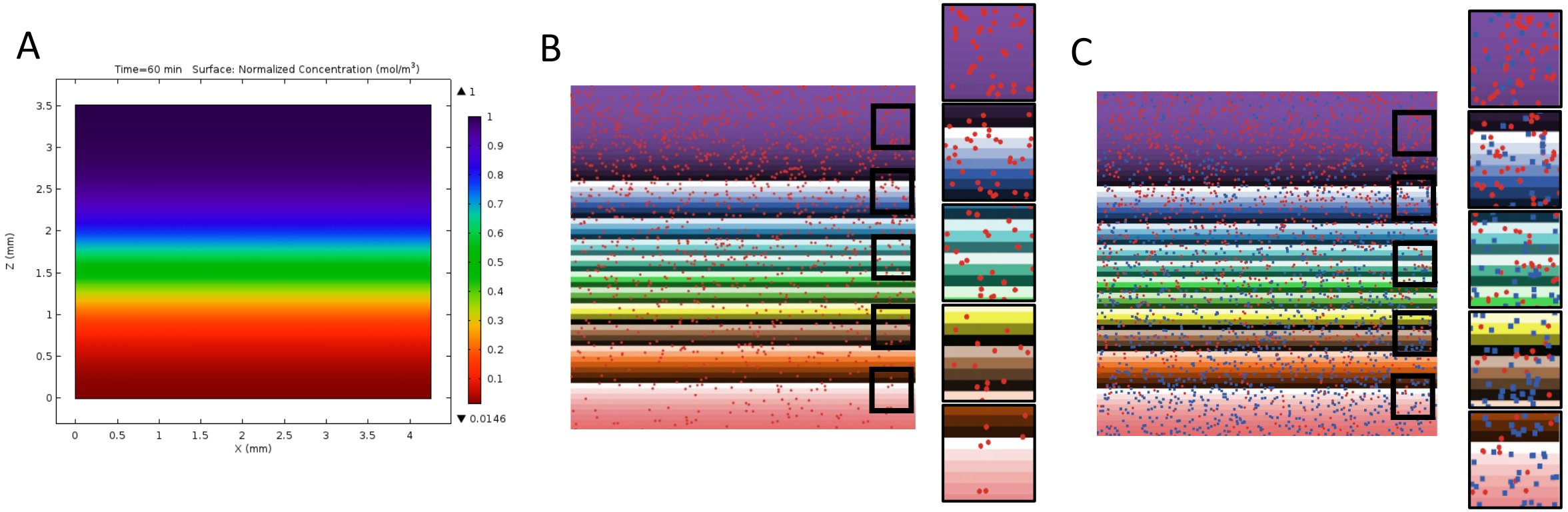

Figure S1| Development of an agent-based model to predict cancer cell response to doxorubicin in 3D tumor bulk to stroma transition environments.
(A) Diffusion-convection concentration gradient developed in Comsol within a simulated 3D hydrogel. **(B)** The agent based model incorporates concentration profiles and cancer cells for time dependent cell viability determination. Single culture condition incorporates varied cancer cell numbers decreasing from the top to the bottom of the gel. Fibroblasts are neglected. **(C)** The agent based model incorporates concentration profiles, fibroblasts, and cancer cells for time dependent cell viability determination. The coculture condition incorporates varied cancer cell numbers, decreasing from the top to the bottom of the gel and varied fibroblast number decreasing from the bottom to the top of the gel.

