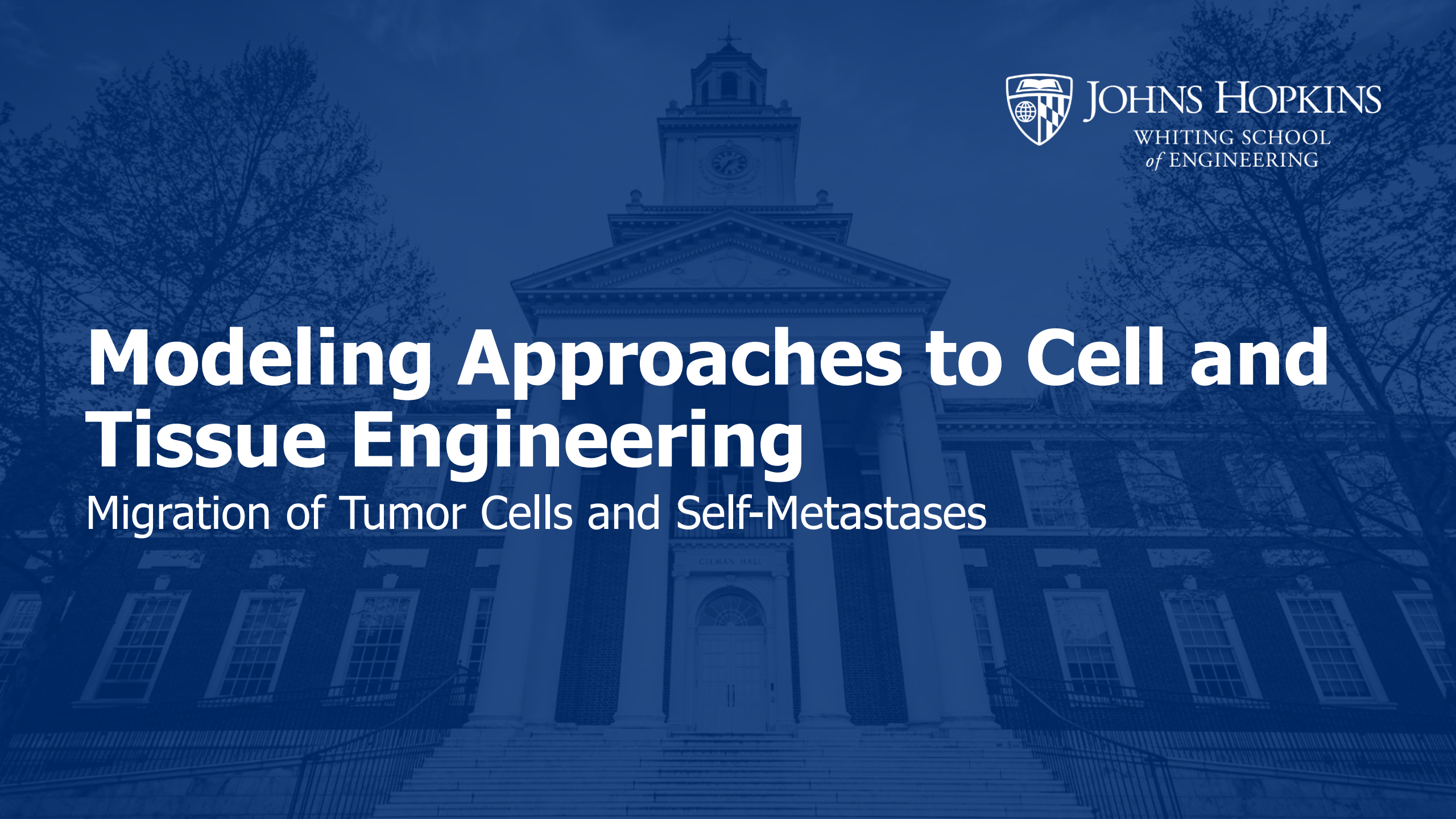

JOHNS HOPKINS
WHITING SCHOOL
of ENGINEERING

Modeling Approaches to Cell and Tissue Engineering

Migration of Tumor Cells and Self-Metastases

Migration of Cancer Cells and Self-Metastases

Alexander A. Spector (From Enderling et al., 2009)

