Angiogenesis Revisited: Cell Biology and Biophysics During Real and Simulated Vascular Growth and Remodeling

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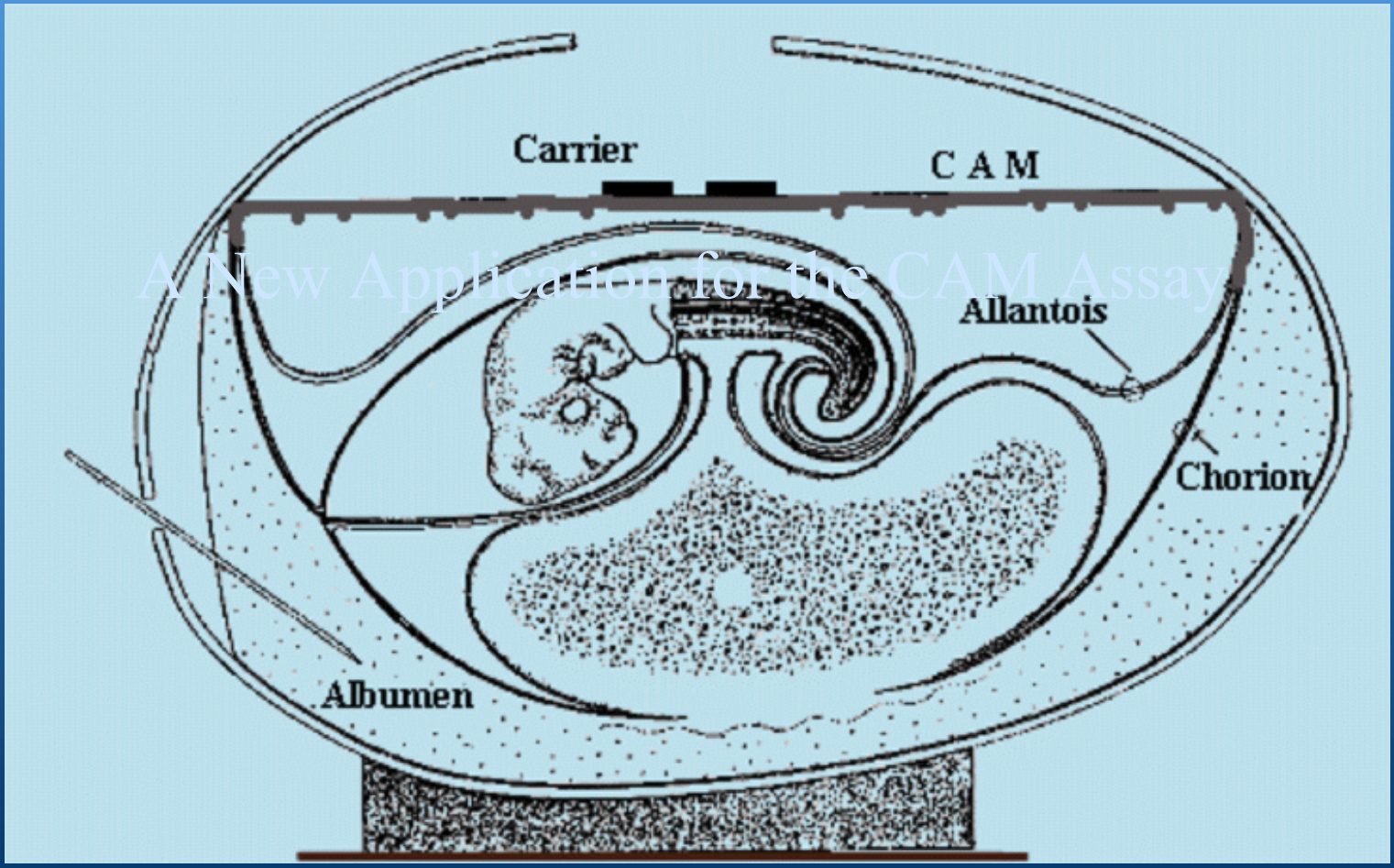
Angiogenesis Research in the Chorio-Allantoic Membrane



Rationale - Why use the CAM ?

- In vivo imaging of a perfused vascular bed.
- Permanently growing and remodeling.
- Assay for angiogenesis-modulating molecules.
- Culture of organ rudiments, xenografts, or biomaterials is well established.

In vivo Imaging of CAM Perfusion

For movies of CAM perfusion and vascular remodeling, visit the website of
Dr. Valentin Djonov, Bern (Switzerland)

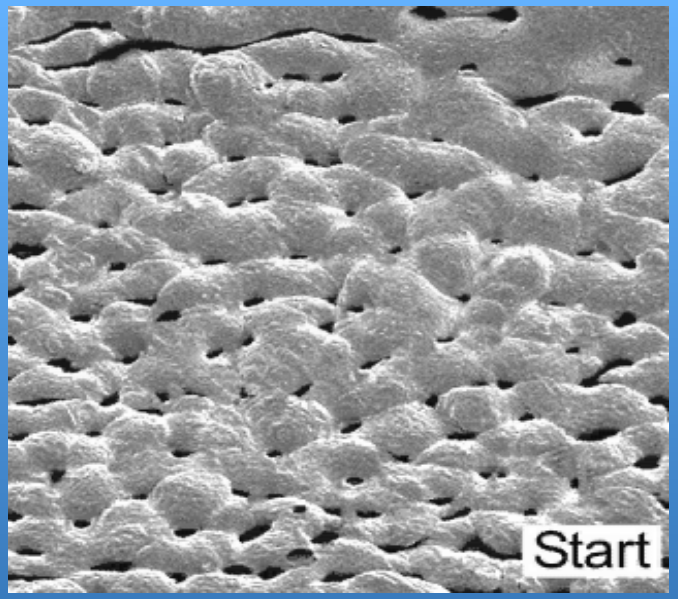
http://anatom1.unibe.ch/angio/

Djonov/Galli/Burri, Anat Embryol 2000

Influences on Angiogensis in the CAM

Growth Factors or Hemodynamics?

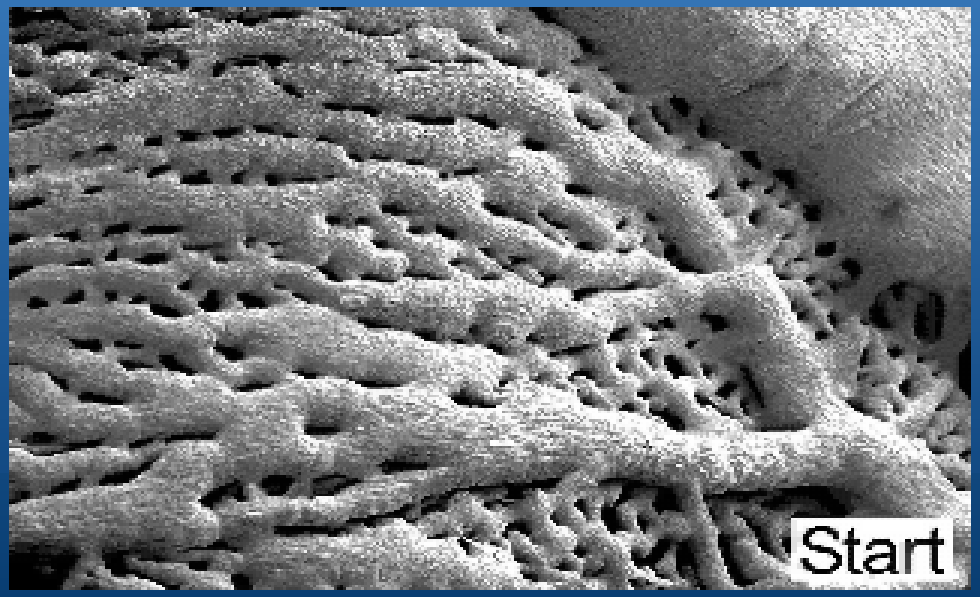
- Hemodynamics
- PDGF-B
- VEGF-A

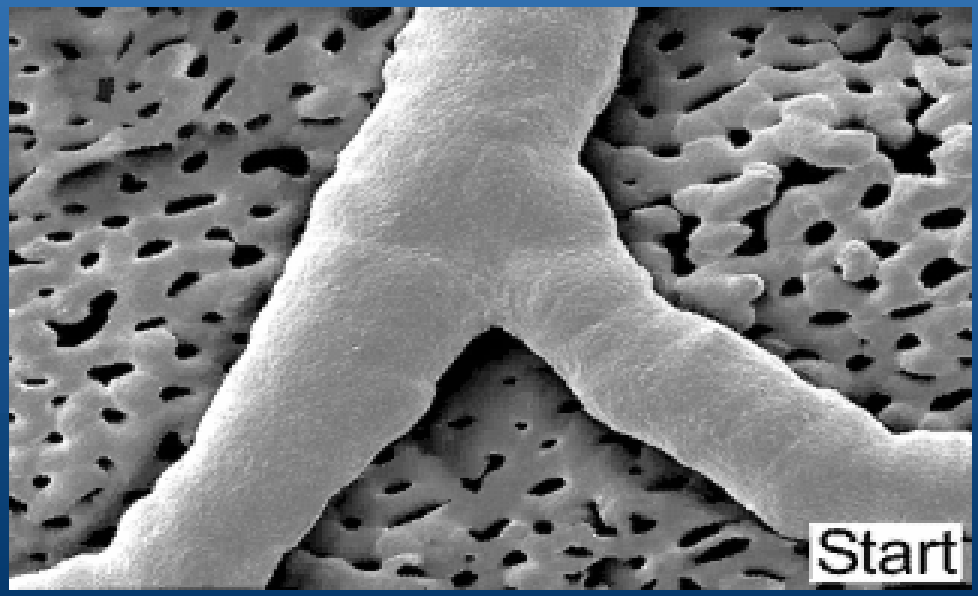


Non-Sprouting Angiogenesis

By means of INTUSSUSCEPTION
(Djonov/Kurz/Burri, Dev Dynam 2002)

