Some insights for the impact of intratumoral heterogeneity on tumor progression

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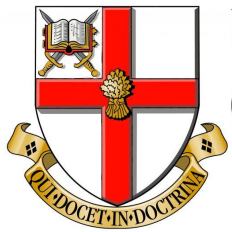

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Overview

The Go or Grow(GoG) System

Due to the migration/proliferation dichotomy, we can distinguish the total population density of cancerous cells ρ in two groups, ρ^p the proliferating cell density and with ρ^m the density of moving cells. Then we end up with the GoG model, **Böttger et al. 2015**,

$$\frac{\partial \rho^m}{\partial t} = \Delta \rho^m + r_{p\to m}(\rho)\rho^m - r_{m\to p}(\rho)\rho^m - r_d \rho^m, \tag{1}$$

$$\frac{\partial \rho^p}{\partial t} = r_b \rho^p (1-\rho^p) + r_{m\to p}(\rho)\rho^p - r_{p\to m}(\rho)\rho^p - r_d \rho^p, \tag{2}$$

where r_b is the birth rate, r_d is the death rate, $r_{p\to m}(\rho)$ is the switch rate from proliferating type to motile type and $r_{m\to p}(\rho)$ is the switch rate from motile type to proliferating type of the cancerous cells.

The Go or Grow(GoG) Single Equation

To obtain a unique equation for $\rho = \rho^m + \rho^p$, we refer to detailed balance condition

$$\rho^p r_{p\to m}(\rho) = \rho^m r_{m\to p}(\rho).$$

Through this condition we can rewrite the preceding system as a single PDE

$$\frac{\partial \rho}{\partial t} = \Delta(r_{p\to m}(\rho)\rho) + r_b r_{m\to p}(\rho)\rho(1-\rho) - r_d\rho. \tag{3}$$

A possible choice of the switching rates is given by, **Böttger et al. 2015**,

$$r_{m\to p}(\rho) = \frac{1}{2}\left(1+\tanh(k(\rho-\theta))\right) := r_s(\rho,k), \tag{4}$$

$$r_{p\to m}(\rho) = 1 - r_s(\rho,k), \tag{5}$$

where the switching parameter k determines how each tumor cell interprets its microenvironment. Then (3) takes the form

$$\frac{\partial \rho}{\partial t} = \Delta((1-r_s(\rho,k))\rho) + r_b r_s(\rho,k)\rho(1-\rho) - r_d\rho. \tag{6}$$

Role of Switching parameter k.