1. Main model parameters
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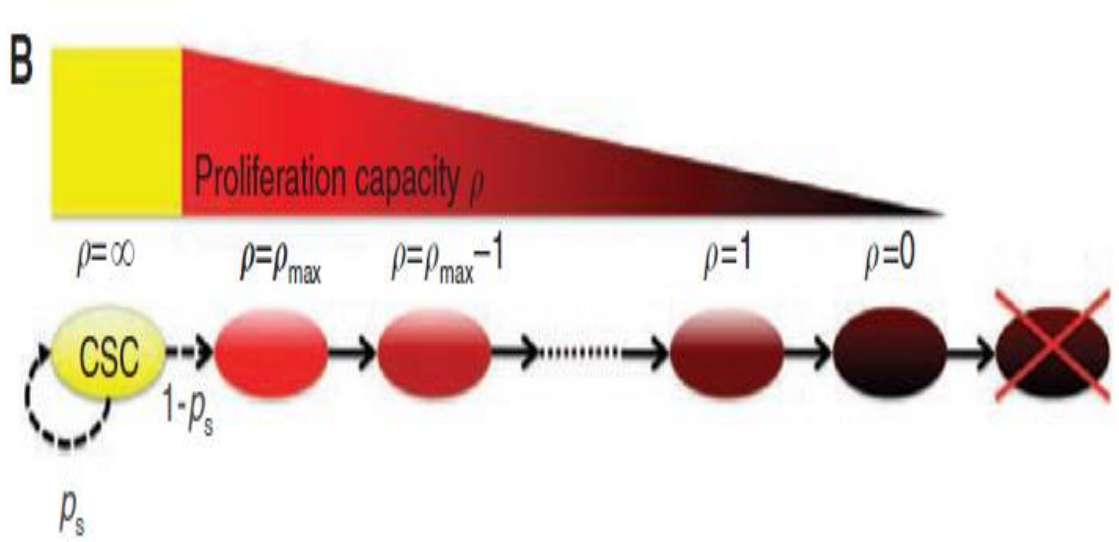
6. Example of the modeling of tumor growth (3-D,b)

