3 Second approach: Agent-based (PhysiCell) model Paul,Hermann

Short intro. 1 pararaph at most. Note difficulty of adding interstitial flow at this scale. Kasia Rejnia did it with IBcell, but very small domains. Hermann did it in continuum tumor growth model. Jessica did it above in static tumor models. We're doing first-of-its-kind 1 cm2 simulations, hundreds of lobules. So, we use insights from above to come up wtih good approximation.

3.1 Method

Describe the model of several liver lobules. Include overall geometry, overall approach:

1. Model flow as quasi-steady, due to fast time scale
2. Approximate flow as radially symmetric profile in each liver lobules, and extrapolate out to liver boundaries
3. Assume biotransport is

3.1.1 Integrating PVE insights: biotransport model

We model biotransport in the liver tissue based upon the insights gained from the PVE model; see Section **??**. In regions not occupied by tumor tissue, we assume that hepatic blood and interstitial flow are intact. (Hereafter, we refer to hepatic blood and interstitial flow collectively as "flow" for simplicity.) Moreover, we can assume that on the time scale of tissue mechanics (minutes to hours) and tumor cell proliferation (hours, days, and weeks), that flow occurs on a much faster time scale (seconds), and so biotransport is at quasi-steady state. Moreover, we will approximate flow as radially-symmetric in lobules not obstructed by tumor. Thus, we approximate $\mathbf{u} = -u(r)\hat{\mathbf{r}}$, where $\hat{\mathbf{r}}$ is the radial unit vector (oriented outward from the nearest central vein), and $u(r)$ is the non-negative radial speed profile.

We model the transport of a single growth substrate σ (e.g., oxygen or glucose) in the tissue with

$$\frac{\partial \sigma}{\partial t} = -\nabla \cdot \mathbf{J} - \lambda \sigma \tag{1}$$

$$\mathbf{J} = -D\nabla\sigma + \sigma\mathbf{u}, \tag{2}$$

where $\mathbf{J}$ is the growth substrate flux, λ is its consumption rate, and D is its diffusion coefficient, which we assume is constant.

To understand the relative contribution of the diffusional term in unobstructed flow, we nondimensionalize space with scale L, time with scale $\bar{t}$, and the flow with typical magnitude $\bar{u}$. With these scales, Equations 1-2 become

$$\frac{\partial \sigma}{\partial t} = \left(\frac{D\bar{t}}{L^2}\right)\nabla^2\sigma - \left(\frac{\bar{u}\bar{t}}{L}\right)\nabla\cdot(\sigma\mathbf{u}) - (\lambda\bar{t})\,\sigma. \tag{3}$$

Choosing

$$\frac{u\bar{t}}{L} = 1 \text{ and } \lambda\bar{t} = 1 \Longrightarrow \bar{t} = \frac{1}{\lambda} \text{ and } L = \frac{u}{\lambda}, \tag{4}$$

then the nondimensionalized equation becomes

$$\frac{\partial \sigma}{\partial t} = \left(\frac{D\lambda}{\bar{u}^2} \right) \nabla^2 \sigma - \nabla \cdot (\sigma \mathbf{u}) - \sigma. \tag{5}$$

By (Ghaffarizadeh et al. 2016), $D \sim 10^5 \mu\text{m}^2/\text{min}$ and $\lambda \sim 10\ \text{min}^{-1}$. By the PVE work in Section **??** and (Nishii et al. 2016), $\bar{u} \sim 10^{-4}\text{m/sec} \sim 10^4\ \mu\text{m/min}$. The diffusion term has relative order of magnitude

$$\frac{D\lambda}{\bar{u}^2} \sim 10^{-2}. \tag{6}$$

Thus, in unobstructed regions of liver lobule, flow is primarily advective-reactive, and we can simplify the original equation to

$$\frac{\partial \sigma}{\partial t} = -\nabla \cdot (\sigma \mathbf{u}) - \lambda\sigma. \tag{7}$$

