A model for cell migration in non-isotropic fibrin networks with an application to pancreatic tumor islets

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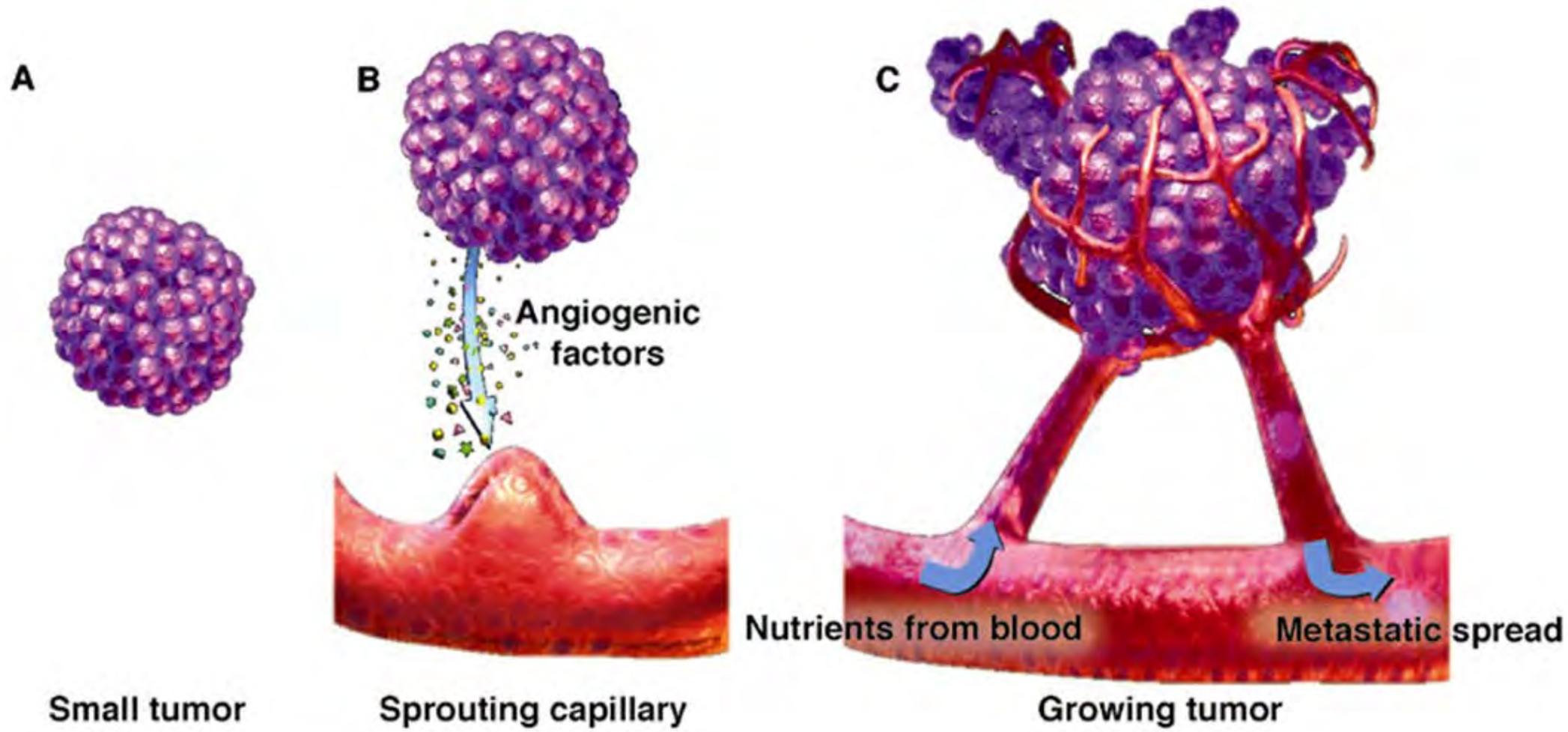
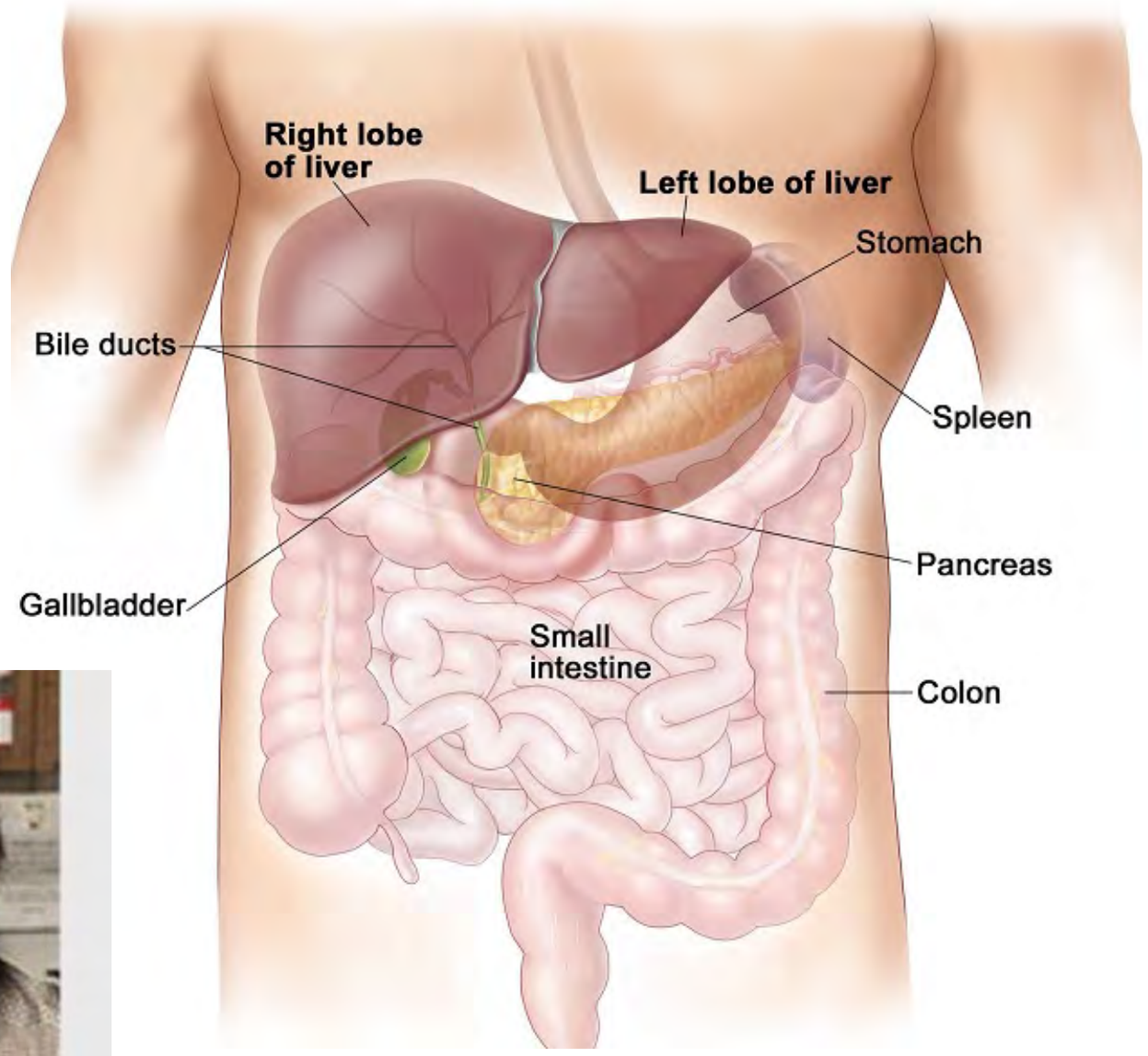
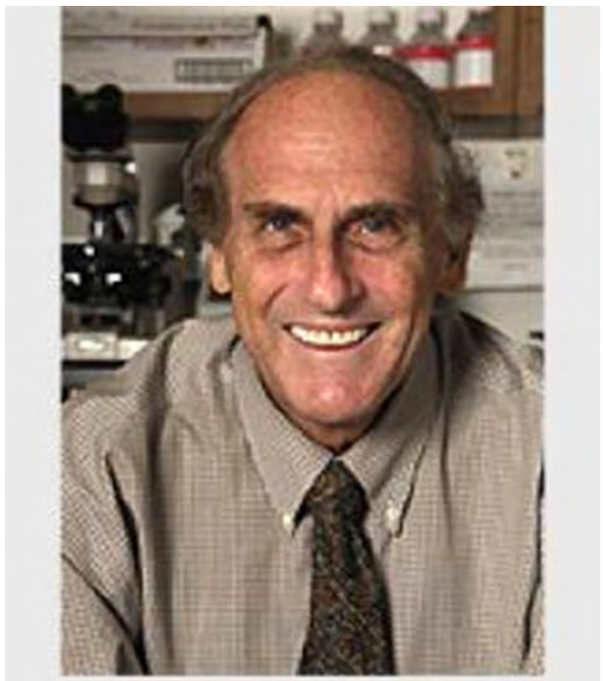
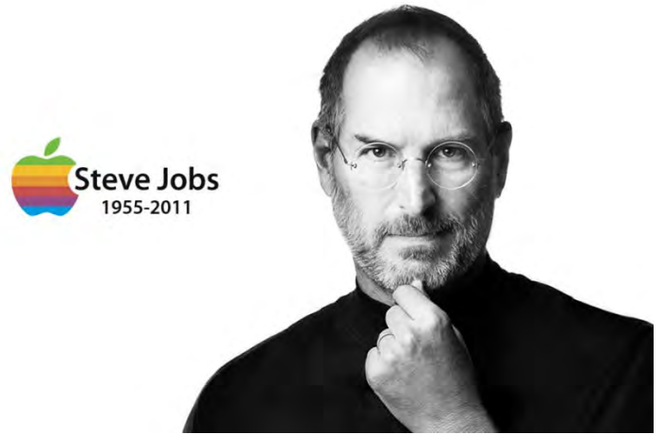
Introduction