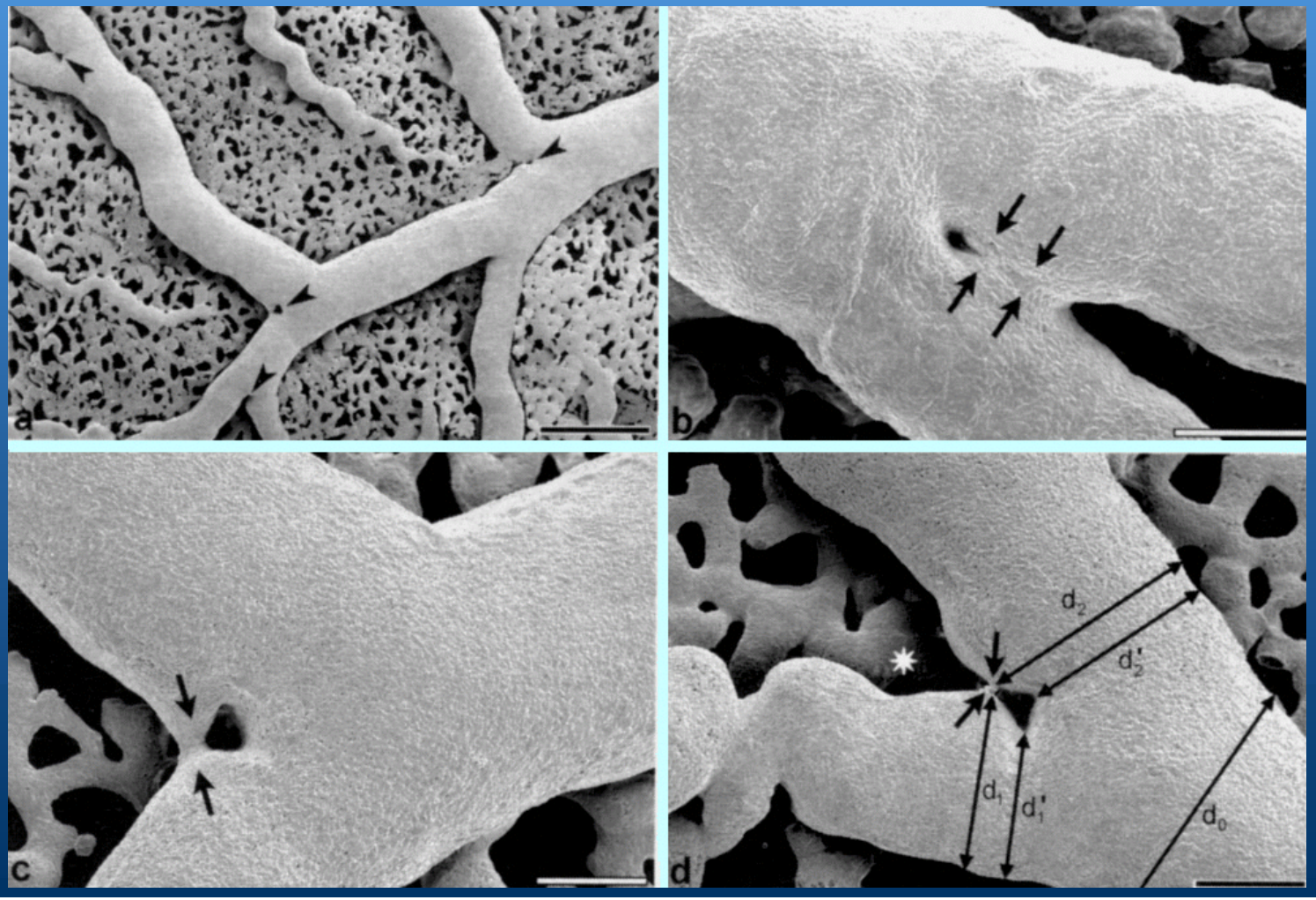
http://anatom1.unibe.ch/nf-djonov/iasim.htm





Non-Sprouting Angiogenesis and Bifurcation Remodeling in the CAM

(Djonov/Kurz/Burri, Dev Dynam 2002)



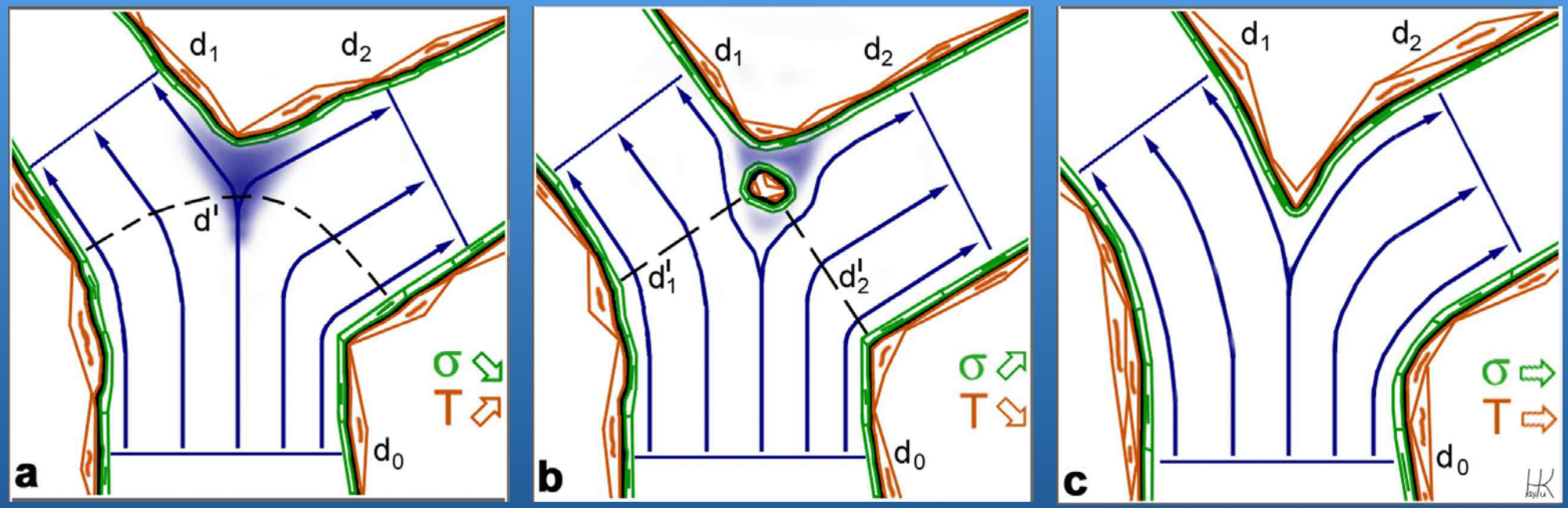
$$d_0^{\Delta} = d_1^{\Delta} + d_2^{\Delta}$$

Theory Predicts
$\Delta = 2.7 \ldots 3.0$

(Kurz & Sandau, Comm Theor Biol 1997)

Intussusceptive Bifurcation Remodeling

Kurz/Burri/Djonov (News Physiol Sci 2003)



Arteries: $\Delta = 2.4 \rightarrow 2.8$ BUT Veins: $\Delta = 3.5 \rightarrow 2.9$

Shear (σ) and Tangential Stress (T) are Essential for Optimisation.

ECs co-operate with PCs and vSCMs during Remodeling.

Desmin and αSM-Actin in the CAM

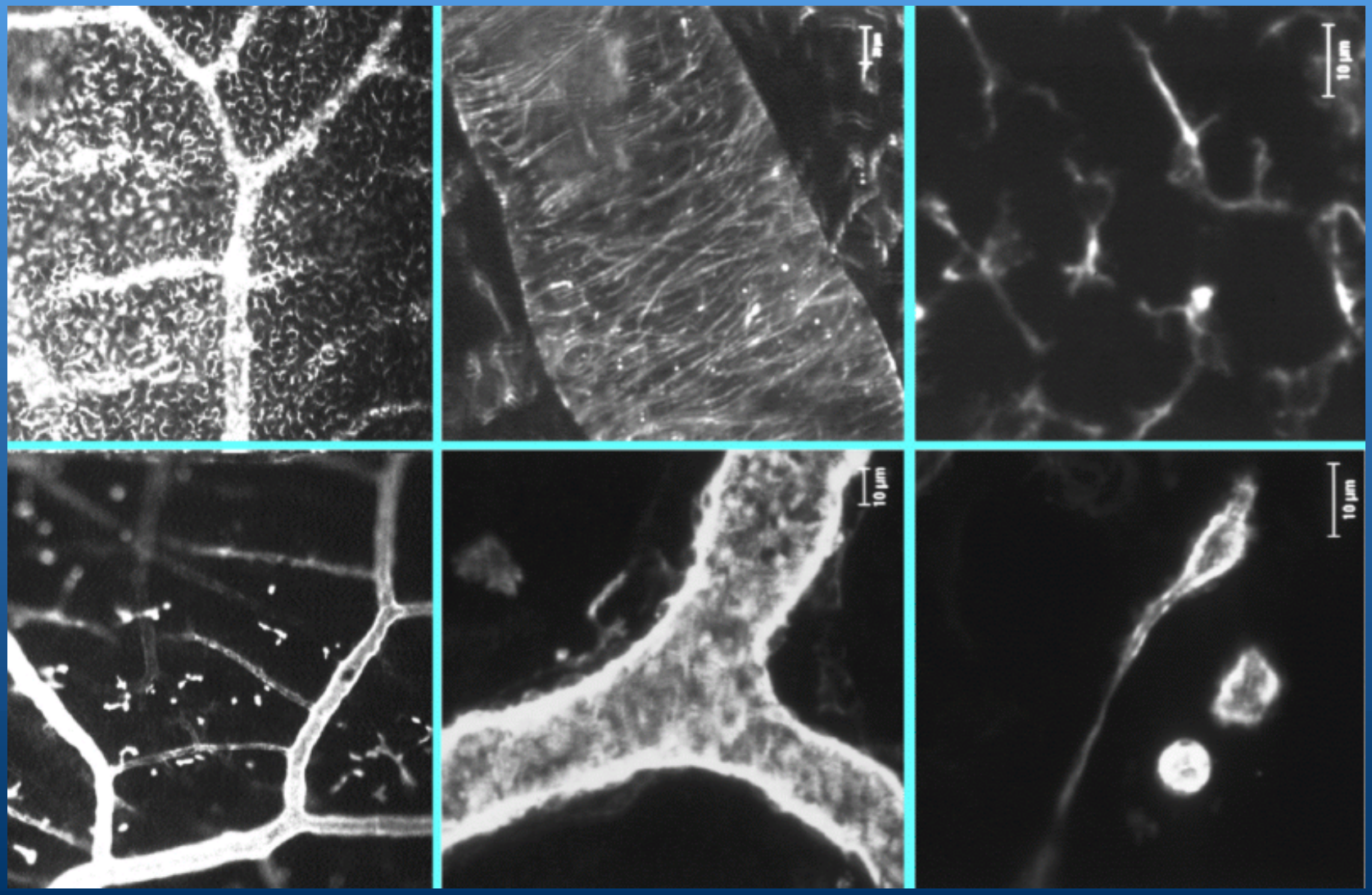
Kurz et al., Histochem Cell Biol 2002

Desmin:

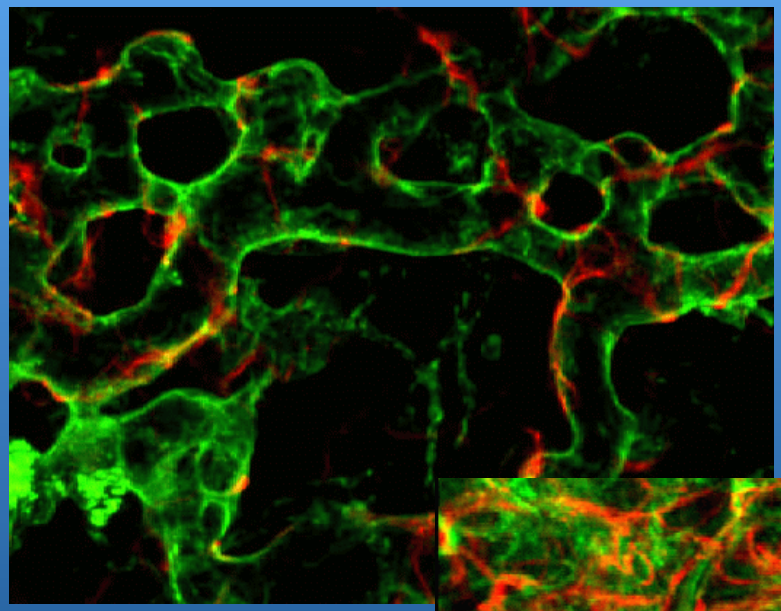
Pericytes

αSMA:

vSMC
Myofibroblasts

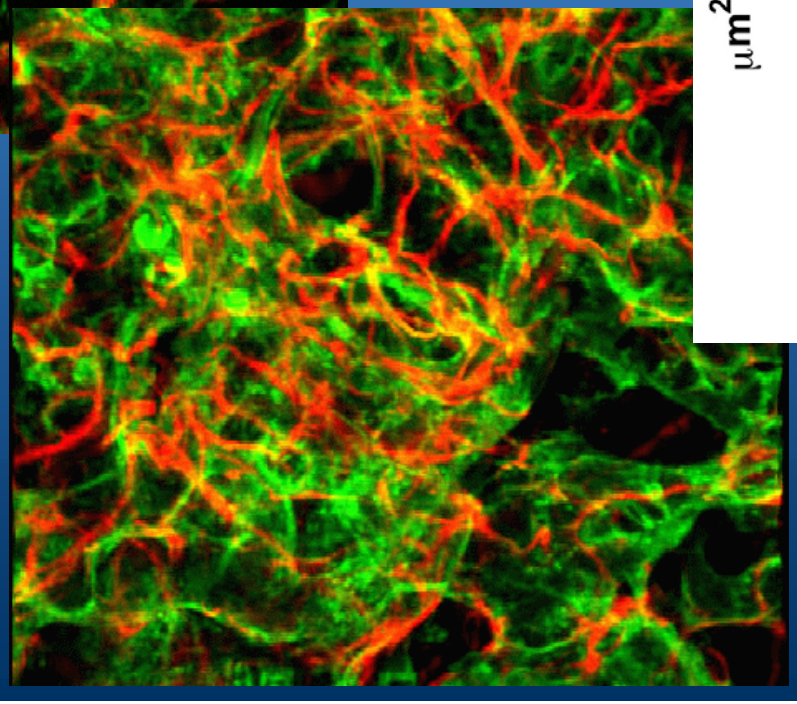


VEGF-A and CAM Remodeling



EC

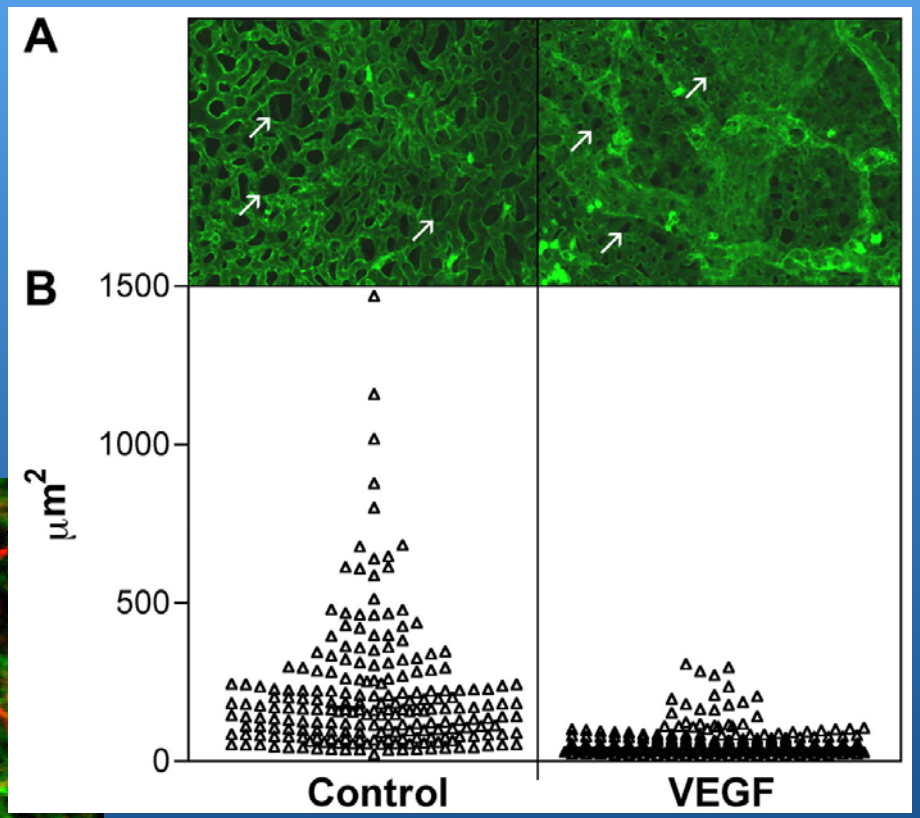
PC



Control

E13 CAM

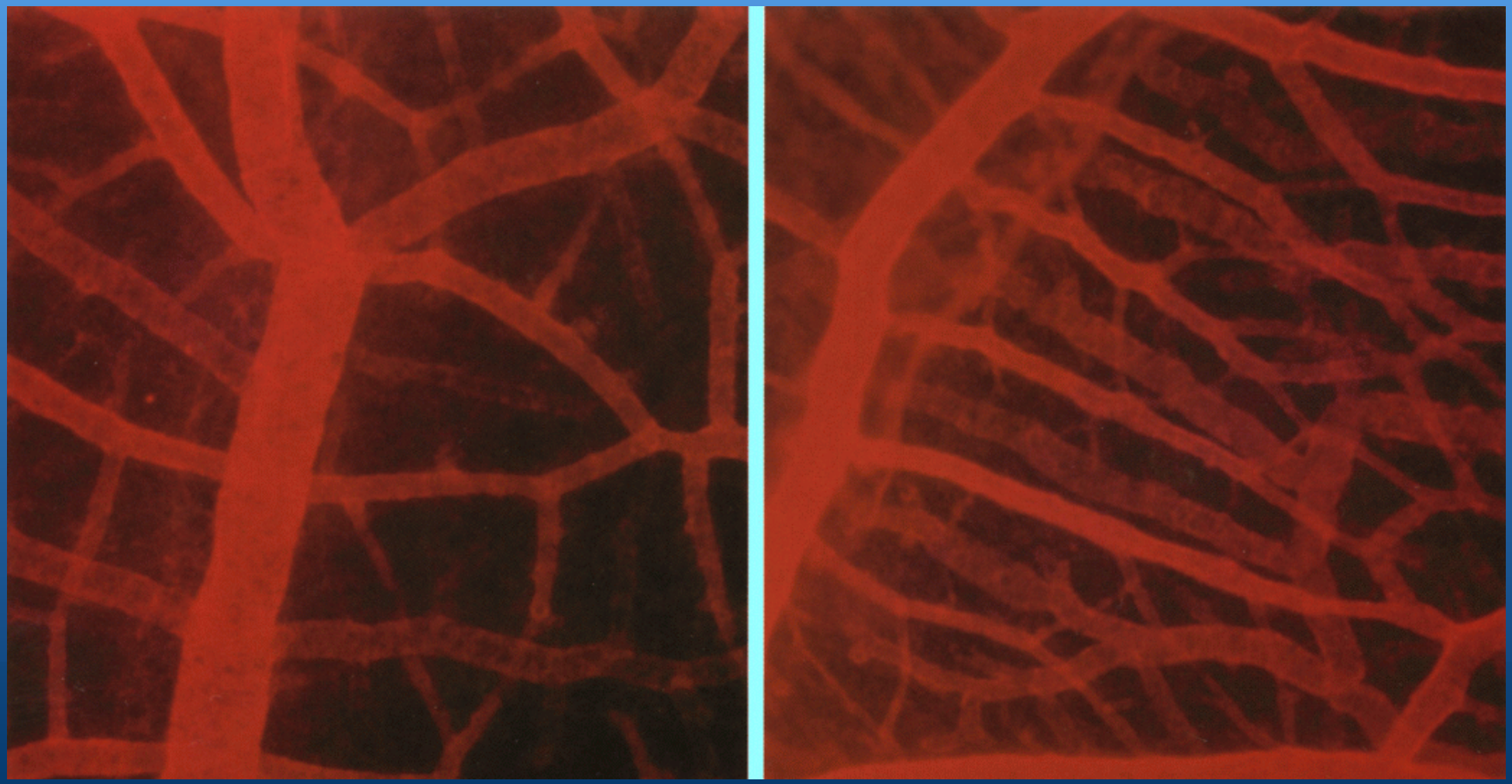
VEGF-A



Kurz et al. (Dev Dynam 1995)
Hagedorn et al. (Submitted, 2003)

PDGF-B and CAM Remodeling

(Oh et al., Histochem Cell Biol 1998)



Control E15 SMA-Cy3 PDGF-BB E15

Results – CAM

Hemodynamics or Growth Factors ?

