AngioFE: Simulation of the Mechanical Regulation of Angiogenesis

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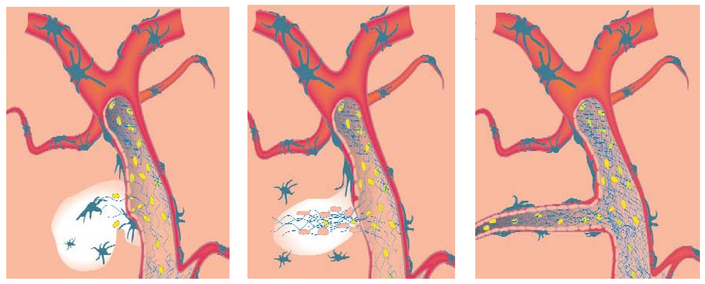
Angiogenesis is the biological process through which new blood vessels form by sprouting off of existing vasculature.

Cells reside within a fibrous protein network known as the extracellular matrix (ECM). Cells interact with the ECM in various ways, in our lab we focus on how forces applied to the ECM affect neovessel behavior during angiogenesis.

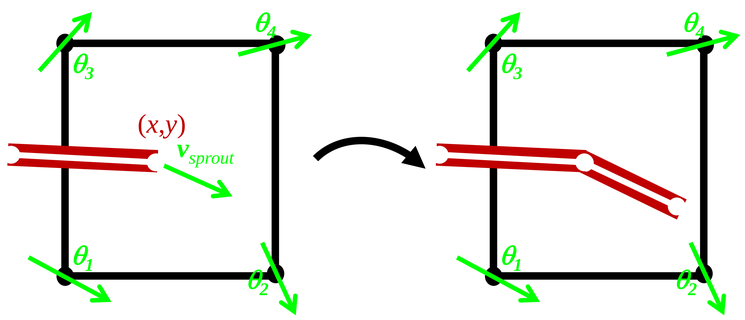


Angiogenesis is regulated by the mechanical interactions with the ECM. As a results, properties of the ECM such as fiber orientation, matrix density, and boundary conditions affect growth. However, the mechanism behind this regulation is poorly understood.

As we try to study this mechanism in the lab, it is often difficult to establish cause-effect relationships across the micro- and macroscale. Therefore, we supplement our experimental efforts with computational modeling. With this computational framework, we can test hypotheses and perform experiments that are not possible in the lab.

Step 1 - Simulate microvessel growth: Microvessels are represented as a series of end-to-end line segments. Simulation occurs within a hexahedral mesh with random collage fiber vectors stored at the nodes.

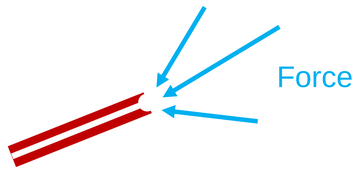
- Elongation involves creating a new line segment at active growth tips. The direction of the new line segment is determined by local collagen fiber orientation. Matrix density affects the rate of growth (more dense, less growth).



$$v_{sprout} = S_1(x,y)\theta_1 + S_2(x,y)\theta_2 + S_3(x,y)\theta_3 + S_4(x,y)\theta_4$$

- Branching, the generation of a new active sprout, was modeled as a random process.
- Anastomosis, the fusing to two neovessels, was permitted for vessels within close proximity.

Step 2 - Assign forces to the sprout tips: Traction applied by neovessel sprouts was represented by a position- and deformation-dependent body force.

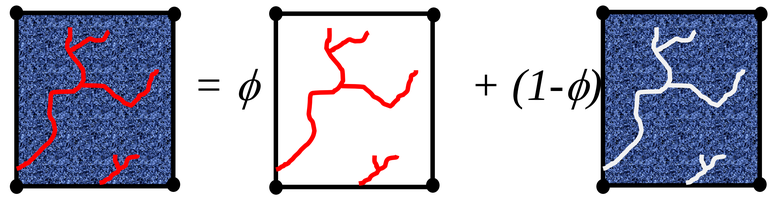


Step 3 - Call FEBio: FEBio in a nonlinear finite element solver specializing in finite strain problems in biomechanics (www.febio.org). We can use FEBio to predict how the ECM deforms given the position and orientation of the sprout forces.

The material model for the vascularized gel is a composite material based on mixture theory. The stress response of the material is a weighted average of the stress response from the microvessel components and the ECM component:

$$\sigma = \phi\,\sigma_{vessel} + (1-\phi)\,\sigma_{ECM}$$

where ϕ is the fraction of element volume occupied by microvessels.



Step 4 - Update vessels and ECM using kinematics:
Microvessels and the ECM are updated into the current configuration using the kinematic results from FEBio.

- Interpolate nodal displacement vectors to vessel using shape functions.
- Update free vectors representing collagen fibers to the current configuration using the deformation gradient tensor.
- Update matrix density using the conservation of mass and the Jacobian (the determinant of the deformation gradient).

Step 5 - Repeat until simulation ends

Simulation of angiogenic microvessel fragments within a long-axis constrained collagen gel:

After simulating 6 days of growth, the geometry of the deformed gel and orientation of the vascular network closely resembled what has been seen in the lab.