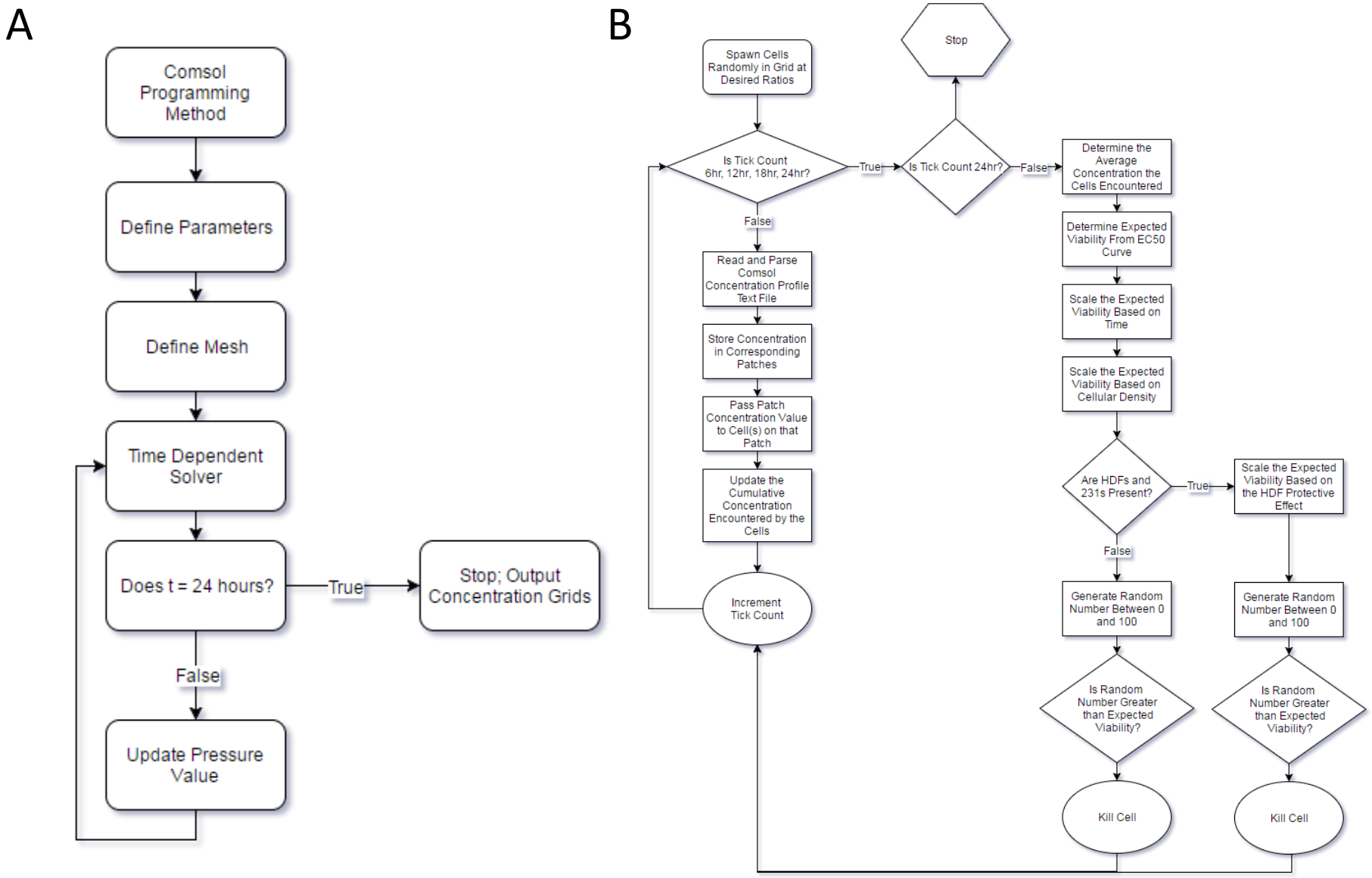

Figure S2| Logic flow charts for *in silico* modelling.
(A) Comsol programing method for development of spatial and time dependent concentration gradients for use in associated agent based models. **(B)** Logic flowchart for agent based models of doxorubicin treatment within collagen/bme hydrogels incorporating Comsol drug concentration profiles and experimental viability equations (Table 2).