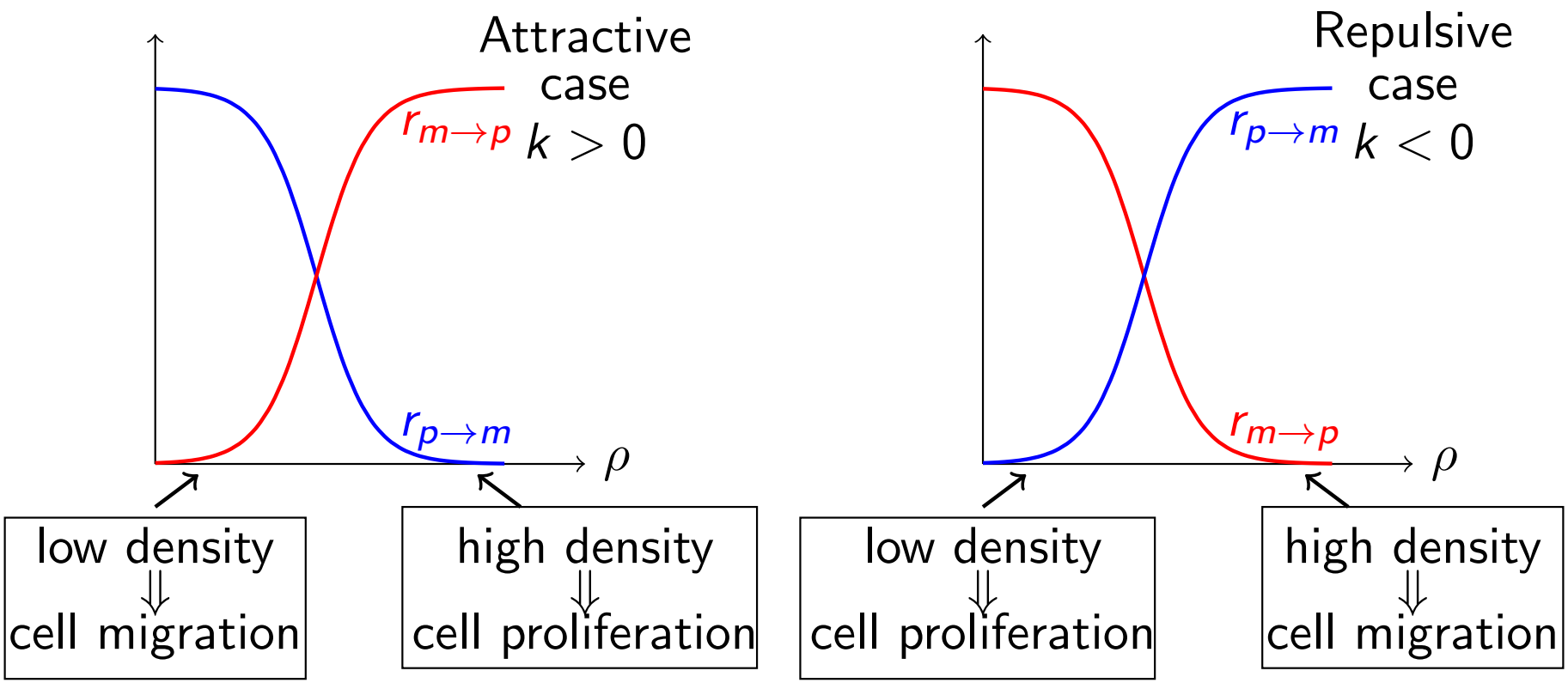

Figure 1: Sketch of cellular mechanism for different kind of phenotypic plasticity. In the left aggregative configuration is represented, while in the right figure, the repulsive configuration is represented, **Böttger et al. 2015**

Allee Effect (Deterministic Case– Constant Heterogeneity)

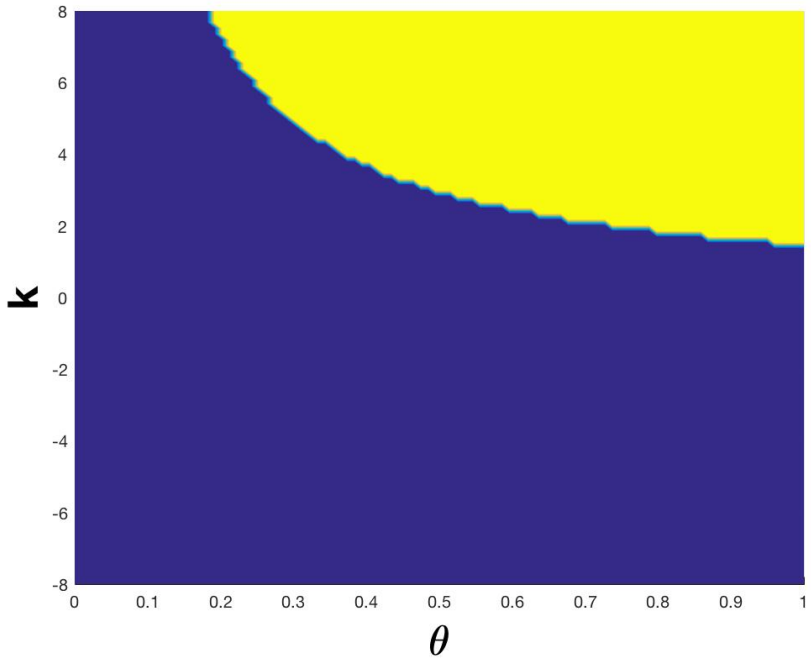

Figure 2: Allee effect in the deterministic system (7)-(8). The yellow area represents the area where 0 is stable for the above system, whereas the blue one depicts the area where 0 becomes unstable, **Böttger et al. 2015**

