1. Introduction
   1. colon cancer metastasizes to the liver. big clinical problem. bad.
   2. unknown impact of TME, but known to impact
   3. new experimental platforms coming online to directly probe dynamics but they can't measure everything
   4. Where do mets most commonly seed? how do they alter the mechanics and flow of the liver? Is diffusion or advection more important in and around the tumor? How do cancer cells impact the surrounding hepatocytes? Tumor cells are often densely packed, but lower cell-cell adhesion. High or low relative permeability, and impact?
   5. math modeling as a way to fill in missing pieces, generate testable hypotheses
   6. past liver models have given limited insights, still not enough for crc mets
   7. In this work, we look at unique insights from two different models: PVE (for flow and mechanics) and ABM (for cell-cell interactions and dynamics). The traditional outlook on multiscale modeling is that small-scale, short-time models give insights for improving larger-scale, long-time models. Typically, an agent-based model is studied in great detail, and used to generate constitutive relations for more efficient, larger-scale continuum models that continue on to long simulation times. In this paper, we demonstrate that the converse can be just as important: that short-time continuum-scale models can give key insights to drive hypotheses in long-timescale, discrete models, which then give further insights to the continuum modeling.
2. Method
   1. PVE model:
      1. Problem geometry,
      2. Equations,
      3. Numerical method.
   2. PhysiCell:
      1. Problem geometry,
      2. Transport via BioFVM,
      3. Cell states (live/dead), cell types (tumor, and parenchyme (no individual hepatocytes and endothelial cells for now), volumes, mechanics via PhysiCell
3. Results
   1. Preliminary result: estimated radial oxygen profile in liver
      1. Solve radial PDE, BCs based on rat for now? , where **u** is the flow field (known by Jessica’s prior work), D is the O2 diffusion coefficient, and lambda is the unknown cell uptake rate in parenchyme. Assume quasi-steady, assume advection is much more than diffusion. Solve analytically in cylindrical coordinates. Choose lambda to match boundary conditions.
      2. This will be our pO2 conditions in regions with intact flow.
   2. Insights from the PVE model
      1. Starting assumptions hypotheses (discussion of unknown porosity, pressure source/sink)
         1. Previous tumor simulations and data show that small tumors tend to be in rapid growth with no necrosis.
         2. Prior models show that rapidly proliferating cells are a fluid pressure sink (lowengrub phase field, our volume model), so assume pressure sink for small tumors.
         3. Converse: big tumors are often necrotic, necrotic cells are shrinking and losing volume, so a fluid pressure source.
         4. Position unknown. Impact on flow, mechanics not yet studied.
      2. Parameter space investigation (Jessica, please reorder / rewrite)
         1. Low tumor permeability
            1. Tumor seed (50 micron diameter, about 8 packed cells), pressure sink, varied initial tumor position from portal triad to middle to edge. Show impact on flow, mechanics at tumor-tissue boundary.
            2. Small tumor (200 micron diameter, about 118 packed cells), pressure sink, varied initial tumor position.
            3. Small tumor (200 micron diameter), pressure source, varied initial tumor position
            4. Medium tumor (400 micron, about 472 packed cells), pressure source, varied initial tumor position
         2. High tumor permeability
            1. Tumor seed (50 micron diameter, about 8 packed cells), pressure sink, varied initial tumor position from portal triad to middle to edge. Show impact on flow, mechanics at tumor-tissue boundary.
            2. Small tumor (200 micron diameter, about 118 packed cells), pressure sink, varied initial tumor position.
            3. Small tumor (200 micron diameter), pressure source, varied initial tumor position
            4. Medium tumor (400 micron, about 472 packed cells), pressure source, varied initial tumor position
   3. Insights from the PhysiCell model
      1. Assumptions based on PVE model
         1. Assume the radial oxygen profile (radial outward from portal triads) where flow is intact by PVE model
         2. Assume hepatocyte apoptosis at tumor-parenchyme interface, if high stresses.
      2. Dynamical simulations: several lobules.
         1. Growth from small seed at a few starting locations, low tumor permeability
         2. Growth from a small seed at a few starting locations, high tumor permeability
         3. Smaller 3D version (optional)
         4. More detailed 2D liver geometry (optional)
   4. Refined PVE insights (optional refinement section)
4. Discussion and Future Plans
   1. Lessons learned
   2. Important of open data, open source codes – tricky stuff
   3. Future directions
      1. Need to dynamically couple
      2. Need to add endothelial cells
      3. Need better segmented liver lobule tissue
   4. other?
5. Supplementary Materials
6. Full summary of parameters
   1. PVE parameters
   2. Digital cell lines for HCT116, hepatocytes
   3. Calibration from DCLs
7. Open source software/source code (where applicable)
8. Open simulation output data?