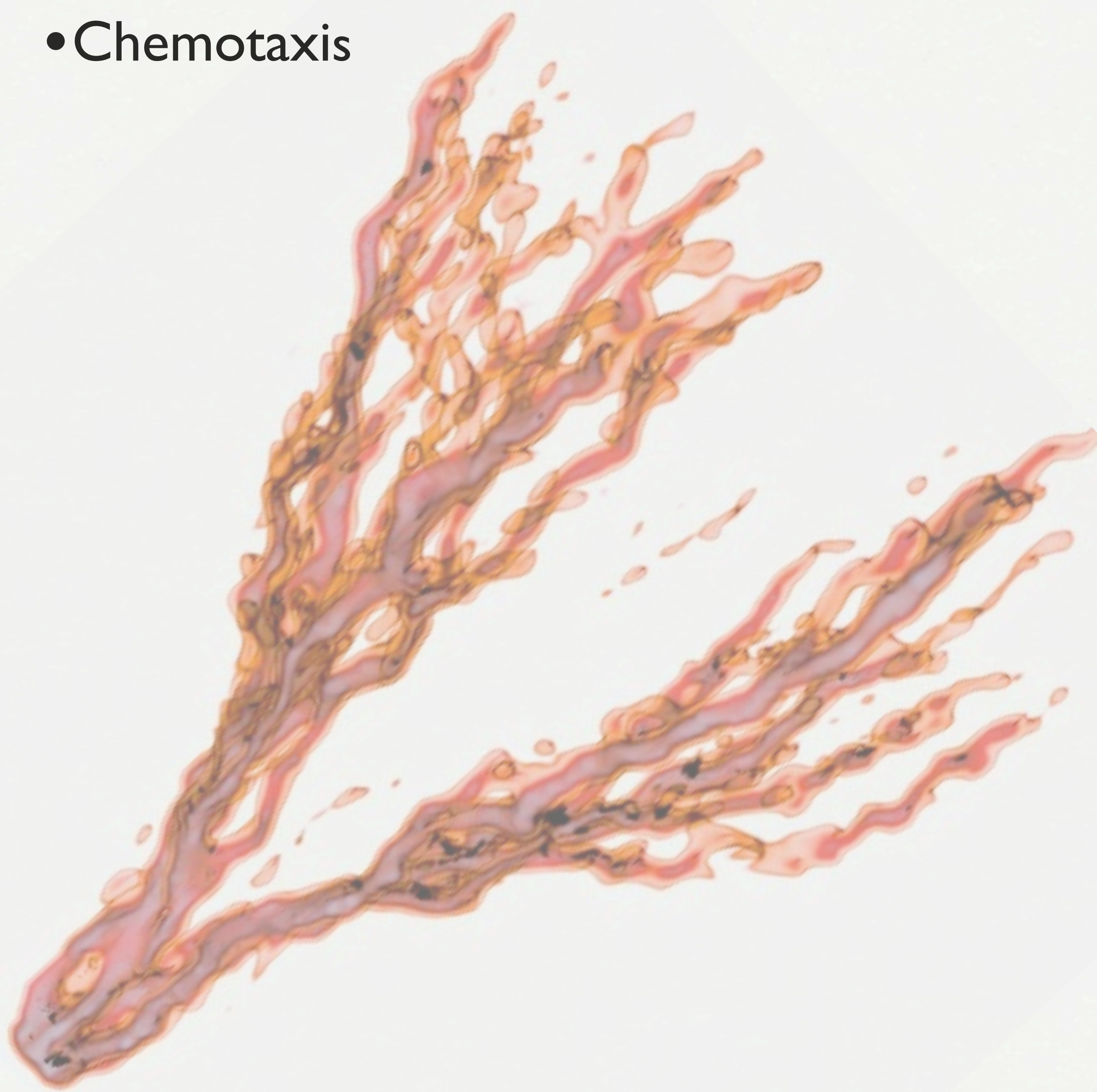
[4] N. D. Kirkpatrick, S. Andreou, J. B. Hoying, and U. Utzinger. Live imaging of collagen remodeling during angiogenesis. *AJP Heart.*. pages 0124.2006-,2007

Continuum Model Approach

Continuum Model of Mesenchymal Cell Migration

Considers:

- Cell-Cell Adhesion
- ECM-Cell Guidance and adhesion
- Pressure
- Chemotaxis



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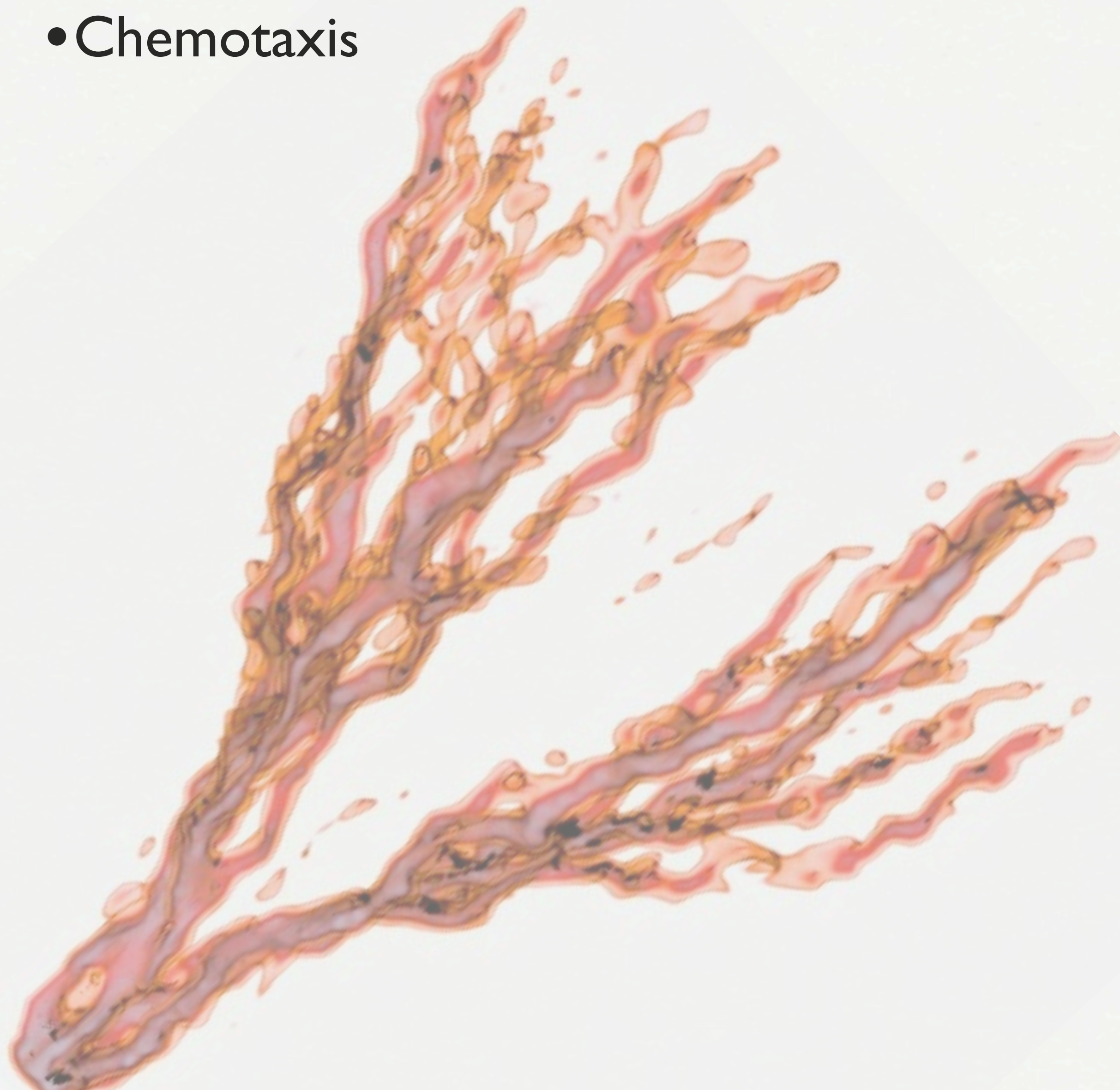

Cell Density:

$$\{\rho_i\}_{i=1}^{\#\text{CellTypes}}$$

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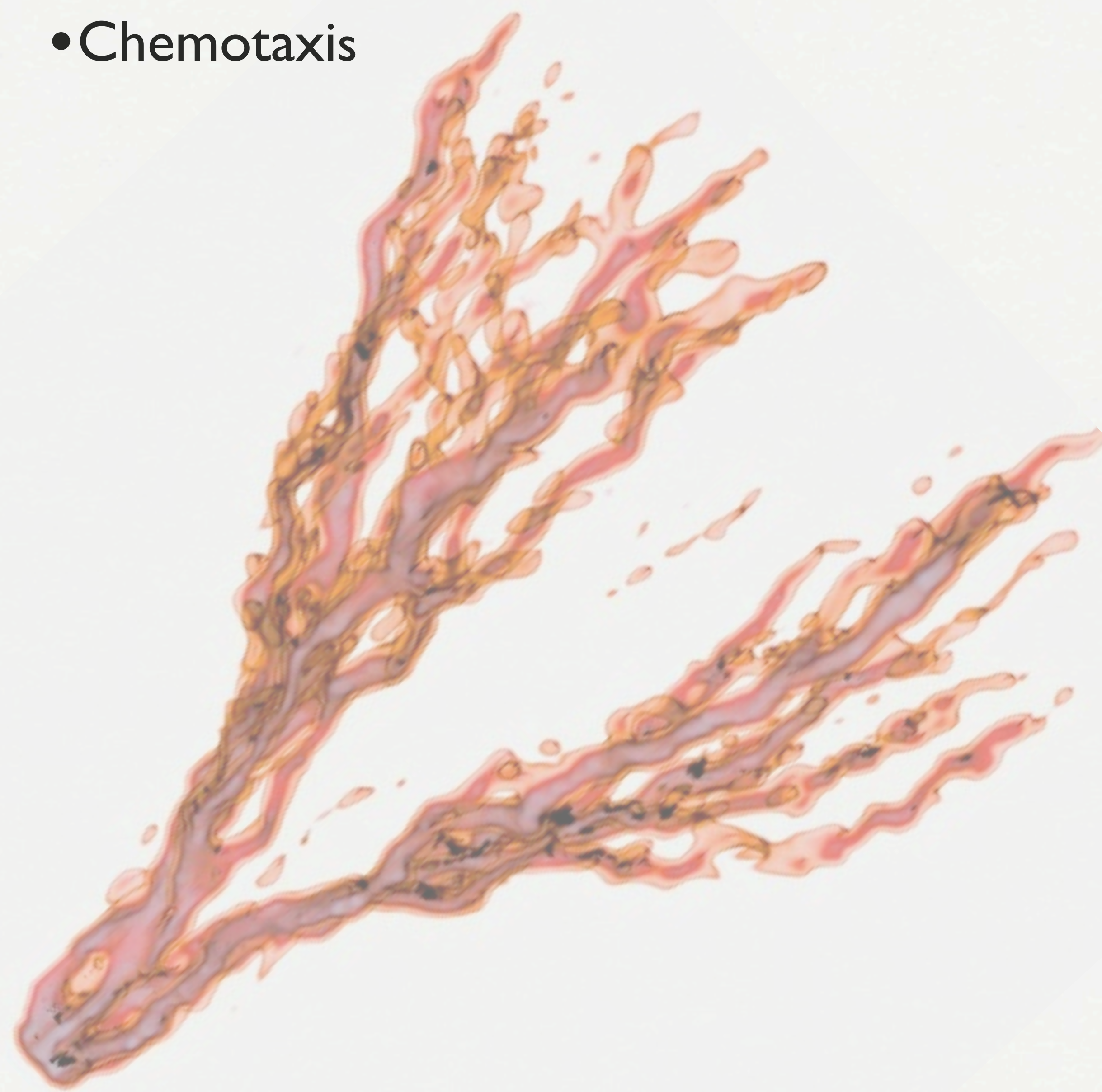

