Dynamics of Tumour Cell Invasion in a Quasi-Critical Regime

Nadia Belmabrouk
In collaboration with Vincent Bansaye, Xavier Erny, and Simon Girel

École de recherche – Chaire MMB, Aussois

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Overview

1. Introduction
   - Biological Framework and Motivation
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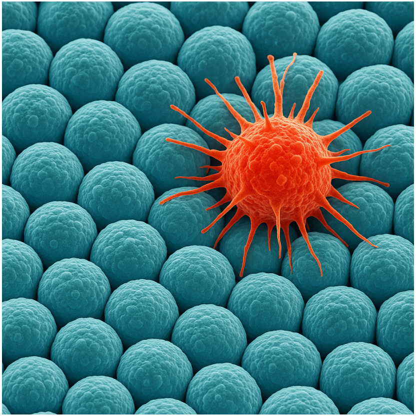
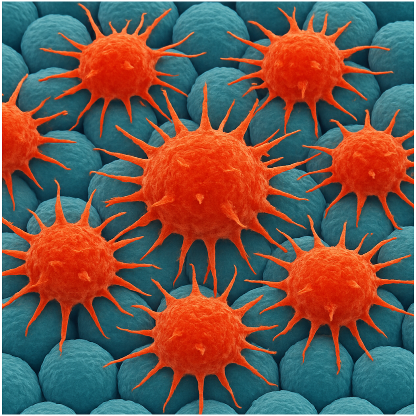
   - Stochastic Invasion Model
   - One-Dimensional Model
2. Invasion Dynamics: Analysis and Results
   - Hitting Time Analysis
   - Trajectory Analysis

Introduction

Biological Framework and Motivation



*Onset of Cancer Cell



*Proliferation and Invasion

Biological Framework and Motivation

One mutant cell introduced in a large resident population at equilibrium.
TGF- protein has a regulatory effect that inhibits the proliferation of resident cells.
Individual birth and death rates:

$$\begin{cases} d_R(x_R, x_M) = d_M(x_R, x_M) = d, \\ b_M(x_R, x_M) = \beta\Big(1 - \frac{x_M + x_R}{C}\Big)_+, \\ b_R(x_R, x_M) = \beta\Big(1 - \frac{\alpha x_M + x_R}{C}\Big)_+, \end{cases}$$

- β is the maximum division rate, where $\beta > d$.
- $\alpha > 1$ models the inhibitory effect on resident cell growth through TGF-proteins.
- C: carrying capacity
- $b_R(x_R^*, 0) = d$, where $x_R^* > 0$, represents the number of resident cells at equilibrium.

Stochastic Invasion Model

1. Bi-type Birth-Death Process
   Consider
   $$N^K(t) = (N_R^K(t), N_M^K(t)) = (n_R, n_M),$$
   K is a scaling parameter and
   $$\begin{aligned}
   (n_R, n_M) &\to (n_R + 1, n_M) && \text{with rate } n_R\, b_R(n_R/K, n_M/K)\\
   (n_R, n_M) &\to (n_R - 1, n_M) && \text{with rate } n_R\, d_R(n_R/K, n_M/K)\\
   (n_R, n_M) &\to (n_R, n_M + 1) && \text{with rate } n_M\, b_M(n_R/K, n_M/K)\\
   (n_R, n_M) &\to (n_R, n_M - 1) && \text{with rate } n_M\, d_M(n_R/K, n_M/K)
   \end{aligned}$$

2. Deterministic System Approximation of $N^K(t)/K$
   $$\begin{cases} x_M'(t) = \Big[b_M(x_R(t), x_M(t)) - d\Big] x_M(t),\\ x_R'(t) = \Big[b_R(x_R(t), x_M(t)) - d\Big] x_R(t). \end{cases}$$

One-Dimensional Model

Let $N_t^K = n$ be the population size at time t, where K is a scaling parameter. The process follows these transition dynamics:

$$n \to n+1 \quad \text{with rate } n\, b(n/K)$$
$$n \to n-1 \quad \text{with rate } n\, d(n/K)$$

where

$$\begin{cases} b(x) = ax + d, & (\text{ individual birth rate}) \\ d(x) = d, & (\text{ individual death rate}). \end{cases}$$

- $N^K(0) = 1$,
- $a > 0$ has an excitatory effect.

