

Supplementary Materials for PVE MODEL:

Impact of tumor-parenchyma biomechanics on liver metastatic progression: a multi-model approach

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1. Material Properties

Model material properties are given in Tables S1-S3. The Young's modulus of the parenchyme was taken as 4.4 kPa and Poisson's ratio as 0.35 (Evans et al. 2013; Nishii et al. 2016). The Young's modulus for tumor tissue was set as 30 kPa (Venkatesh et al. 2008; Lu et al. 2015) and Poisson's ratio was assumed equal to normal tissue. A four-term Prony series expansion was used to model tissue viscoelasticity, with Prony series constants taken from previous nano-indentation experiments on perfused liver tissue (Evans et al. 2013).

At the macroscopic (cm) length scale, tumors have been reported to have higher hydraulic conductivity K relative to the surrounding tissue (Swabb et al. 1974; Netti et al. 2000; Pishko et al. 2011). However, the hydraulic conductivity of smaller tumors on the order of 50-400 μm is unknown. For each tumor size/location combination in the present study, we simulated the effects of high and low hydraulic conductivity in the tumor. For the high hydraulic conductivity case, we used a value of 3.65 times that of normal liver, based on hydraulic conductivity of hepatocarcinoma determined from measurements of (Swabb et al. 1974). For the low hydraulic conductivity case, we used 0.3 times that of normal liver, to span approximately one order of magnitude in our high/low conditions. Normal liver parenchyme hydraulic conductivity was taken as $1.85 \times 10^{-6} \text{ m/s}$ as reported by (Nishii et al. 2016), based on void ratio measurements from histological image analysis. Void ratio, e , is defined as:

$$e = \frac{V_v}{V_s} = \frac{V_v}{V_t - V_v} \quad (\text{Eq. S1})$$

where e is the void ratio, V_v is the void volume, V_s is the volume of solid in the lobule, and V_t is the total volume of the lobule. Void ratio is related to hydraulic conductivity as follows (Nishii et al. 2016):

$$K = \frac{\rho g e r^2}{8\mu(1+e)} \quad (\text{Eq. S2})$$

where K is the hydraulic conductivity (m/s), ρ is fluid density (kg/m^3), g is gravitational acceleration (m/s^2), e is the void ratio, r is the average radius of a sinusoid (m), and μ is the dynamic viscosity of the permeating fluid ($\text{Pa}\cdot\text{s}$).

Table S1. Elastic constants for parenchyme and tumor. Materials are assumed isotropic.

	Parenchyme	Tumor
Elastic Modulus (kPa)	4.4	30
Poisson's ratio	0.35	0.35

Table S2. Viscoelastic constants (same values used for parenchyme and tumor).

Term	g_i (dim)	τ_i (sec)
1	0.53	2.00E-05
2	0.376	1
3	0.027	7.65
4	0.01	100

Table S3. Hydraulic conductivity and related properties

Property	Parenchyme	Tumor, High Hydraulic Conductivity	Tumor, Low Hydraulic Conductivity
Hydraulic Conductivity (m/s)	1.85E-06	6.75E-06	5.50E-07
Void Ratio	0.8	1.55	0.052
Specific Weight of Fluid (kg/m ³)	9855	9855	9855

2. Boundary Conditions

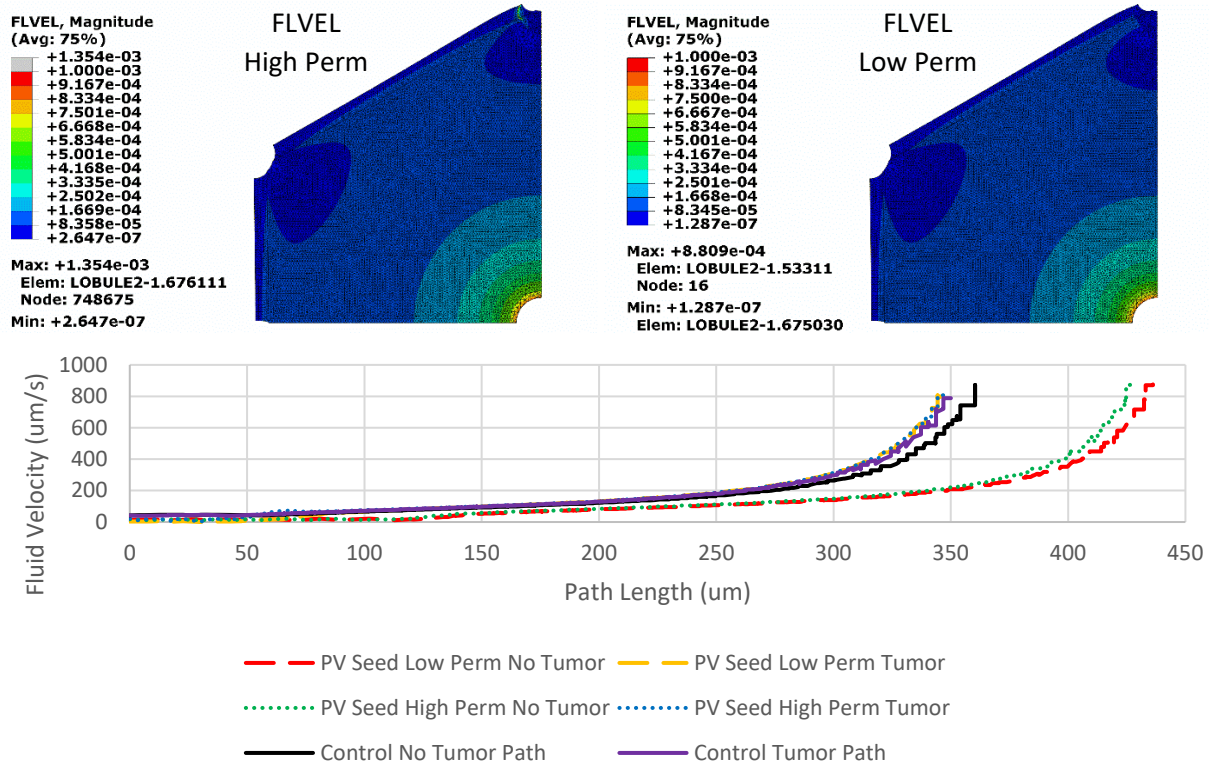
As noted in the manuscript, one-quarter of the hexagonal lobule was modeled to minimize computational cost; therefore symmetric boundary conditions were applied to the *X*, *Y*, and *Z* planes (see Model Geometry). Following the work of (Bonfiglio et al. 2010), the model assumed uniform expansion in the axial direction (in the *XY* plane) and no expansion in the longitudinal (*Z*) direction. Pressure in the CV surface was set to zero to serve as a pressure sink, and pressures in the terminal portal vein (tPV) and pre-terminal portal vein (pre-tPV) were set to 2.23 mmHg (297.3 Pa) above the CV pressure so that the physiological pressure difference was preserved (Nishii et al. 2016). The pressure condition at the tumor boundary varied depending on tumor size (Table S4). A total of 13 model runs were performed, varying tumor position and size, pressure condition at the tumor boundary, and tumor permeability relative to surrounding parenchyme (Table S4). Lastly, a control model was created with no tumor but with identical parenchyme properties and vascular pressure boundary conditions, to serve as a basis for comparison.

Table S4. Variable parameters for finite element model runs.