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Evolution of Cell density:

random fluctuation

$$\frac{\partial \rho_i}{\partial t} + \nabla \cdot (\mathbf{a}_i \rho) = \kappa_i \Delta \rho_i + R(\rho)$$

migrative response

creation/death

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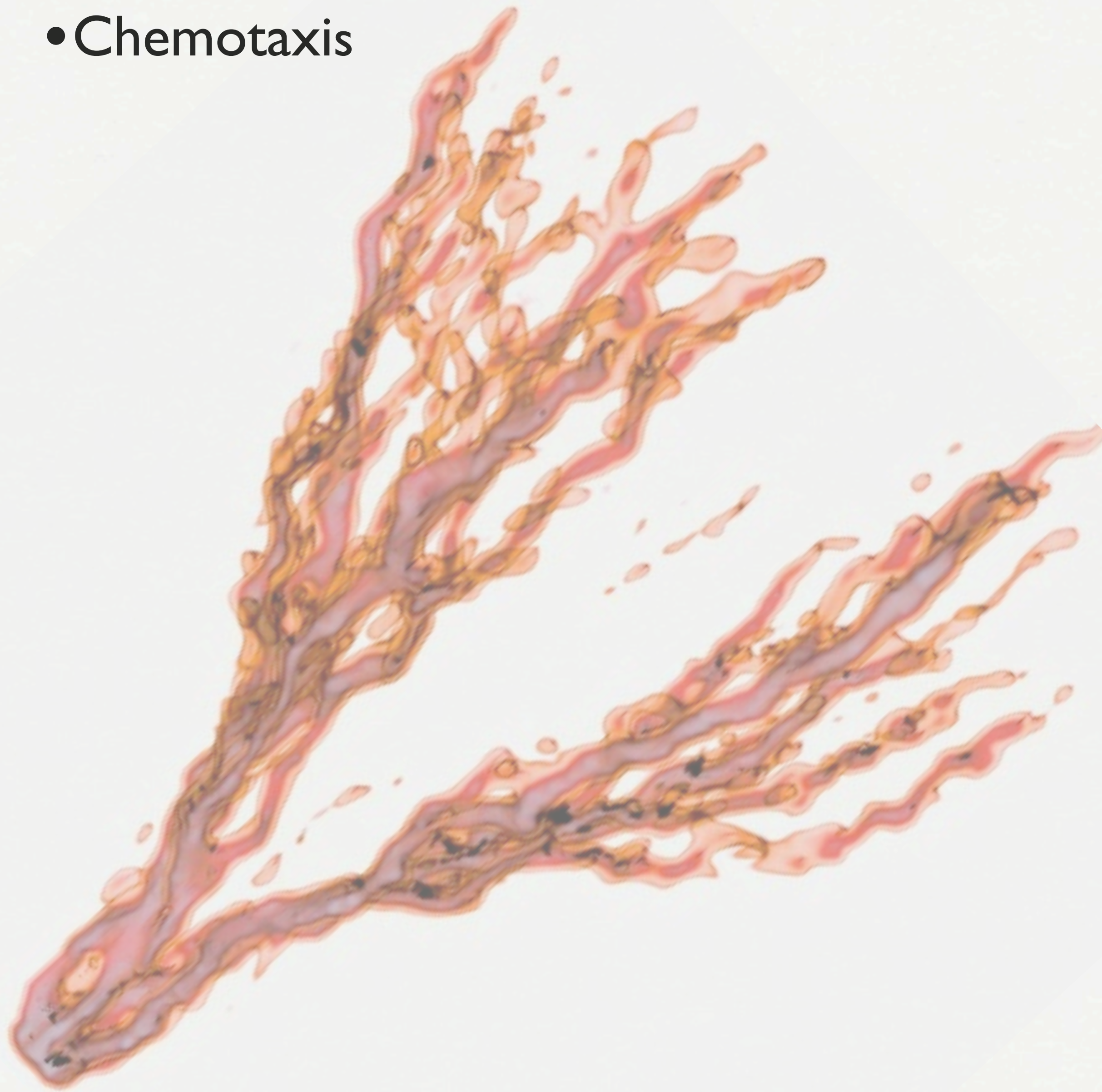

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$$\frac{\partial \rho_i}{\partial t} + \nabla \cdot (\mathbf{a}_i \rho) = \kappa_i \Delta \rho_i + R(\rho)$$

migrative response; random fluctuation; creation/death

Migrative Response:

$$\mathbf{a}_i = \mathbf{a}_i^{c/c} + \mathbf{a}_i^{\phi,e} + \mathbf{a}^p.$$

cell-cell adhesion; chemotaxis inside ECM; cell density pressure

Continuum Model: Cell-Cell Adhesion

Model Approach:

- Cells ρ_i secrete adhesion signal f_i
- Short range diffusion establishing adhesion gradient
- Cells Respond to adhesion signal by migration upwards the adhesion signal.
- Inter and intra Cell-Type response can vary

Adhesion Signal:

$$\frac{\partial f_i}{\partial t} = D_i \Delta f_i + \alpha_i \left(1 - \frac{f_i}{f_{i,max}}\right) \rho_i - \mu_i f_i$$

diffusion   released by CellType   decay

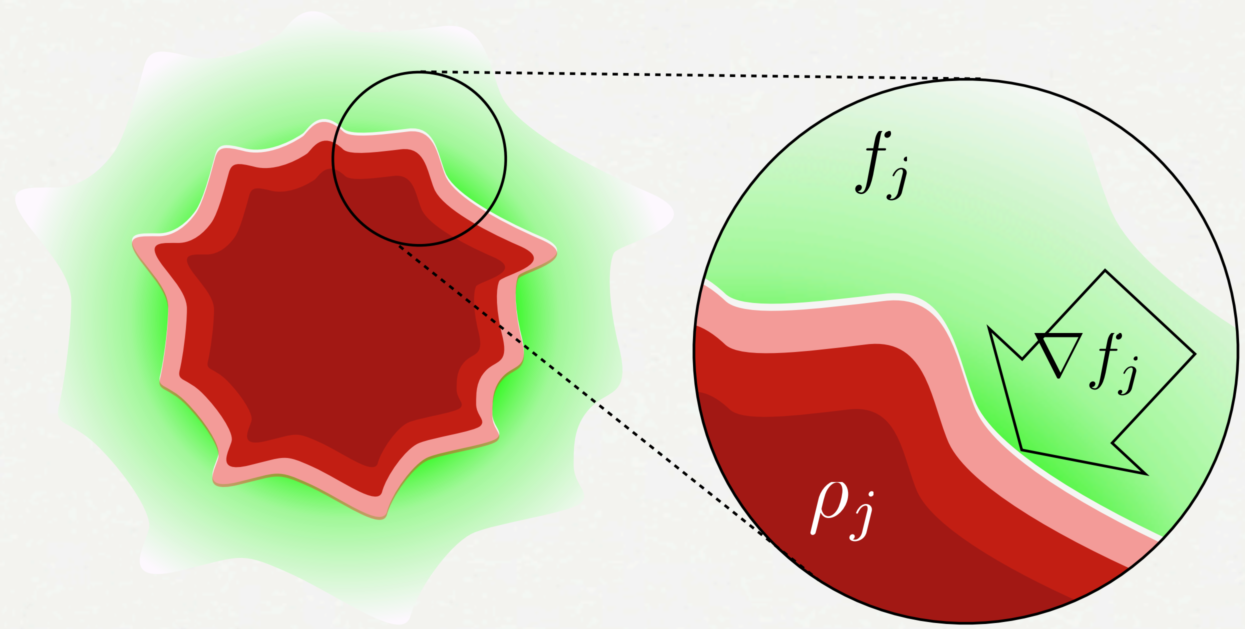
Cell Response:

$$\mathbf{a}_i^{c/c} = \sum_j^{\#\text{CellTypes}} \kappa_{ij} L\left(f_j, df_j\right) \nabla f_j$$

threshold function

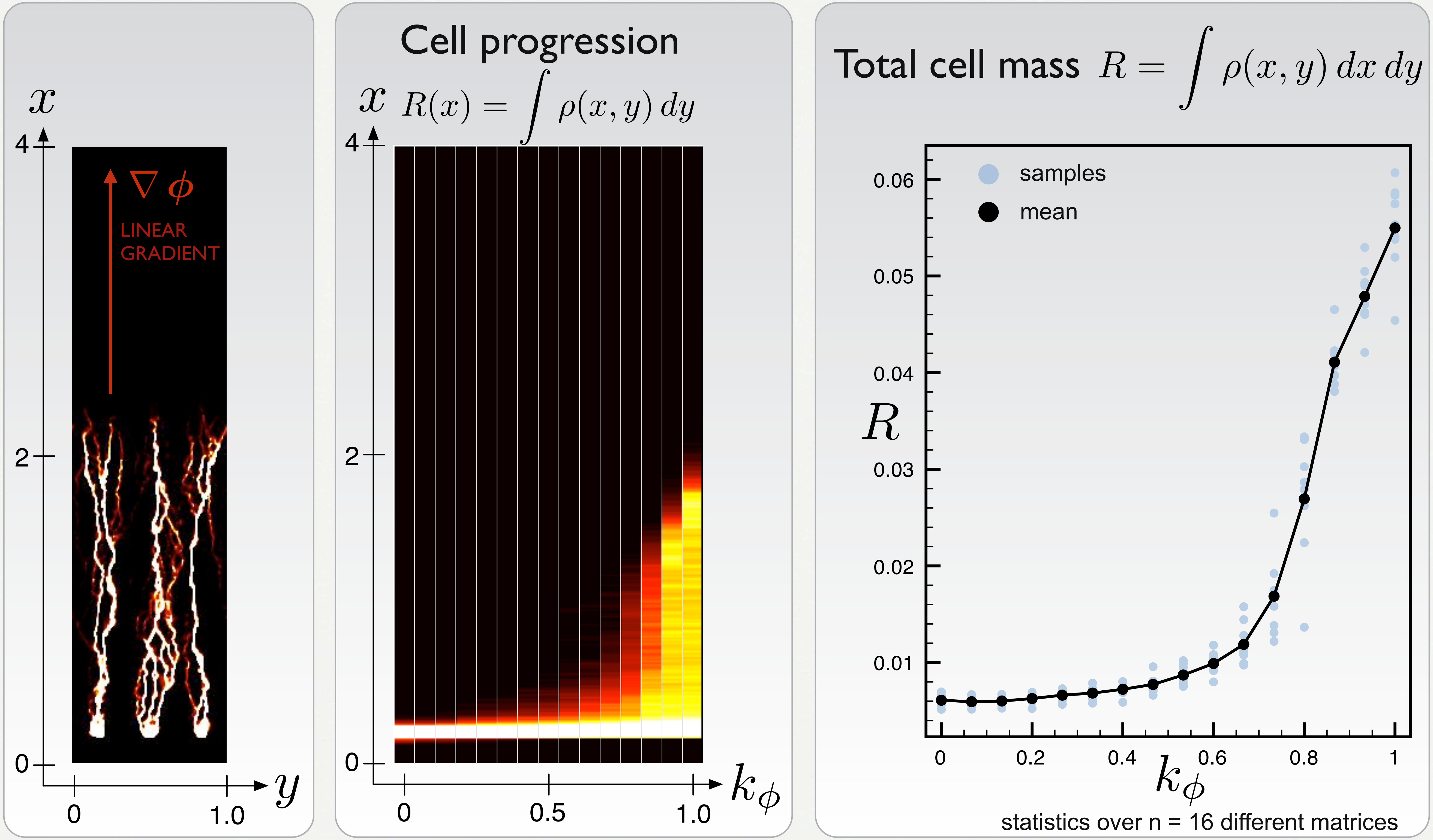
differential response

signal gradient



Result: Sprouting is non-linear

Given a chemotactic response strength k_ϕ how far do the cells migrate?

