Supplemental Materials

**Derivation of diffusion within a concentrated solution**

For a dilute solution, flux of a solute in the x-direction is proportional to the diffusion coefficient and the gradient of concentration, as defined by Fick’s law

\[ J_{i,x} = -D_{ij} \frac{dc_i}{dx} \]  
(Eq. S1)

In a concentrated solution, solute-solute interactions can no longer be ignored, therefore the driving force for flux is not concentration gradient, but the gradient in chemical potential.

\[ J_{i,x} = \frac{d\mu_i}{RT} \frac{d\mu_i}{dx} \]  
(Eq. S2)

where \( \mu_i \) is the chemical potential described by

\[ \mu_i = \mu_i^0 + RT \ln(\gamma_i \chi_i) \]  
(Eq. S3)

where \( \mu_i^0 \) is the reference chemical potential, \( \gamma_i \) is the activity coefficient for the solute-solute (cell-cell) interactions, and \( \chi_i \) is the mole fraction of the cells (Truskey et al., 2004). \( \mu_i^0 \) can be arbitrarily set to zero and \( RT \) is constant, therefore

\[ J_{i,x} = -\frac{D_{ij}c_i}{RT} \left( \frac{d\ln(\gamma_i \chi_i)}{dx} \right) = -D_{ij}c_i \left( \frac{d\ln(\gamma_i \chi_i)}{dx} \right) \]  
(Eq. S4)

By the chain rule

\[ J_{i,x} = -\frac{D_{ij}c_i}{\gamma_i \chi_i} \left( \frac{d(\gamma_i \chi_i)}{dx} \right) \]  
(Eq. S5)

By the product rule

\[ J_{i,x} = -\frac{D_{ij}c_i}{\gamma_i \chi_i} \left( \chi_i \frac{dy_i}{dx} + \gamma_i \frac{d\chi_i}{dx} \right) \]  
(Eq. S6)

Assuming \( y_i \) is a function of \( \chi_i \)

\[ \frac{dy_i}{dx} = \frac{dy_i}{d\chi_i} \frac{d\chi_i}{dx} \]  
(Eq. S7)

Therefore
\[ J_{i,x} = -\frac{D_{ij}c_i}{\gamma_i\chi_i} \left( \chi_i \frac{d\gamma_i}{d\chi_i} + \gamma_i \right) \frac{d\chi_i}{dx} \]  
(Eq. S8)

\[ C_i = \chi_i C \]  
(Eq. S9)

where \( C \) is the total molar concentration of all species, then

\[ J_{i,x} = -D_{ij}C \left( \frac{\chi_i}{\gamma_i} \frac{d\gamma_i}{d\chi_i} + 1 \right) \frac{d\chi_i}{dx} \]  
(Eq. S10)

Using the fact that the derivative of the natural log of \( y \) is \( 1/y \) we can simplify the problem to

\[ J_{i,x} = -D_{ij}C \left( \frac{d\ln\gamma_i}{d\ln\chi_i} + 1 \right) \frac{d\chi_i}{dx} \]  
(Eq. S11)

and by differentiating Eq. S9,

\[ C \frac{d\chi_i}{dx} = \frac{dC_i}{dx} \]  
(Eq. S12)

so that

\[ J_{i,x} = -D_{ij} \frac{dC_i}{dx} \left( \frac{d\ln\gamma_i}{d\ln\chi_i} + 1 \right) \]  
(Eq. S13)

\[ D_{app} = -\frac{J_{i,x}}{\frac{dC_i}{dx}} = D_{ij} \left( \frac{d\ln\gamma_i}{d\ln\chi_i} + 1 \right) \]  
(Eq. S14)

Assuming a simple linear relationship between \( \gamma_i \) and \( \chi_i \) where the intercept is 1 (dilute solutions are assumed to be ideal with an activity coefficient of 1)

\[ \gamma_i = \beta \chi_i + 1 \]  
(Eq. S15)

and simplifying with the chain rule, we get

\[ D_{app} = D_{ij} \left( \frac{\beta \chi_i}{\beta \chi_i + 1} + 1 \right) \]  
(Eq. S16)

The maximum interaction would occur when mole fraction \( \chi_i \) equals 1. As \( \beta \) tends to infinity we approach the upper limit of \( D_{app} \) where

\[ \beta \rightarrow \infty \]

\[ D_{app} \rightarrow 2D_{ij} \]  
(Eq. S17)
Thus, a classic thermodynamic approach for concentrated solutions that uses an activity coefficient model predicts at most a 2-fold effect of crowding on the apparent diffusion coefficient.