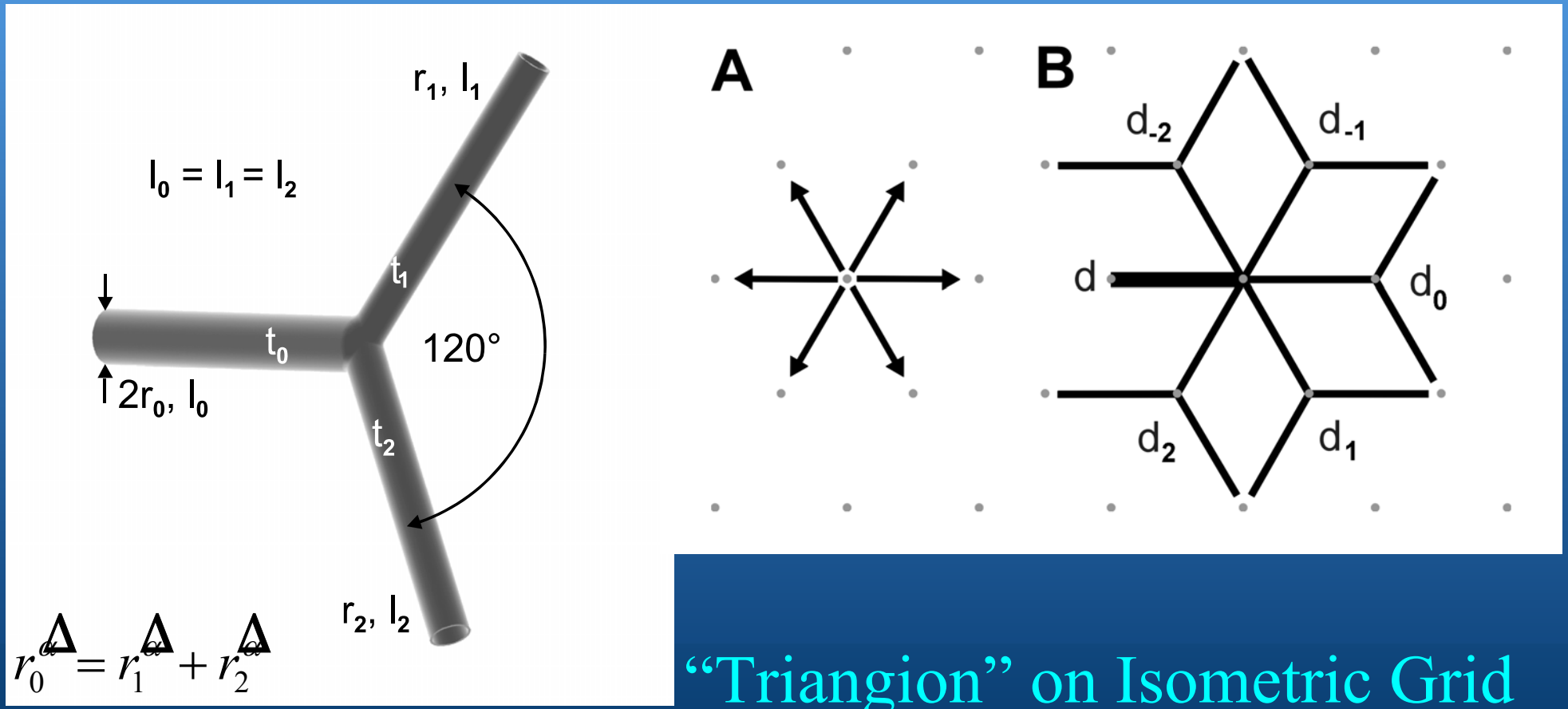
- VEGF-A and PDGF-B strongly influence angiogenesis and remodeling in the CAM.
- Hemodynamics, e.g., flow and pressure, are critical for non-sprouting angiogenesis and optimization of network ramifications.
- EC and PC /vSMC interact during non-sprouting angiogenesis, in response to physical and chemical signals

Rationale - Why Simulate ?

Sandau/Kurz, J Microsc 1994; Gödde/Kurz, Dev Dynam 2002

- Predict **local** relationships between vascular patterns and transport properties.
- Understand the **global** design of fluid transport systems.
- Assess growth / remodeling and transport in vascular therapies and bioartificial tissues.