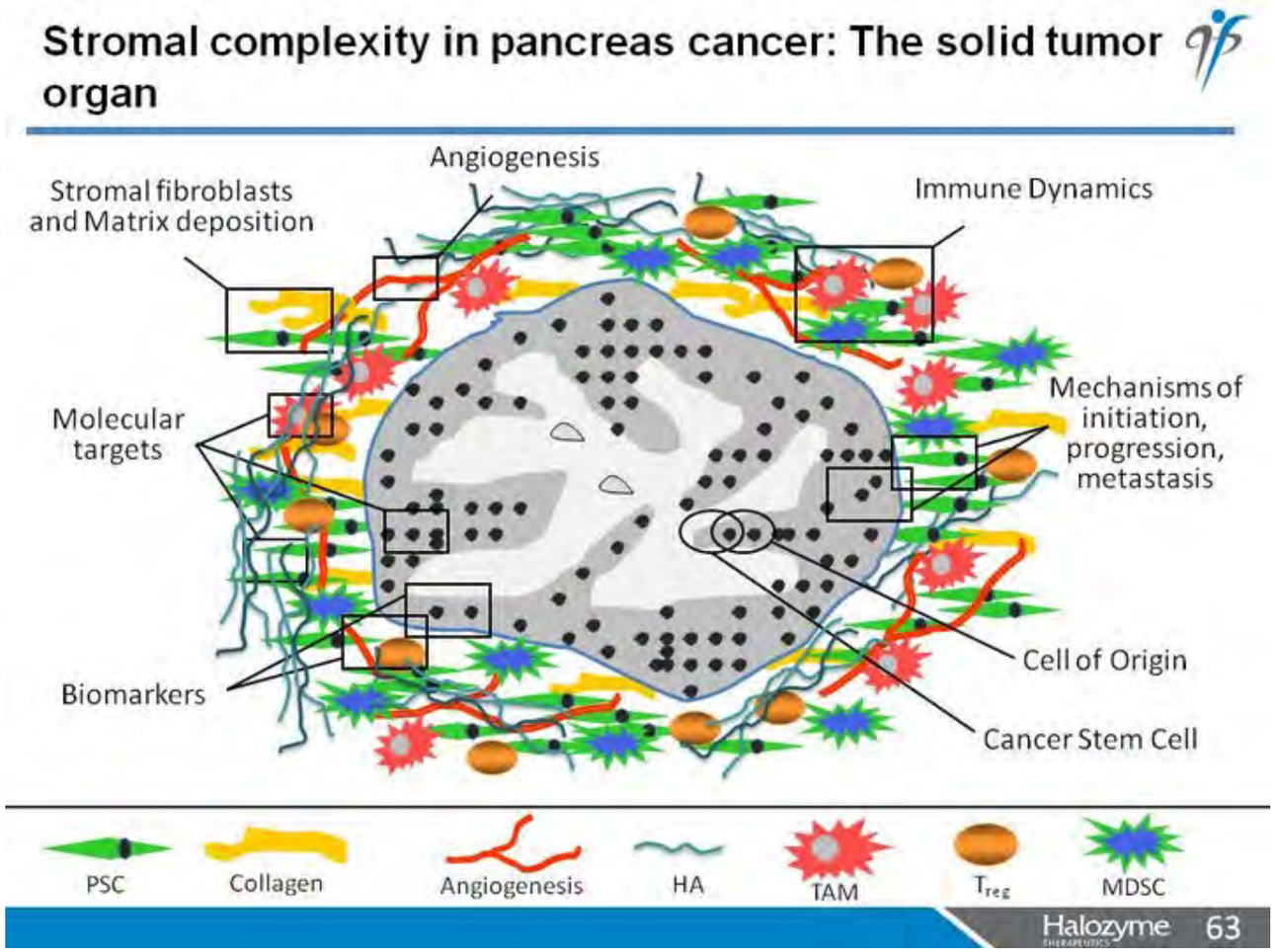




Ralph M. Steinman
The Rockefeller University



Pancreatic cancer



Lethal characteristics:

- 5-year survival rate < 5%
- Immune tolerance
- No angiogenesis
- Desmoplastic stroma
- Prognosis is really poor
- …

Mathematical model

The displacement of epithelial and cancer cells:

- Strain energy density

$$M_i^0 = \frac{1}{2\pi^2}\frac{F_i^2}{E_s(\mathbf{r}_i)R^4},\ for\ i \in \{1,...,n\}, \tag{1}$$

$$M(\mathbf{r}_i) = M_i^0 + \sum_{j=1_{j\neq i}}^{n} M_j^0 exp\{-\lambda_j \frac{\parallel \mathbf{r}_i - \mathbf{r}_j \parallel}{R}\} \tag{2}$$

- Mechanical contact

$$M^{ij} = \frac{4}{15\sqrt{2}}\frac{E}{\pi}(\frac{h}{R})^{\frac{5}{2}} \tag{3}$$

- Migration of cells

$$\hat{M}_i(\mathbf{r}) = M(\mathbf{r}_i) - \sum_{j\in\{i_1,,...,i_n\}} M^{ij} \tag{4}$$

$$for\ i \in \{1,...,n\}$$

$$\mathbf{r}_i^t = \mathbf{r}_i^{t-1} + \Delta t \alpha_i \hat{M}_i(\mathbf{r}^t) + \sqrt{2D}\Delta\mathbf{W} \tag{5}$$

Mathematical model

Displacement of T lymphocytes:

- Chemokine model

$$c(\mathbf{r}) = -\sum_{j \in \mathbb{K}(t)} \frac{\gamma_j(t)}{2\pi D} log \parallel \mathbf{r} - \mathbf{r}_j(t) \parallel, \quad j \in \mathbb{K}(t) \tag{1}$$