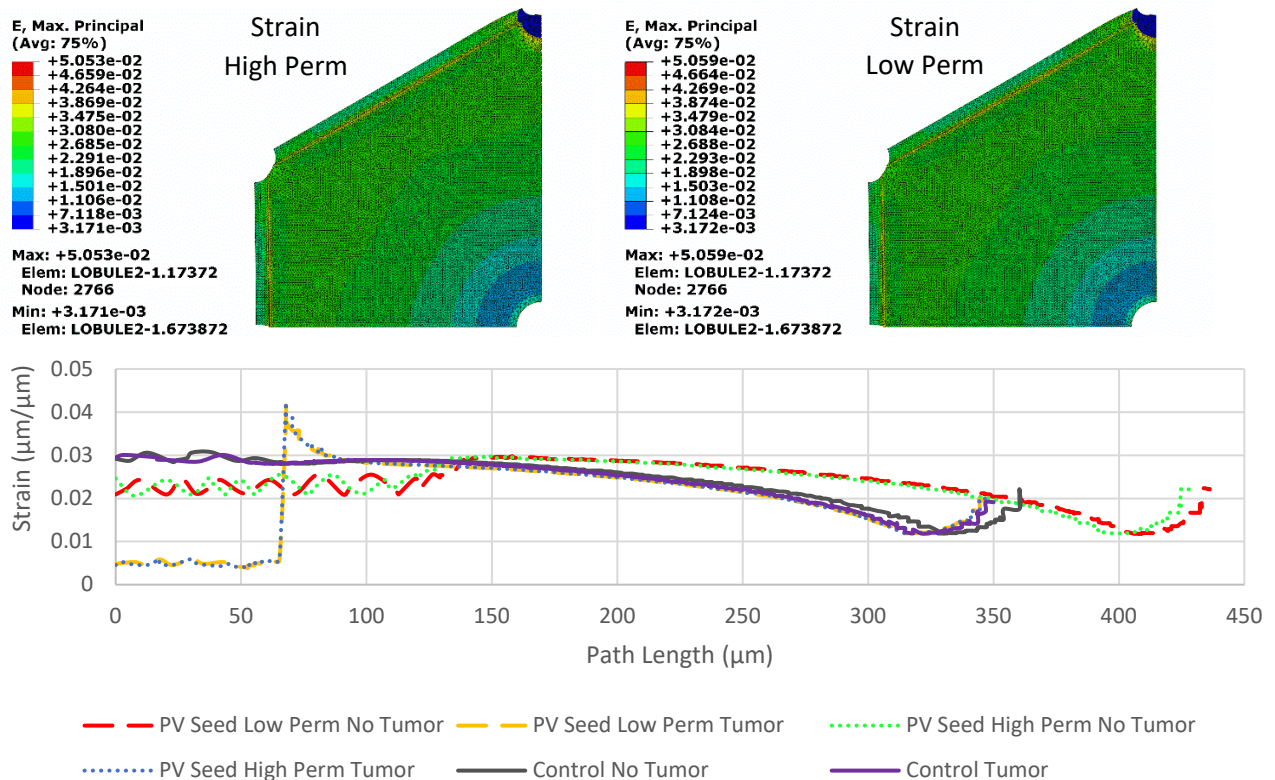
Model Run	Tumor Position	Tumor Size (diam., μm)	Tumor as Pressure Source or Sink (Pa)	Tumor Hydraulic Conductivity (m/s)
1	Center	Seed (50)	Neutral	Low (5.50E-07)
2	Center	Seed (50)	Neutral	High (6.75E-06)
3	Center	Small (200)	Sink (0)	Low (5.50E-07)
4	Center	Small (200)	Sink (0)	High (6.75E-06)
5	Portal	Seed (50)	Neutral	Low (5.50E-07)
6	Portal	Seed (50)	Neutral	High (6.75E-06)
7	Portal	Small (200)	Sink (0)	Low (5.50E-07)
8	Portal	Small (200)	Sink (0)	High (6.75E-06)
9	Portal	Medium (400)	Source (600)	Low (5.50E-07)
10	Portal	Medium (400)	Source (600)	High (6.75E-06)
11	Portal	Medium (400)	Neutral	Low (5.50E-07)
12	Portal	Medium (400)	Neutral	High (6.75E-06)
13	Control	No Tumor	N/A	Parenchyme (1.85E-06)

3. Fluid Velocity, Strain, Stress, and Pore Fluid Pressure Results

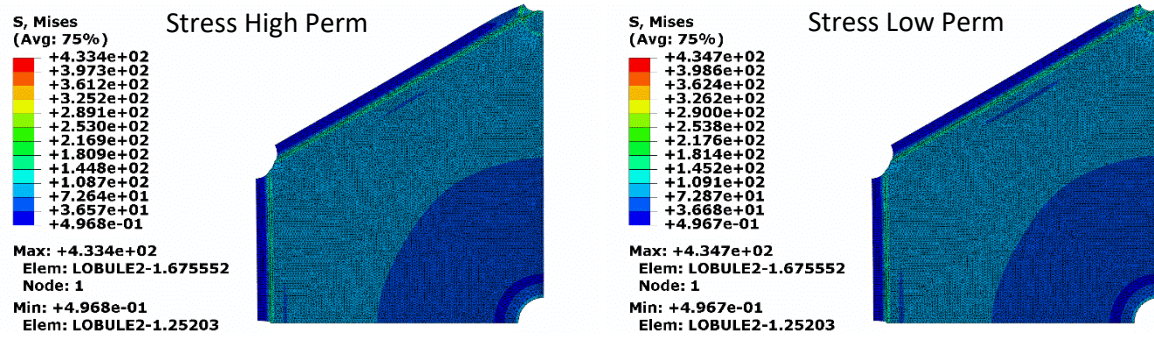
(A)



(B)



(C)



(D)

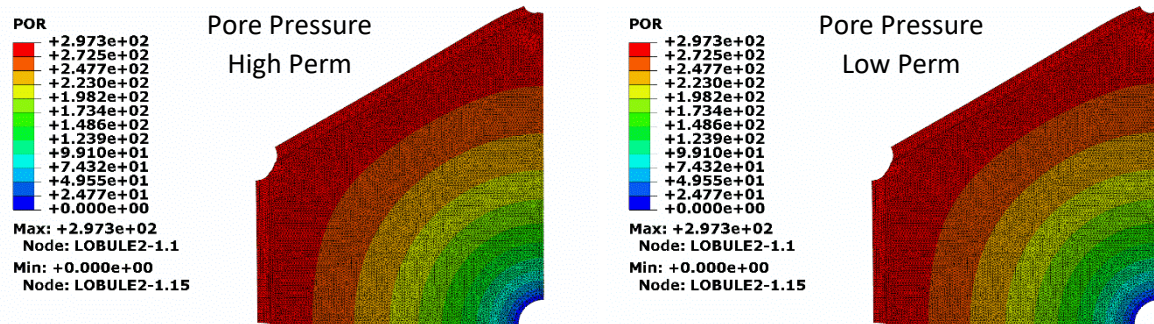
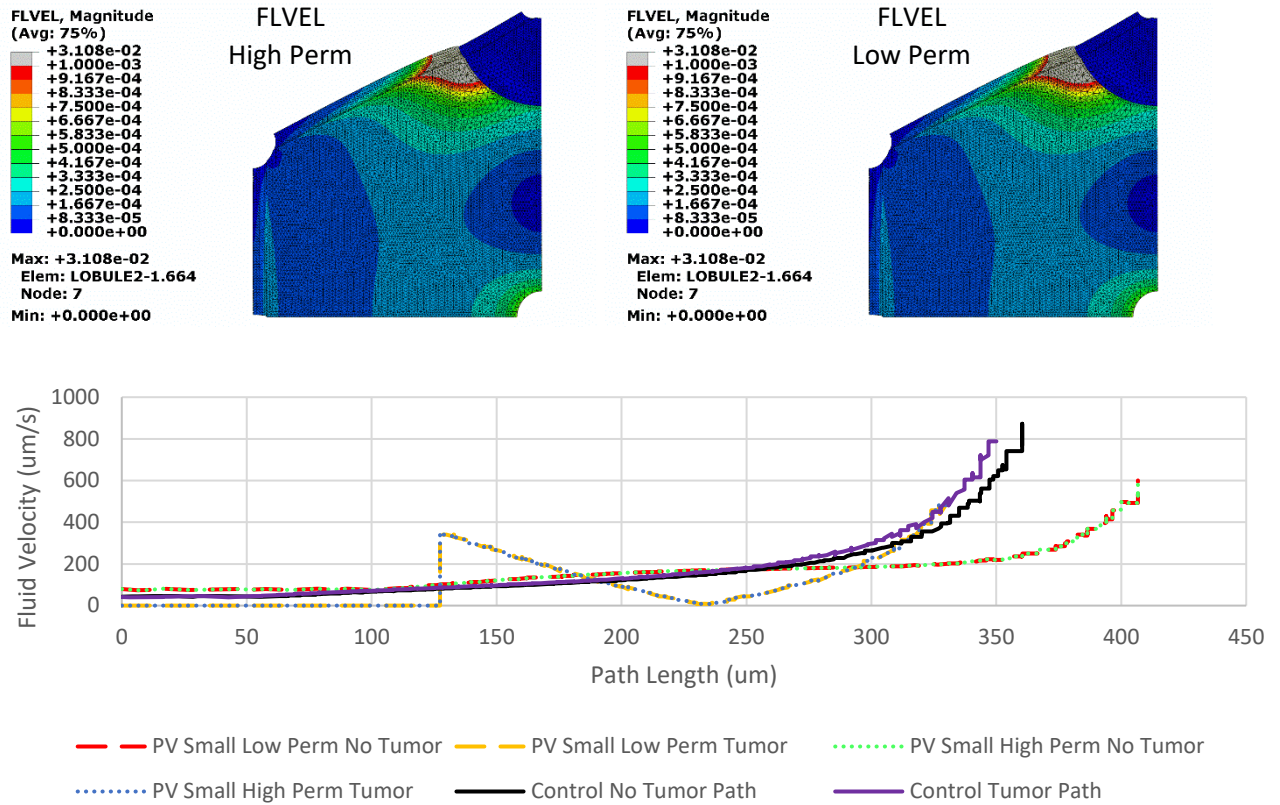
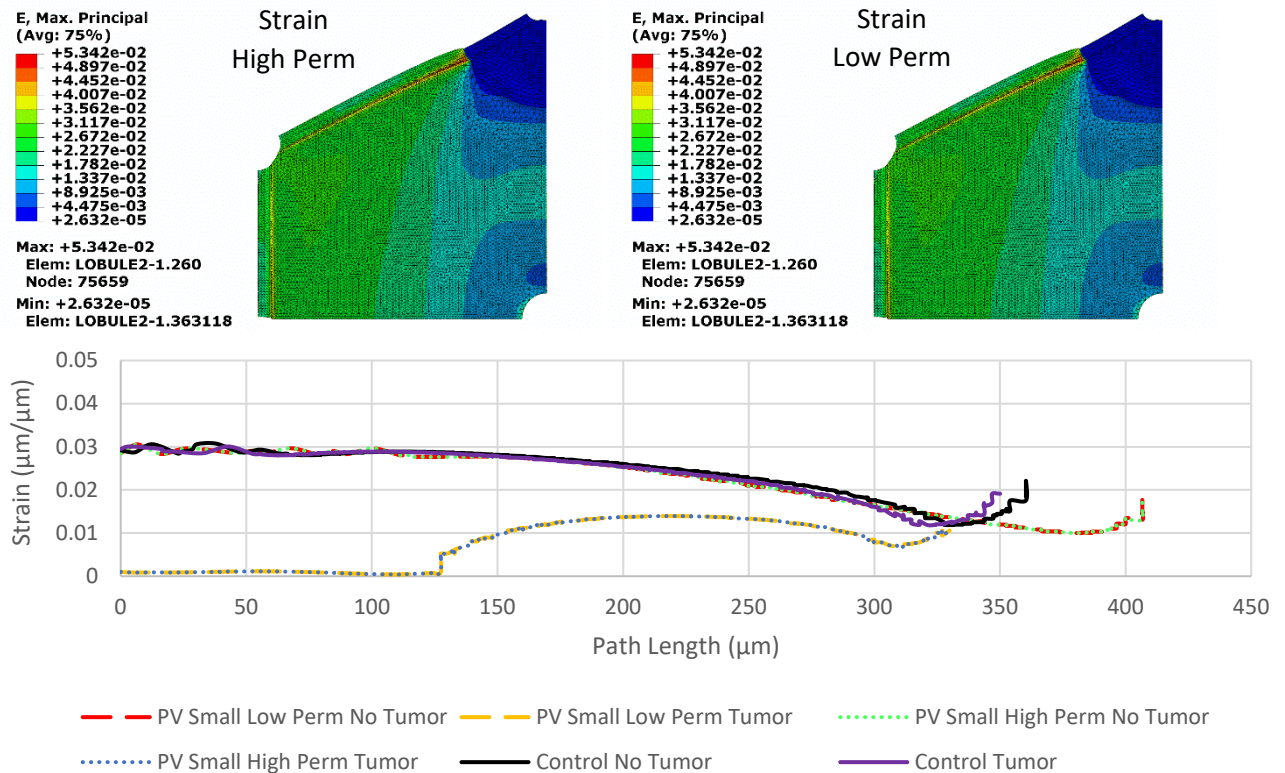


