Spatial Moran Model with Mutation

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Joint work with

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Model

State of the process at time t is $\eta_t : \mathbb{Z}^d \to \{0, 1, 2, \ldots\}$

$0 =$ wild type, $1 =$ premailgnant, $2 =$ malignant

Type i cells have fitness $(1 + s)^i$

Birth-death dynamics: Cells reproduce with a rate equal to their fitness and then replace one of its $2d$ nearest neighbors cells at random with its progeny, which inherits the parental fitness.

Type i cells also mutate to type $i + 1$ cells at rate u_{i+1}.

Biased Voter Model

Only 1's and 0's, no mutation.

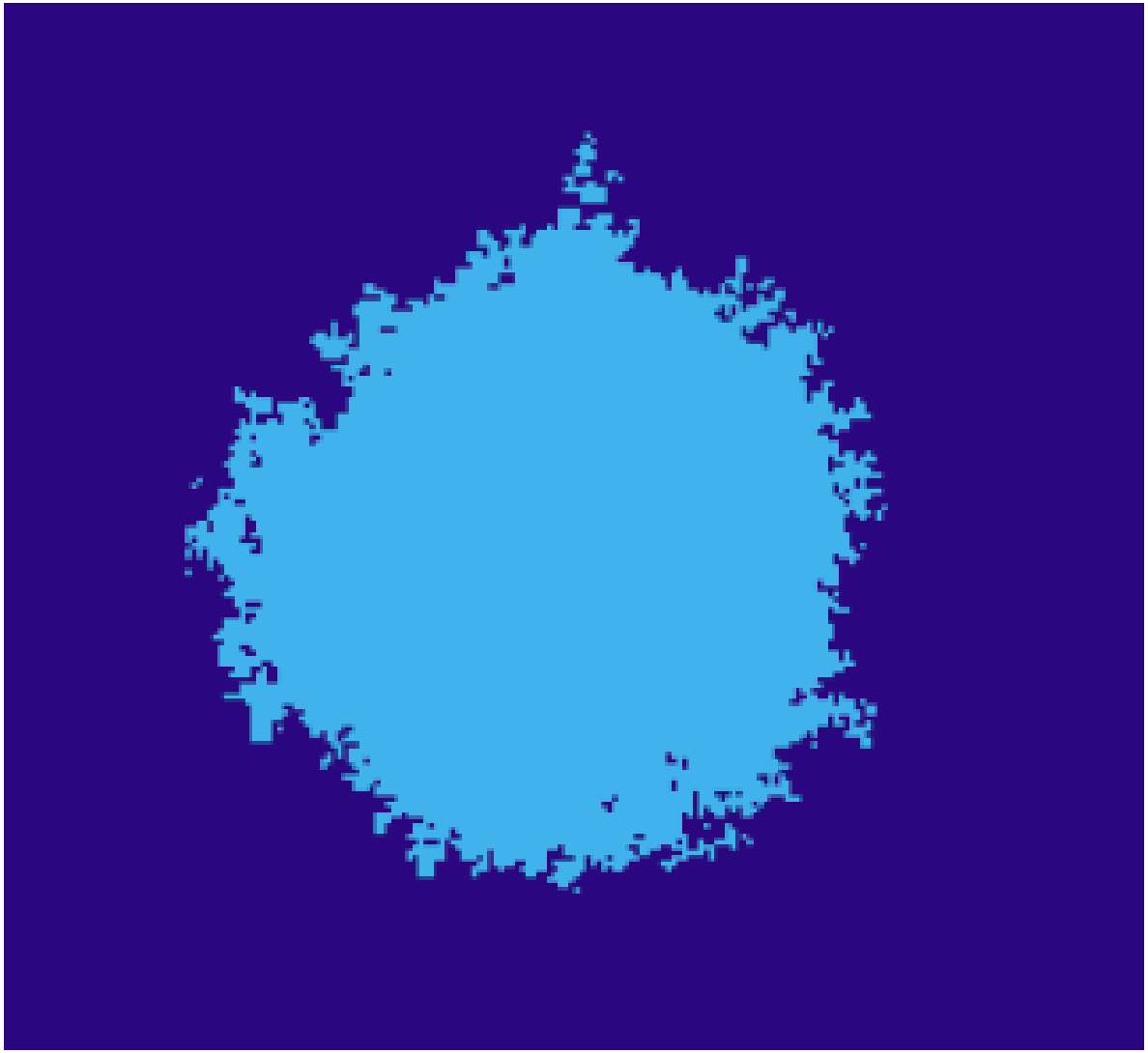
ξ_t^0 process when initially there is a single 1 at the origin at time 0.

Let T_0 be the extinction time. $P_1(T_0 = \infty) = s/(1+s)$.