Context, Challenges, and Objectives

- We start from a quasi-critical regime.
- We study invasion dynamics (i.e., the transition from 1 to K).
- Problem: the probability of invasion tends to 0.
- Solution: We study the law $\mathbf{E}^x\Big(F((N_s^K)_{0\leq s\leq t})|N_t^K>0\Big)$.
- Challenges: We identify three regimes:
  - one close to 1 : $[1,\sqrt{K}]$,
  - intermediate regime : $[\sqrt{K},K^{1/2+\epsilon}]$,
  - one close to K : $[K^{1/2+\epsilon},K]$.

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Invasion Dynamics: Analysis and Results

Invasion Dynamics: Analysis and Results

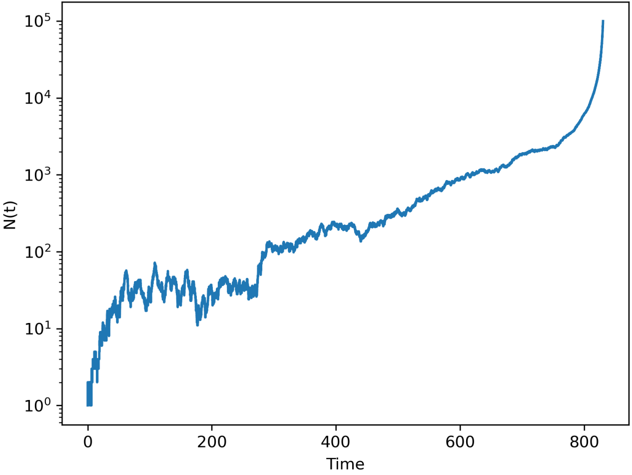
Hitting Time Analysis

Consider the hitting time

$$T_n = \inf\{t > 0 \ : \ N_t^K = n\}.$$

We quantify the following probabilities:

1. $\mathbb{P}_{\lfloor K^\alpha \rfloor}\left(T_0^K < T^K_{\lfloor \sqrt{K} \rfloor}\right) \underset{K\to\infty}{\longrightarrow} 1$, for $\alpha < 1/2$.
2. $\mathbb{P}_{\lfloor \sqrt{K} \rfloor}\left(T_0^K < T^K_K\right) \underset{K\to\infty}{\longrightarrow} l$, with $l \in]0,1[$.
3. $\mathbb{P}_{\lfloor K^\beta \rfloor}\left(T_0^K < T^K_K\right) \underset{K\to\infty}{\longrightarrow} 0$, for $\beta > 1/2$.



Cell number evolution

Trajectory Analysis (From 1 to $\sqrt{K}$)

Probability change of measure

Consider Y^K defined by its semigroup:

$$\mathcal{P}_t^Y f(x) = \frac{1}{x}\mathbb{E}^x \left[e^{-\int_0^t (d-b)(\frac{N_s^K}{K})ds} N_t^K f(N_t^K) \right],$$

where f is a bounded continuous function.

Lemma

The law of $(N_s^K)_{0\leq s\leq t}$ conditioned on survival is characterized by

$$\mathbf{E}^x\Big(F((N_s^K)_{0\leq s\leq t}) | N_t^K > 0\Big) = \frac{\mathbf{E}^x\left(\frac{F((Y_s^K)_{0\leq s\leq t})}{Y_t^K \exp(\int_0^t (d-b)(\frac{Y_s^K}{K})ds}\right)}{\mathbf{E}^x\left(\frac{1}{Y_t^K \exp(\int_0^t (d-b)(\frac{Y_s^K}{K}))ds}\right)}$$

Trajectory Analysis (From 1 to $\sqrt{K}$)

We will now explore the study of

$$W_u^K = \frac{1}{K^\alpha} Y_{uK^\alpha}^K.$$

- **Generator of** A^{W^K} :

$$A^{W^K} f(w) = 2df'(w) + \frac{aw}{K^{1-\alpha}} f'(w) + \frac{aw}{K^{1-2\alpha}} f'(w) + wdf"(w) + \frac{aw^2}{2K^{1-\alpha}} f"(w) + \frac{aw}{2K} f"(w) + o\left(\frac{1}{K^\alpha}\right)$$

Trajectory Analysis (From 1 to $\sqrt{K}$)