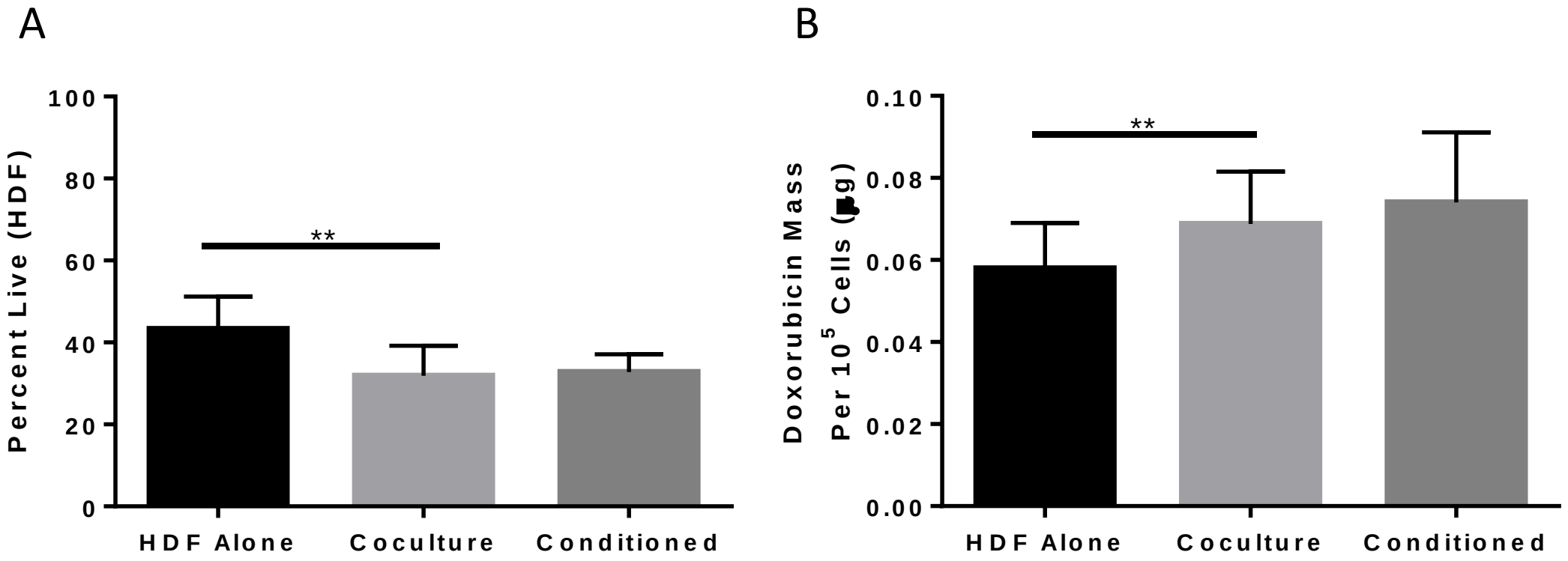

Figure S3| Fibroblast viability is lessened in the presence of cancer cells within hanging-well 2D culture

MDA-MB-231 cells and HDFs are cocultured independent of contact for 24 hours prior to 10uM doxorubicin treatment. In the conditioned experimental group, the 231s are removed prior to dosing chemotherapy. **(A)** Percentage of live HDFs after 6 hours of doxorubicin chemotherapy treatment (n=5). **(**B) Uptake of doxorubicin following 6 hours of treatment, here the total mass of uptake accounts for ~10% of the total available extracellular doxorubicin (n=6). Data are represented as mean ±SEM. ** $p<0.01$, by post-hoc paired t-test following two-way ANOVA