Bramson and Griffeath Shape Theorem. For any $\epsilon > 0$, there is a $t_\epsilon(\omega)$ so that on $\{T_0 = \infty\}$ we have

$$(1-\epsilon)tD \cap \mathbb{Z}^d \subset \xi_t \subset (1+\epsilon)tD \quad \text{for } t \geq t_\epsilon(\omega).$$

Simulation of biased voter model



Speeds

Let e_1 be the first unit vector, $[-c_d(s)e_1, c_d(s)e_1]$ intersection of D with the x axis. Using ideas of Durrett and Zähle (2007):.

Theorem. *As $s \to 0$ we have*

$$c_d(s) \sim \begin{cases} s/2 & d = 1 \\ \sqrt{(\pi/4)s/\log(1/s)} & d = 2 \\ \sqrt{\beta_d s}/d & d \geq 3, \end{cases}$$

where β_d is the probability that two d dimensional simple random walks started at 0 and $e_1 = (1, 0, \ldots 0)$ never hit.

$d = 3$. $C\sqrt{s}$ speed for $\partial u/\partial t = \partial^2 u/\partial x^2 + su(1-u)$ and for branching Brownian motion.

$d = 2$. $s = 0.025$. Formula 0.0729, simulation 0.0715 ± 0.0043.

An important quantity

On $\mathbb{Z}^d$ we say a mutation is successful if the family it starts does not die out. To define this notation on a torus with $N = L^d$ sites:

$$\ell(s) = \begin{cases} s^{-2} & d = 1, \\ s^{-1}\log(1/s) & d = 2, \\ s^{-1} & d \geq 3 \end{cases}$$

Lemma. *For $\delta > 0$ there exists M such that the probability an unsuccessful type 1 family on $\mathbb{Z}^d$ will last for time $\geq M\ell(s)$ or will escape from a cube of radius $M\ell(s)^{1/2}$ is $\leq \delta s$.*

σ_1 Time to first successful type 1 mutation

$$P(\sigma_1 > t/Nu_1 s) \to e^{-t}$$

"Proof" Mutations occur at rate Nu_1, are successful with probability $\to s$.

Technicality: How do we know that successive attempts don't interfere with each other?

A clumsy proof

Divide space-time into boxes with side $[M\ell(s)]^{1/2}$ in space, $M\ell(s)$ in time

- (A0) $u_1\ell(s)^{(d+2)/2} \to 0$ **(at most one mutation per box)**
- (A0') $N/(\ell(s))^{d/2} \to \infty$. **(boxes fit in torus)**

Theorem. Assume (A0) and (A0').

$$P(\sigma_1 > t/Nu_1 s) \to e^{-t}$$

Open Problem. Get rid of (A0) which is not satisfied in some applications.

Values of constants

$N = 10^6$ cells in 1 cm^2, 10^9 in 1 cm^3.

Mutation rate 5×10^{-10} per nucleotide per cell division but there can be hundreds of mutations that will knock out a gene, and a large number of genes that can be mutated to knock out a metabolic pathway.
$u_i = 10^{-9}$ to 10^{-5}

Suppose $s = 0.01$, $d = 2$ (colon, bladder, epithelial tissues)

- (A0) $u_1 \ell(s)^{(d+2)/2} = 0.1$ when $u_1 = 10^{-6.362}$
- (A0') $N/(\ell(s))^{d/2} = 10$ when $N = 10^{3.663}$