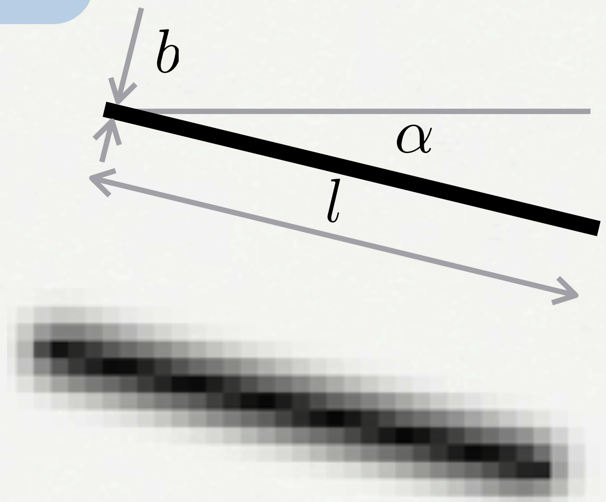


Modeling the ECM

Fibers:

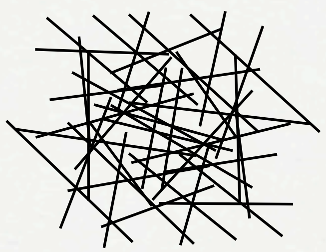
- straight
- random direction
- distribution of lengths

$$l = l_0 \, 2^{m\,z}$$
$$\alpha \in \mathcal{U}([0, \pi])$$
$$z \in \mathcal{N}(0, 1)$$

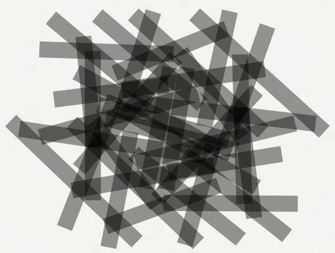


Representation:

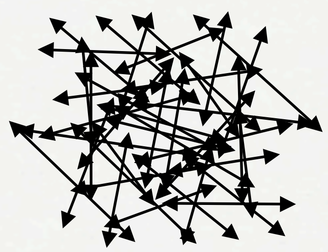
- indicator field: E_X
- density field: E_ρ
- directional field: $\mathbf{K}$



E_X



E_ρ



$\mathbf{K}$

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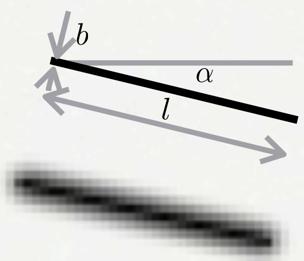
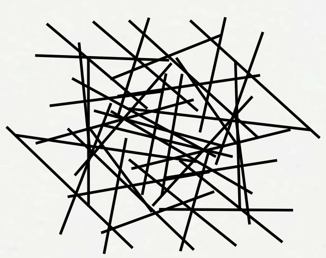
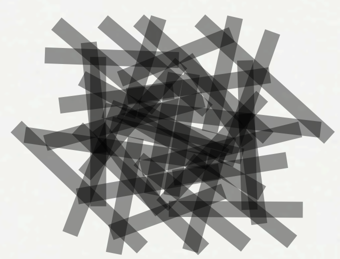
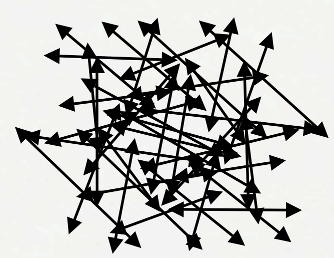




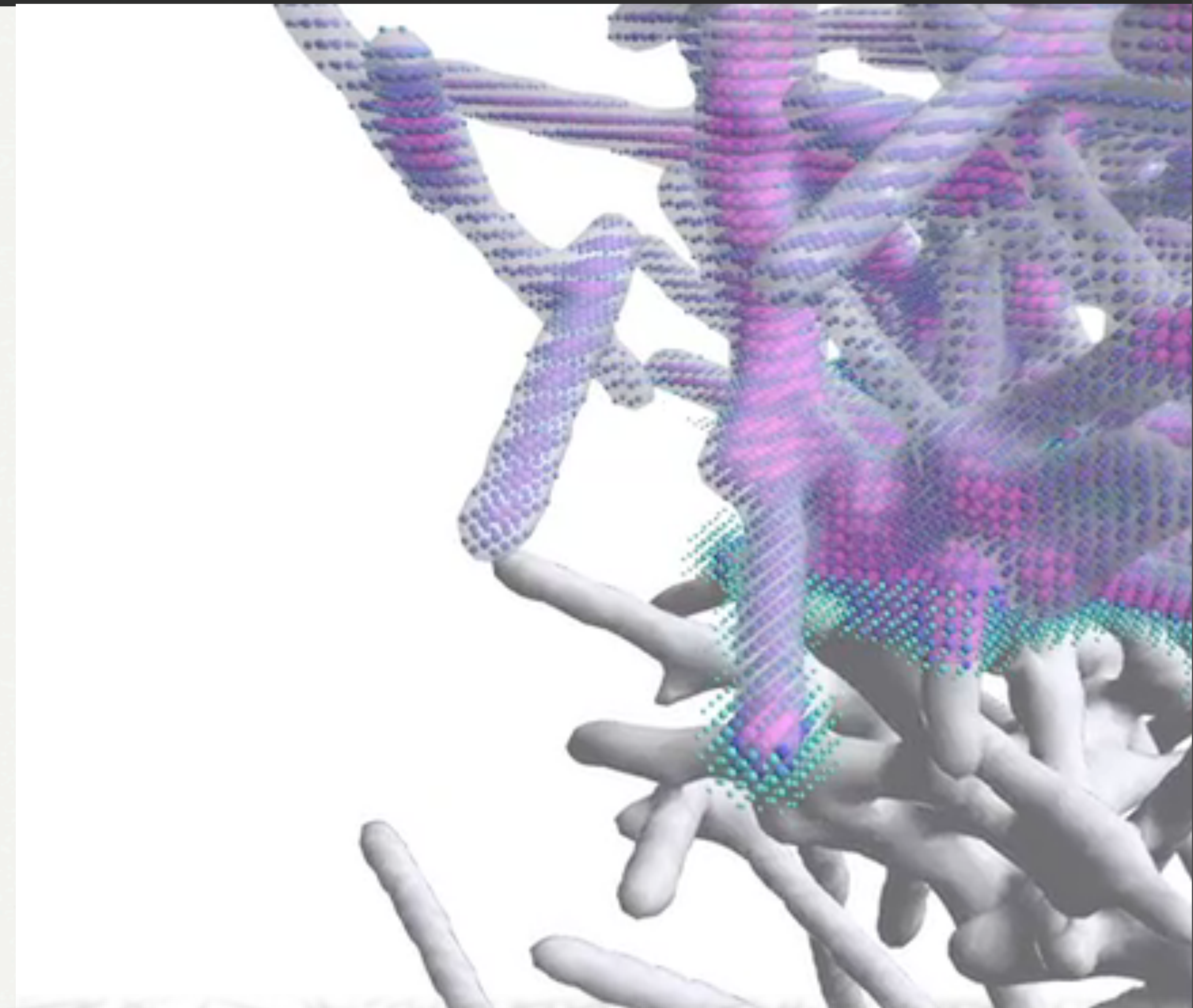
E_X



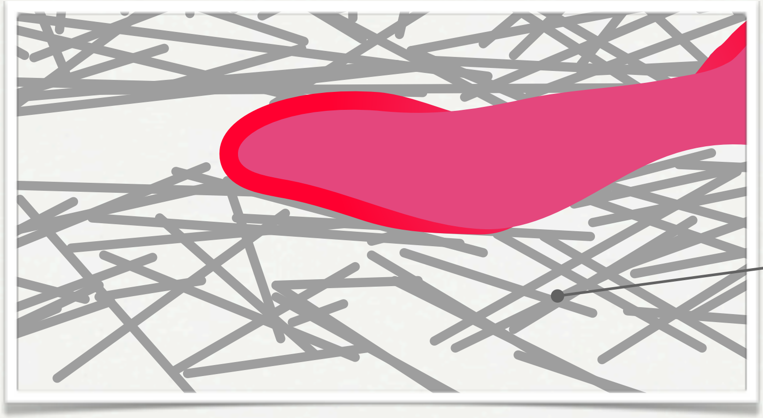
E_ρ



$\mathbf{K}$

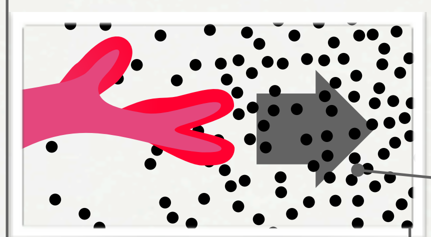


Matrix-aware Chemotaxis - Tip Cells



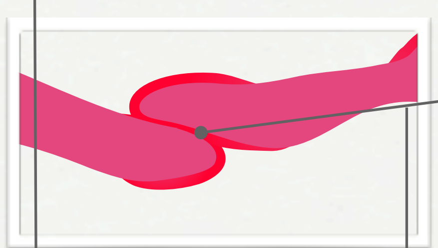
Cells are guided by extracellular matrix

transmembrane CAMs: integrins,...)
facilitates migration



Cells sense chemical gradients

gradients of "chemoattractant" serve as migratory cues



Cells stick to cells

gradient of "haptotactic" molecules serve as migration cues

Migration Speed

$$\mathbf{a} = \alpha\left(E_\rho\right)\underline{\mathbf{T}}\left(w_V \nabla \Psi + w_F \nabla \Phi_b\right)$$

Matrix-aware Chemotaxis - CONTINUUM

Cells will attach to fibers if they are aligned with the chemotactic cue $\nabla\phi$

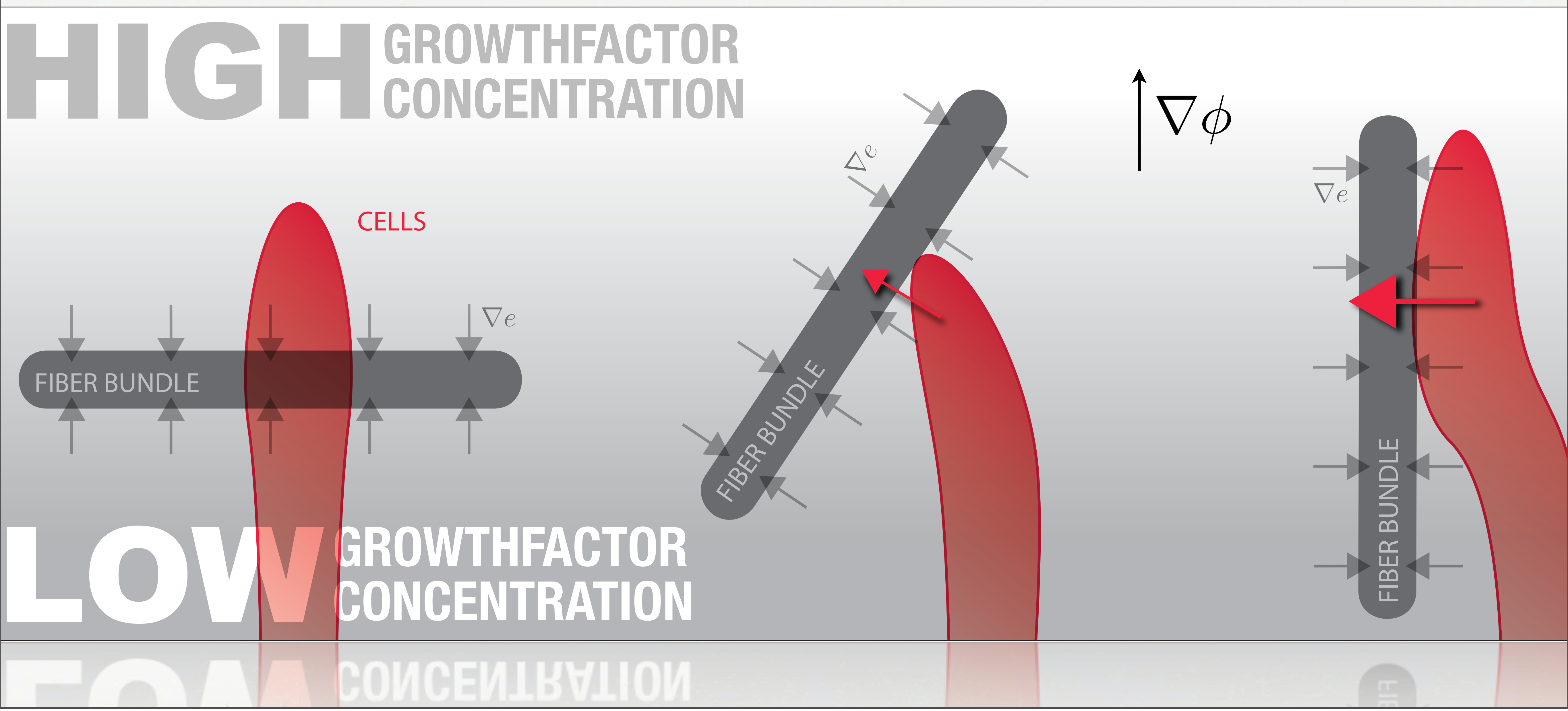
$$\mathbf{a}^{\phi,e} = \left[\left(1 - \left|\frac{\nabla e}{|\nabla e|} \cdot \frac{\nabla \phi}{|\nabla \phi|}\right|\right) \nabla e + \nabla \phi\right] (e + e_0)(e_\infty - e)$$

CELL-MATRIX ADHESION

CHEMOTACTIC RESPONSE

ECM GUIDANCE

ECM MODULATION



Angiogenesis : *in silico*

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Matrix-bound VEGF - Simulation