$$\frac{d\rho}{dt} = r_b r_s(\rho, k)\rho(1-\rho) - r_d\rho := F(\rho), t \in (0, T], \tag{7}$$

$$\rho(0) = \rho_0. \tag{8}$$

Data driven motivation for introduction of heterogeneity

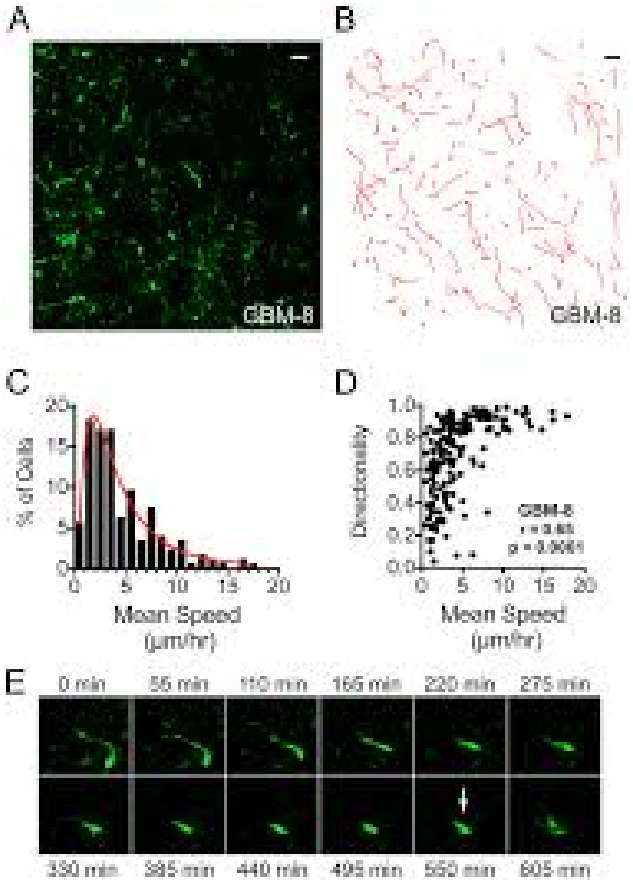

Figure 3: High temporal resolution path tracking highlights intratumoral heterogeneity of speed and directionality of tumor cell migration in focal micro-regions, **J. J. Parker et. al 2018**.

Intrinsic Heterogeneity as Noise

• Main Assumption: The phenotypic switch is in-homogeneously regulated through the glioma cell populations.
Then the desirable heterogeneous regulation is realised by k following a probability distribution, i.e. we heuristically take

$$k \mapsto k_0 + \text{Noise} := \xi_t.$$

Thus (7)-(8) takes the form

$$\frac{d\rho}{dt} = F(\rho, \xi_t), t \in (0, T],$$
$$\rho(0) = \rho_0$$

which is not so well behaved since F is a nonlinear function.

Approximation of White Noise

We consider the following approximation of the White Noise ξ_t

$$\xi_t^N = \sum_{i=1}^{N} \alpha_i^N \mathbb{1}_{A_i^N}(t) \quad \text{where} \quad \alpha_i^N = \frac{B_{\frac{i-1}{N}T+\Delta_N} - B_{\frac{i-1}{N}T}}{\Delta_N} \sim \mathcal{N}(0, N), \tag{9}$$

where B_j are Brownian motions and

$$A_i^N = \left[\frac{(i-1)}{N}T, \frac{i}{N}T\right], \ i = 1, \ldots, N.$$

Therefore we end up with the following well posed system

$$\frac{d\rho^N}{dt} = F(\rho^N, \xi_t^N(\omega)), t \in (0, T], \ \omega \in \Omega = \text{probability space} \tag{10}$$

$$\rho^N(0) = \rho_0. \tag{11}$$

Convergence as $N \to \infty$ (White Noise)