Figure S9. Images for the 50 μ m diameter tumor seed centered at the portal vein. Tumor was not set as a pressure source or sink. Images for (A) fluid velocity, (B) strain, (C) stress, and (D) pore pressure distribution throughout the quarter lobule. Graphs represent the fluid velocity and strain in the “tumor” and “no tumor” paths.

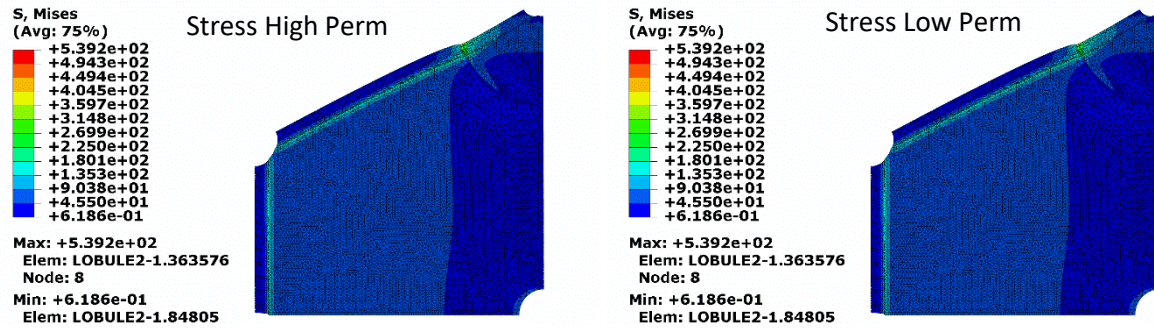
(A)



(B)



(C)



(D)