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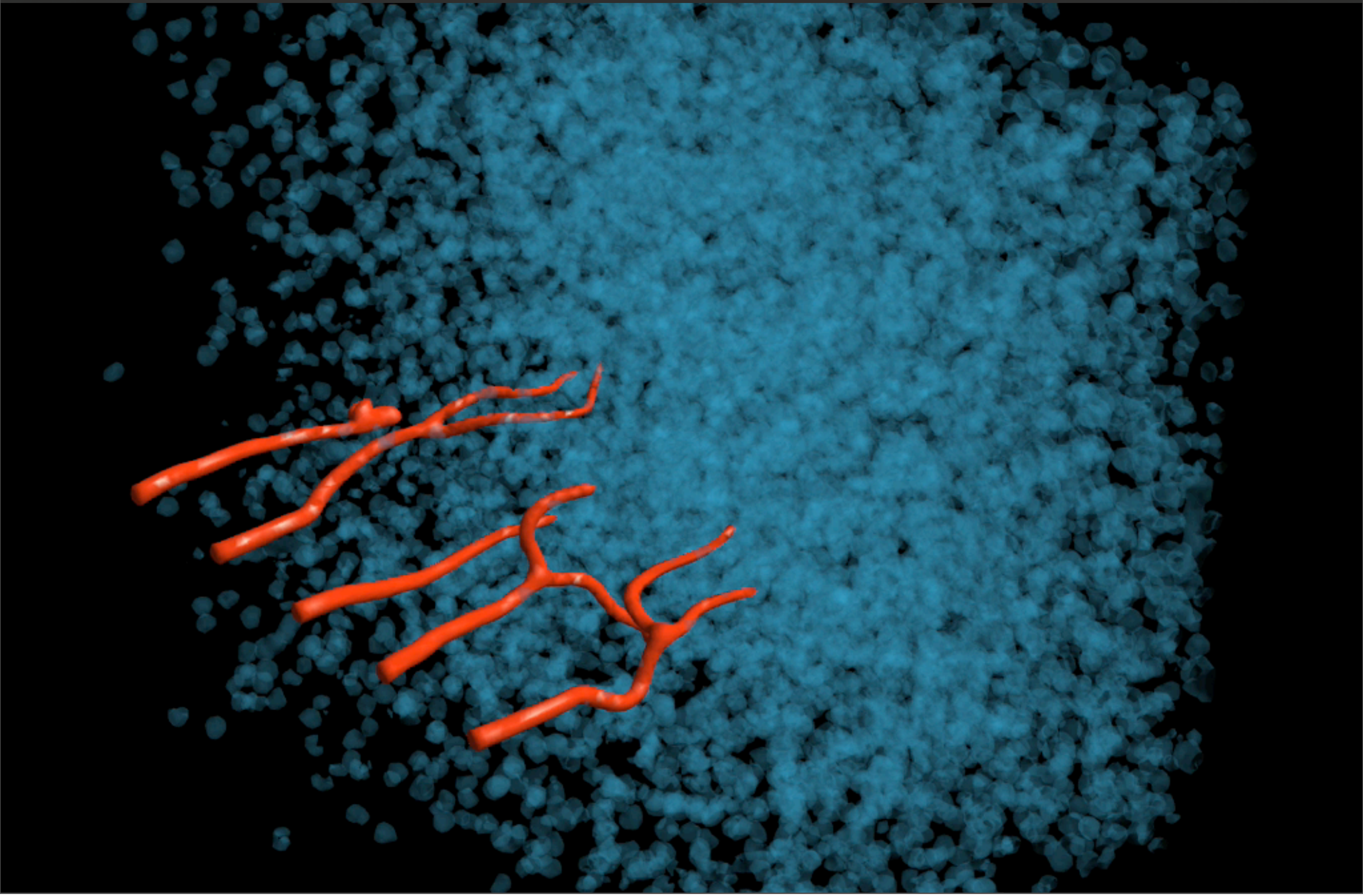
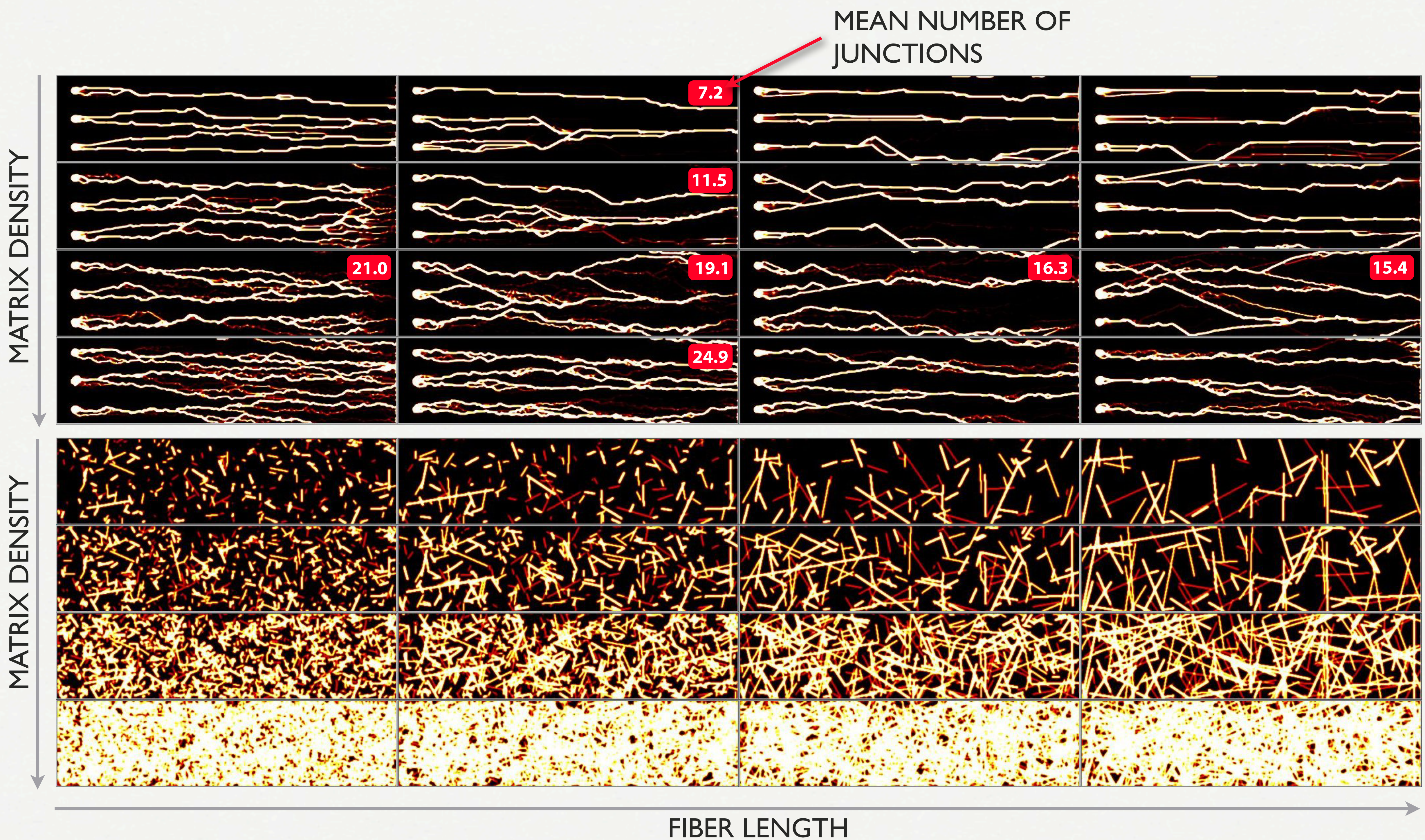
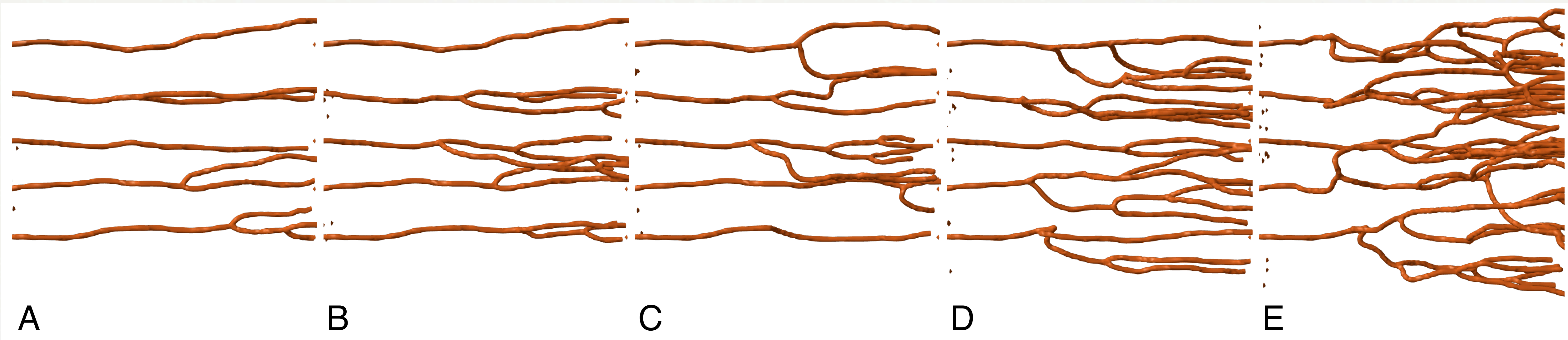


Effect of Matrix structure on branching - Mesenchymal cells



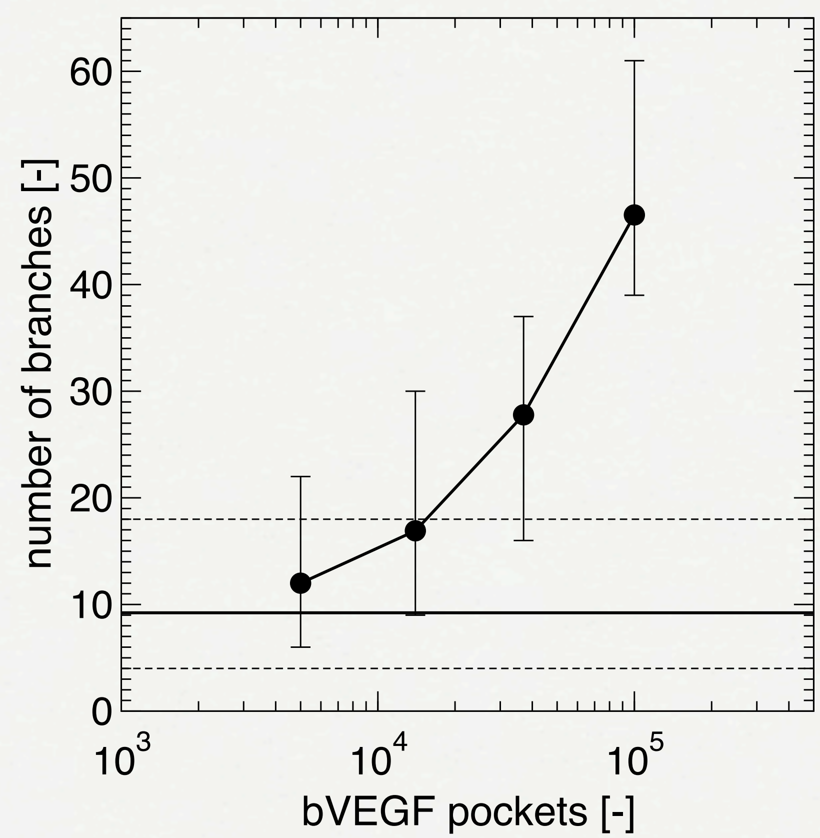
statistics over n = 50 different matrices
junctions identified with AngioQuant