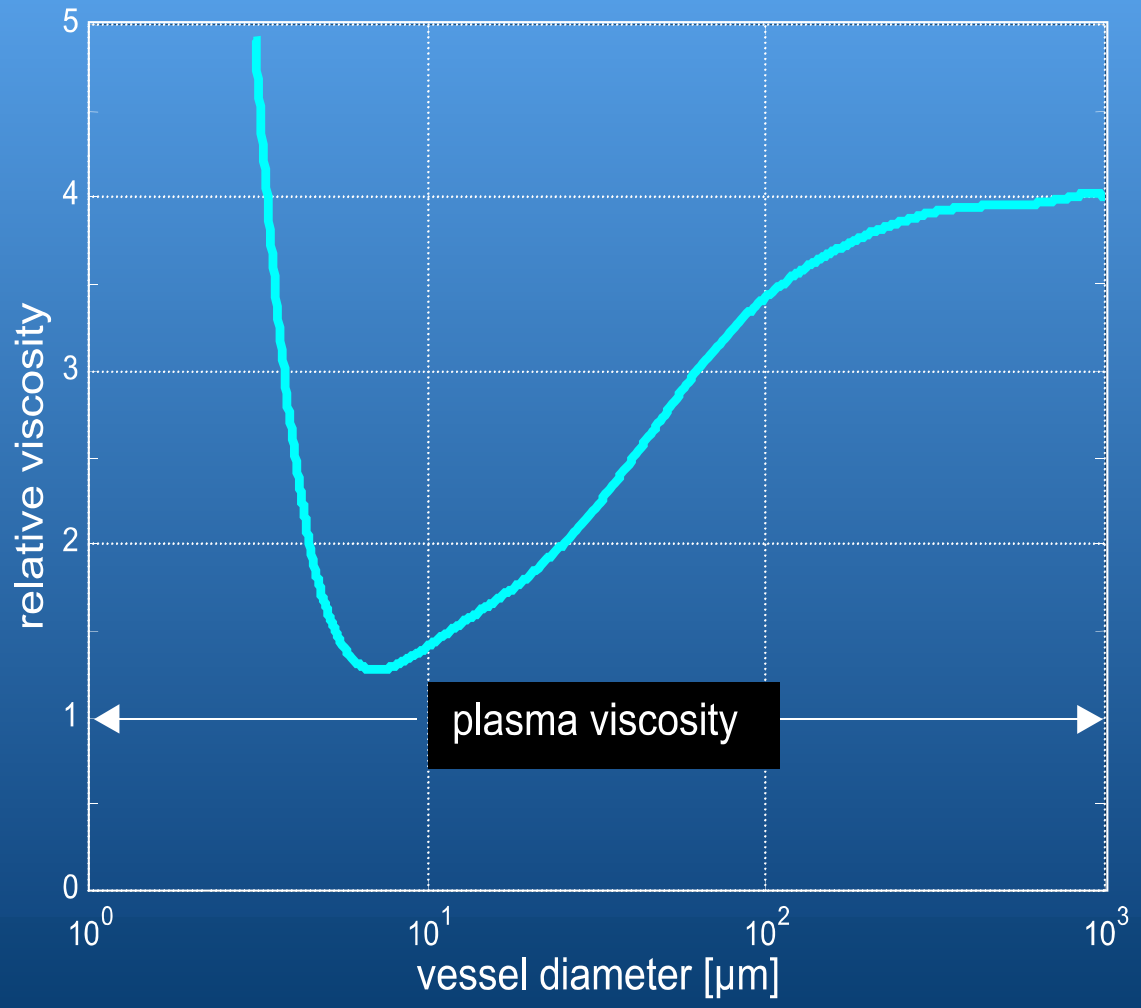
Geometric Definitions



"Triangion" on Isometric Grid

Δ: Bifurcation Exponent

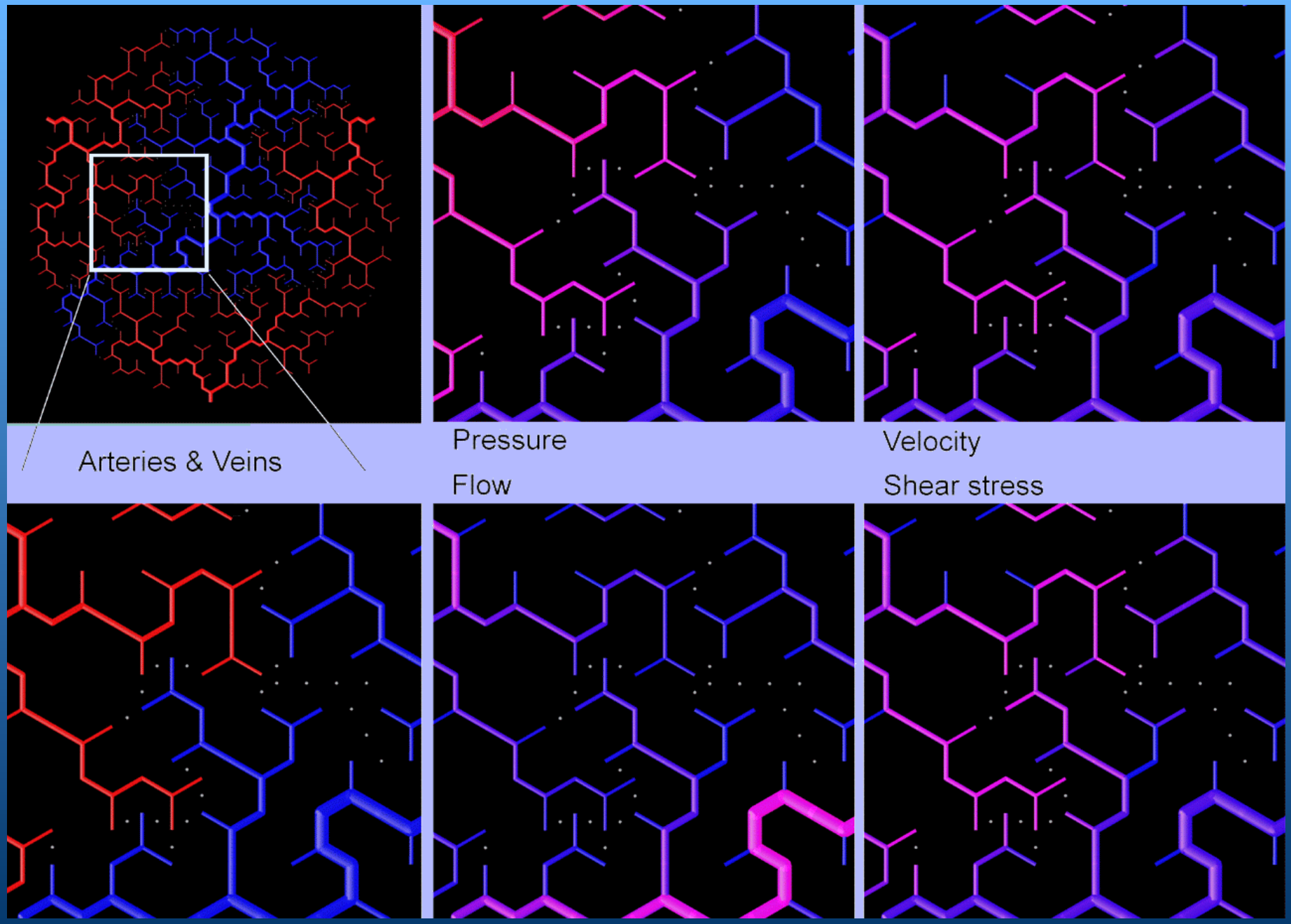
Biophysical Definitions



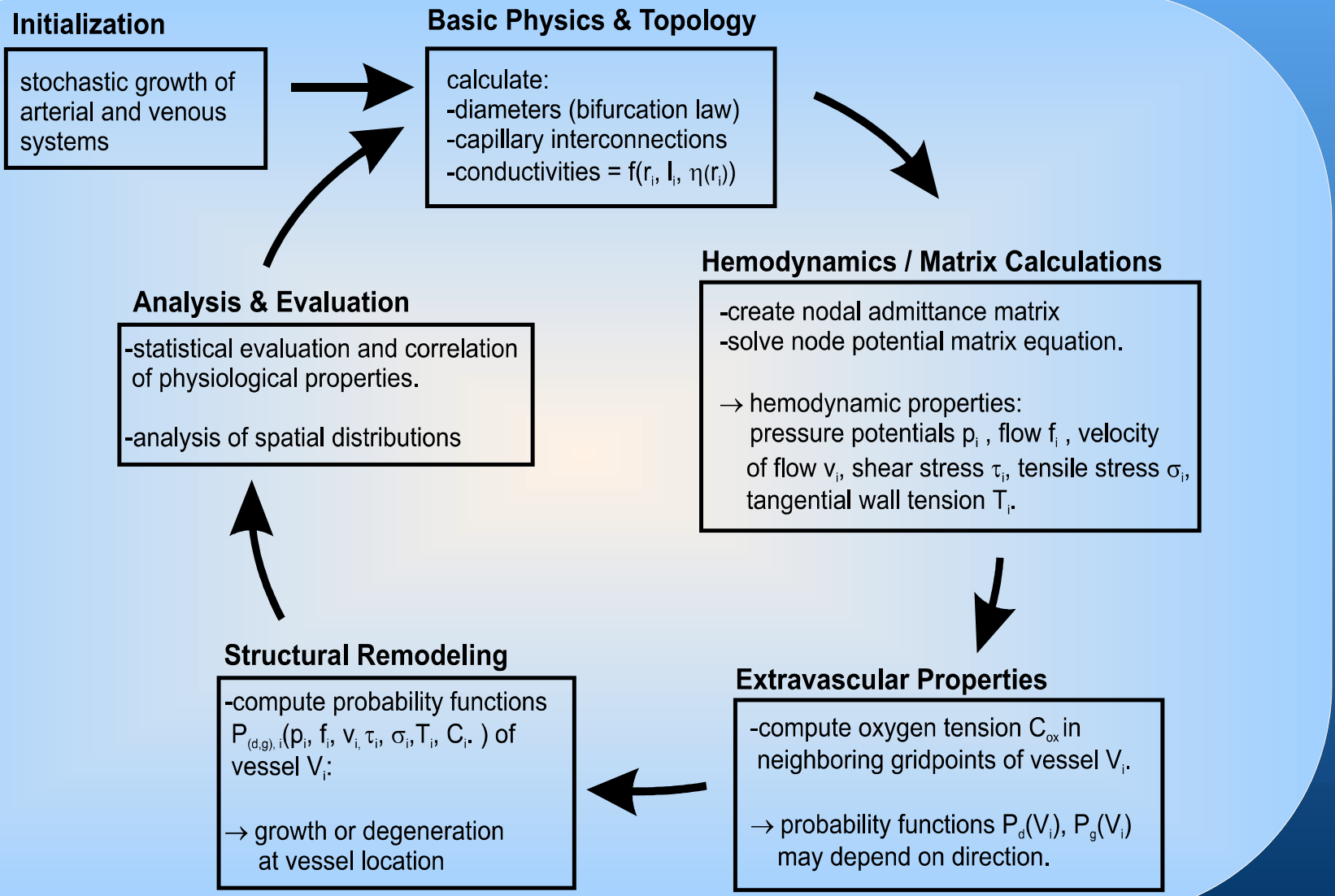
Fahraeus-Lindqvist Effect

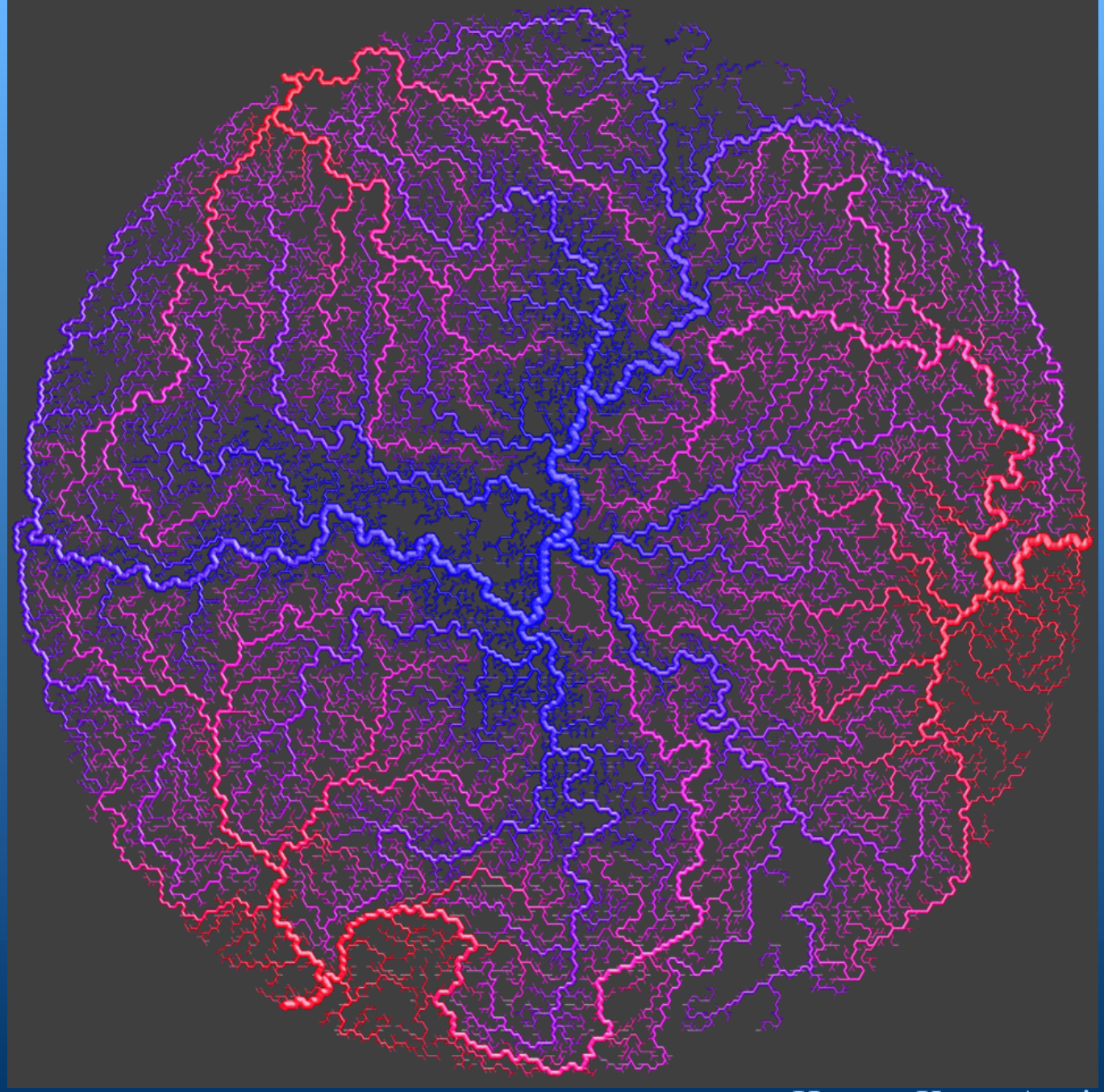
$$P_g(\tau_i) = \frac{\tau_i - \tau_{\min}}{\tau_{\max} - \tau_{\min}}$$

Growth or regression probability related to shear stress (or flow, pressure, pO_2, ...)