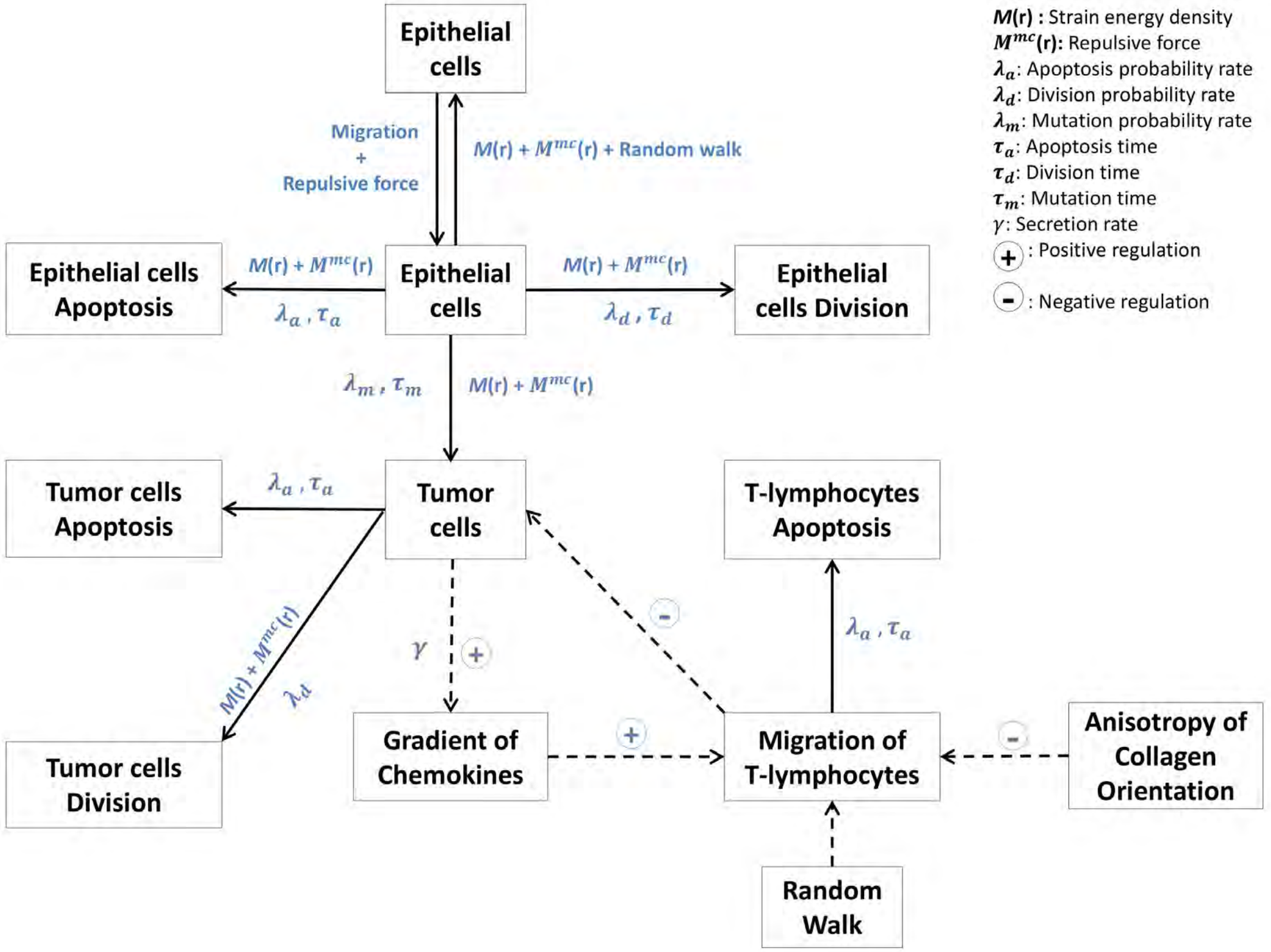
- Non-isotropy collagen network

$$\Psi(t, \mathbf{x}) = \begin{pmatrix} \Psi_{xx} & \Psi_{xy} \\ \Psi_{xy} & \Psi_{yy} \end{pmatrix} \tag{2}$$

$$\Psi = e^{-ks} \lambda_1 \mathbf{v_1} \mathbf{v_1}^T + \lambda_2 \mathbf{v_2} \mathbf{v_2}^T \tag{3}$$