Results: Matrix bound VEGF perturbs Vasculature

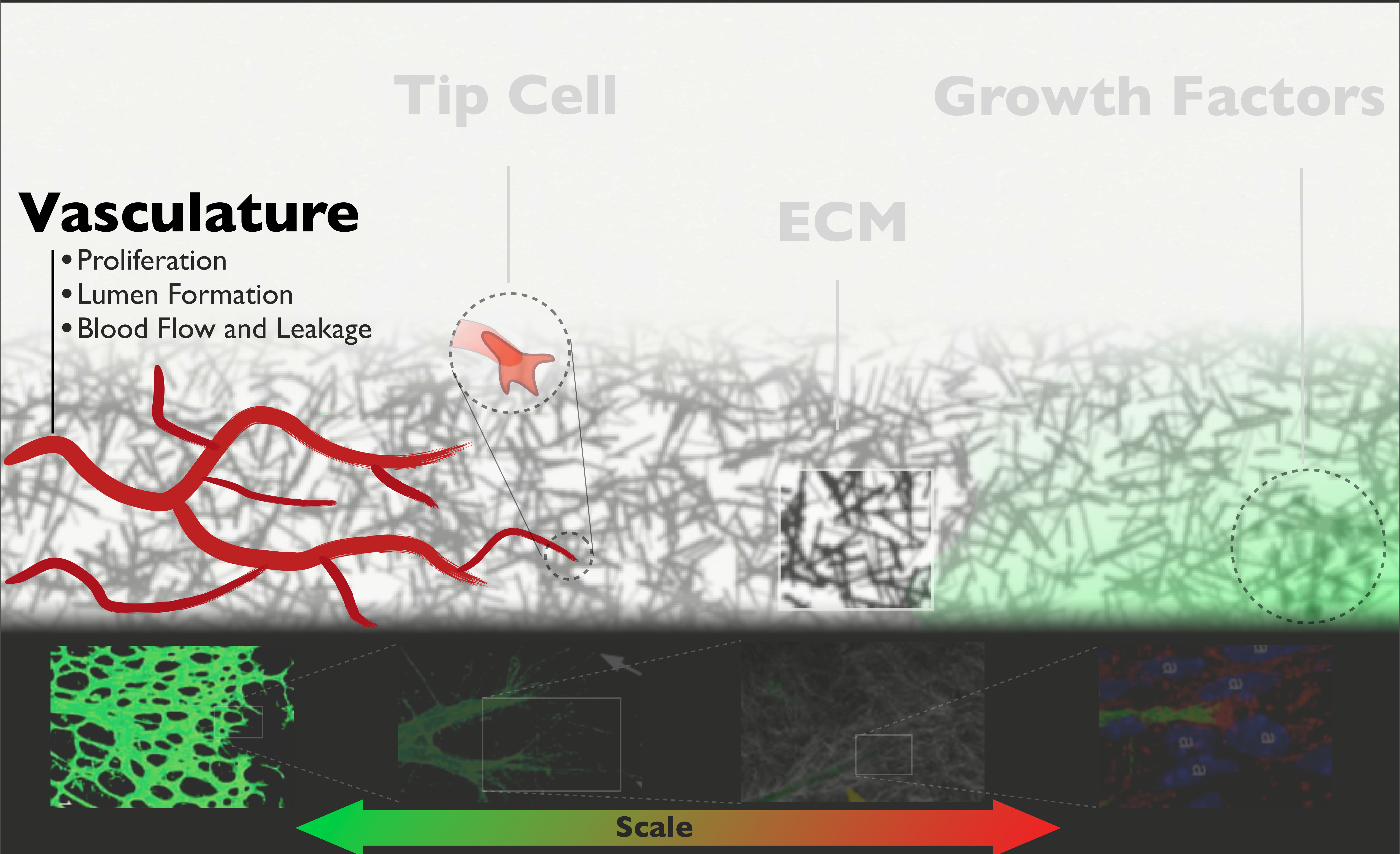


DISTRIBUTED VEGF POCKETS:

A: 0, B: 500, C: 1’400, E: 10’000



The Extra-Cellular Matrix



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Lumen Formation and Maturation

Endothelial Cells:

$$\frac{\partial c_{ec}}{\partial t} + v_{ec}\nabla c_{ec} = \begin{cases} \chi_{ec} c_s c_{ec} \frac{c_{tot,max} - c_{tot}}{c_{tot,max} - c_{tot,rlx}} & \text{if } c_{tot} > c_{tot,rlx} \\ \chi_{ec} c_s c_{ec} & \text{otherwise} \end{cases}$$

Proliferation Signal:

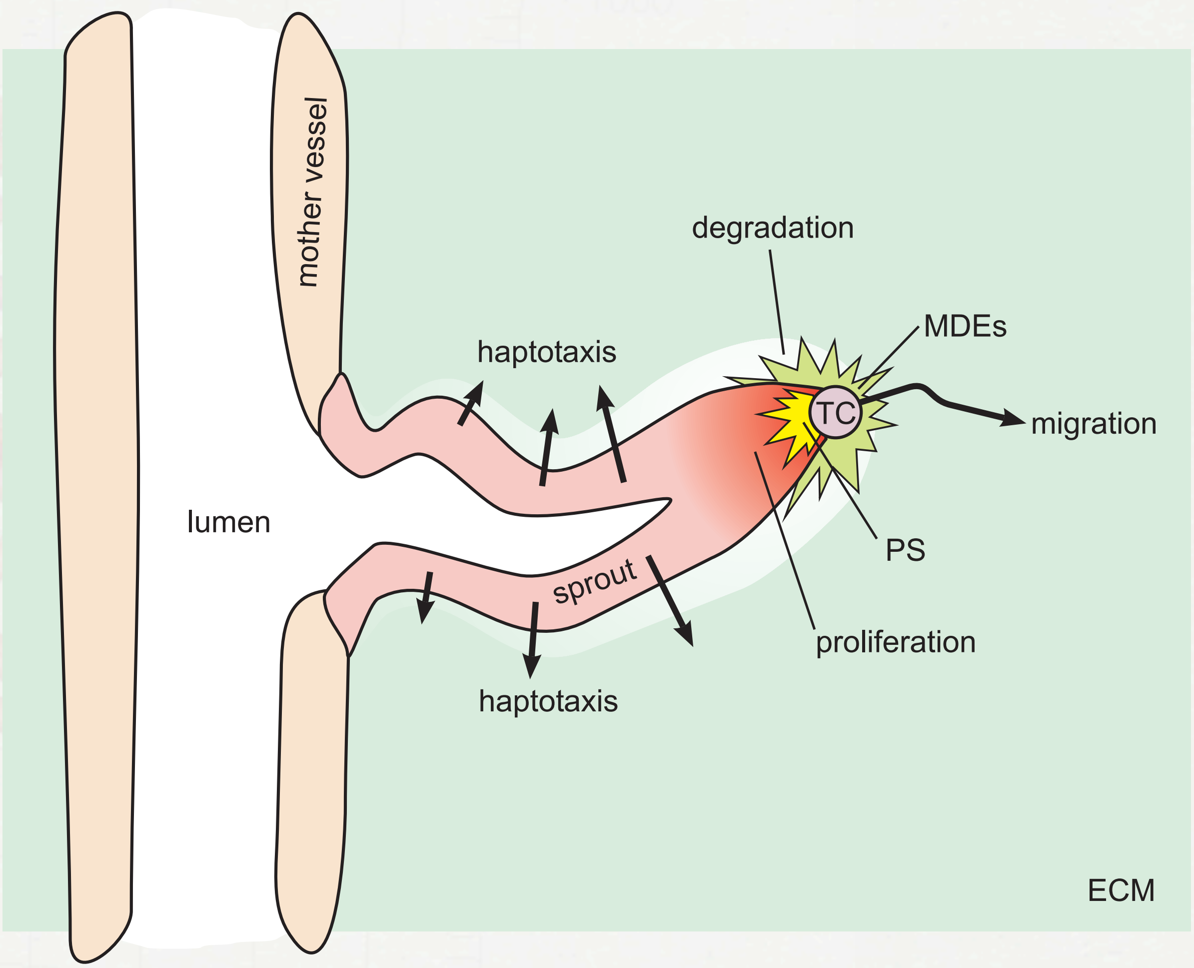
$$\frac{\partial c_s}{\partial t} + v_{ec}\nabla c_s = c_{tot} D_s \Delta c_s + \alpha_{s,tc} c_{tc} - \beta_{s,ec} c_{ec} c_s - \gamma_s c_s$$

Fibronectin:

$$\frac{\partial c_f}{\partial t} = \begin{cases} \alpha_{f,ec} c_{ec} & \text{if } c_f < c_{f,max} \\ 0 & \text{otherwise} \end{cases} - \beta_{f,m} c_m c_f$$

Matrix Degrading Enzymes:

$$\frac{\partial c_m}{\partial t} = D_m \Delta c_m + \alpha_{m,tc} c_{tc} c_m - \gamma_m c_m$$



Lumen Formation and Maturation: Simulation

[10] Kamei et al. Endothelial tubes assemble from intracellular vacuoles *in vivo,* Nature 442, 453- 456, 2006

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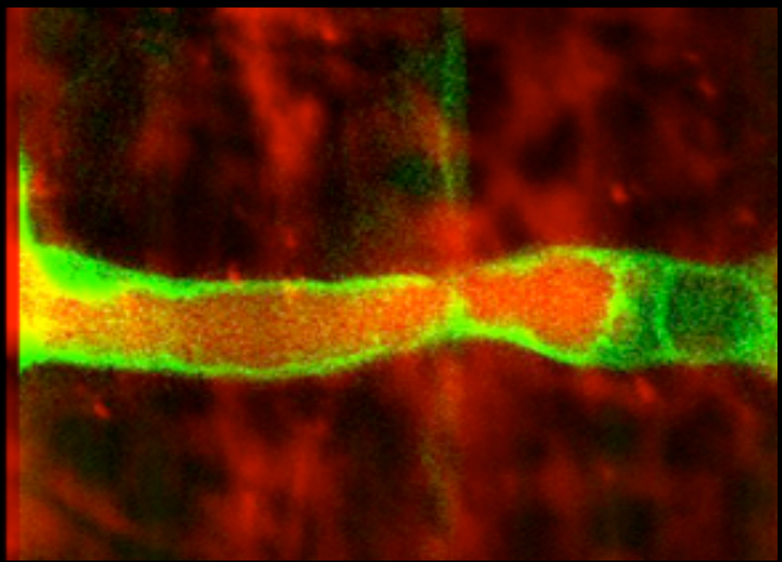

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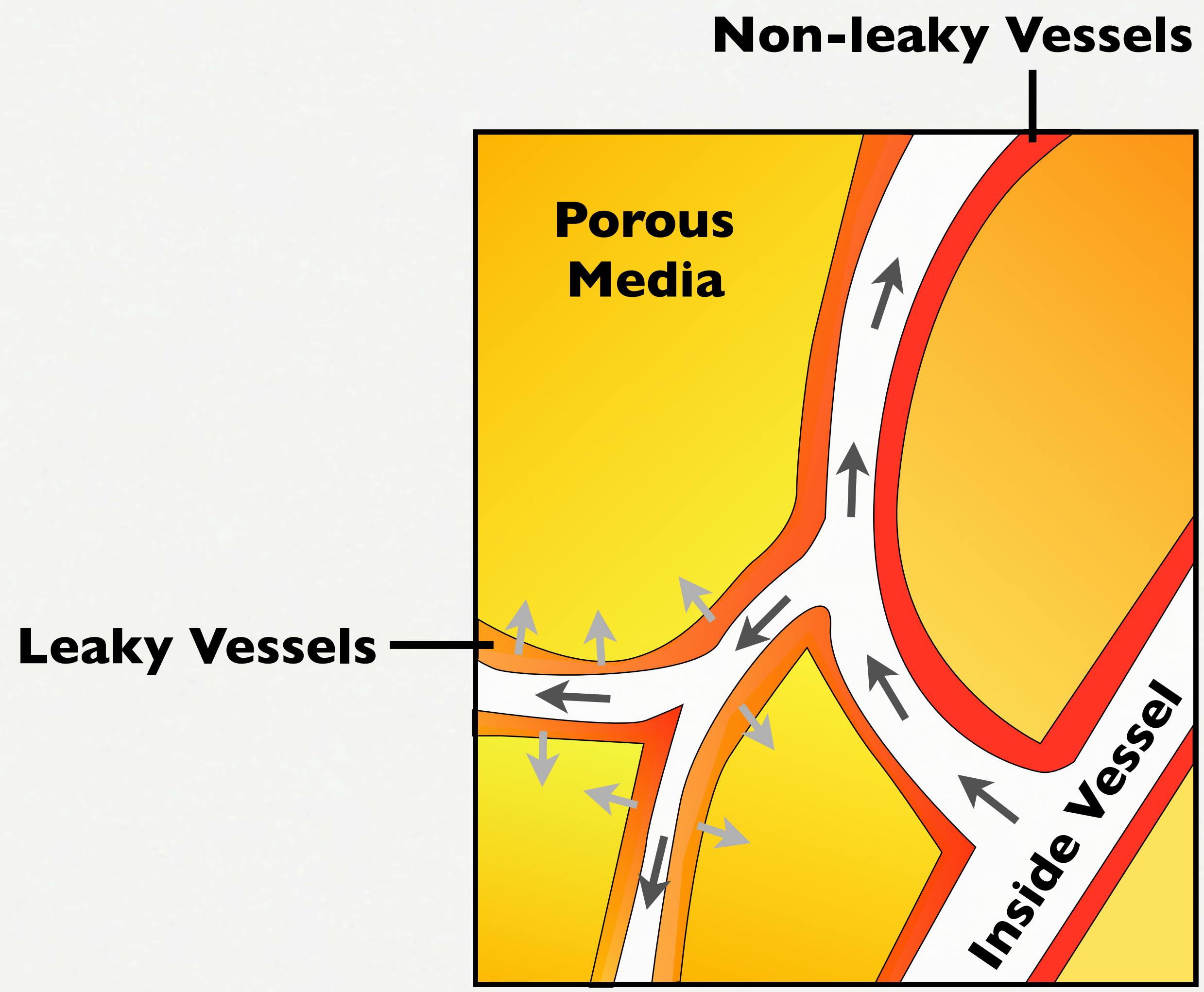
Blood Flow in Complex Geometries