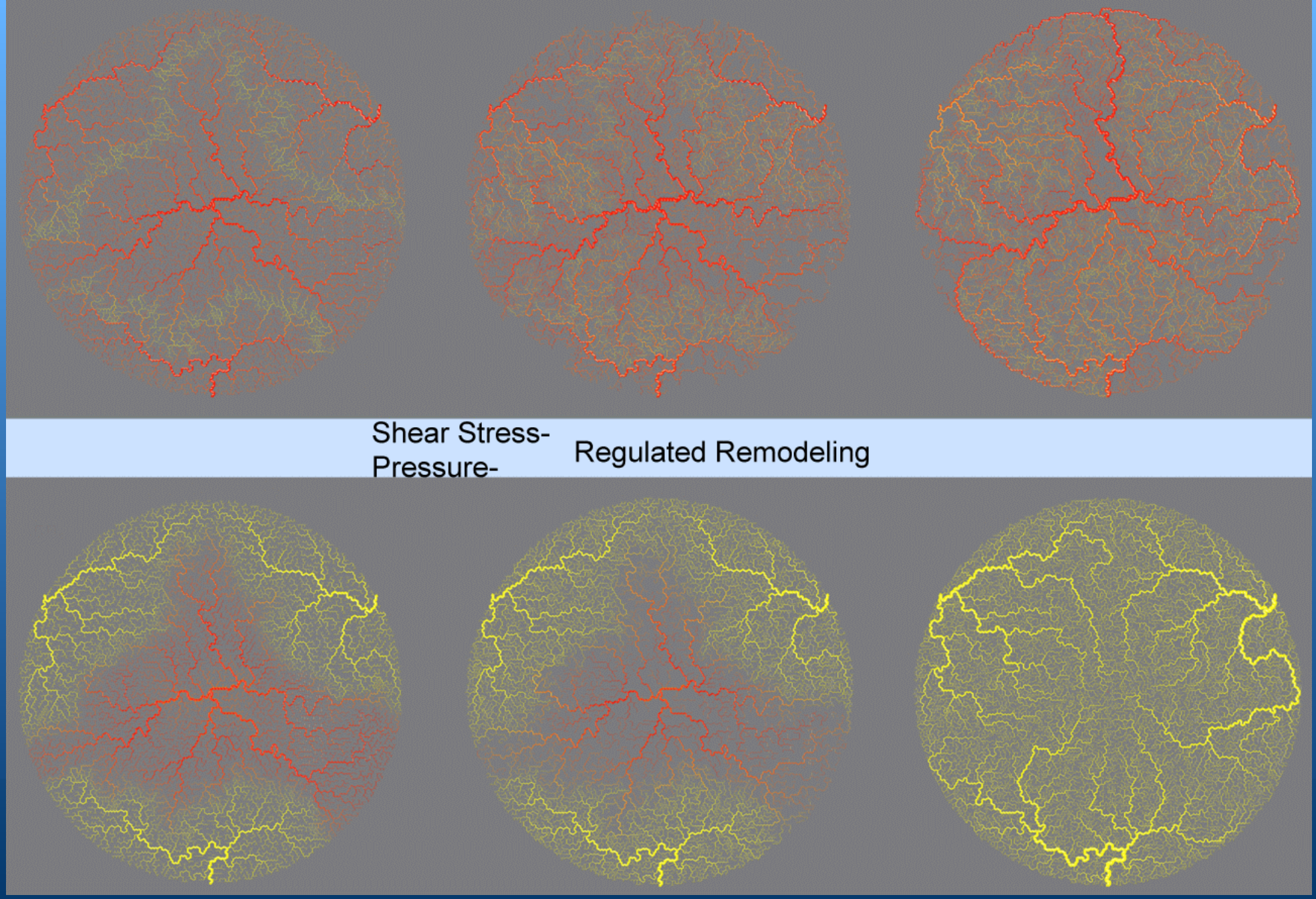

Arteries & Veins
Pressure
Flow
Velocity
Shear stress

Simulation via Iterative Processing

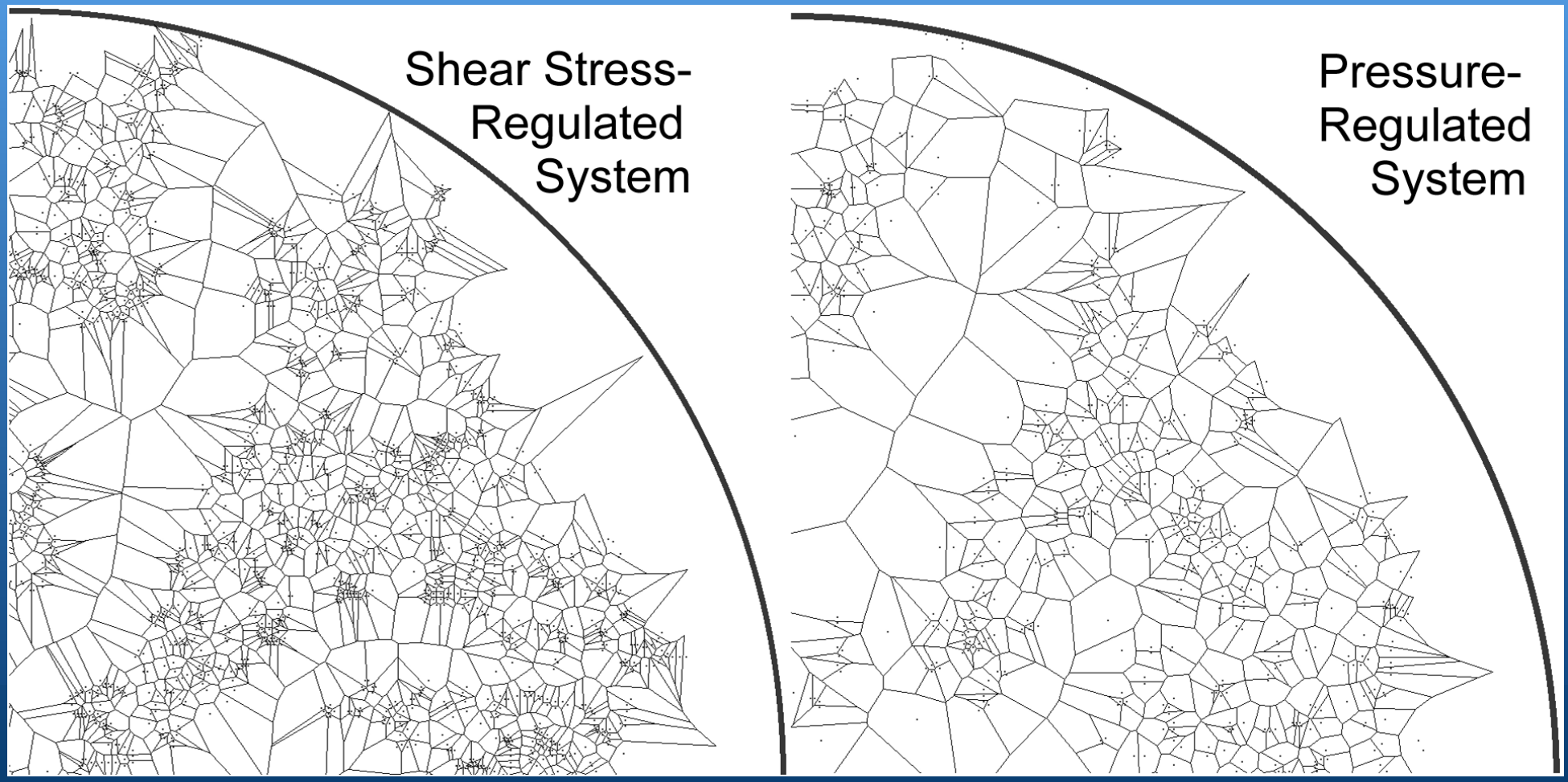




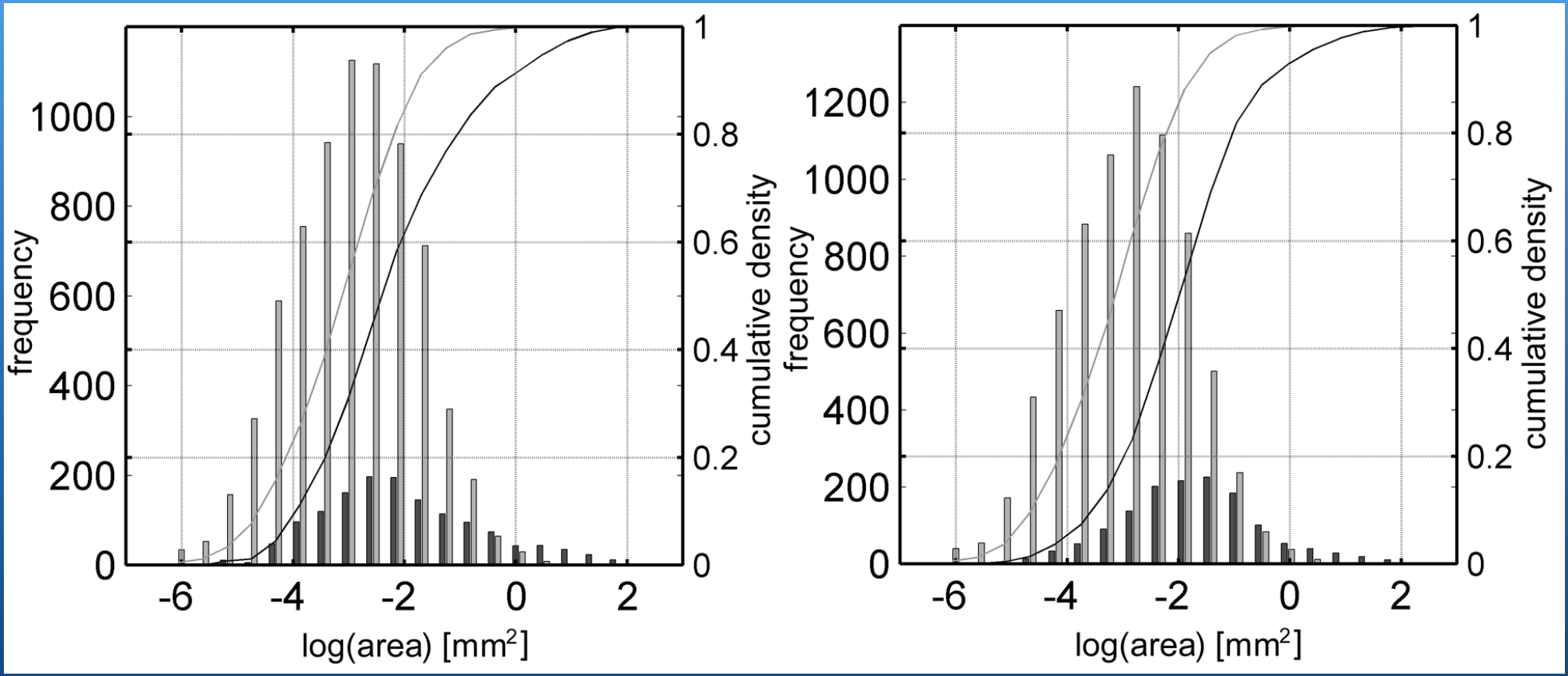
Haymo Kurz: Angiogenesis Revisited


Shear Stress-
Pressure-
Regulated Remodeling