- Migration of T lymphocytes

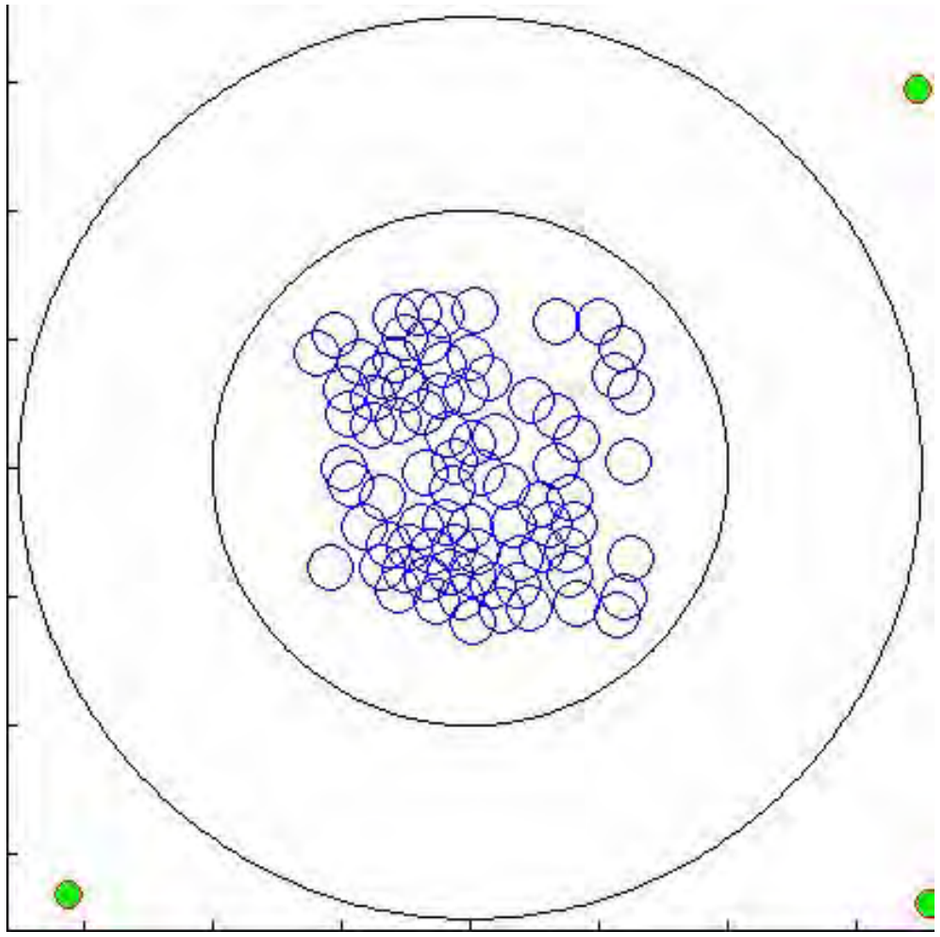
$$\mathbf{r}_j^t = \mathbf{r}_j^{t-1} + \Psi[\bigtriangledown c(t, \mathbf{x}_j^{t-1}) \triangle t + \sqrt{2D} \triangle \mathbf{W}] - \sum_{l \in \{l_1, l_2, \ldots, l_k\}} M^{jl} \triangle t, \quad j, l \in \mathbb{T}(t) \tag{4}$$

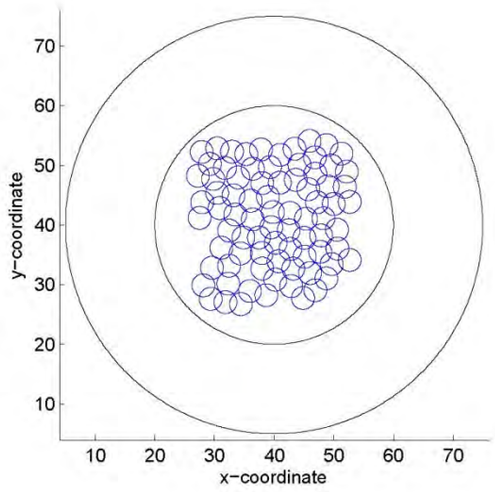


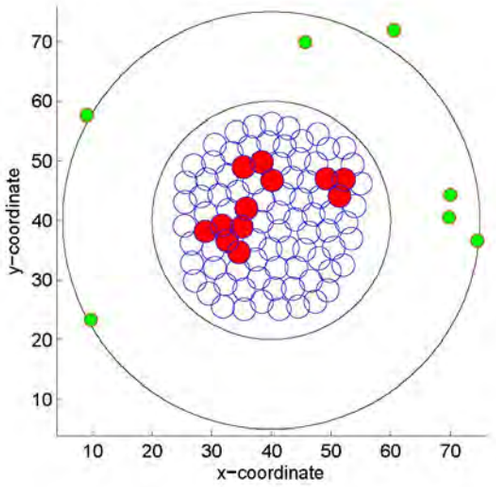
$M(\mathbf{r})$: Strain energy density
$M^{mc}(\mathbf{r})$: Repulsive force
λ_a: Apoptosis probability rate
λ_d: Division probability rate
λ_m: Mutation probability rate
τ_a: Apoptosis time
τ_d: Division time
τ_m: Mutation time
γ: Secretion rate
(+) : Positive regulation
(-) : Negative regulation

Figure 2. Schematic representation of the cross-talk among the epithelial cells, cancer cell and immune cells in the microenvironment of a pancreatic tumor islet.