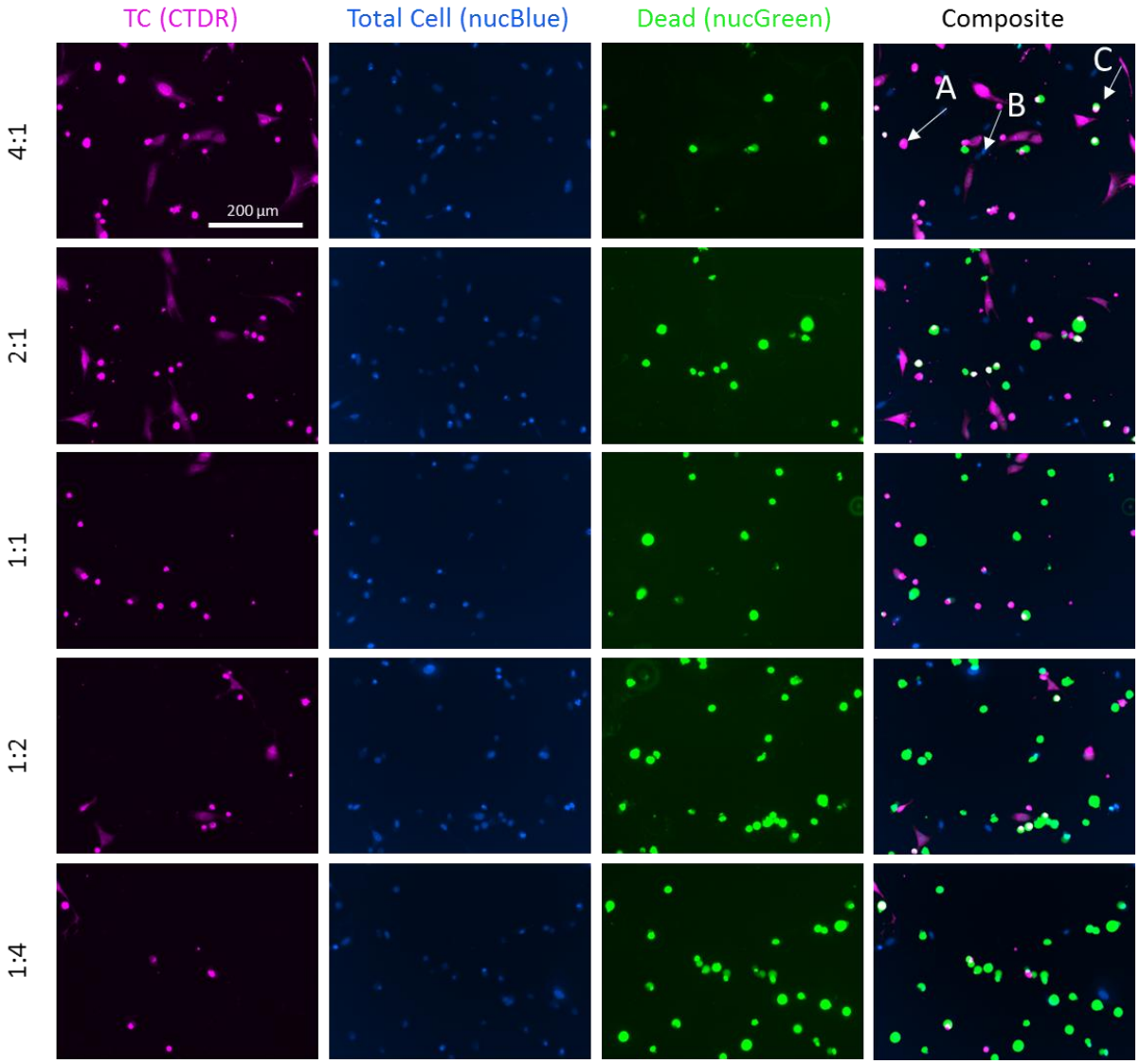

Figure S4| Sample panel for image analysis in 2D coculture experiments.
Sample images for live/dead analysis within 2D coculture systems (See Figure 2a). Here the experimental conditions are portrayed. The first column indicates the total cancer cells stained with deep red cell tracker. The second column indicates the total nuclei of all cells stained with a nucBlue indicator. The third column indicates dead cells labelled with nucGreen. The fourth column shows the composite image. Dead cancer cells were determined by localization of all three channels **(C)**. **(B)** Indicates a fibroblast cell, and **(A)** indicates a cancer cell.