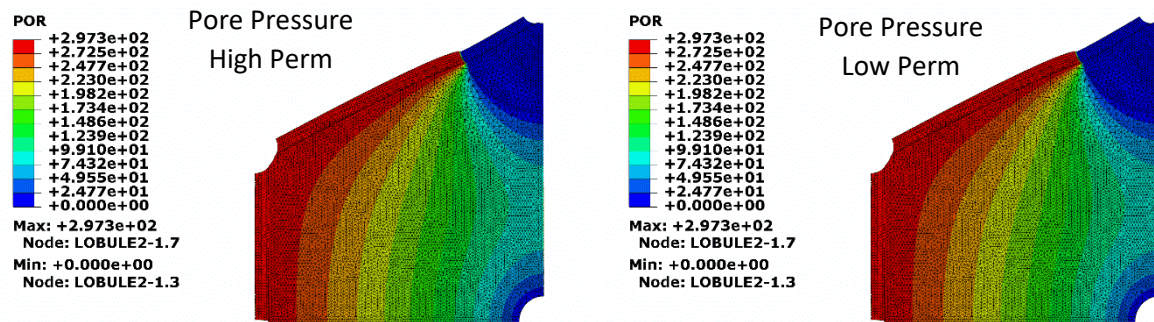
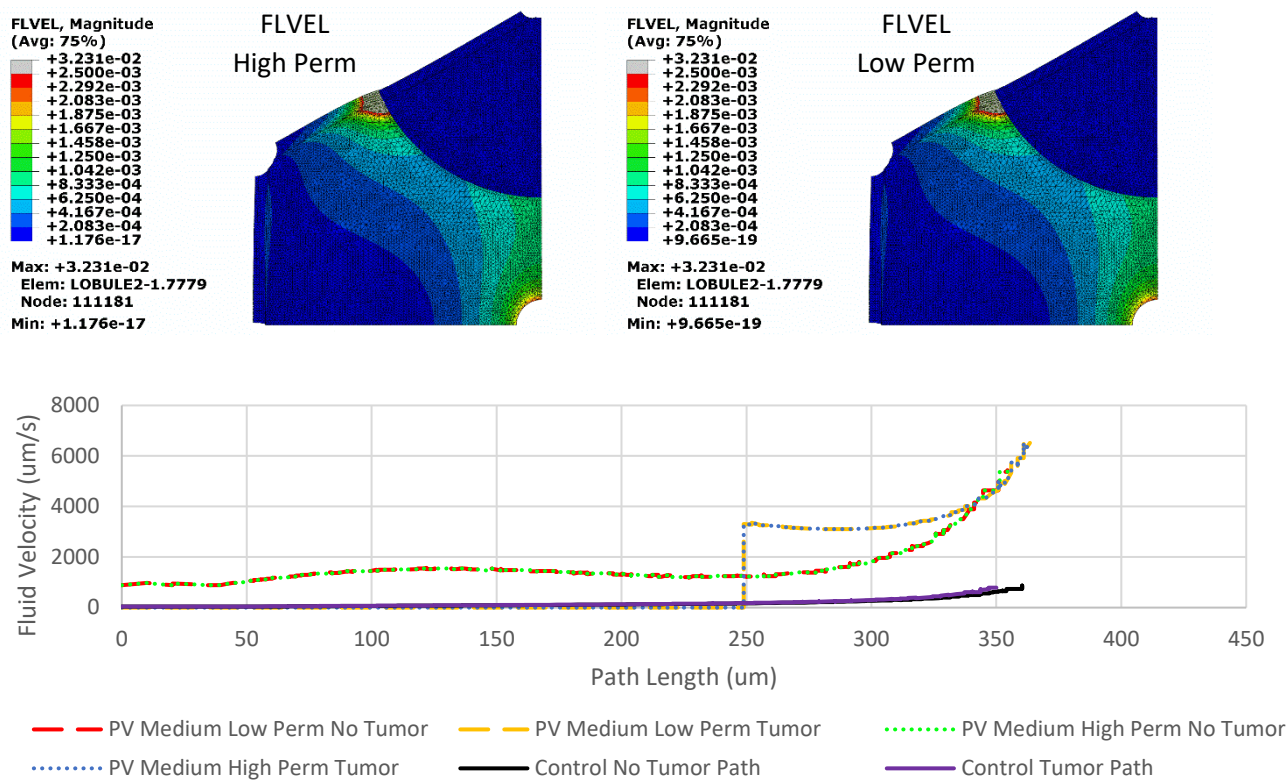
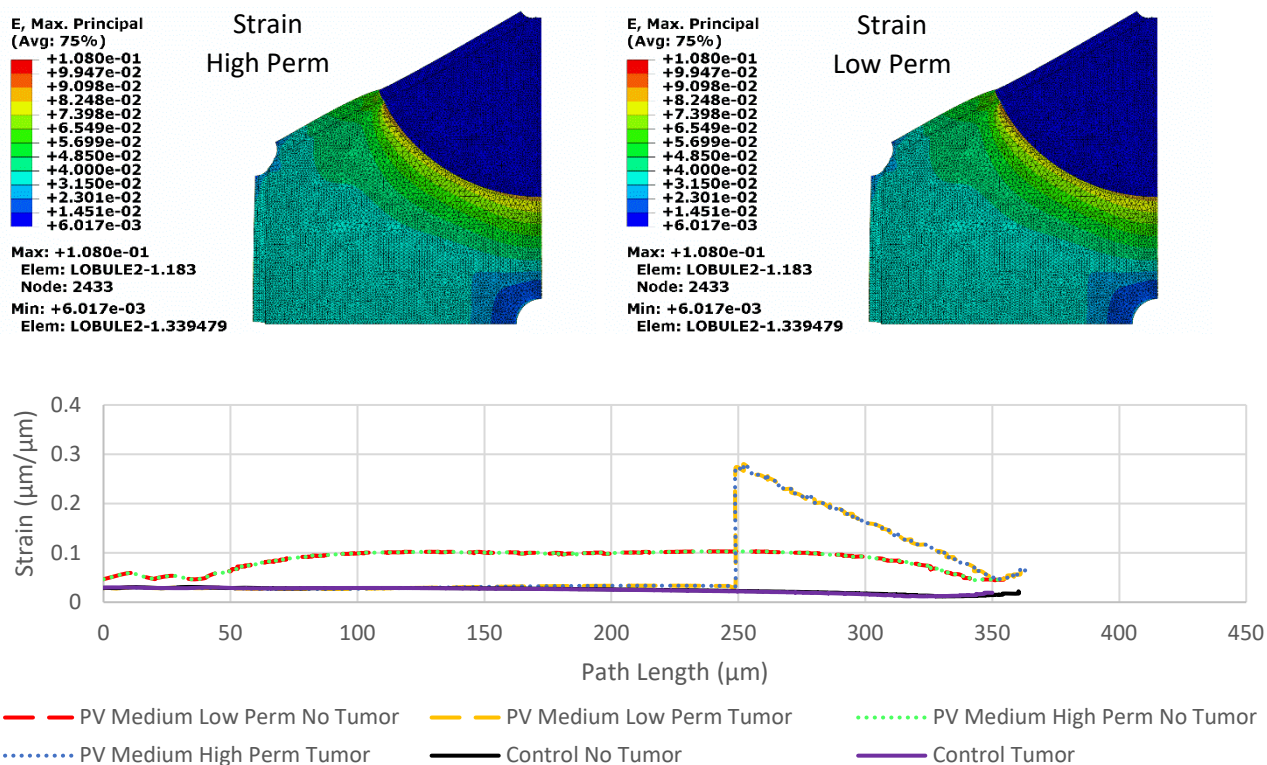


Figure S10. Images for the 200 μ m diameter tumor centered at the portal vein. Tumor was set as a pressure sink. Images for (A) fluid velocity, (B) strain, (B) stress, and (D) pore pressure distribution throughout the quarter lobule. Graphs represent the fluid velocity and strain in the “tumor” and “no tumor” paths.

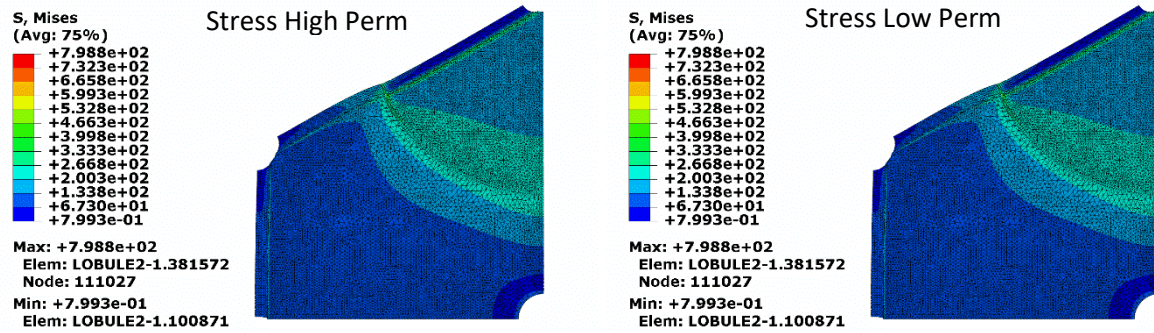
(A)



(B)



(C)



(D)