Theorem

Let ξ_t^N be the process described by (9). Then the solution trajectories ρ_t^N of

$$\begin{cases} \frac{\partial \rho^N}{\partial t} = r_b r_s(\rho^N, \xi_t^N)\rho^N(1-\rho^N) - r_d\rho^N, \\ 0 \leq \rho(0) = \rho_0 \leq 1, \end{cases}$$

converge uniformly in time and almost surely to the solution ρ of the following ODE problem

$$\begin{cases} \frac{d\rho}{dt} = \frac{1}{2} r_b \rho(1-\rho) - r_d\rho \\ 0 \leq \rho^N(0) = \rho_0 \leq 1. \end{cases} \tag{12}$$

Namely,

$$\lim_{N\to\infty} \sup_{t\in[0,T]} |\rho_t^N - \rho_t| = 0 \quad a.s. .$$

Elimination of Allee Effect (White Noise)

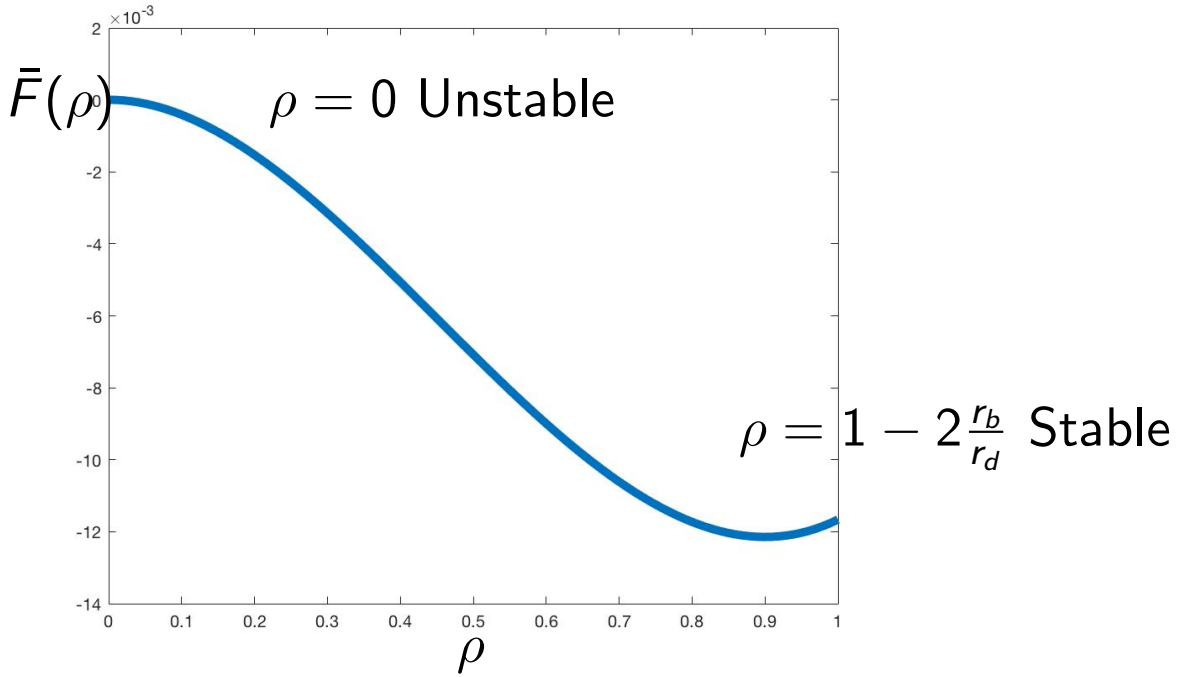

Figure 4: Plot of the potential of equation (12), namely $\bar{F}(\rho) := \frac{1}{2} r_b \rho(1-\rho) - r_d \rho$ with $r_b = 0.1$ and $r_d = 0.02$.