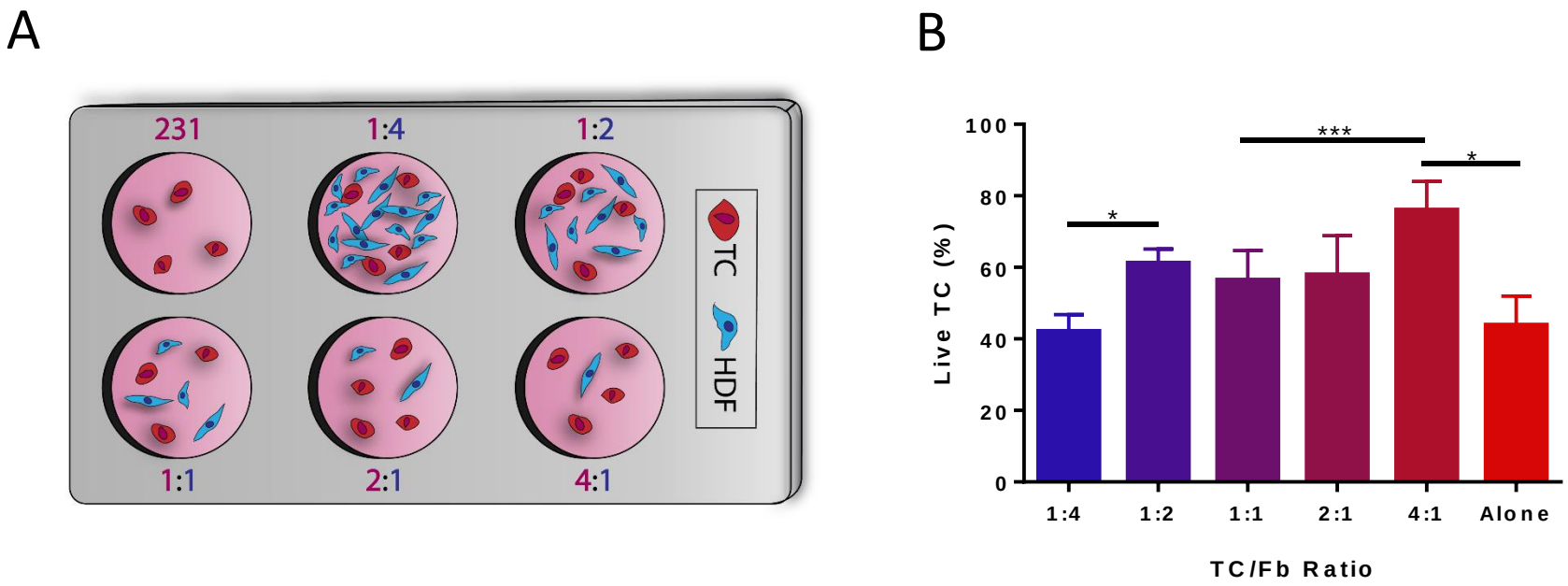

Figure S5| In single co-culture, the ratio of tumor cells to fibroblasts alters the viability of tumor cells in response to doxorubicin treatment. **(A)** Schematic of constant total cancer cell seeding density: Cells were seeded in a culture dish with the total number of cancer cells held constant. Fibroblast cell numbers were adjusted relative to the cancer cells. Fibroblasts are represented in blue, cancer cells in red. **(B)** Live TCs assessed by nuclear dead stain +/- doxorubicin (10µM) after doxorubicin application for 6 hours with varied ratios of TC:Fb in 2D (n=3). Data are represented as mean ±SEM. *p<0.05, ****p<0.0001 by post-hoc unpaired t-tests following two-way ANOVA.