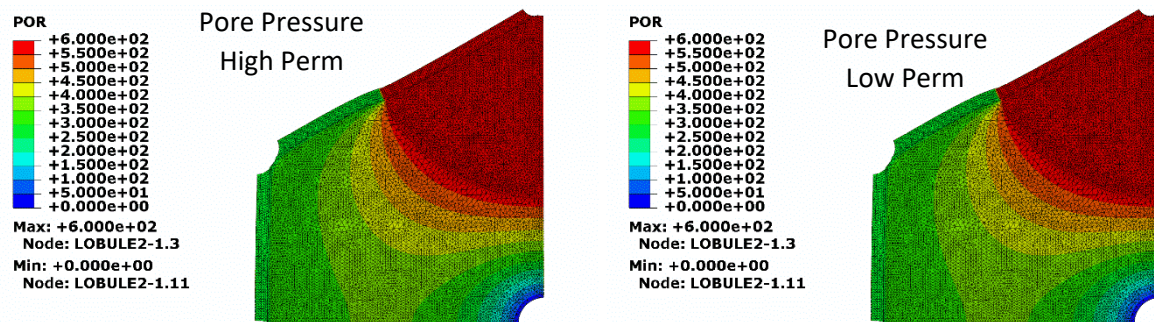
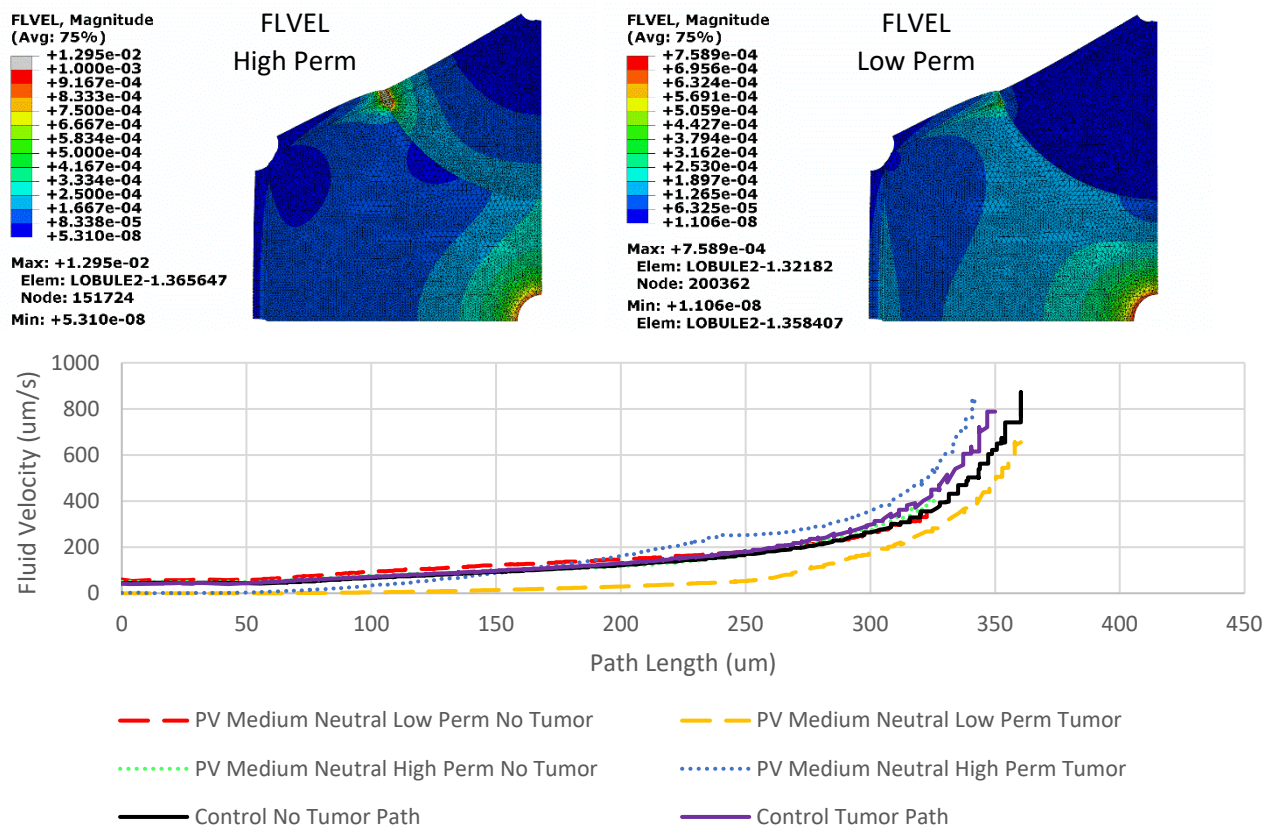
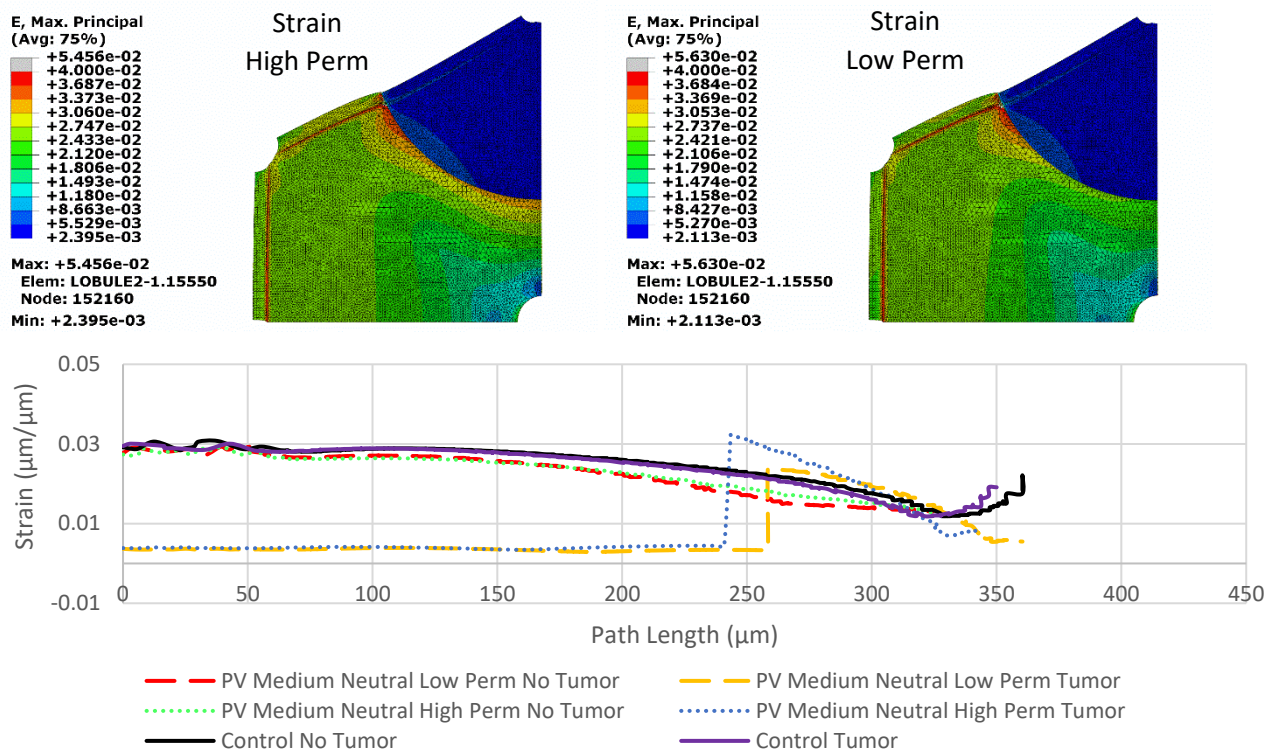


Figure S11. Images for the 400 μ m diameter tumor centered at the portal vein. Tumor was set as a 600 Pa pressure source. Images for (A) fluid velocity, (B) strain, (C) stress, and (D) pore pressure distribution throughout the quarter lobule. Graphs represent the fluid velocity and strain in the “tumor” and “no tumor” paths. Note the scale of fluid velocity and strain is much higher than other models.

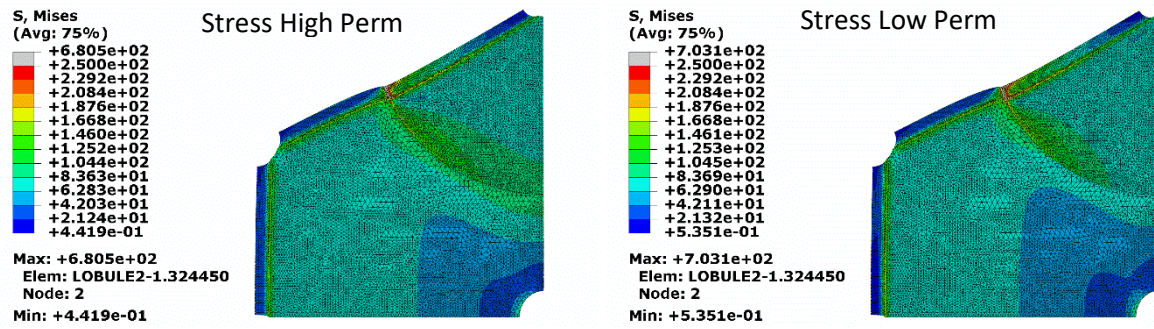
(A)



(B)



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(D)