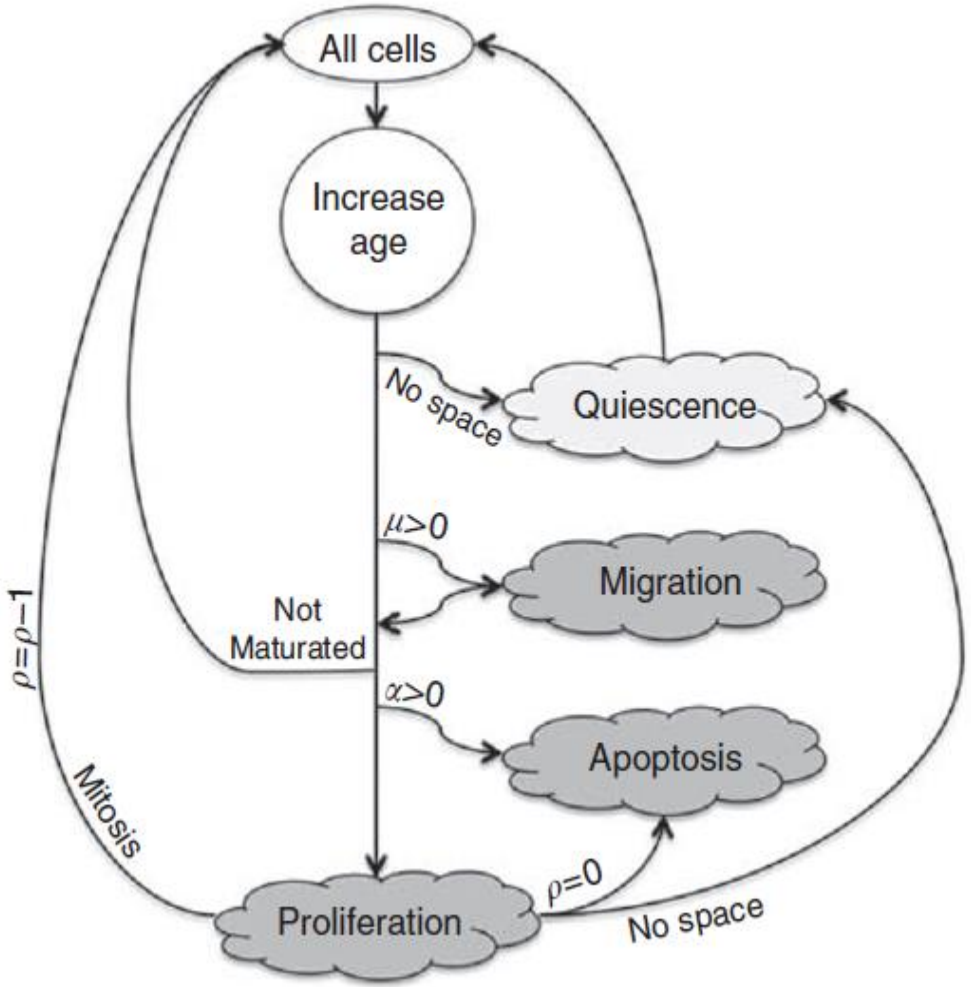
Cancer Stem Cell Division

Figure 1. In light of evidence for a small cancer stem cell fraction in the tumour mass, we further assume that stem cells either divide symmetrically to produce another stem cell with a small probability, ρs, or divide asymmetrically with probability, 1 – ρs, to produce a stem cell and a non-stem progeny cell with proliferation capacity ρmax. A default value, ρs = 1%, was selected as representative, reflecting the order of magnitude of stem cell frequency observed in solid tumours (Visvader and Lindeman, 2008), and, as we later discuss, the surprising insensitivity of the basic tumour growth characteristics for ρs values ranging from 1 to 50% and beyond. If non-stem cells divide, their proliferation capacity ρ decreases by 1, and the daughter cells inherit the new ρ (Figure 1B). Eventually, these cells exhaust their proliferative capacity and cease dividing.



Tumor Cell Proliferation and Migration

Figure 2. With equal likelihoods, cells can migrate randomly into one of the adjacent available lattice points (a typical rate being 0.00635 mm /h or about μ= 15 cell widths per day (Maini et al, 2004) or remain stationary. At each time of potential proliferation, we further assume that cancer cell death occurs spontaneously and randomly among non-stem cells with probability α. Different sources of spontaneous cancer cell death exist; for instance, spontaneous cell apoptosis (Meggiato et al, 2000) has been estimated to be in the order of 1 – 25% in breast cancer (Ehemann et al, 2003). A schematic of the cell life cycle scheme in our computational model is shown in Figure 2. We run each stochastic simulation for t =20 x 365 days, that is, 20 years, unless the domain becomes confluent.



Example of the Modeling of Tumor Growth and Self-Metastases (2-D Case)