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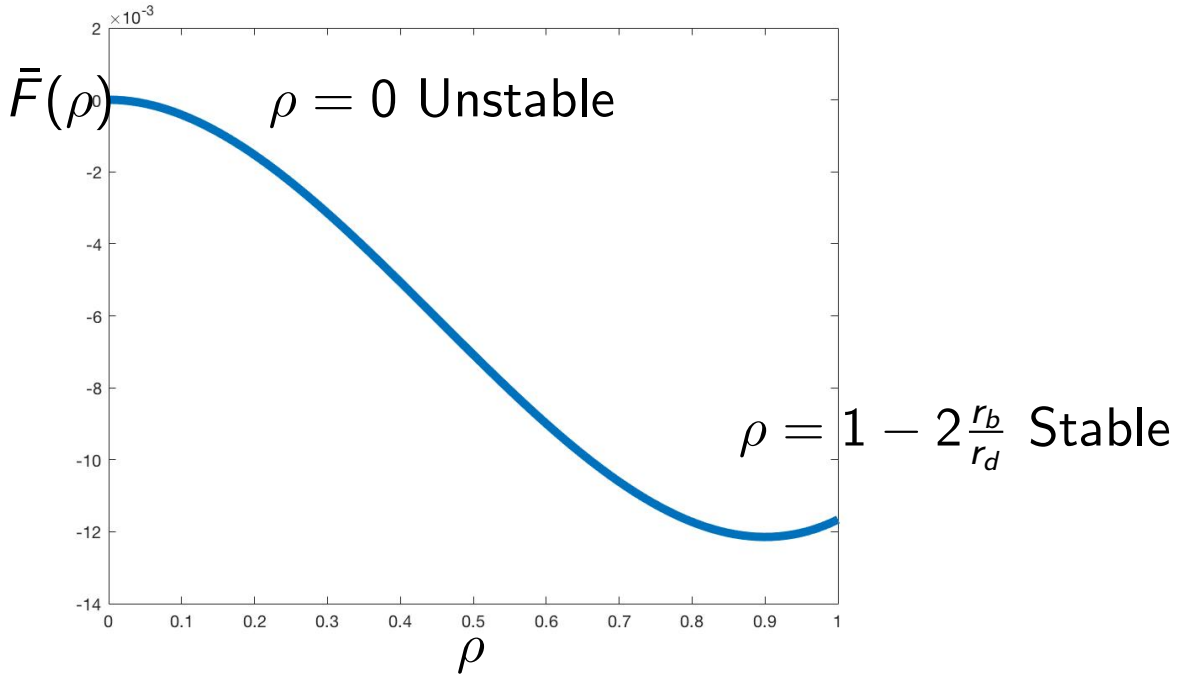

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- The strength of White Noise is so big that annihilates any other influence and force the system to return to a monostable configuration!

ξ_t =Gaussian Noise

By clinical data provided in **J. J. Parker et. al 2018** we get that the mean speed of cells follows a lognormal distribution $\implies k \sim \mathcal{N}(\mu_1, D_1)$. Therefore we consider

$$\xi_t^D = \xi_t \sim \mathcal{N}(\mu, D), D = \text{ noise strength.}$$

Approximation of Gaussian Noise

We consider the following approximation of the Gaussian Noise ξ_t

$$\xi_t^{D,N} = \sum_{i=1}^{N} \alpha_i^N \mathbb{1}_{A_i^N}(t) \quad \text{where} \quad \alpha_i^N \sim \mathcal{N}(\mu, D), \tag{13}$$

and thus we end up with the model

$$\frac{\partial \rho^{D,N}}{\partial t} = r_b r_s(\rho^{D,N}, \xi_t^{D,N})\rho^{D,N}(1-\rho^{D,N}) - r_d \rho^{D,N} := \bar{F}(\rho), \tag{14}$$

$$0 \leq \rho^{D,N}(0) = \rho_0 \leq 1. \tag{15}$$

Convergence as $N \to \infty$ (Gaussian Noise)