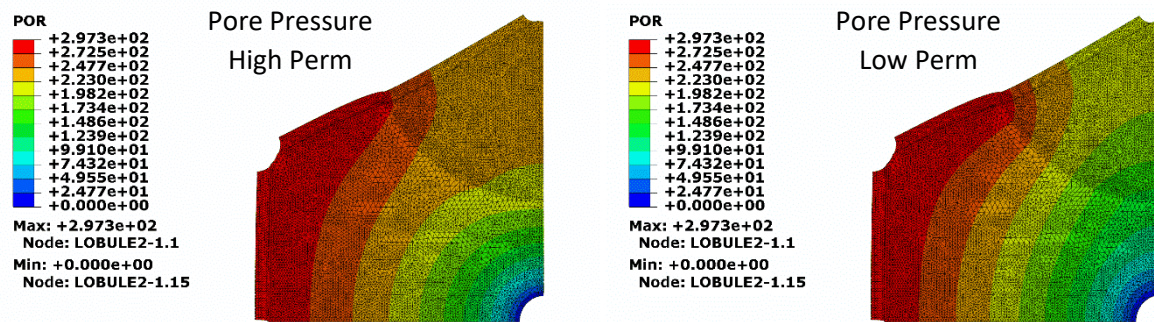
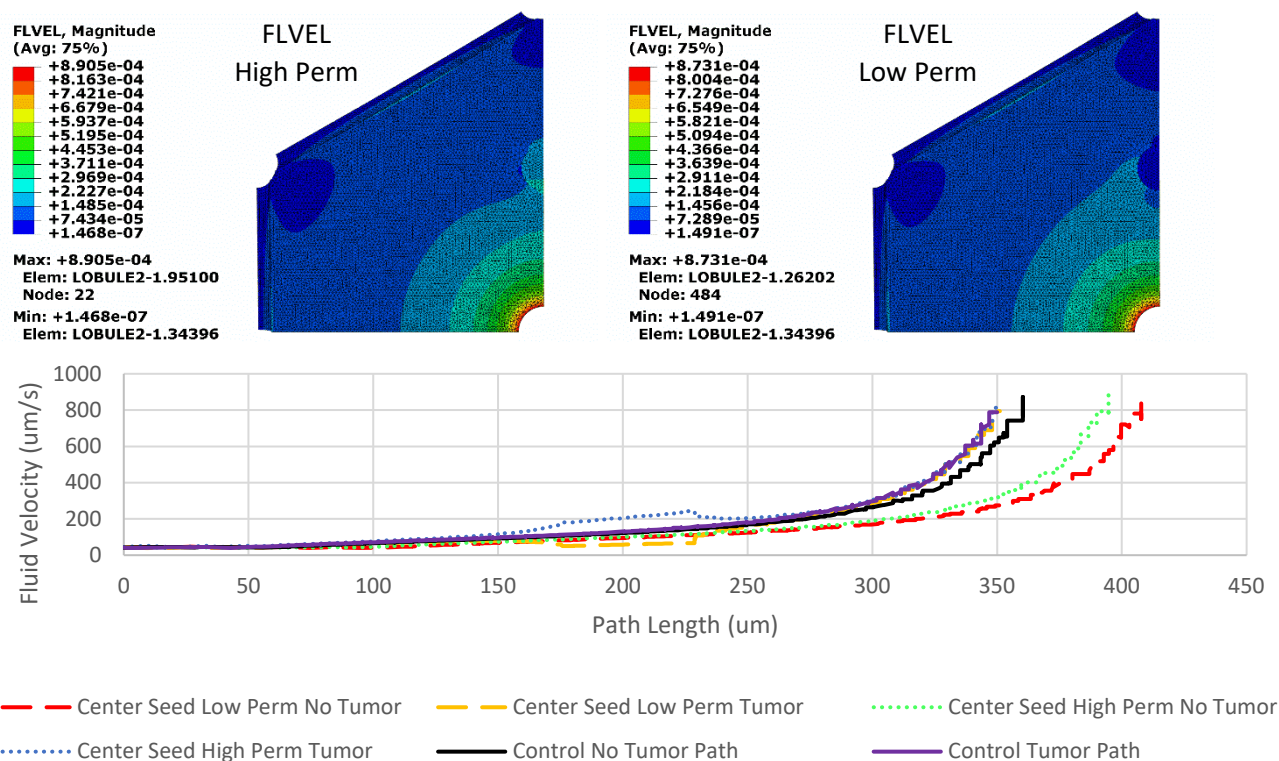
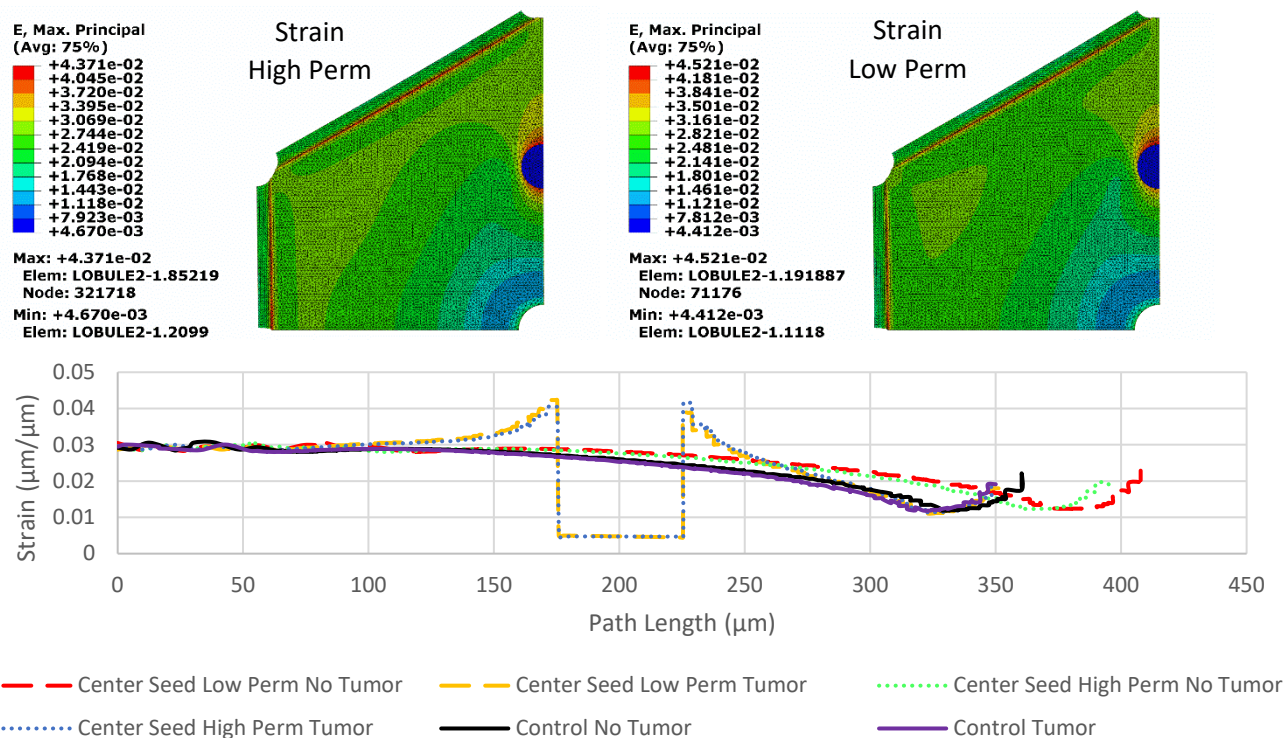


Figure S12. Images for the 400 μ m diameter tumor centered at the portal vein. Tumor was not set as a pressure source or sink. Images for (A) fluid velocity, (B) strain, (C) stress, and (D) pore pressure distribution throughout the quarter lobule. Graphs represent the fluid velocity and strain in the “tumor” and “no tumor” paths.

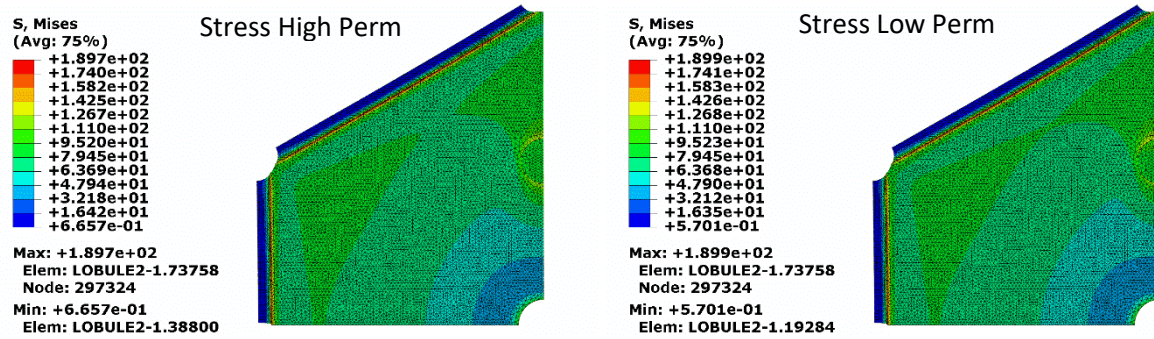
(A)



(B)