Reference
Supplemental Figure 1. Progeny trees of simple overlapping model

Sample outputs of simulations for all 15 parameter sets tested in the simple overlapping model. Rows display identical input diffusion coefficients. Columns display identical input proliferation rates. The time scale of each column is adjusted to display the time needed to achieve six generations of cell division for that particular nominal proliferation rate. Black curves indicate individual cell centroid locations, and red dots indicate the time and location of a division event.
Supplemental Figure 2. Progeny trees of the overlapping + carrying capacity model

Sample outputs of simulations for all 15 parameter sets tested in the overlapping + carrying capacity (cc) model. Rows display identical input diffusion coefficients. Columns display identical input proliferation rates. The time scale of each column is adjusted to display the time needed to achieve six generations of cell division for that particular nominal proliferation rate. Black curves indicate individual cell centroid locations, and red dots indicate the time and location of a division event.
Supplemental Figure 3. Progeny trees of the non-overlapping model

Sample outputs of simulations for all 15 parameter sets tested in the non-overlapping model. Rows display identical input diffusion coefficients. Columns display identical input proliferation rates. The time scale of each column is adjusted to display the time needed to achieve six generations of cell division for that particular nominal proliferation rate. Black curves indicate individual cell centroid locations, and red dots indicate the time and location of a division event.
Supplemental Figure 4. Long term behavior of simulations
Progeny trees for the overlapping+cc model and the non-overlapping model evaluated at $p_0=1000$ divisions/month with varying diffusion values as indicated on the figure. Jammed behavior continues at long times for the non-overlapping model and an effective convective velocity allows cells to spread faster than in the overlapping+cc model. In the non-overlapping model, proliferating cells (red dots) are only present at the tumor edges, while they are present throughout the tumor in the overlapping+cc model.
Supplemental Figure 5. Effect of simulation time interval on cell velocity estimates

Plots of velocity versus distance from the tumor edge evaluated at different time intervals. All values are measured from the same set of simulations for the non-overlapping model with input parameters \( D_0 = 20 \, \mu\text{m}^2/\text{hour} \) and \( p_0 = 10 \) divisions/month. Only \( \Delta t \) is varied for the calculation of instantaneous velocity. As \( \Delta t \) is increased, the data become less noisy, due to longer time averaging in the velocity calculation, and a ballistic tumor front becomes apparent. The simulations show that the results are insensitive to the time step used.
Supplemental Figure 6. Tumor velocity in non-overlapping model compared to Fisher’s Approximation

Velocity data of the non-overlapping model were compared to theoretical tumor margin velocities based on the Fisher Approximation \( (v = \sqrt{2pD}) \). Values in the heatmap are calculated as the ratio of simulated data to theoretical approximation to show the fold-increase in velocity with the non-overlapping assumptions.
Supplemental Movie Captions

**Supplemental Movie 1. Simulation of the simple overlapping model**
Movie of a sample simulation output of the simple overlapping model evaluated at $D_0=20\ \mu \text{m}^2/\text{hour \ and\ } p_0=10$ divisions/month. Each cell is represented by two spheres of the same color that gradually separate as the cell grows. A cell division event is indicated by a change in color.

**Supplemental Movie 2. Simulation of the overlapping \+ carrying capacity model**
Movie of a sample simulation output of the overlapping \+ carrying capacity model with parameter values and color rendering as in Movie 1.

**Supplemental Movie 3. Simulation of the non-overlapping model**
Movie of a sample simulation output of the non-overlapping model with parameter values and color rendering as in Movie 1.