For $\alpha = \frac{1}{2}$, we obtain the following Feller diffusion :

$$dW_t = (2d + aW_t)dt + \sqrt{2dW_t}dB_t$$

Back to the original process

$$\mathbb{E}^x\left(\left(F\left(\frac{N^K_{\sqrt{K}s}}{\sqrt{K}}\right)_{s\leq t}\right)|N^K_{\sqrt{K}t} > 0\right) = \frac{\mathbb{E}^x\left(\frac{\left(F\left(W^K_s\right)_{s\leq t}\right)}{W^K_t\left(\exp\int_0^t aW^K_v dv\right)}\right)}{\mathbb{E}^x\left(\frac{1}{W^K_t\left(\exp\int_0^t aW^K_v dv\right)}\right)}$$

To be continued! 

Trajectory Analysis from $K^{1/2+\epsilon}$ to K

Dynamical System Approximation

Let x_K be the solution of the ODE:

$$x'_K(t) = x_K(t)(b-d)(x_K(t)),$$

where x_K may depend on K through its initial condition.

We introduce, for $0 < x_K(0) < v_K$,

$$\tau^K := \inf\{t \geq 0 \ : \ x_K(t) = v_K\}.$$

Trajectory Analysis from $K^{1/2+\epsilon}$ to K

Consider $X^K(t) = \frac{N^K(t)}{K}$ is the population density.

Theorem

For all $\eta > 0$,

$$\mathbb{P}\Big(\sup_{t \leq \tau^K} \left| \frac{X^K(t)}{x_K(t)} - 1 \right| > \eta \Big) \leq \frac{1}{\eta} C \frac{v_K}{K^{1/2} x_K(0)^2}$$

1. We deduce that, starting from the initial condition $x_K(0) = K^{-1/4+\epsilon}$, we can reach the order of K.
2. We repeat the same process until we reach the limit $K^{-1/2}$ for $X^K(0)$, ($K^{1/2}$ for $N^K(0)$).

Trajectory analysis from $(K^{1/2}$ to $K^{1/2+\epsilon})$

$$N_0^K = \lfloor K^{1/2} \rfloor.$$

Let us introduce the process:

$$\zeta_t^K := K^{-1/2} N^K_{K^{1/2}t},$$

and define $(\bar{\zeta}_t)_t$ as the solution of the stochastic differential equation:

$$d\bar{\zeta}_t = a\,\bar{\zeta}_t^2\,dt + \sqrt{2\,b\,\bar{\zeta}_t}\,dB_t.$$

Consider

$$T(K^\epsilon) := \inf\left\{t \geq 0 \;:\; \bar{\zeta}(t) = K^\epsilon\right\},$$

We have

$$\left|A^{\zeta^K} g(x) - A^{\bar{\zeta}} g(x)\right| \leq C\,K^{-1/2}\left(1 + x^2\right)\left(||g''||_\infty + ||g'''||_\infty\right).$$

Conclusion

Probability of Invasion	Approximated Model	Dynamics
$\mathbb{P}_{\lfloor K^{\alpha} \rfloor}\left(T_0^K > T^K_{\lfloor \sqrt{K} \rfloor}\right) \underset{K\to\infty}{\longrightarrow} 0$, for $\alpha < 1/2$.	$\mathbf{E}^x\left(F((N_s^K)_{0\leq s\leq t})\vert N_t^K > 0\right)$	$\mathrm{d}W_t = (2d + aW_t)dt + \sqrt{2dW_t}dB_t$
$\mathbb{P}_{\lfloor \sqrt{K} \rfloor}\left(T_0^K > T_K^K\right) \underset{K\to\infty}{\longrightarrow} l$, with $l \in]0,1[$.	$\zeta_t^K := K^{-1/2} N^K_{K^{1/2}t}$	$\mathrm{d}\bar{\zeta}_t = a\,\bar{\zeta}_t^2\,dt + \sqrt{2\,b\,\bar{\zeta}_t}\,dB_t$.
$\mathbb{P}_{\lfloor K^{\beta} \rfloor}\left(T_0^K < T_K^K\right) \underset{K\to\infty}{\longrightarrow} 1$, for $\beta > 1/2$.	$\frac{N^K(t)}{K}$	$\mathrm{x}'_K(t) = x_K(t)(b-d)(x_K(t))$,

Thank You!