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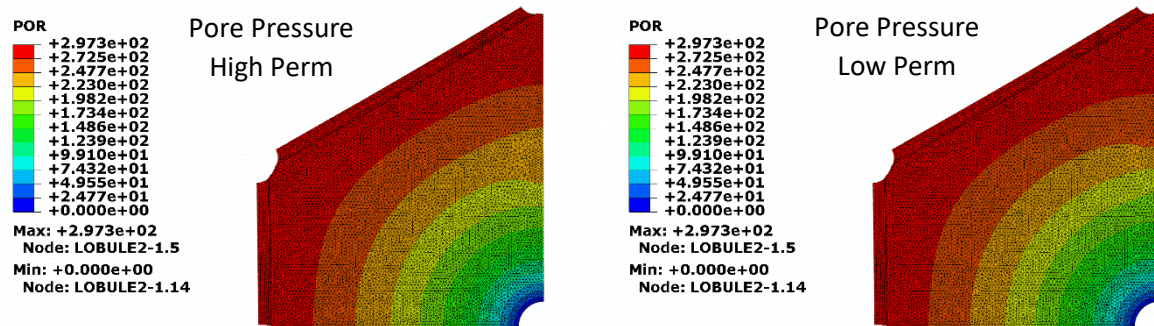
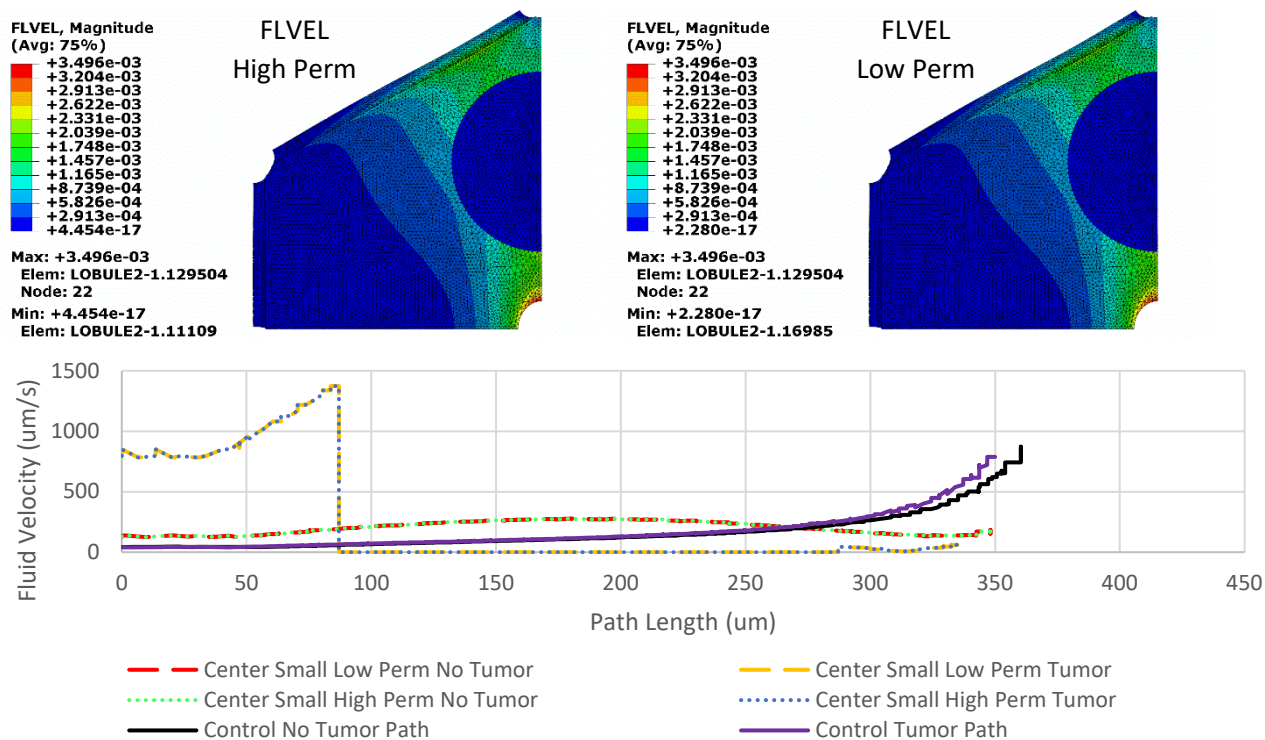
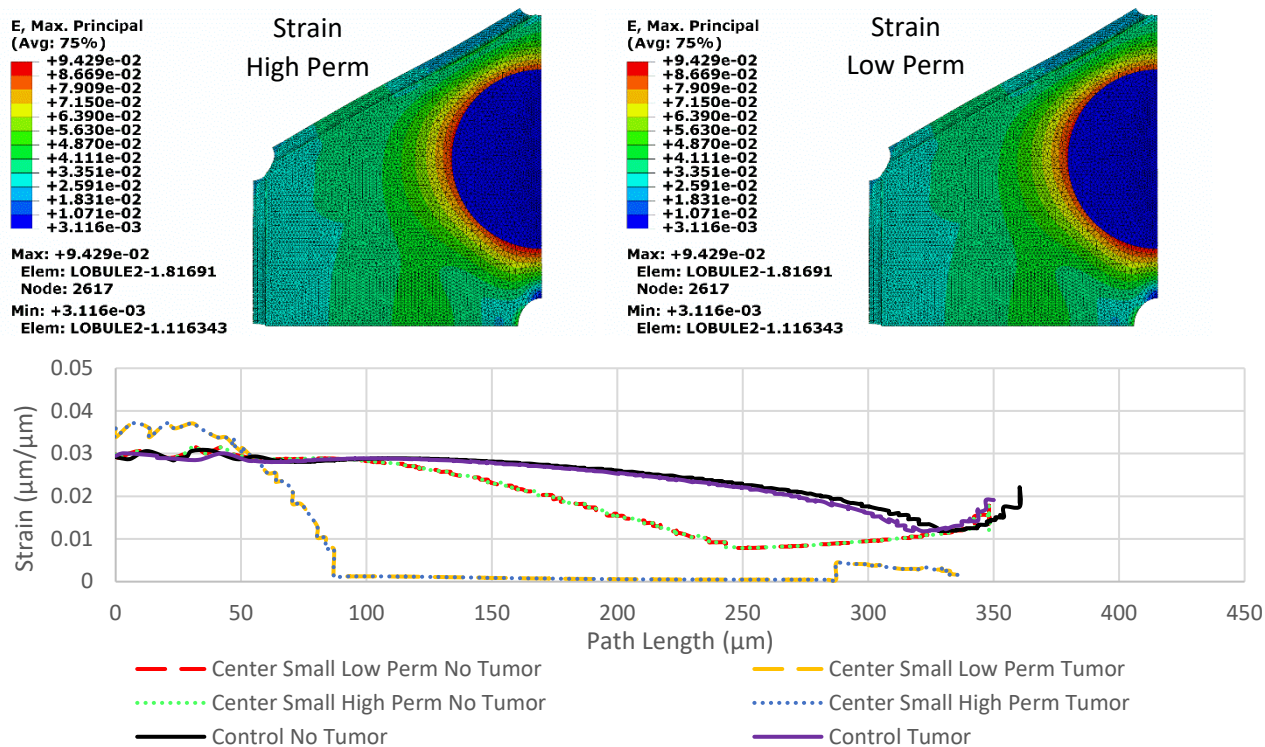


Figure S13. Images for the 50 μ m diameter tumor seed centered between the portal vein and central vein. Tumor was not set as a pressure source or sink. Images for (A) fluid velocity, (B) strain, (C) stress, and (D) pore pressure distribution throughout the quarter lobule. Graphs represent the fluid velocity and strain in the “tumor” and “no tumor” paths.

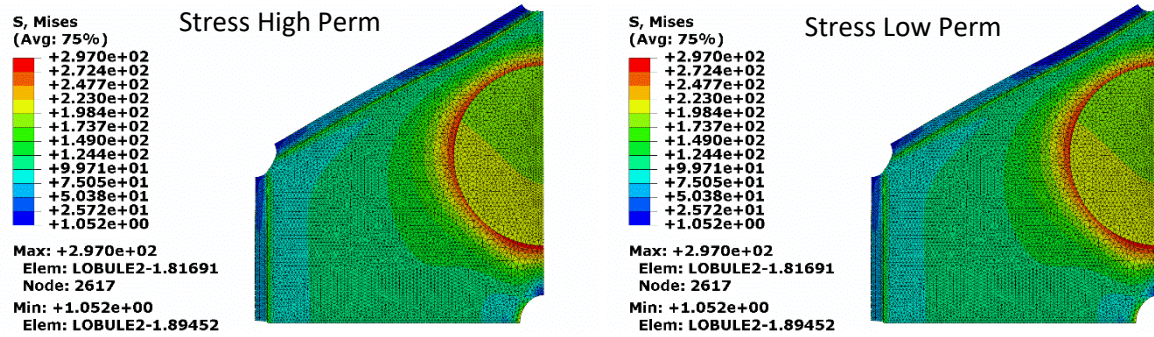
(A)



(B)