Next, assuming incompressible flow ($\nabla \cdot \mathbf{u} = 0$) and that $\mathbf{u} \approx -u(r)\hat{\mathbf{r}}$, we have

$$\frac{\partial \sigma}{\partial t} = u(r) \nabla\sigma \cdot \hat{\mathbf{r}} - \lambda\sigma \tag{8}$$

$$= u(r) \frac{\partial \sigma}{\partial r} - \lambda\sigma. \tag{9}$$

Under quasi-steady conditions, $\sigma = \sigma(r)$, and we have

$$0 = \sigma'(r) - \frac{\lambda}{u(r)}\sigma, \Longrightarrow \tag{10}$$

whose analytical solution is given by

$$\sigma(r) = ce^{\lambda \int_0^r \frac{1}{u(s)} ds} \tag{11}$$

for some constant c.

For simplicity, we will approximate the flow profiles in Section **??** with the form

$$u(r) \approx ae^{-br} \tag{12}$$

for constants a and b. Notice that $u(0) = a$ and $u(R) = ae^{-bR} = u(0)e^{-bR}$, whereby

$$b = -\frac{\ln\left(\frac{u(R)}{u(0)}\right)}{R}. \tag{13}$$

For consistency with the PVE model, we set $R = 400\ \mu\text{m}$.

For this simplified form, we have

$$\sigma(r) \approx ce^{\frac{\lambda}{ab}\left(e^{br}-1\right)}. \tag{14}$$

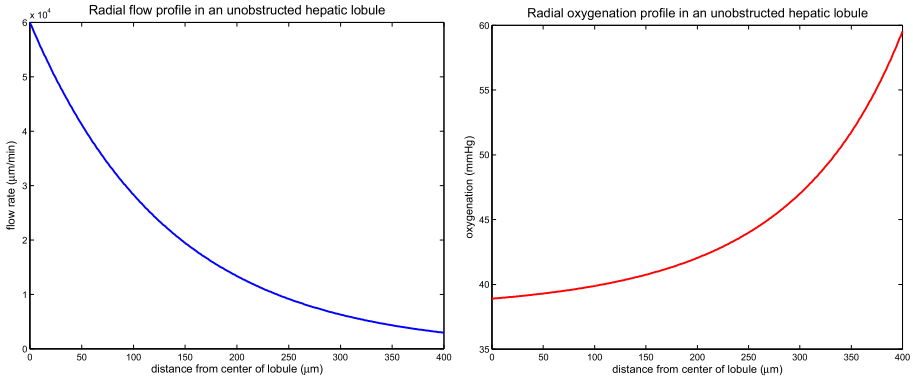

Fig. 3 Sample flow profile (left) and oxygenation profile (right) in a hepatic lobule, under the flow assumptions derived from the PVE model.

In Section **??**, we see that $\frac{u(R)}{u(0)}$ is on the order of 0.01 to 0.1, so we choose 0.05. Thus, $b \sim 0.0075\,\mu\text{m}^{-1}$ by Equation 13. Moreover, $u(0) = a \sim 10^{-3}$ m/sec $= 6 \times 10^4\,\mu$m/min. Tsukada and Suematsu (2012) reports that liver oxygenation is approximately 38.9 mmHg in central venules, 48.2 mmHg in sinusoids, and 59.8 mmHg in portal venules. So, we set $\sigma(0) = 38.9$ mmHg:

$$u(r) = 6 \times 10^4 e^{-0.0075r} \tag{15}$$

$$\sigma(r) = 38.9e^{0.0223\left(e^{0.0075r}-1\right)}. \tag{16}$$

We plot the radial flow and oxygenation profiles for these parameters in a hepatic lobule with radius $R = 400\,\mu$m in Fig. 3; note that $\sigma(R) \approx 60$ mmHg, comparable to the portal venule oxygenation reported in Tsukada and Suematsu (2012).