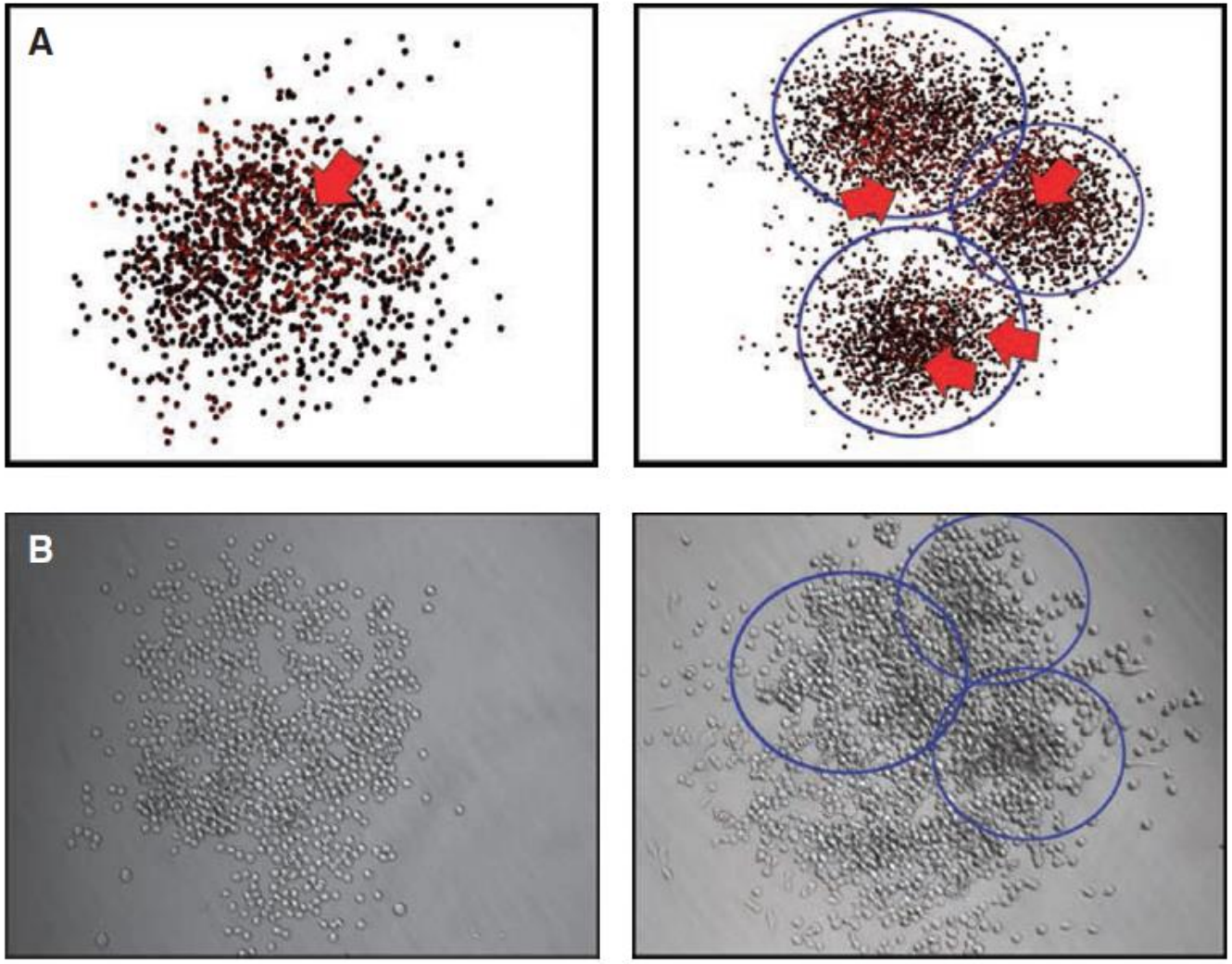


Figure 3. (A) All the common features of cell growth, including initial formation of gaps in tumour clones (left) and growth by self-seeding of clones (right), can readily be explained by basic cell kinetics. The arrows indicate locations of cancer stem cells in the simulation with parameters, ρ=10, α=5% and ps ¼ 1%. (B) Shown for comparison are tumourigenically transformed murine lung fibroblasts displaying migration-dependent clusterings arising from a single-plated cell per well.