Results







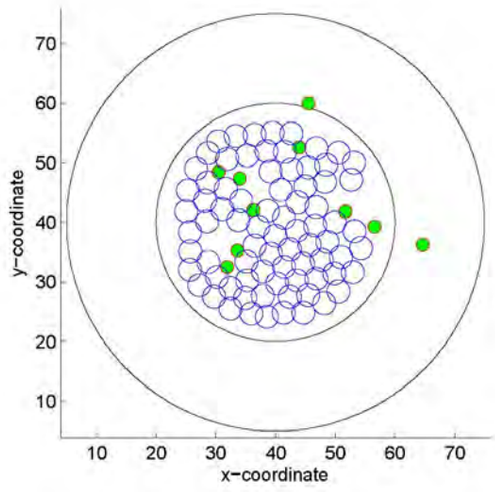
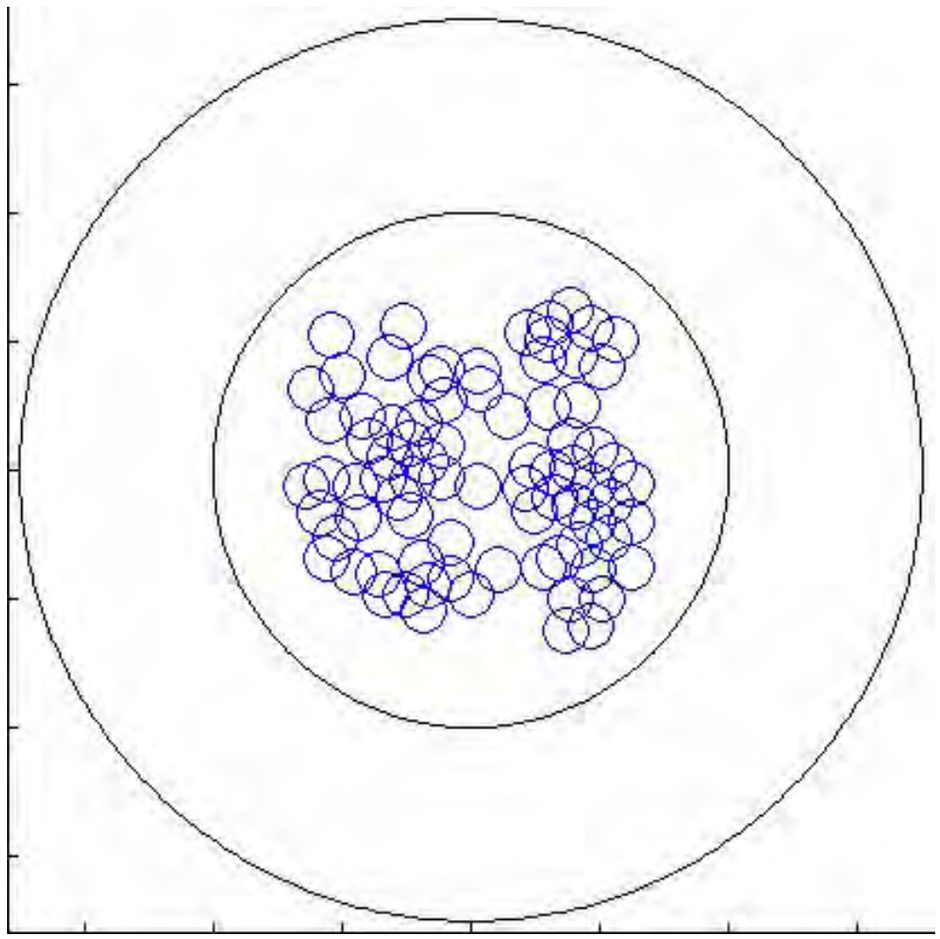
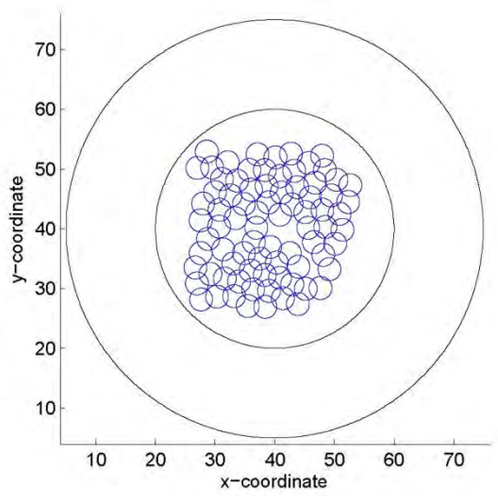
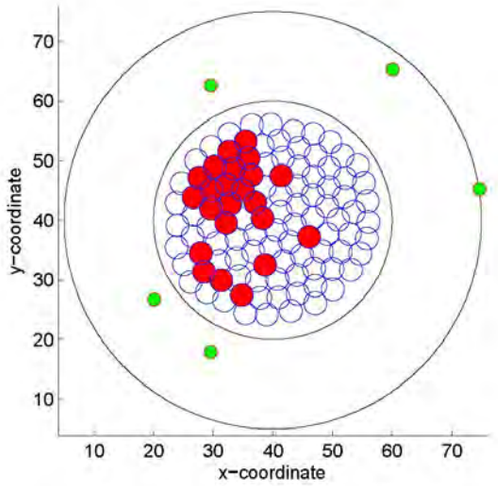


