Simulating fibrin clot mechanics using finite element methods

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Thrombi

- Fibrin mesh interior to blood vessels
- Impede blood flow
- r-tPA affects body systemically
- Could cause haemorrhage

Sonothrombolysis

- High-amplitude pulsed ultrasound
- Microbubble-assisted
- Targeted, non-systemic dissolution of thrombi through mechanical & chemical action of inertial cavitation
- Possible drug delivery

Objectives

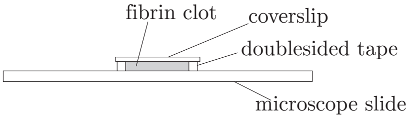
- Model interaction between fibrin and microbubbles
- Need:
  1. Detailed structure of fibrin mesh
  2. Mechanics of microbubbles
- Fibrin:
  1. Fabricating idealised clot
  2. Confocal imaging
  3. 3D printing
  4. Stress analysis in ANSYS
- Microbubble:
  1. Nonlinear response to sound field
  2. Model using Rayleigh-Plesset equation
- Goal: model bubbles tunnelling through thrombus

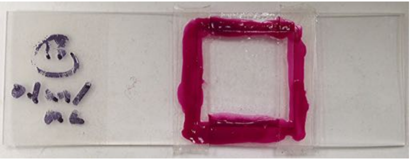
Clot fabrication

Ingredients

- Fibrinogen
- Alexa Fluor 488
- Tris buffer
- $CaCl_2$
- Thrombin: 0.1–1.0 unit/mL

Inject into microscope slide chamber





Confocal micrographs

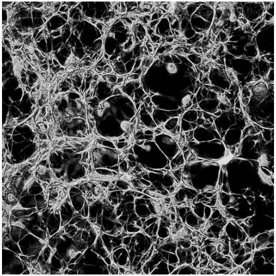


Figure: 0.1 unit/mL thrombin.

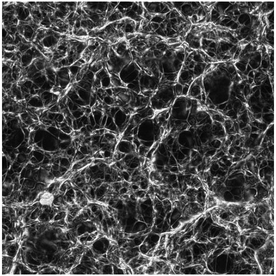


Figure: 0.5 unit/mL thrombin.

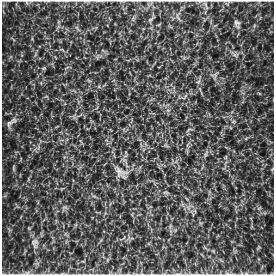


Figure: 1.0 unit/mL thrombin.

3D prints

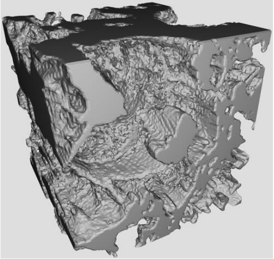


Figure: 0.1 unit/mL thrombin.

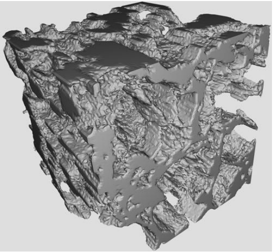


Figure: 0.5 unit/mL thrombin.

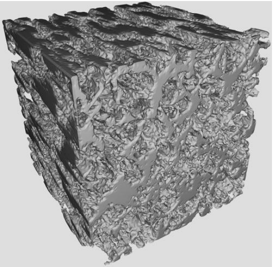
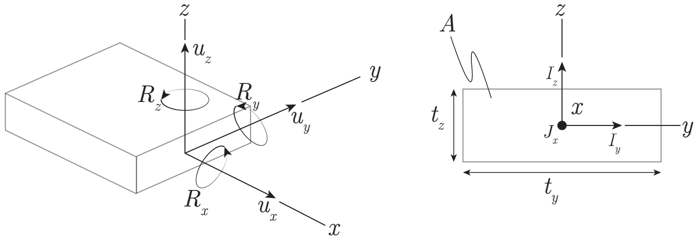


Figure: 1.0 unit/mL thrombin.