Theorem

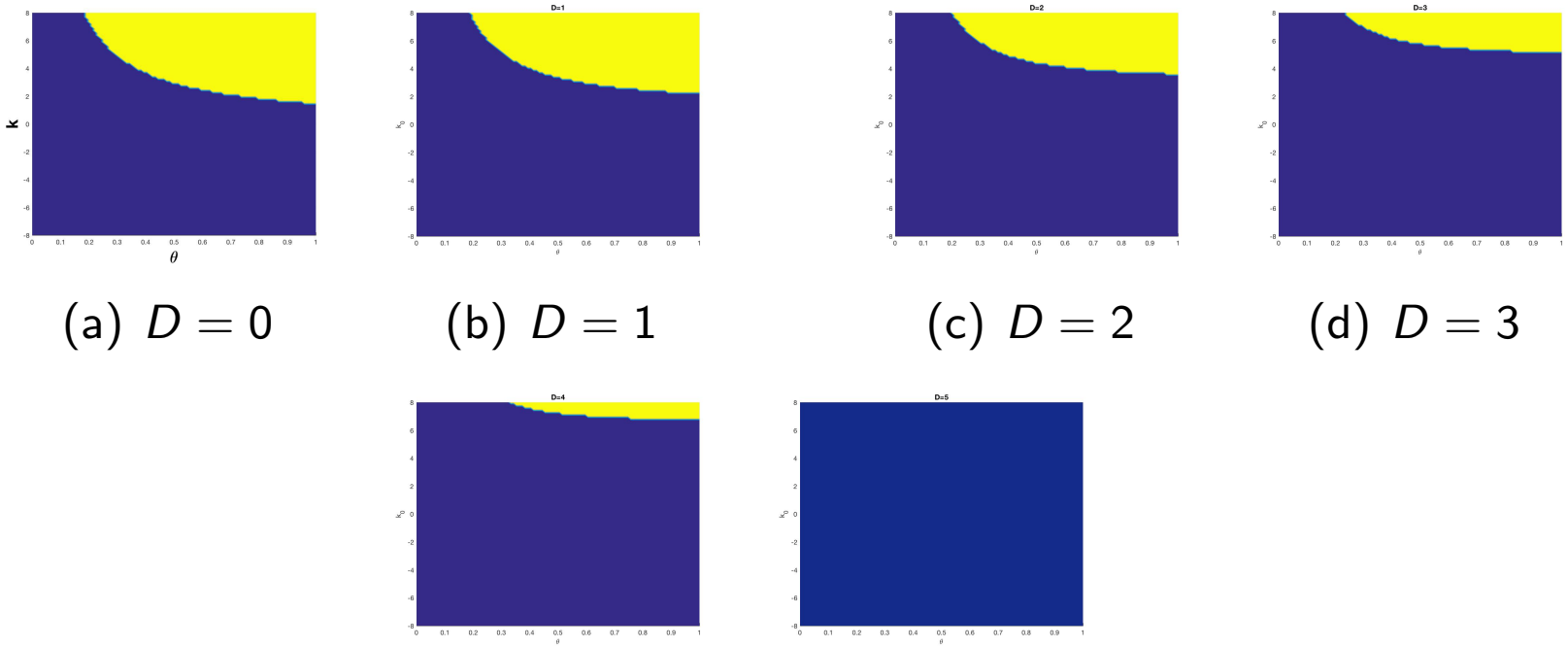
Assume that $\xi_t^{D,N}$ *is given by* (13). *Then each solution trajectory of* (14)-(15) *converges uniformly in time and almost surely to the unique solution of*

$$\begin{cases} \frac{d\rho^D}{dt} = \mathbb{E}\left[f^D(\rho^D)\right] r_b \rho^D (1-\rho^D) - r_d \rho^D \\ 0 \leq \rho^D(0) = \rho_0 \leq 1, \end{cases} \tag{16}$$