Governing Equations:

- Navier-Stokes equation for incompressible flow
- Brinkmann penalization method

$$\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla)\,\mathbf{u} = -\frac{\nabla p}{\rho} + \nu \nabla^2 \mathbf{u} + \frac{1}{\eta}\chi\left(\mathbf{u}_{BD} - \mathbf{u}\right) + \frac{f}{\rho}$$

$$\nabla \cdot \mathbf{u} = 0$$



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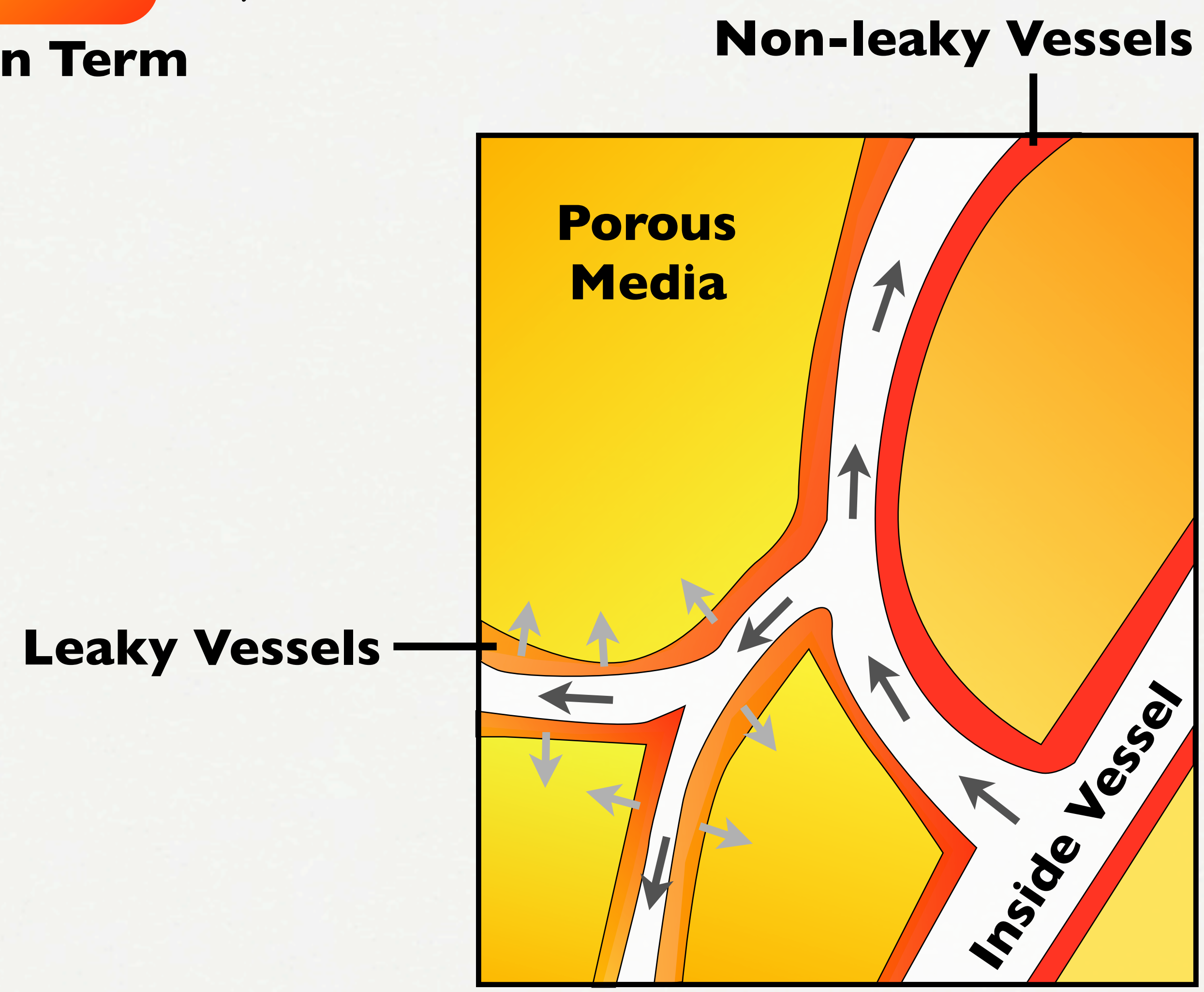
$$\nabla \cdot \mathbf{u} = 0$$

Penalization Term

Penalization Method:

- Complex geometries
  - flow in vessels
- Porous media
  - flow through leaky vessels
  - flow into tissue
- Moving boundaries
  - flow in growing vessel network



Blood Flow in Complex Geometries: Simulation

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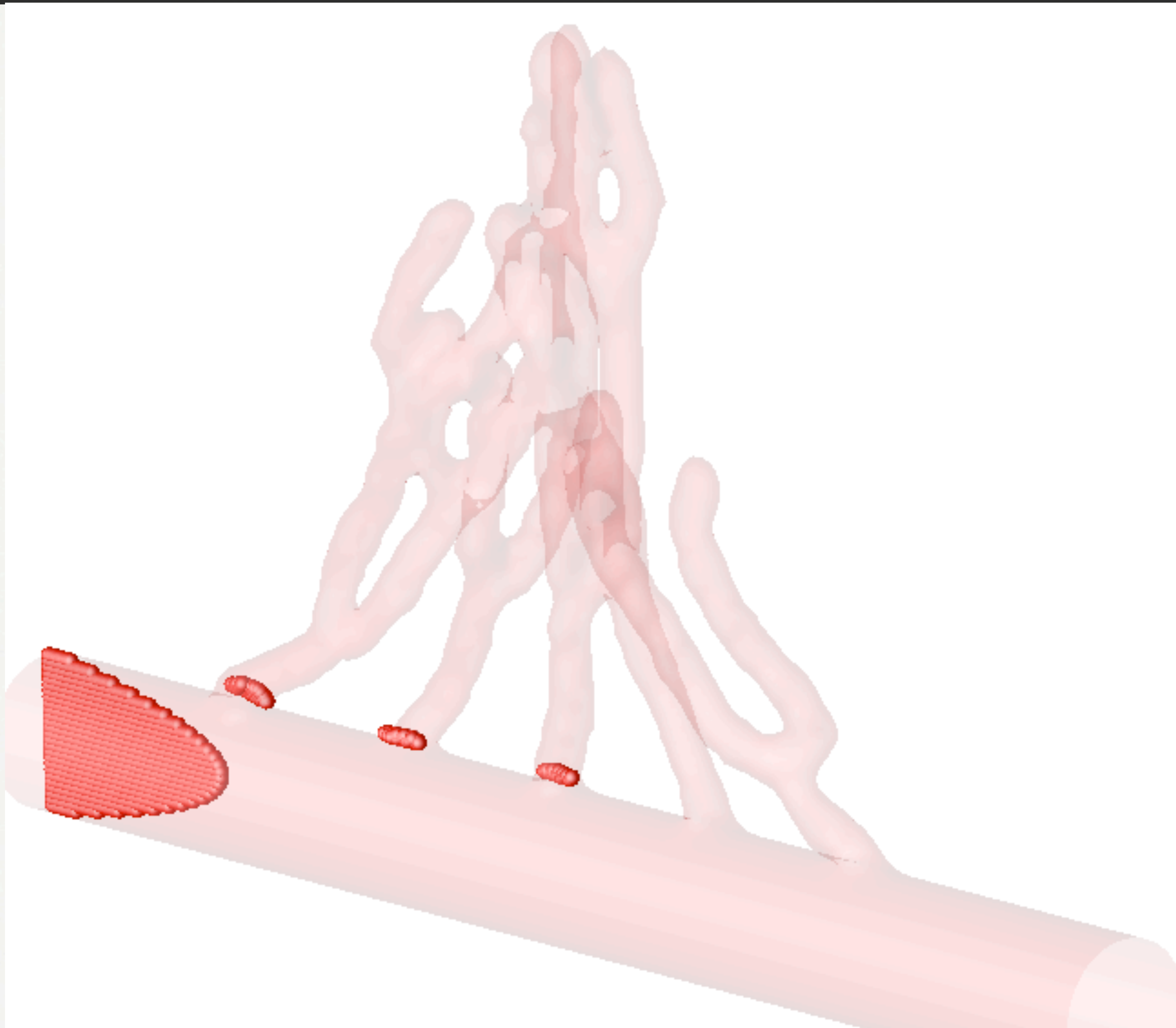
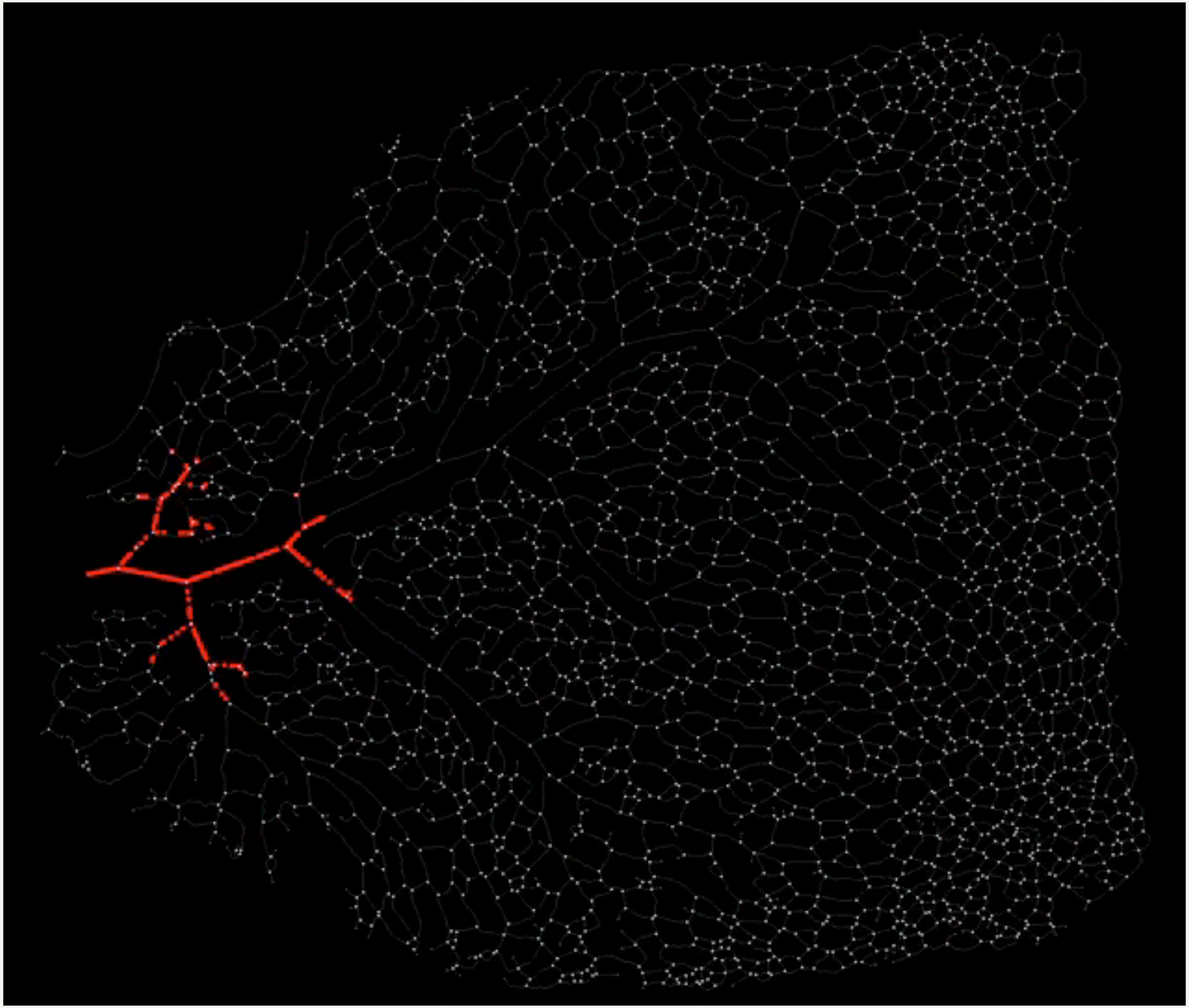
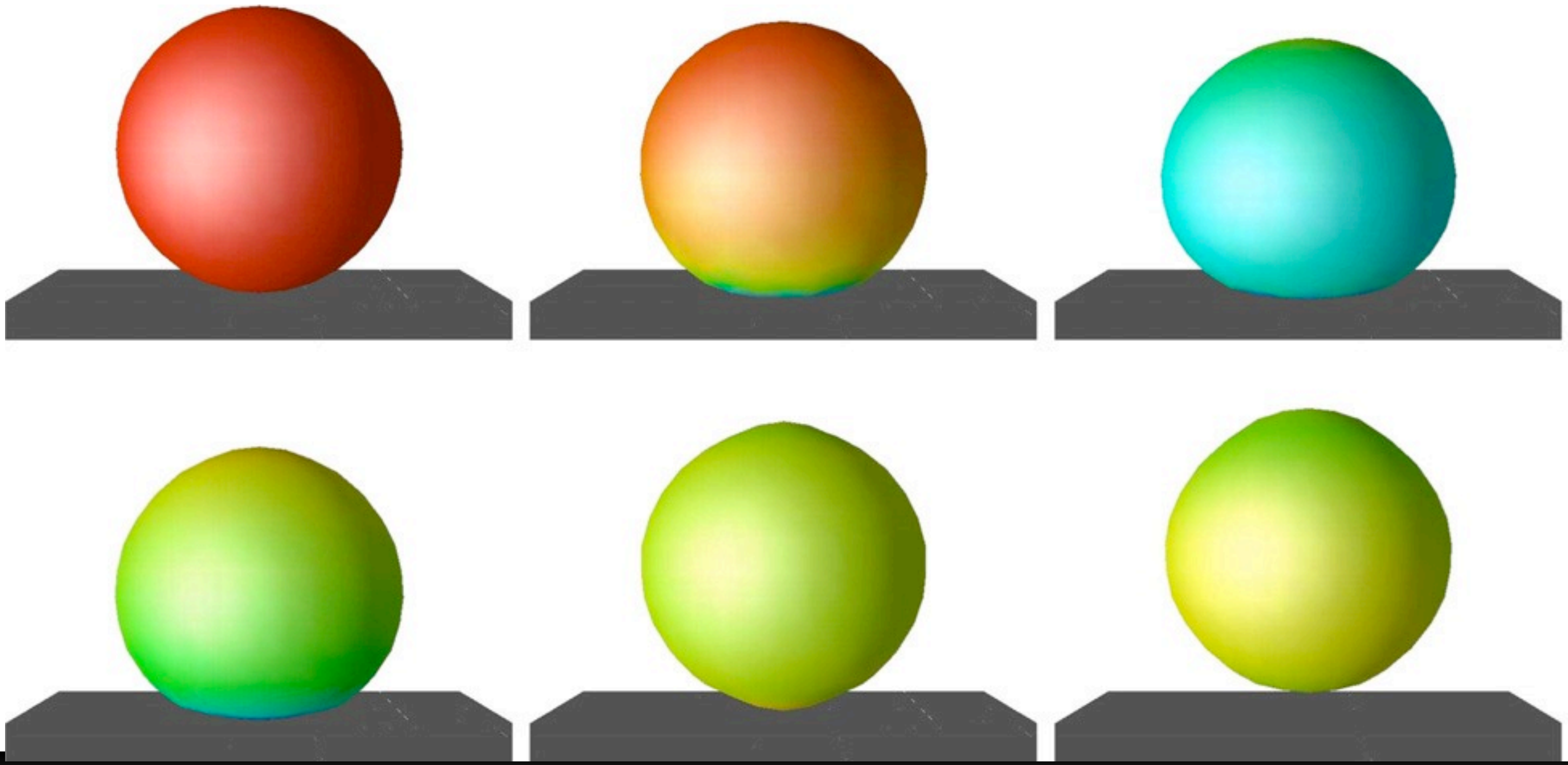