Beam4



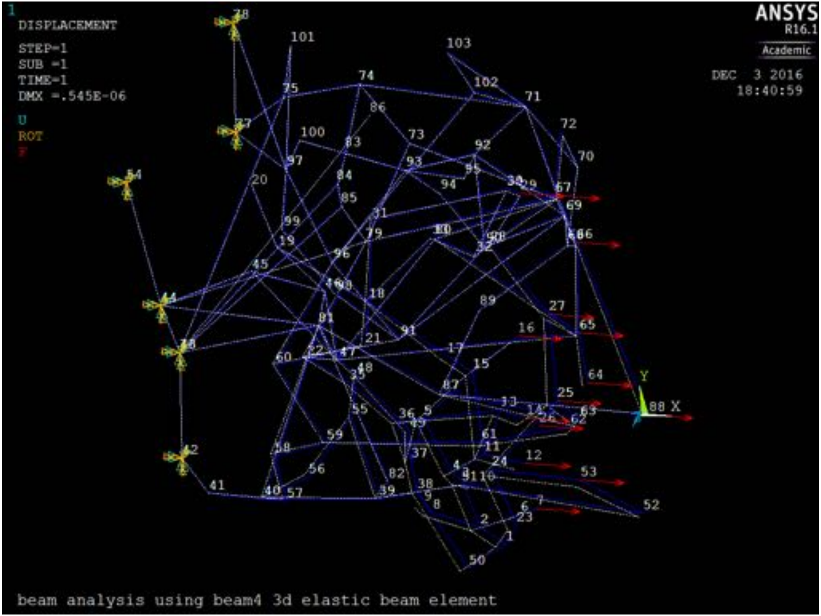
- $A = \pi r^2 = 1.046 \times 10^{-12}$ m^2
- $I_y = I_z = \frac{1}{4}\pi r^4 = 8.71 \times 10^{-26}$ m^4
- $t_y = t_z = 2r = 1.154 \times 10^{-6}$ m
- $J_x = \frac{1}{2}\pi r^4 = 1.741 \times 10^{-25}$ m^4
- $E = 5 \times 10^6$ Pa [Guthold et al., 2007]
- $\nu = 0.4999999$ [Wufsus et al., 2015]

ANSYS

Simulation

- Apply 1×10^{-9} N axial load
- Find average nodal displacements
- Calculate effective Young's modulus from $E = \sigma/\epsilon$

E_x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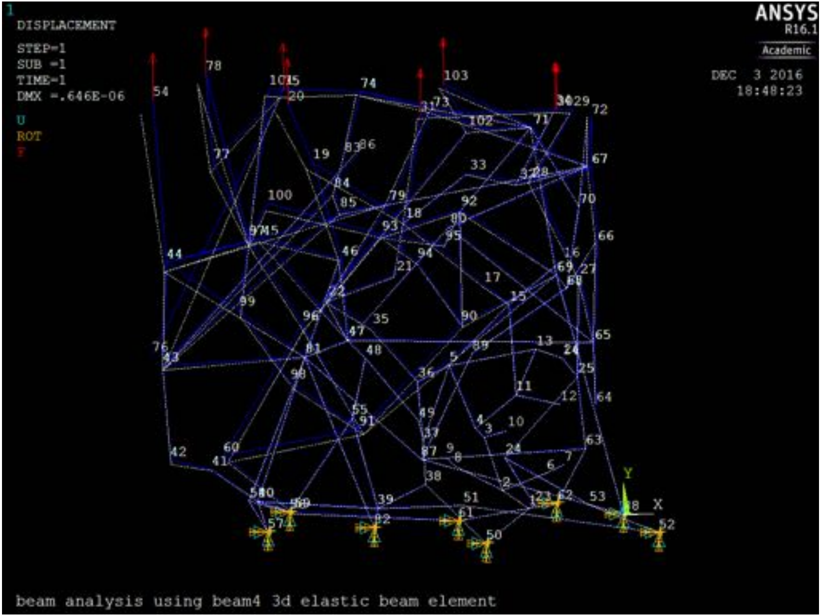
beam analysis using beam4 3d elastic beam element

E_y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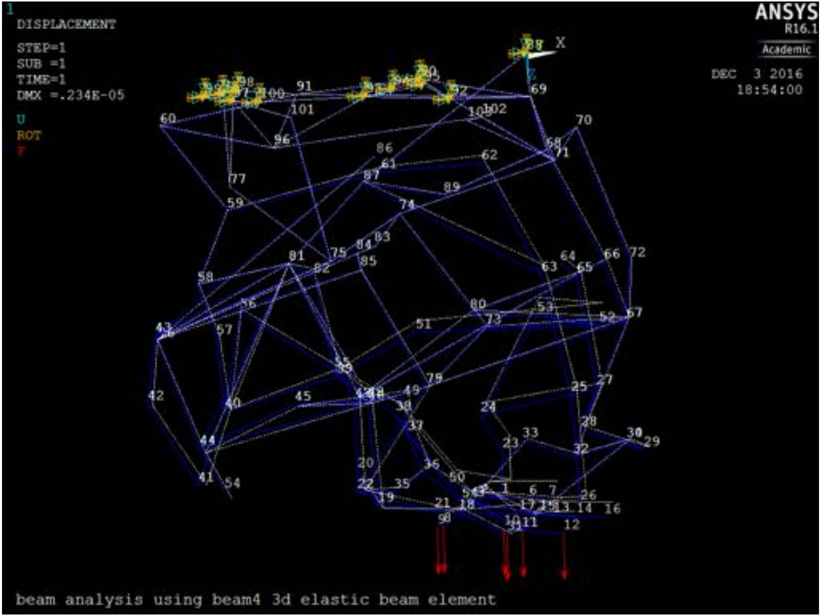
E_z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beam analysis using beam4 3d elastic beam element

Results

Effective bulk stiffness

1. $\sigma_x = 0.409$ Pa
2. $\epsilon_x = 3.60 \times 10^{-3}$
3. $E_x = \frac{\sigma_x}{\epsilon_x} = 113.5$ Pa

1. $\sigma_y = 0.409$ Pa
2. $\epsilon_y = 3.75 \times 10^{-3}$
3. $E_y = \frac{\sigma_y}{\epsilon_y} = 109.1$ Pa

1. $\sigma_z = 0.426$ Pa
2. $\epsilon_z = 2.63 \times 10^{-2}$
3. $E_z = \frac{\sigma_z}{\epsilon_z} = 16.17$ Pa

E_z is smallest!