where

$$f^D(x)[y] = \begin{cases} 0, & y \leq 0, \\ sign(x-\theta) \frac{2e^{-\left(\left(\frac{\tanh^{-1}(2y-1)}{(x-\theta)} - k_0\right)\frac{1}{D\sqrt{2}}\right)^2}}{D\sqrt{2\pi}(x-\theta)(1-(2y-1)^2)}, & y \in (0,1), \\ 0, & y \geq 1. \end{cases}$$

Elimination of Allee Effect (Gaussian Noise)



(a) $D = 0$ (b) $D = 1$ (c) $D = 2$ (d) $D = 3$

(e) $D = 4$ (f) $D = 5$

Figure 5: Plot of the indicator function $S_{t_0}(\theta, k_0, D)$. In yellow area there holds $\mathrm{St}_0(\theta, k_0, D) = 1$, whilst $S_{t_0}(\theta, k_0, D) = 0$ in blue area.

$$S_{t_0}(\theta, k_0, D) = \begin{cases} 1 & \text{If 0 is stable for the system (16)} \\ 0 & \text{If 0 is unstable for the system (16)} \end{cases}$$

Probability of Tumor's Extinction (Gaussian Noise)

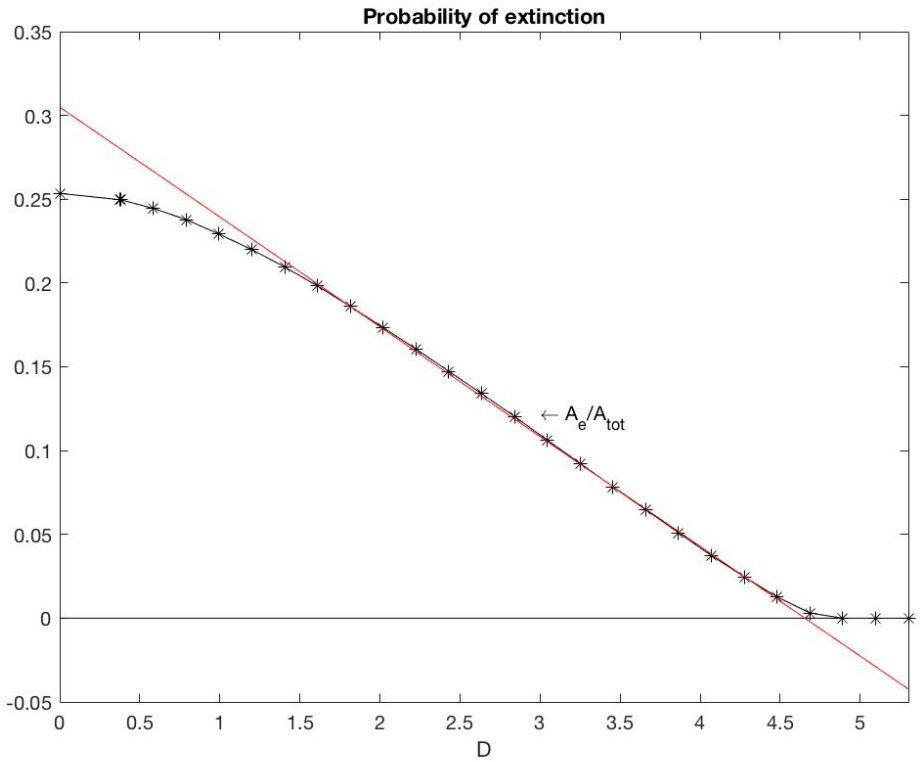


Figure 6: Probability of extinction: $\frac{A_e}{A_{tot}}$ as a function of variance D. Notably this probability decreases almost linearly as D inreases.