“Blood Flow” in Image Extracted Networks





PARTICLES AND SOLIDS

Governing Equations

Lagrangian Formulation

Isothermal Compressible Viscous Fluid

Continuity equation

$$\frac{D\rho_l}{Dt} = -\rho_l \nabla \cdot u_l$$

Momentum equation

$$\rho_l \frac{Du_l}{Dt} = -\nabla p_l + \nabla \tau_l$$

Constitutive model

$$p_l = RT_0 \rho_l$$

$$\tau_{l,ij} = \mu \left(\frac{\partial u_{l,i}}{\partial x_j} - \frac{\partial u_{l,i}}{\partial x_j} - \frac{2}{3}\delta_{i,j} \frac{\partial u_{l,k}}{\partial x_k} \right)$$

Elastic Solid

$$\frac{D\rho_s}{Dt} = -\rho_s \nabla \cdot u_s$$

$$\rho_s \frac{Du_s}{Dt} = \nabla . \sigma_s = \nabla . \left(-p_s I + S\right)$$

Linear

$$p_s = c_0^2 \left(\rho_s - \rho_0\right)$$

$$\frac{DS}{Dt} = 2\mu \left(\dot{\epsilon} - \tfrac{1}{3}\delta_{ij} \dot{\epsilon}_{ij} \right)$$

$$\dot{\epsilon} = \tfrac{1}{2}\left(\nabla u + (\nabla u)^T\right)$$

Nonlinear

$$\sigma_s = f(F)$$

$$\frac{DF}{Dt} = \frac{\partial u}{\partial x} F$$

Particle Equations - Fluid

Set of ODEs

Isothermal Compressible Viscous Fluid

$$\frac{dx_p}{dt} = u_p$$

Equation of motion

$$\frac{d\rho_p}{dt} = -\rho_p \langle \nabla \cdot u \rangle_p$$

Continuity equation

$$\rho_p \frac{du_p}{dt} = -\langle \nabla p \rangle_p + \langle \nabla \tau \rangle_p$$

Momentum equation

$$p_p = RT_0 \rho_p$$

$$\tau_{ij,p} = \mu \left(\left\langle \frac{\partial u_i}{\partial x_j} \right\rangle_p - \left\langle \frac{\partial u_i}{\partial x_j} \right\rangle_p - \frac{2}{3} \delta_{i,j} \left\langle \frac{\partial u_k}{\partial x_k} \right\rangle_p \right)$$

Constitutive model

$\langle \; \rangle_p$:Approximation on particle p

Particle Equations - Solid

Set of ODEs

Elastic Solid

Equation of motion

$$\frac{dx_p}{dt} = u_p$$

Continuity equation

$$\frac{d\rho_p}{dt} = -\rho_p \langle \nabla \cdot u \rangle_p$$

Momentum equation

$$\rho_p \frac{du_p}{dt} = \langle \nabla . \sigma \rangle_p = -\langle \nabla p \rangle_p + \langle \nabla . S \rangle_p$$

Constitutive model

Linear

$$p_p = c_0^2 (\rho_p - \rho_0)$$

$$\frac{dS_p}{dt} = 2\mu \left(\dot{\epsilon}_p - \tfrac{1}{3} \delta_{ij} \dot{\epsilon}_{ij,p} \right)$$

$$\dot{\epsilon}_p = \tfrac{1}{2} \left(\langle \nabla u \rangle_p + \langle \nabla u \rangle_p^T \right)$$

Nonlinear

$$\sigma_p = f(F_p)$$

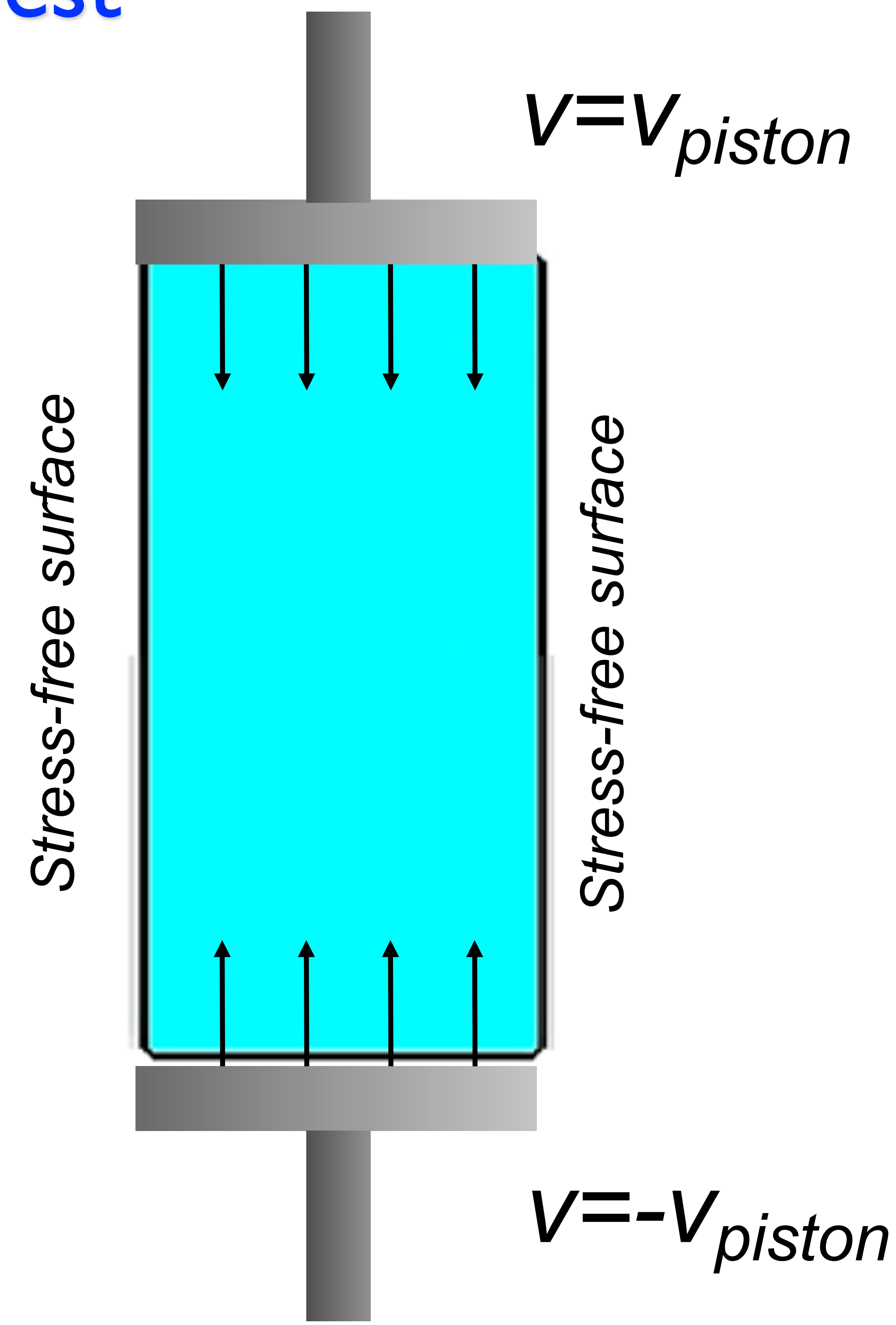
$$\frac{dF_p}{dt} = \left\langle \frac{\partial u}{\partial x} \right\rangle_p F_p$$

$\langle \; \rangle_p$:Approximation on particle p

Particle Simulation of Elastic Solid

Plane Strain Compression Test

- Pistons move with constant velocity
- Elastic solid fixed to the pistons
- Highly dynamic deformation of large extent