Figure 3. The tumor islet without collagen under a strong immune reaction







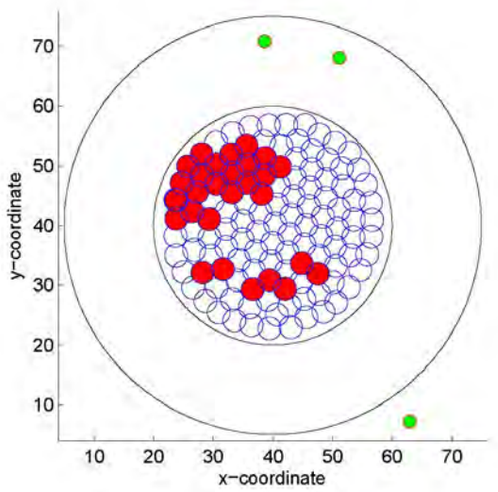
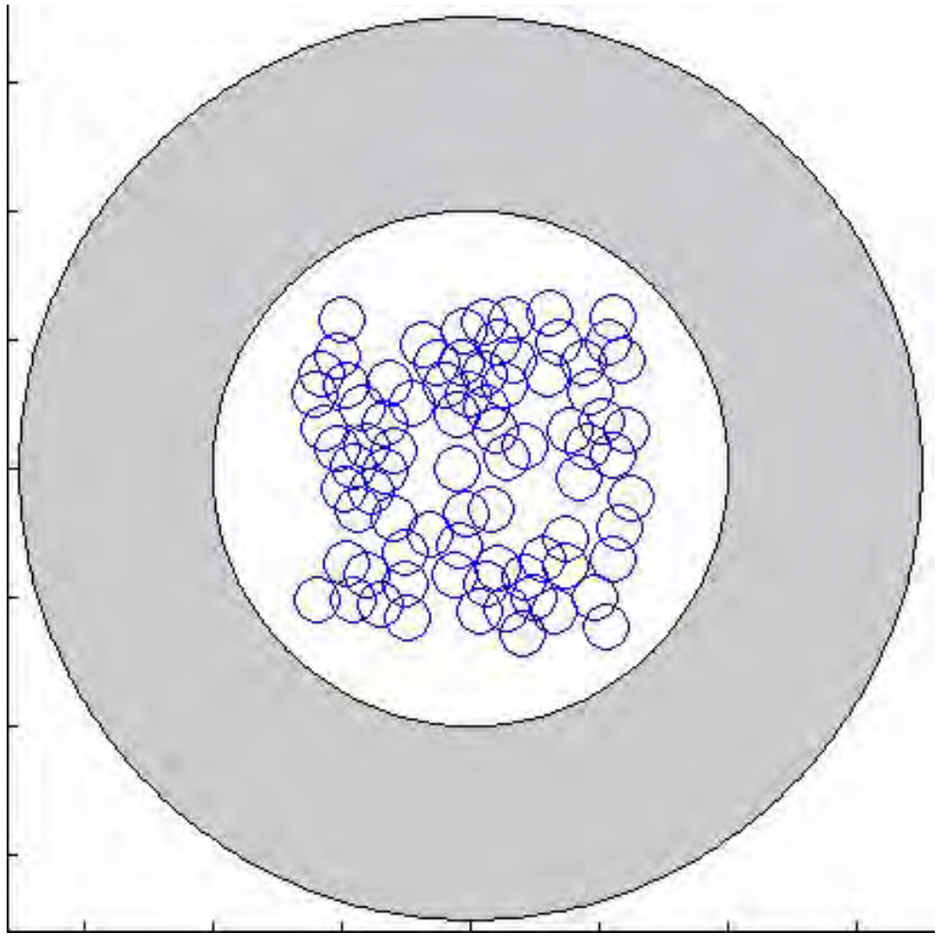
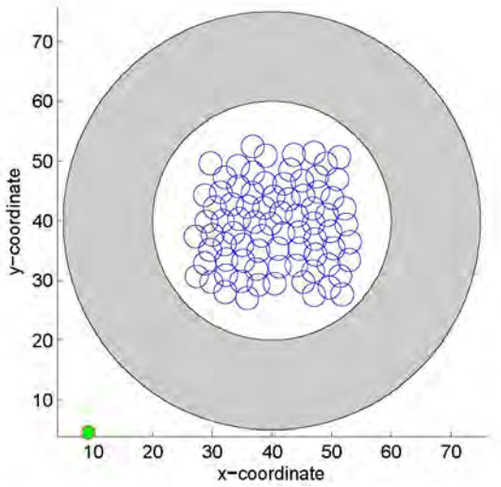
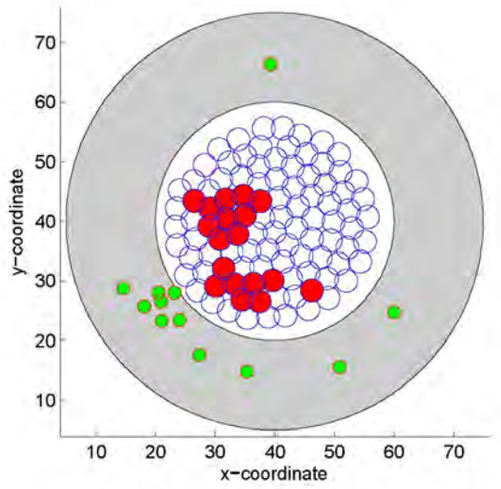