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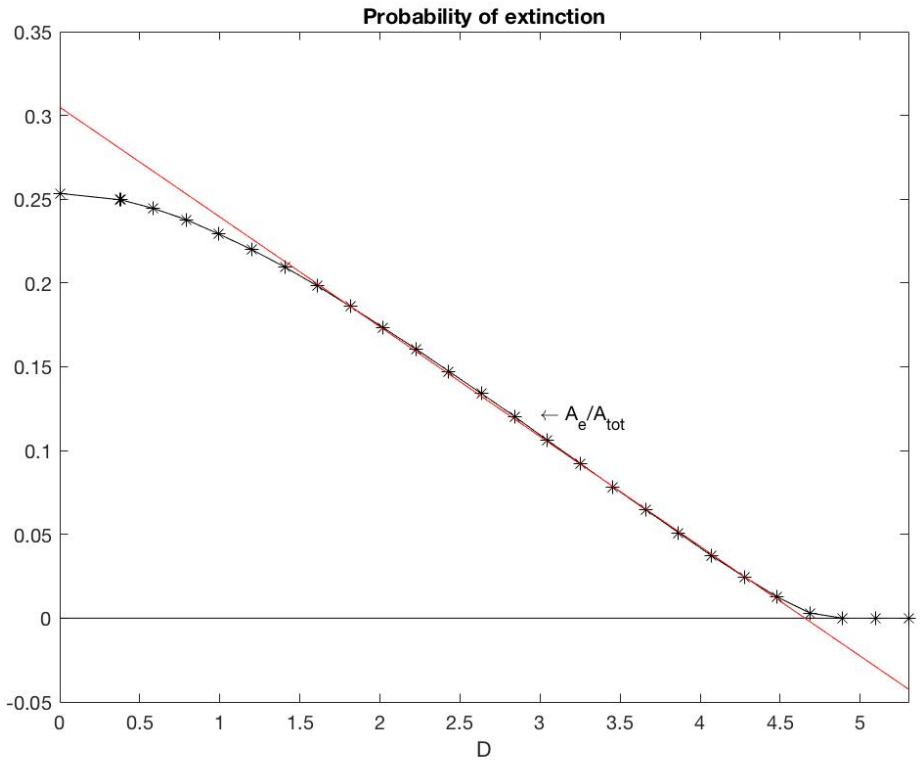

Figure 6: Probability of extinction: $\frac{A_e}{A_{tot}}$ as a function of variance D. Notably this probability decreases almost linearly as D inreases.

- There is a critical level of heterogeineity (or noise magnitude e.g. $D = 5$,) above which the tumor survives.

Spatio-temporal GoG model (White Noise)

Theorem

For every $T > 0$ the unique solution ρ^N of problem

$$\frac{\partial \rho^N}{\partial t} = \Delta((1 - r_s(\rho^N, \xi_t^N))\rho^N) + F(\rho^N, \xi_t^N),\ (x,t) \in D_T := D \times (0,T),$$
$$\rho^N(x,t) = 0, \quad (x,t) \in \Gamma_T := \partial D \times (0,T),$$
$$0 \leq \rho^N(x,0) = \rho_0(x) \leq 1, \quad x \in D,$$

converges as $N \to \infty$ into $\mathcal{H}_T = C\left(0,T; L^2(D)\right)$ to the unique solution of the average problem

$$\frac{\partial \rho}{\partial t} = \frac{1}{2}\Delta\rho + \bar{F}(\rho),\ (x,t) \in D_T,$$
$$\rho(x,t) = 0, \quad (x,t) \in \Gamma_T,$$
$$0 \leq \rho(x,0) = \rho_0(x) \leq 1, \quad x \in D.$$

Summary

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• Linear stability analysis for spatial-temporal GoG models again reveals the existence of a critical threshold of heterogeneity above which the glioblastoma tumor survives.

• Therefore the provided stochastic models predict that: the higher the heterogeneity of the microenvironment of the cancerous cells is then the higher the probability of survival of the tumor becomes.

Key References

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Thank you for your attention!