Tissue Tessellation

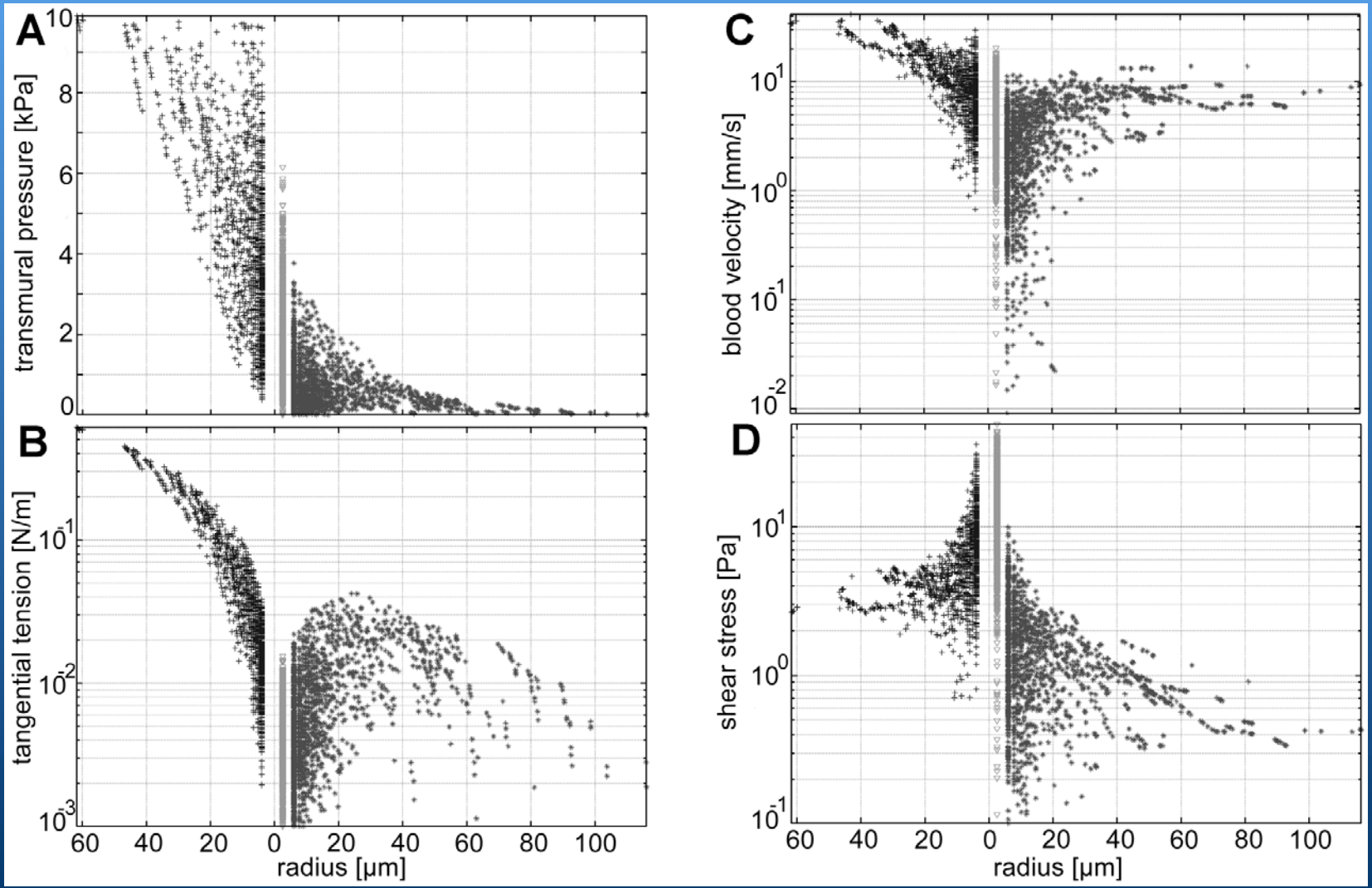


Tissue Tessellation

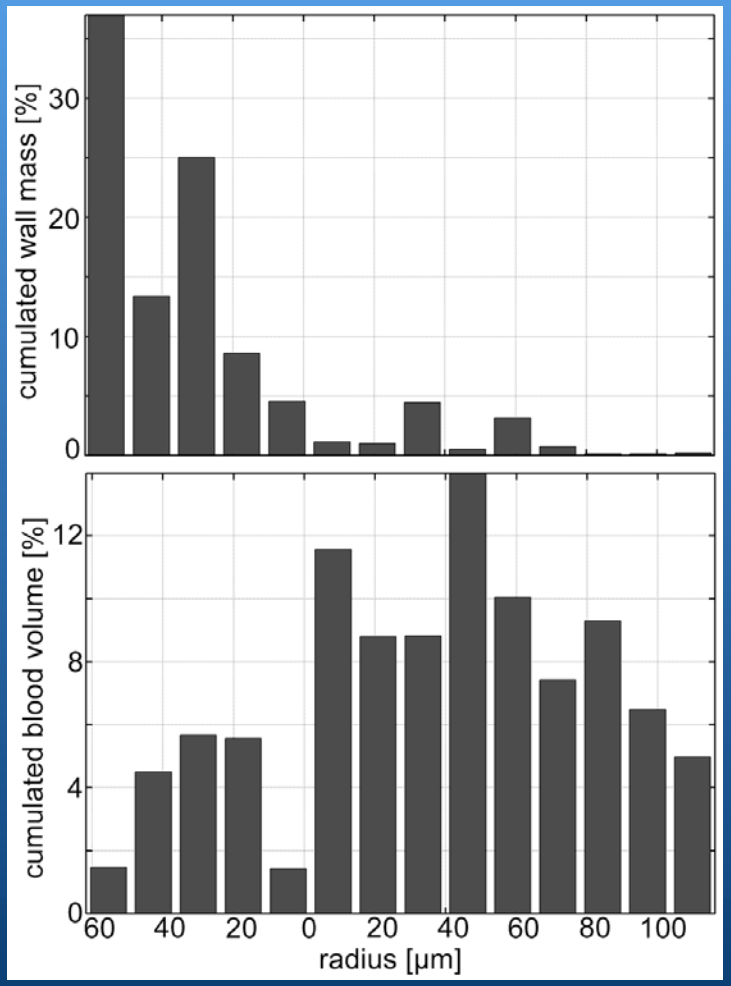


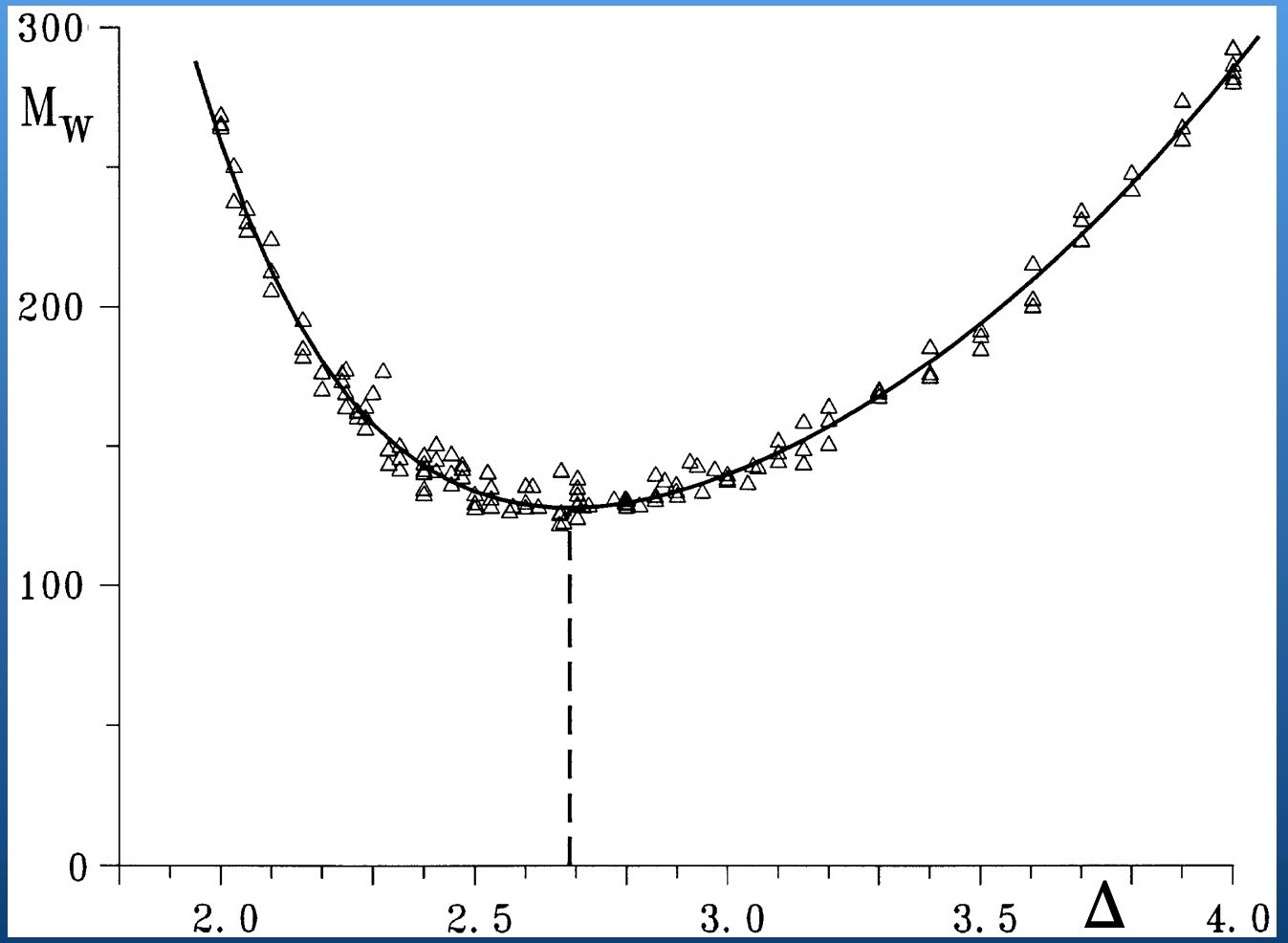
Log(area) = -1.96 ±1.36(initial) to -2.85 ±1.06(remodeled) Log(area) = -2.85 ±1.06(shear) vs. -1.68 ± 1.21(pressure)