Particle Simulation of Elastic Solid

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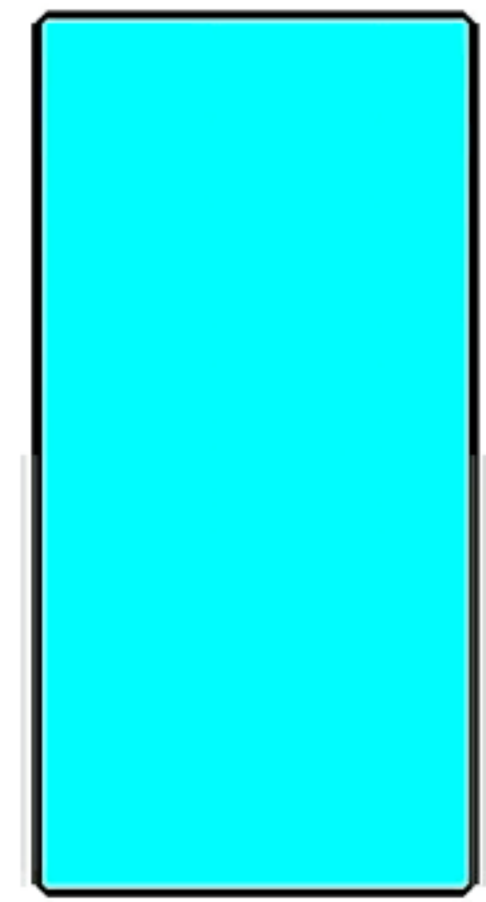


Plane Strain Compression Test

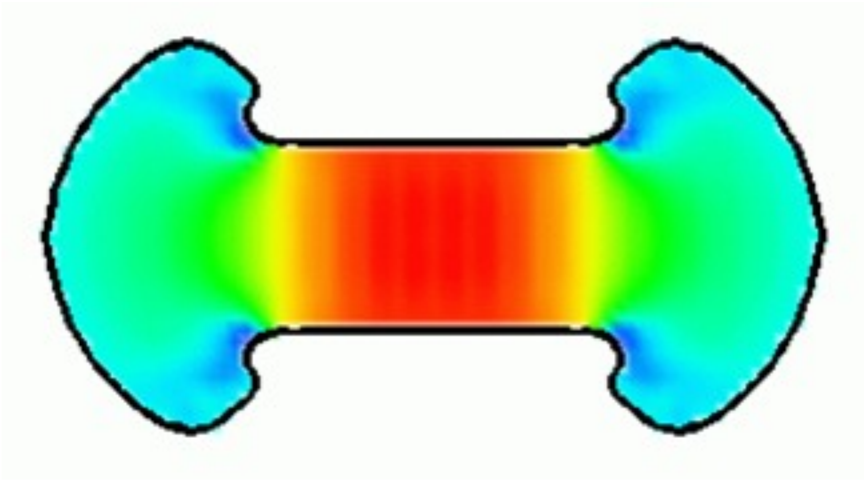
Redistributed Particle solution

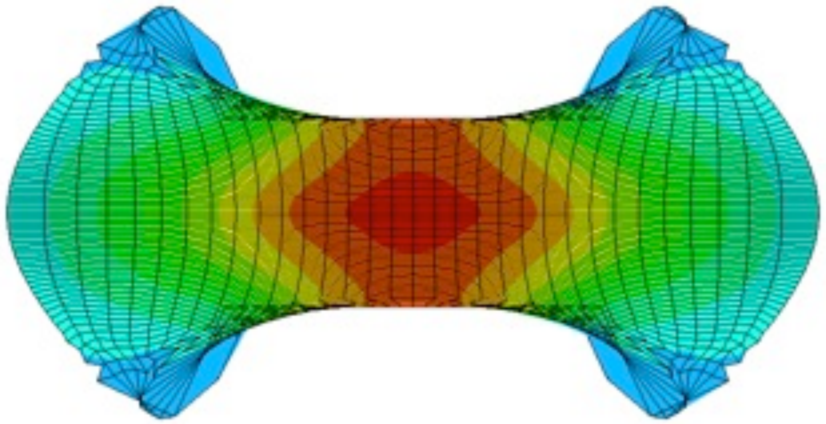
FEM solution (ABAQUS 6.4/ Explicit)

Linear Elasticity

Young's Modulus =100
Poisson ratio=0.49 ~2000

particles/nodes



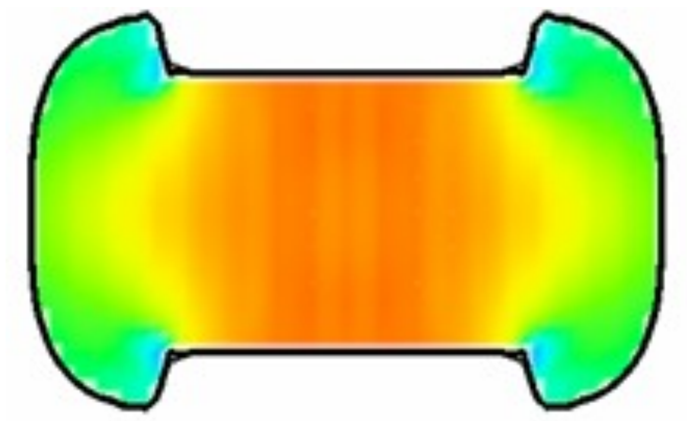


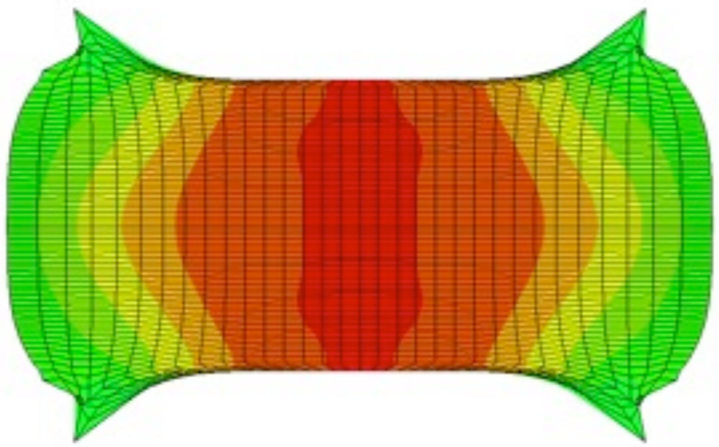
Nonlinear Elasticity

Hyperelastic Material

C_{10}=2.2, D=0.001

~2000 particles/nodes



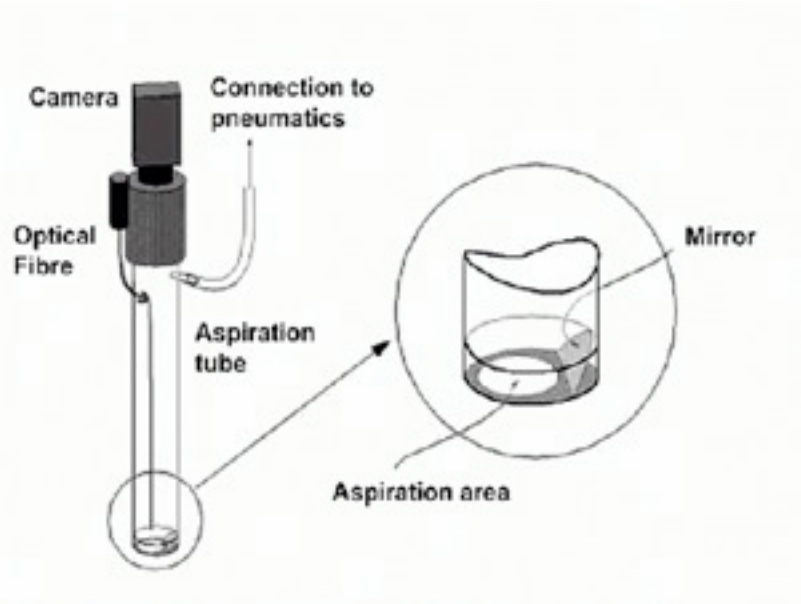


S.E. Hieber and P. Koumoutsakos A Lagrangian particle method for the simulation of linear and nonlinear elastic models of soft tissue. *al., J. Comp. Physics, accepted*

Simulation of Liver Tissue

Aspiration Test

- Experiment to determine constitutive models for biological tissue
- A vacuum created in the aspiration devices causes the tissue to form a bubble
- The height of the tissue bubble determines the parameters of the nonlinear model

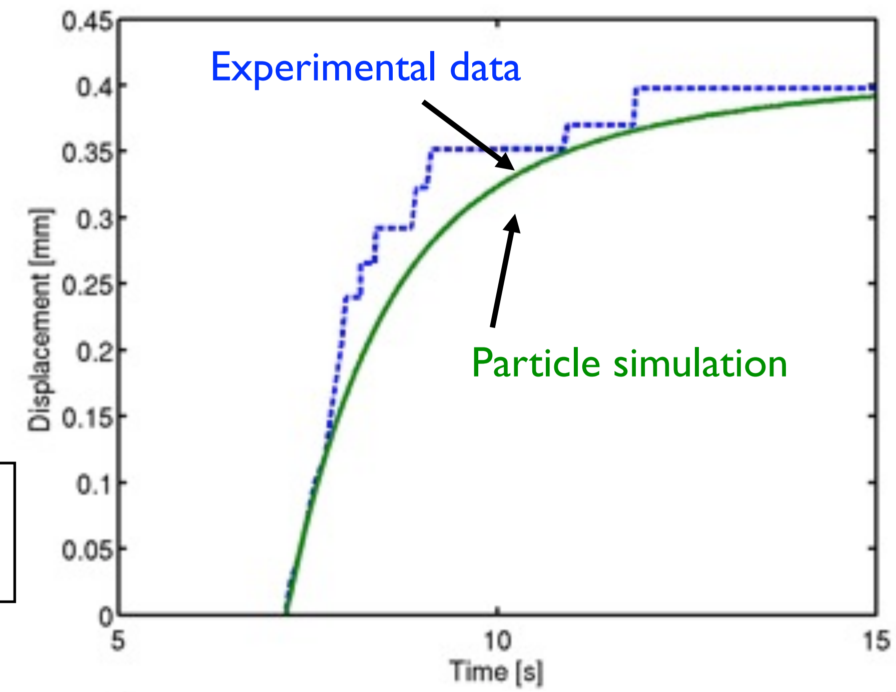


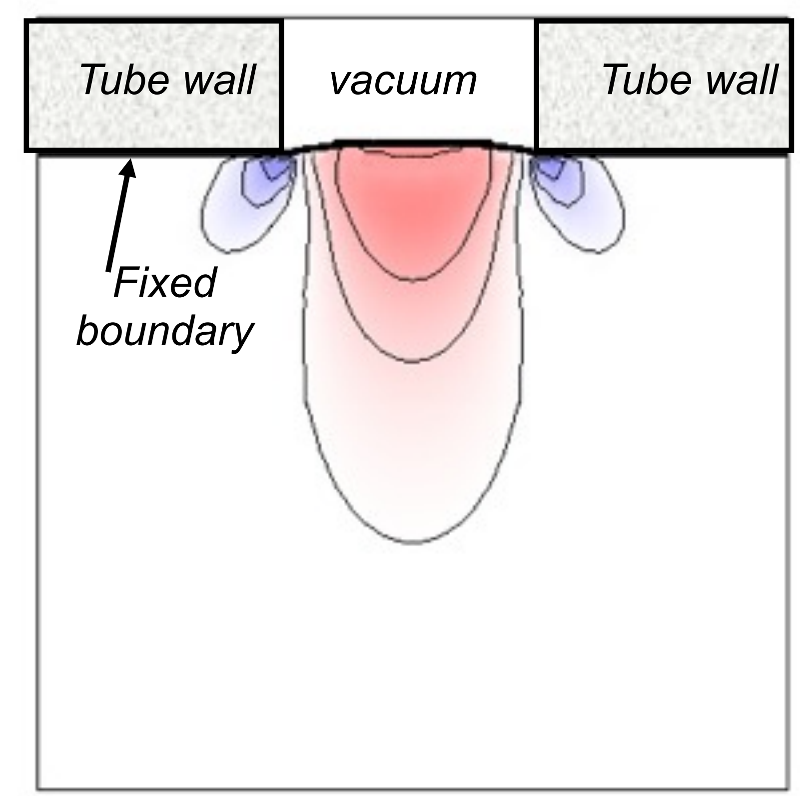
Nava et al., Technology and Health Care,2004, vol.12,269-280

Particle Simulation of Aspiration Test

- **Experiment and nonlinear model from Nava *et al.* (2004)**
- **3D Particle simulation using ~10^5 particles**
- **Good agreement with experimental results in the tissue displacement**

Tissue Displacement





Stretch distribution

Experimental Data and Model from *Nava et al., Technology and Health Care,2004, vol 12,269-280*


Bergdorf
Walther
Rossinelli
Chatelain
Hedjazialhosseini