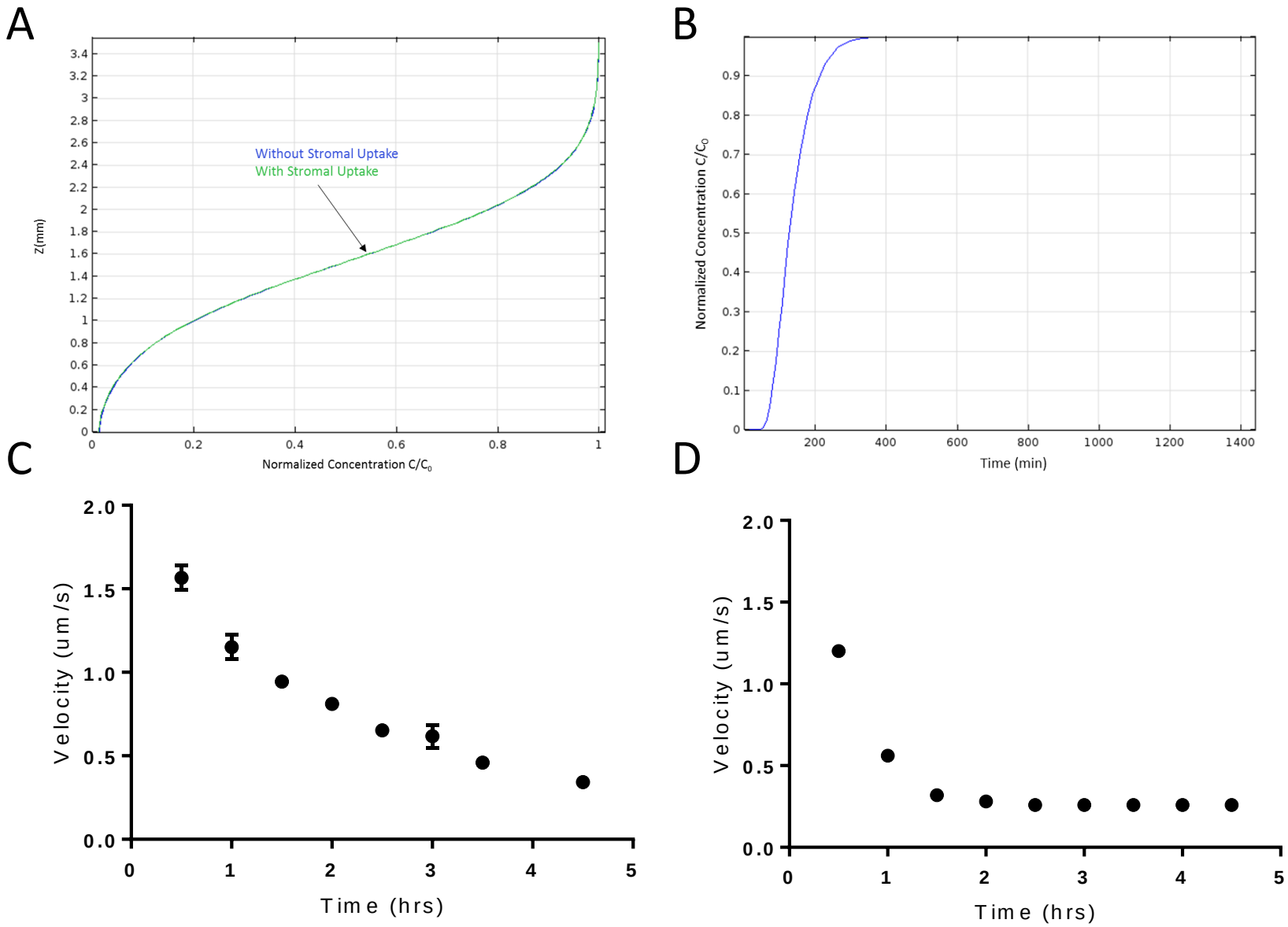

Figure S6| Velocity and concentration profiles characterization in 3D gels.
(A) Normalized Comsol drug concentration within a simulated cancer cell and fibroblast coculture hydrogel at varied depths with and without a stromal uptake reaction term at 60 minutes of simulation. (R = 2.75e-7 mol/(m^3*s)). **(B)** Minimum concentration in the hydrogel over time; saturation is reached at 350 minutes of simulation. **(C)** Superficial velocity within the 3D breast mimetic hydrogels determined from volume collected at the bottom of the transwell (n=6). Data are represented as mean ±SEM. **(C)** superficial velocity output from Comsol model.