Local Properties

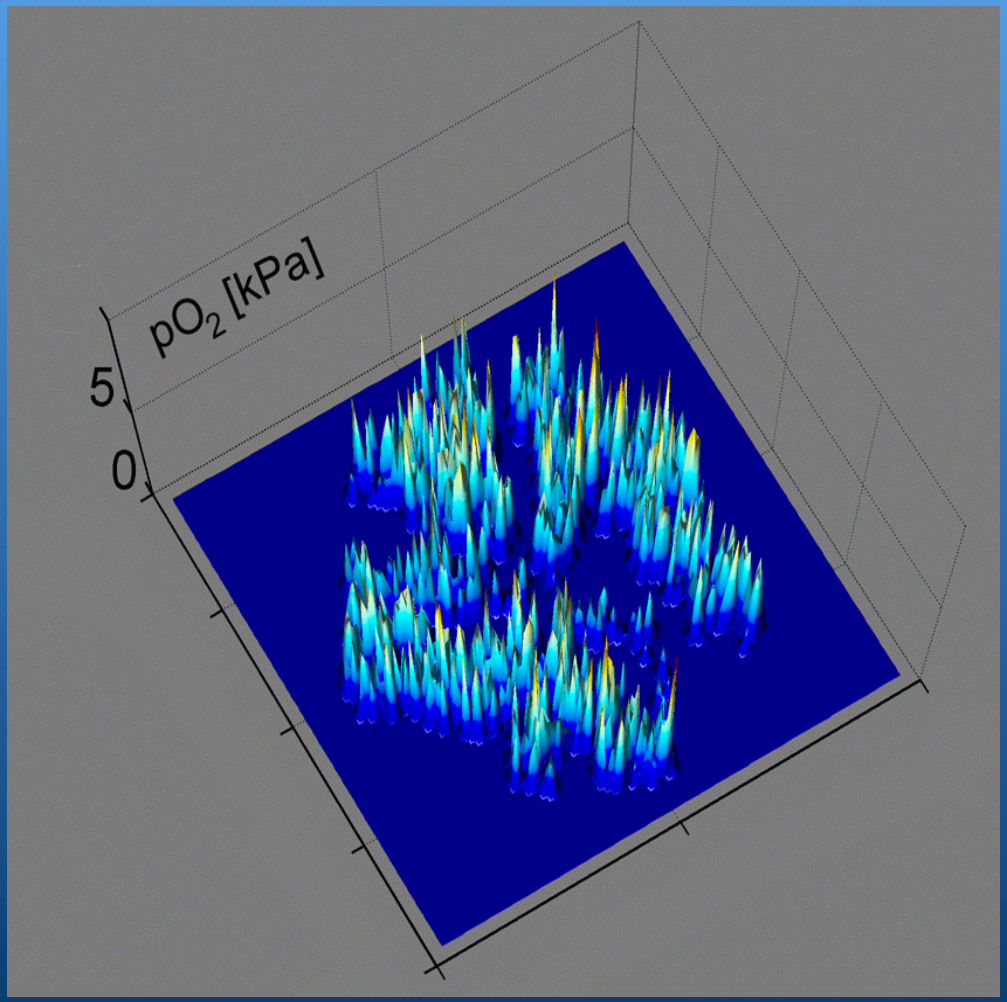


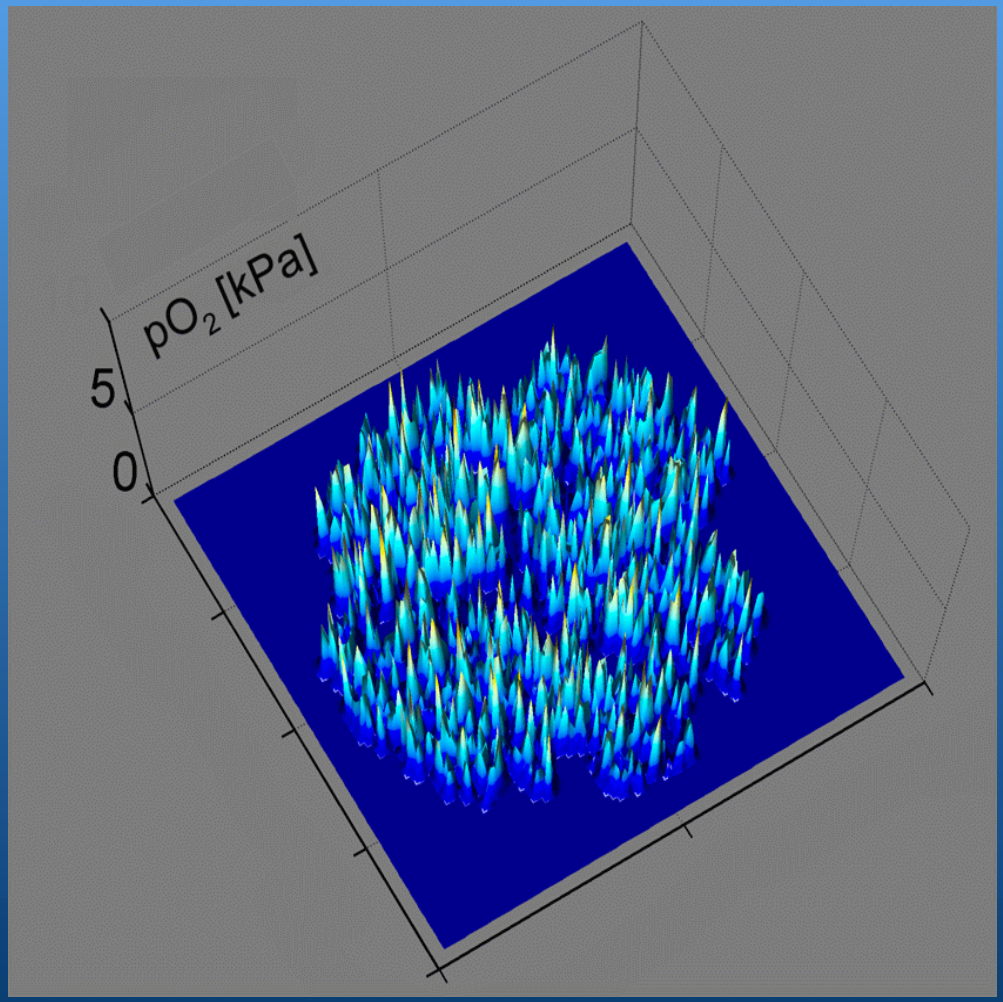
Global Properties



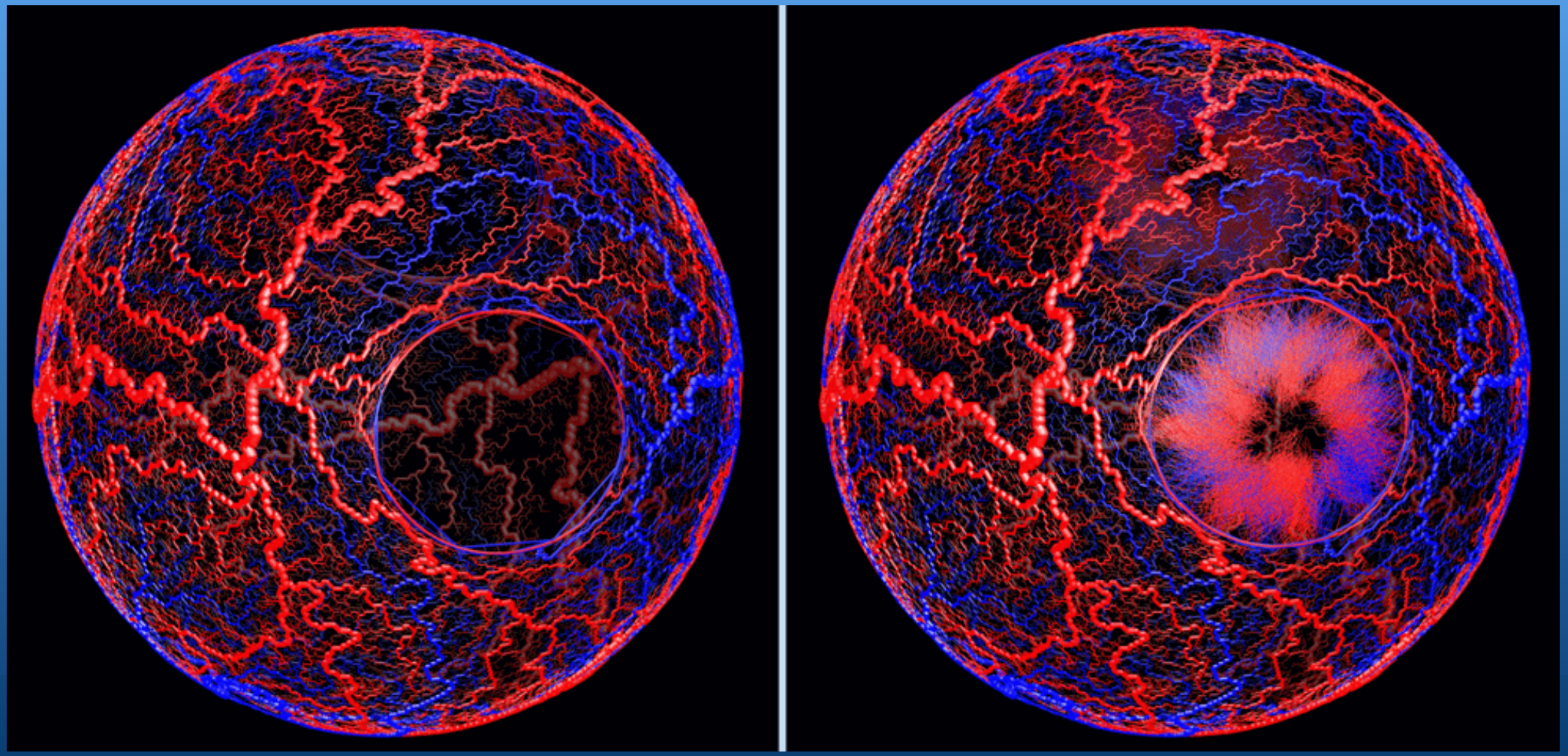


Oxygen Partial Pressure





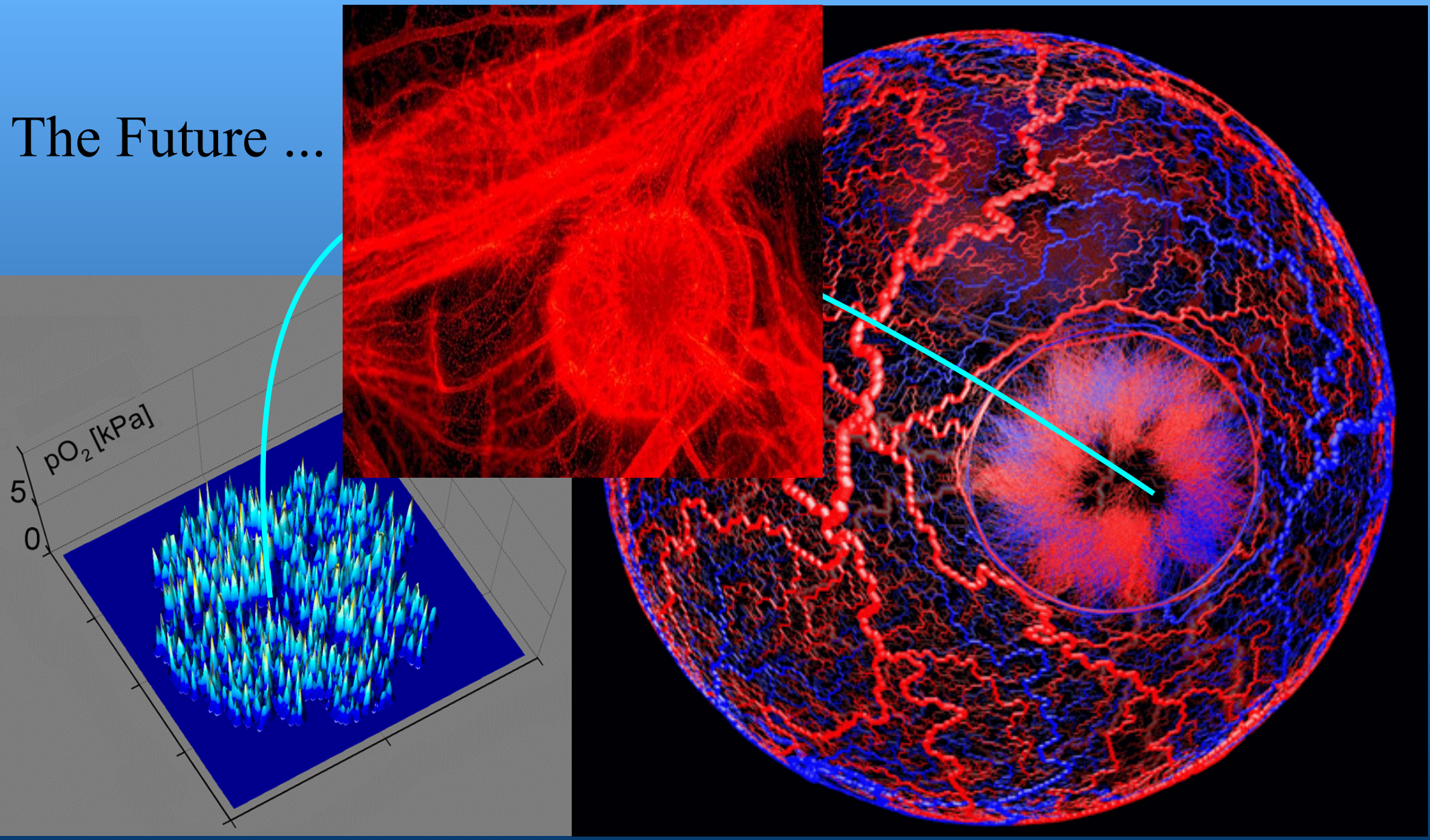
Tumor or Engineered Angiogenesis



Results - Simulation

- First model with interdigitating arteries and veins, generated via shear stress-regulated remodeling.
- Realistic local and global, structural and functional properties.
- Predictive value for anti- or pro-angiogenic therapies, and for tissue engineering of vascularized bioartificial organs to be studied.

The Future ...



But – will we ever be able to program a unifying model that simulates all, or at least the most, typical variants of vascular beds ?

- Probably Not ! Why?
- 3-D Growth and Remodeling Difficult
- Inherent Complexity (of Cells)
- Emergent Complexity (of Vascular Patterns)

Reality and Simulation of Angiogenesis

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