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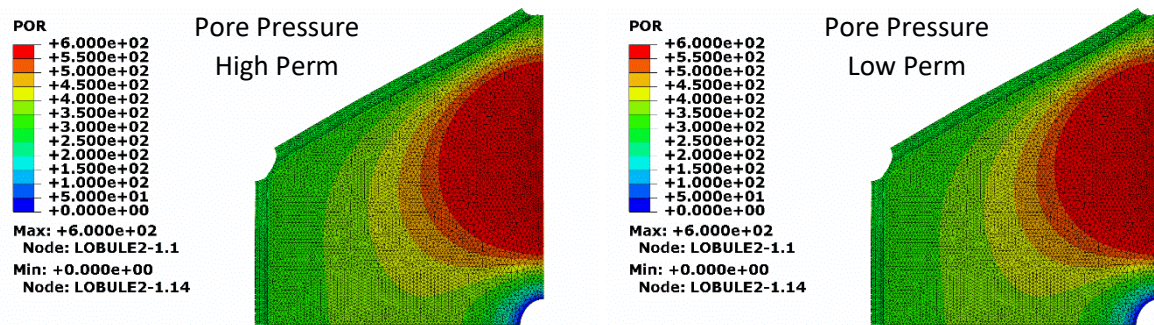
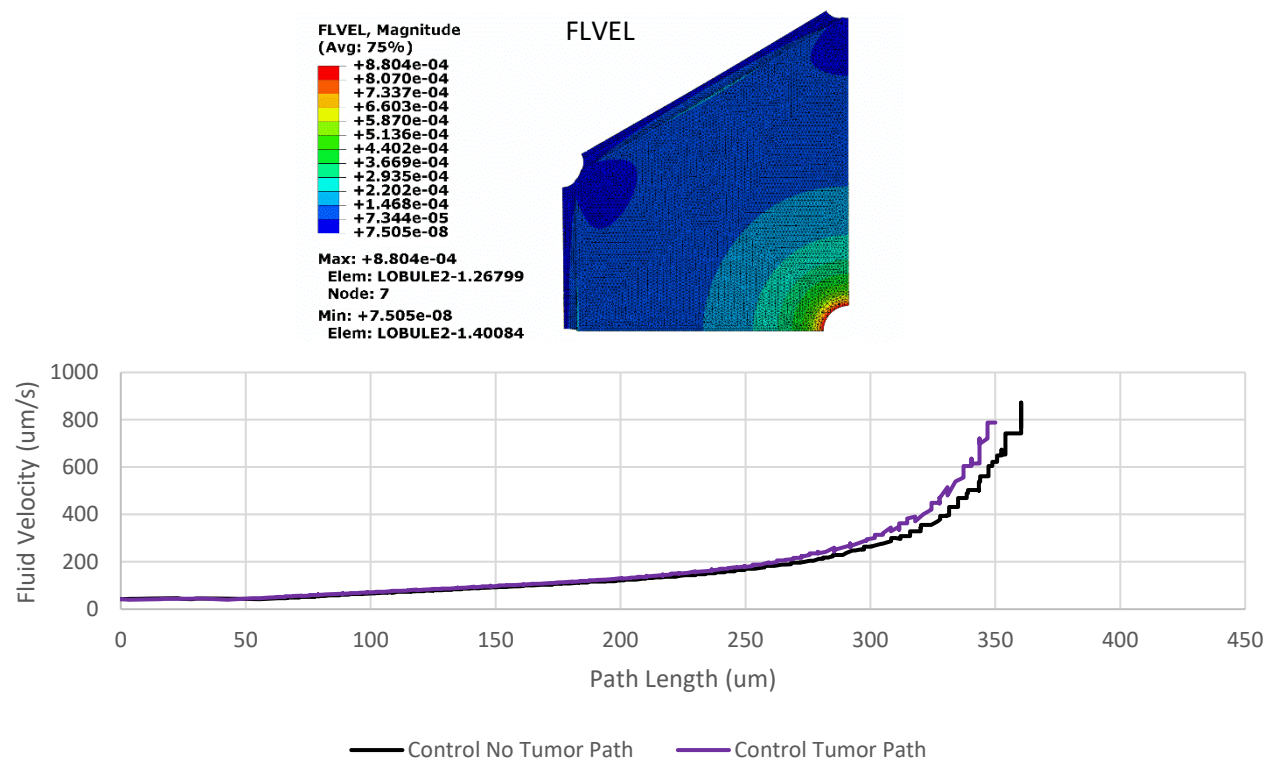
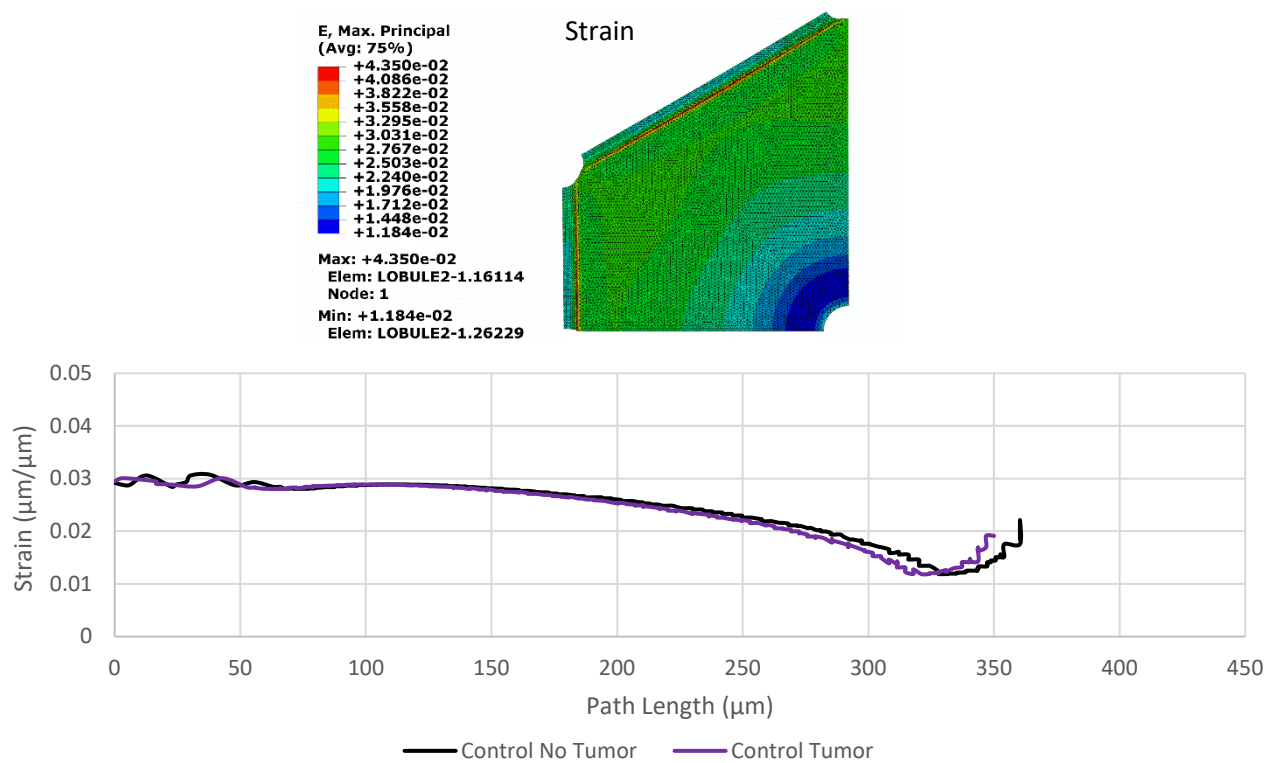


Figure S14. Images for the 200 μm diameter tumor seed centered between the portal vein and central vein. Tumor was set as a pressure sink. Images for (A) fluid velocity, (B) strain, (C) stress, and (D) pore pressure distribution throughout the quarter lobule. Graphs represent the fluid velocity and strain in the “tumor” and “no tumor” paths. Note the scale of fluid velocity is higher than other models.

(A)



(B)



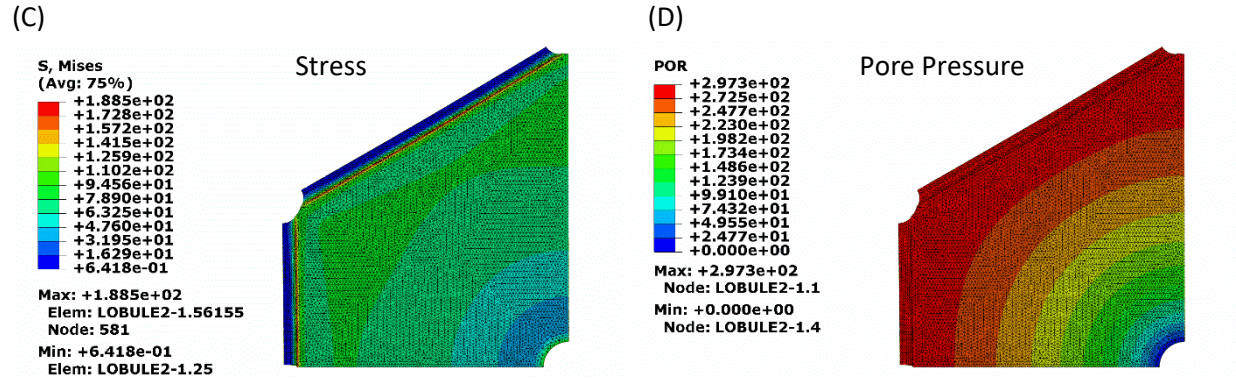


Figure S15. Images for the control lobule (there is no tumor anywhere in this model). Images for (A) fluid velocity, (B) strain, (C) stress, and (D) pore pressure distribution throughout the quarter lobule. Graphs represent the fluid velocity and strain in the “tumor” and “no tumor” paths (to keep path notation consistent with plots above). Data for control fluid velocity and strain can be found in other model graphs, but is also displayed here for clarity.

Supplemental Materials Bibliography

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