- 10 times more deformation in Z
- Could be related to bias towards Z seen in 3D print

Modelling microbubbles

Rayleigh-Plesset

$$R\ddot{R} + \frac{3\dot{R}^2}{2}$$
$$= \frac{1}{\rho}\left\{\left(p_0 + \frac{2\sigma}{R_0} - p_v\right)\left(\frac{R_0}{R}\right)^{3\kappa} + p_v - \frac{2\sigma}{R} - \frac{4\eta\dot{R}}{R} - p_0 - P(t)\right\}$$

Radius-time curves

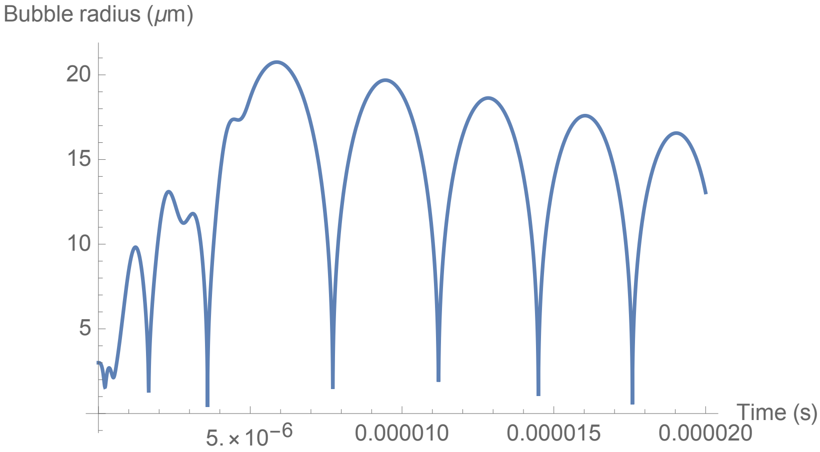

Figure: $P_A = 500$kPa, f=1.0MHz, $R_0 = 3\mu$m.

Radius-time curves

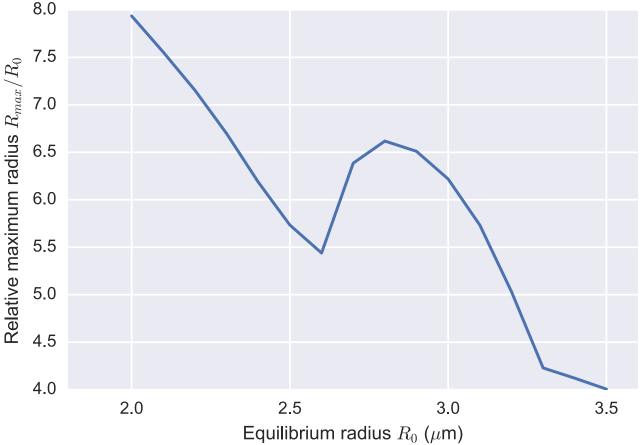

Figure: $P_A = 500$kPa, f=1.0MHz, $R_0 = 2.0$–3.5μm; R_{max}/R_0 is maximised at $R_0 = 2.8\mu$m; strange behaviour at $R_0 \leq 2.6\mu$m.

What I have learnt

- It *is* possible to reconstruct 3D models of fibrin meshes from confocal slices
- Increasing thrombin concentration reduces porosity and increases density of said meshes
- My clot model is least stiff in Z
- Procedure is useful though has problems

Next steps

- Make higher resolution 3D prints
- Integrate results from Rayleigh-Plesset equation into my clot model
- First approximation: ignore clot-bubble reciprocal action
- *Maybe*: automate node generation

References

Guthold, M., Liu, W., Sparks, E. A., Jawerth, L. M., Peng, L., Falvo, M., Superfine, R., Hantgan, R. R., and Lord, S. T., 2007. “A Comparison of the Mechanical and Structural Properties of Fibrin Fibers with Other Protein Fibers”. *Cell Biochem. Biophys.*, **49**(3), Oct., pp. 165181.

Wufsus, A., Rana, K., Brown, A., Dorgan, J., Liberatore, M., and Neeves, K., 2015. “Elastic Behavior and Platelet Retraction in Low- and High-Density Fibrin Gels”. *Biophys. J.*, **108**(1), Jan., pp. 173183.