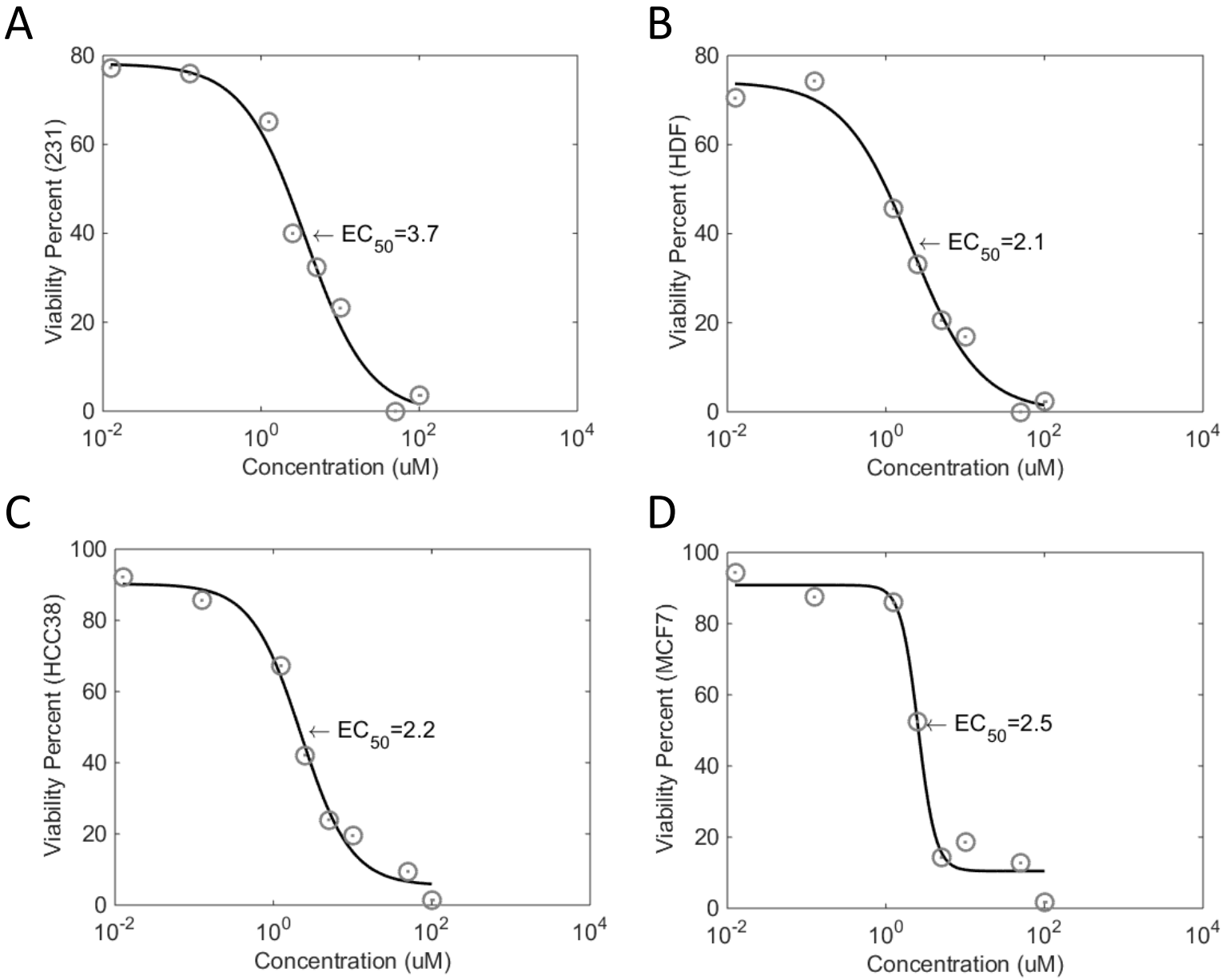

Figure S7| 2D doxorubicin EC50 curves for HDFs and MDA-MB-231 incorporated into the agent based models
(A) Dose response curves following 24 hours of treatment for **(A)** MDAMB231, **(B)** HDF, **(C)** HCC38, and **(D)** MCF7 cells at varied concentrations of doxorubicin (n=3). Data are represented as the mean of 3 independent trials. Curve fits were determined using an EC50 curve fitting Matlab algorithm.

