**Next steps spheroid model.**

Features to include in minimal model

1. Cell-cell (CC) contacts vs cell-matrix (CM) contacts. Cells adhere both to each other and to the matrix. High CC is associated with fluid (dense) phase. ‘Open space’ (matrix without cells) around (part of) a cell promotes (increases) CM and suppresses CC.
2. Motility. Cells with higher CM move actively. The direction seems to be mostly radially outward. The mechanism for this is rho/rac activation by extracellular matrix stiffness. The idea is that when cells experience high ECM stiffness, this promotes the formation of more actin for stress fibers, which are needed for propulsion. Thus more matrix exposure also (via a pathway) promotes higher motility.
3. Initially, there is a uniform density of mostly collagenous ECM. Cells deposit fibronectin ECM and do so more in the core of the spheroid. Question: how do we identify core cells, geometrically (distance from center of mass < some value) or in terms of local structure (cell density, # of cell-cell contacts?). Cells in the core deposit fibronectin but only in the thin spaces between cells. This is not enough to stiffen under force, so does not promote motility. It may however produce enough CM to hold off cell death.
4. Invasion: leaders and followers. Leaders drill a hole through the (collagen) matrix, adhere strongly with CC to followers making it easier for followers to take the same path. Observation (mostly in the treated systems iirc): invasion fingers disintegrate (become ‘gas-like’) suggesting that the CM cues override CC more strongly in this case?
5. Survival: low oxygen promotes cell death. High CM promotes cell survival. Need to include a threshold low-oxygen tolerance that is lower for high CM.

Starting point could be the ECM modification + Leader/Follower system described here (includes anisotropy of matrix, fiber orientation, density). Leaders can modify matrix.

<https://nanohub.org/resources/physicellecm>

Need to look into matrix degradation/production implementation here. Can we reproduce the ‘tunnel digging’?

Should first try to reproduce normal spheroid growth and then see which parameters are likely changed by interventions (radiation/genetic).

What is the role of fibronectin?

We do not need to manually distinguish Leader/Follower, but make use of the coupling between CC or CM with