Example of the Modeling of Tumor Growth and Self-Metastases (3-D Case)

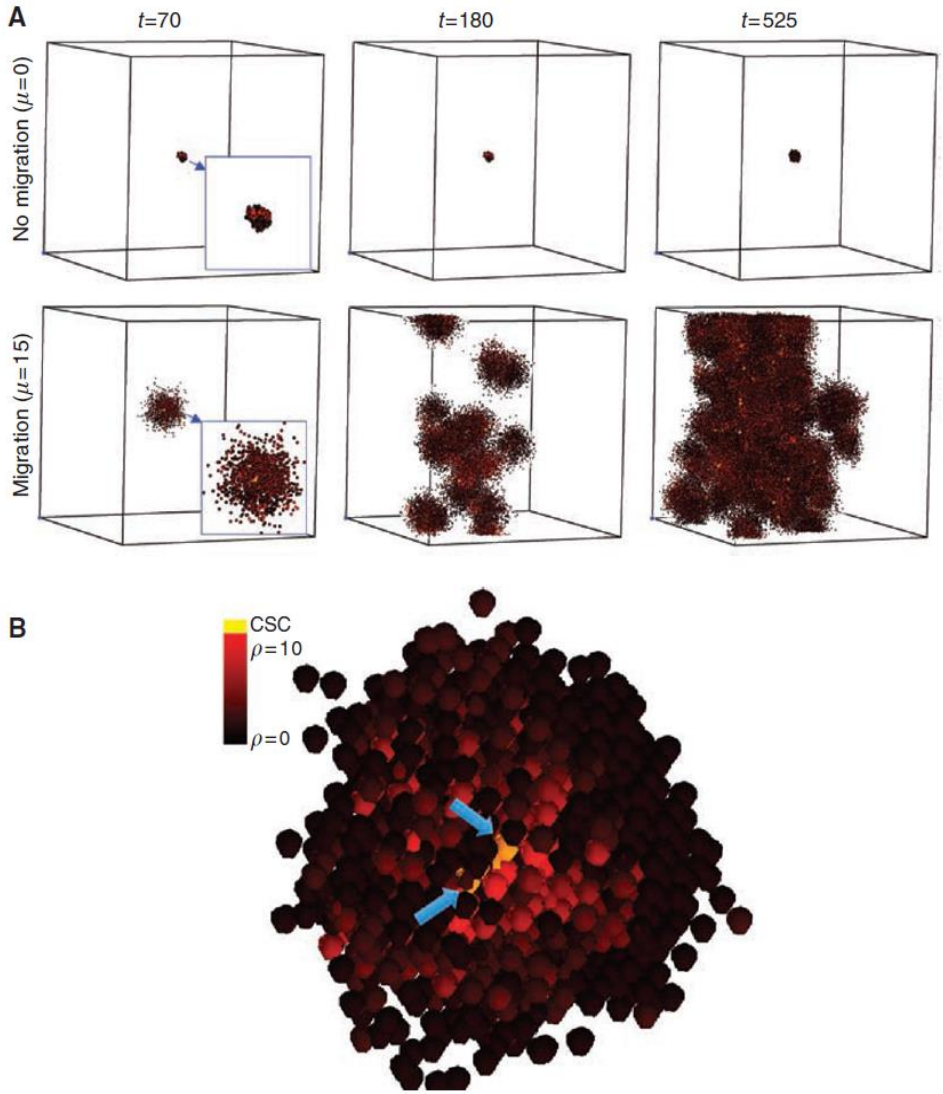


Figure 7. Three-dimensional simulations elucidating the pivotal role of migration in tumour growth and progression. (A) Without migration (μ=0, top row), no cells can be shed from the tumour to form foci of micrometastases and the tumour remains dormant. Cancer cell migration (μ=15, bottom row) is necessary to exhibit tumour growth and progression over time (t=70, 180, 525 days, left to right) through the formation of self-metastases. (B) High-resolution visualization of a representative three-dimensional tumour cluster after cancer stem cell (CSC) (yellow) has divided (arrows). Both stem cells are in the core of the tumour cluster with a radial proliferation capacity gradient.