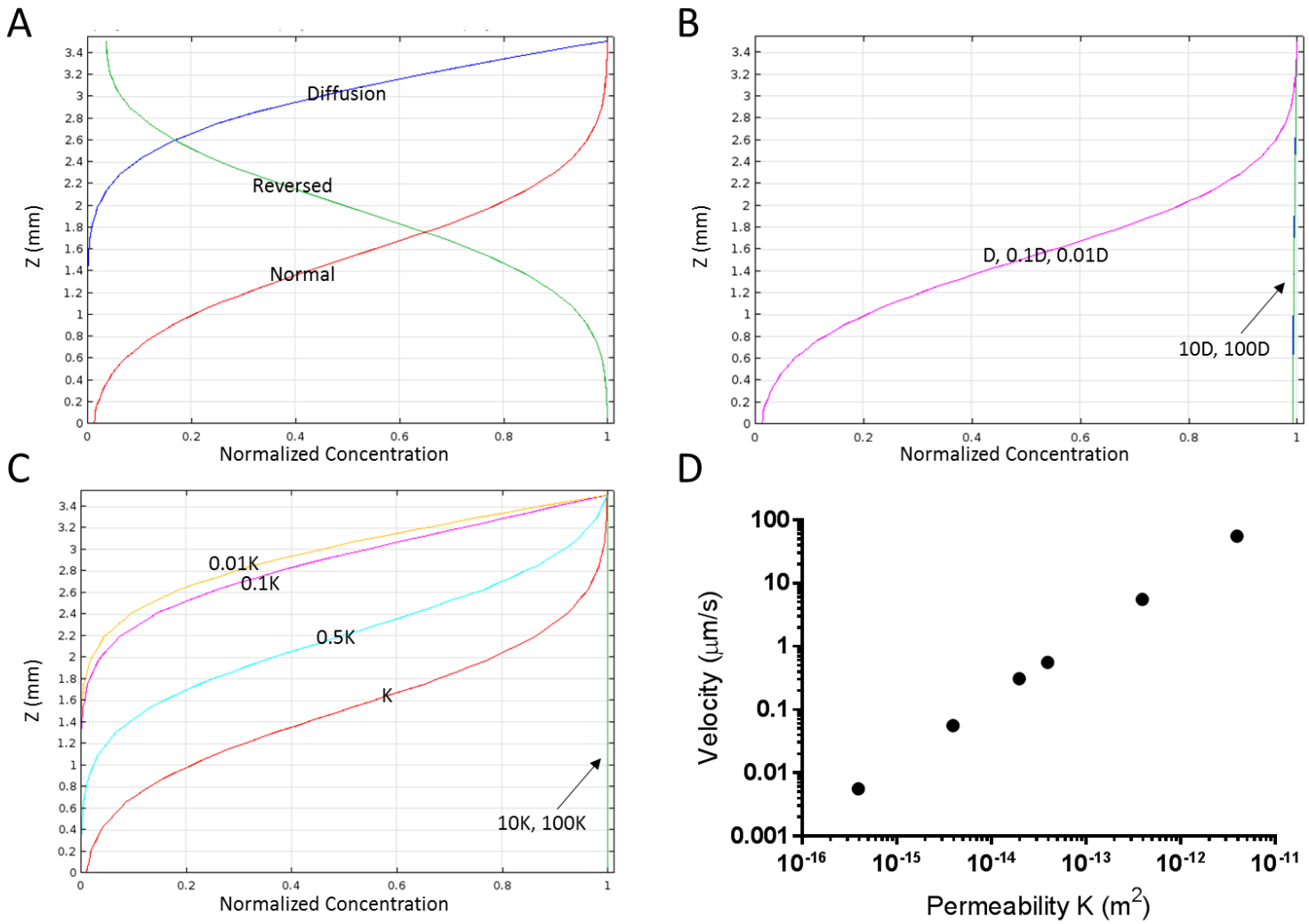

Figure S8| The agent-based model reveals complex interactions between transport properties and concentration profiles. Normalized drug concentration within a simulated cancer cell and fibroblast coculture layered gel at varied depths for varied **(A)** types of transport, **(B)** diffusion coefficients, and **(C)** permeability coefficients. Data is represented at 60 minutes. D indicates baseline diffusion coefficient value (6 e^{-11} [m^2/s]), and K represents baseline permeability coefficient value (3.19 e^{-14} [m^2]). **(D)** Simulated fold changes in permeability relate to comparable fold changes in fluid velocity through the simulated hydrogel. The arrow indicates the baseline permeability (3.19 e^{-14} [m^2])