Figure 4. The tumor islet without collagen under a weak immune reaction







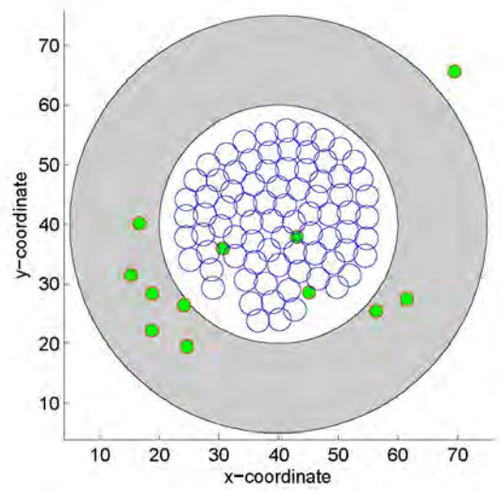
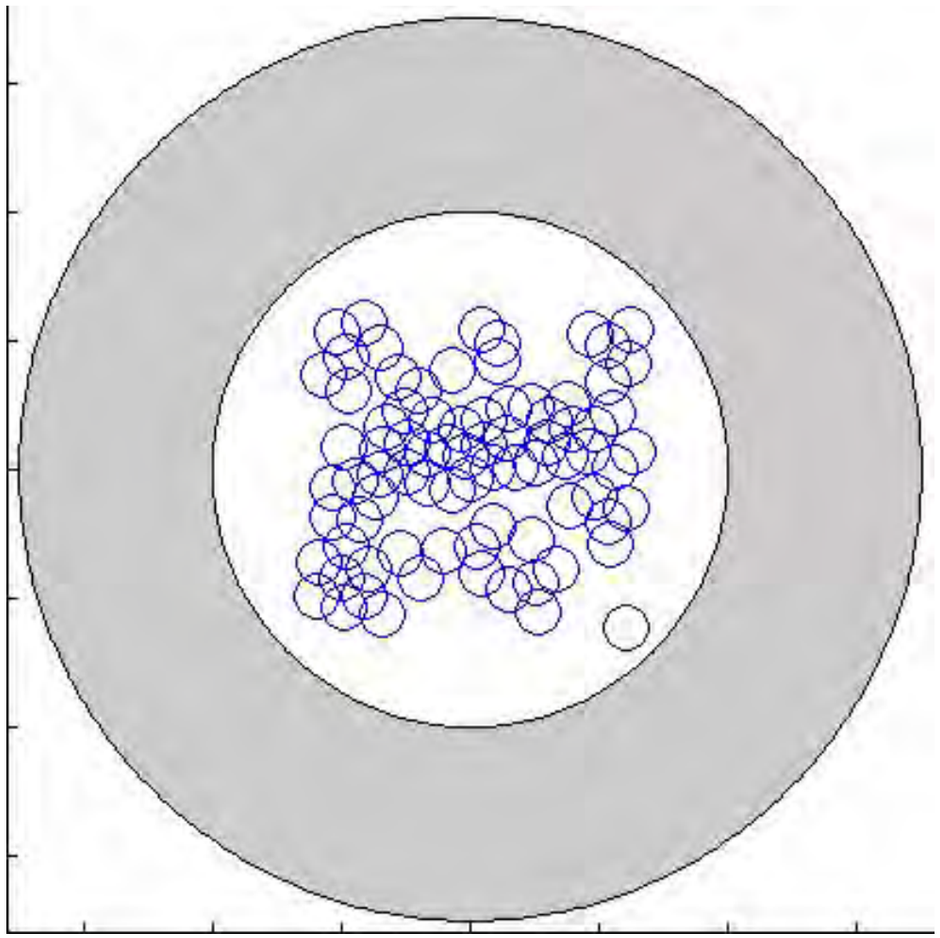
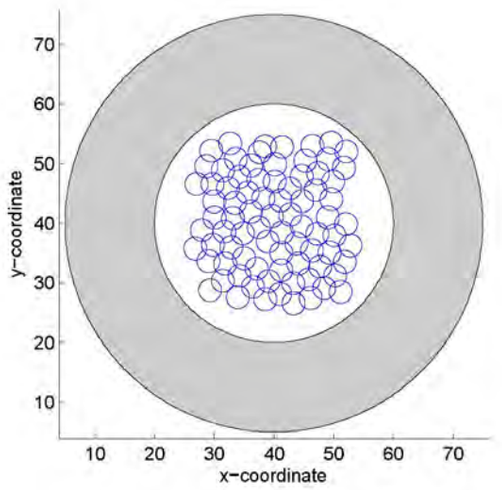
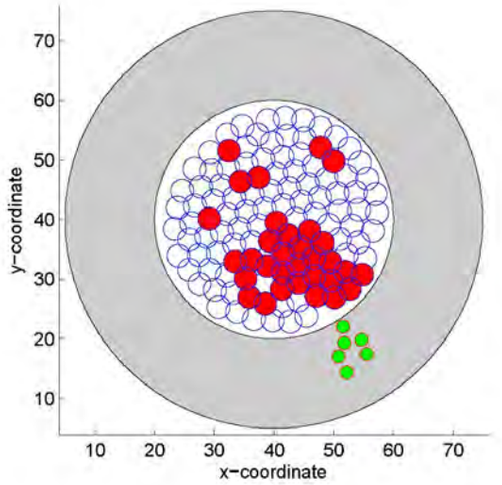


Figure 5. The tumor islet with collagen under a strong immune reaction







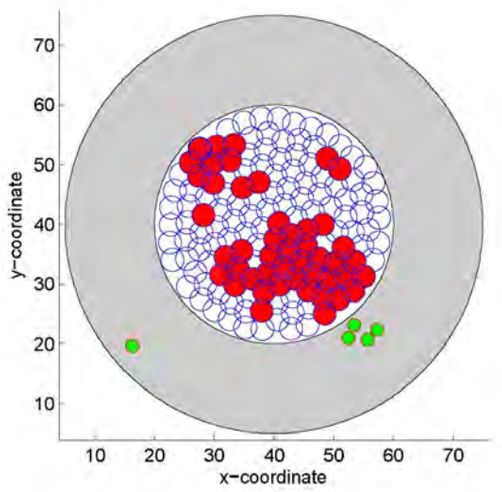


Figure 6. The tumor islet with collagen under a weak immune reaction

Discussion

The model quantifies the delay of invasion of T-cells into the cancer-effected area, and hence it quantifies the increase in time to battle the cancer cells

The model predicts the unlimited proliferation of carcinoma cells if the immune system is weak, and a state of equilibrium where cancer cells are eliminated if the immune system is sufficiently strong

The obstructing effect of stromal ECM increases with the increase of k value which is used to denote a measure for the amount that anisotropy contributed to T-cell migration.

Thanks for your attention !

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