Proof by simulation

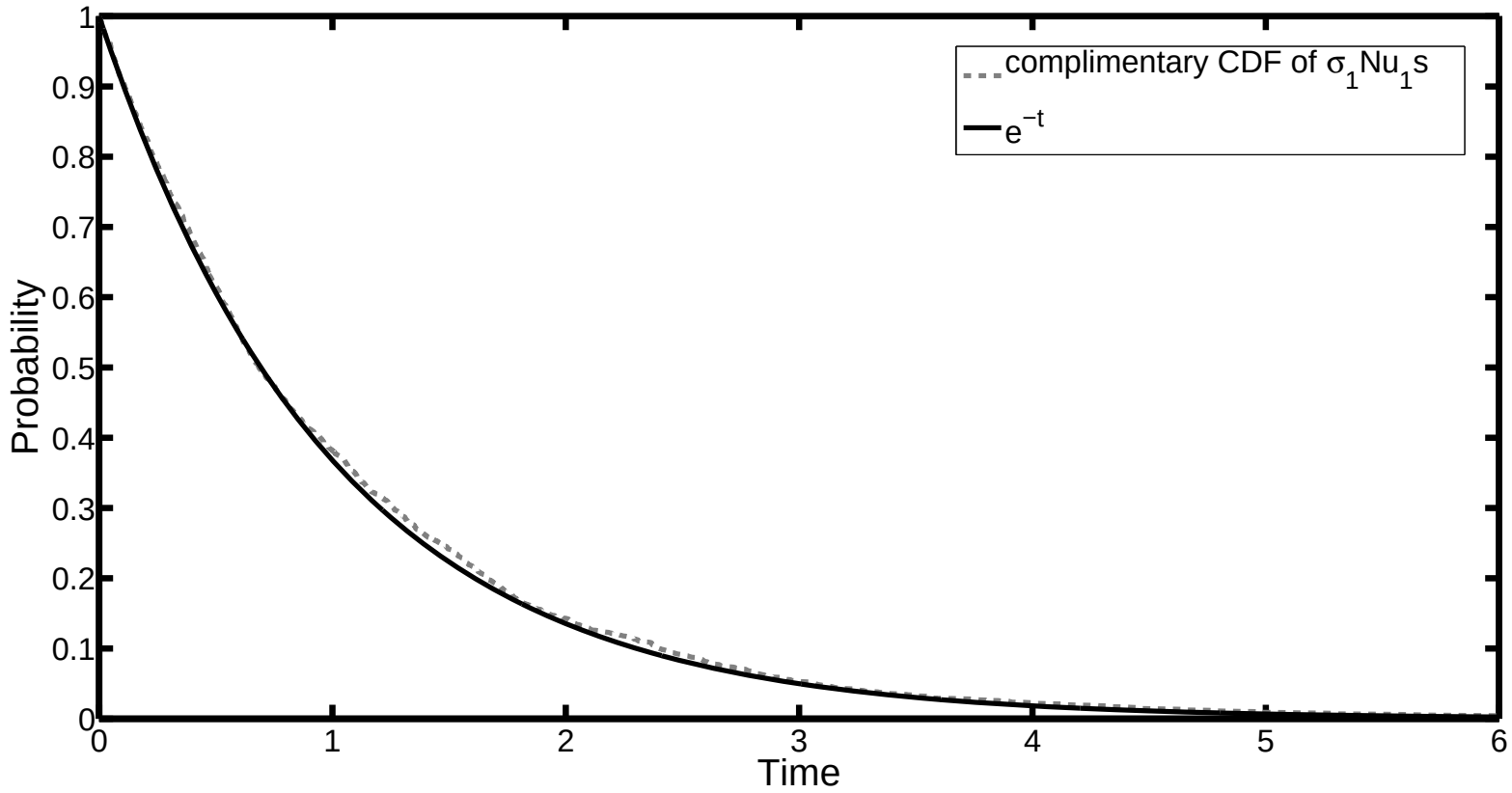


Figure: $N = 10^{5.5}$, $u_1 = 8 \times 10^{-8}$, $s = 0.01$

Simplified model on the torus $[0, L)^d$

Assumption I. Successful type 1's grow deterministically

$$\text{region covered by 1's} \quad \chi_t = \bigcup_{i=1}^{k} B_{x_i,(t-t_i)c_d(s)}.$$

Assumption II. We ignore the effect of unsuccessful type 1 and unsuccessful type 2 mutations on the growth of the successful type 1's.

Assumption III. Successful type 2 mutations occur at rate:

$$\lambda_2(x,t) = 1_{\{x\in\chi_t\}} u_2 s + 1_{\{x\in\chi_t^c\}} u_1 I(s) u_2 s$$

where $I(s) = E(\int_0^{T_0} |\xi_t^0|\, dt | T_0 < \infty)$.

σ_2, First case

The successful type 2 comes from the first successful type 1 family.

At $t_2 = (c_d^d u_2 s)^{-1/(d+1)}$ the family has space-time volume

$$\int_0^{t_2} (c_d r)^d \, dr = \Theta(1/u_2 s).$$

the radius is $c_d t_2 = (c_d/u_2 s)^{-1/(d+1)}$. For this ball to fit inside our torus, we need to have

$$(A1) \qquad (c_d/u_2 s)^{d/(d+1)} \ll L^d = N.$$

(A1), (A2), (A3) are ugly but have simple explanations.

Theorem 3. *If we assume,*

$$(A1) \qquad \left(\frac{c_d}{u_2 s}\right)^{d/(d+1)} \ll N \ll \frac{(c_d^d u_2 s)^{1/d+1}}{u_1 s} \qquad (A2)$$

and (A3) $u_2 \ll 1/\ell(s)$ *then as* $s \to 0$

$$P(\sigma_2 > t/Nu_1 s) \to \exp(-t)$$

(A1) growing ball fits in torus (previous slide)

(A2) $t_2 = \sigma_2 - \sigma_1 \ll \sigma_1$

(A3) Successful type 2 does not come from a type 1 family that dies out.

Simulation of spatial Moran model (not simplified)

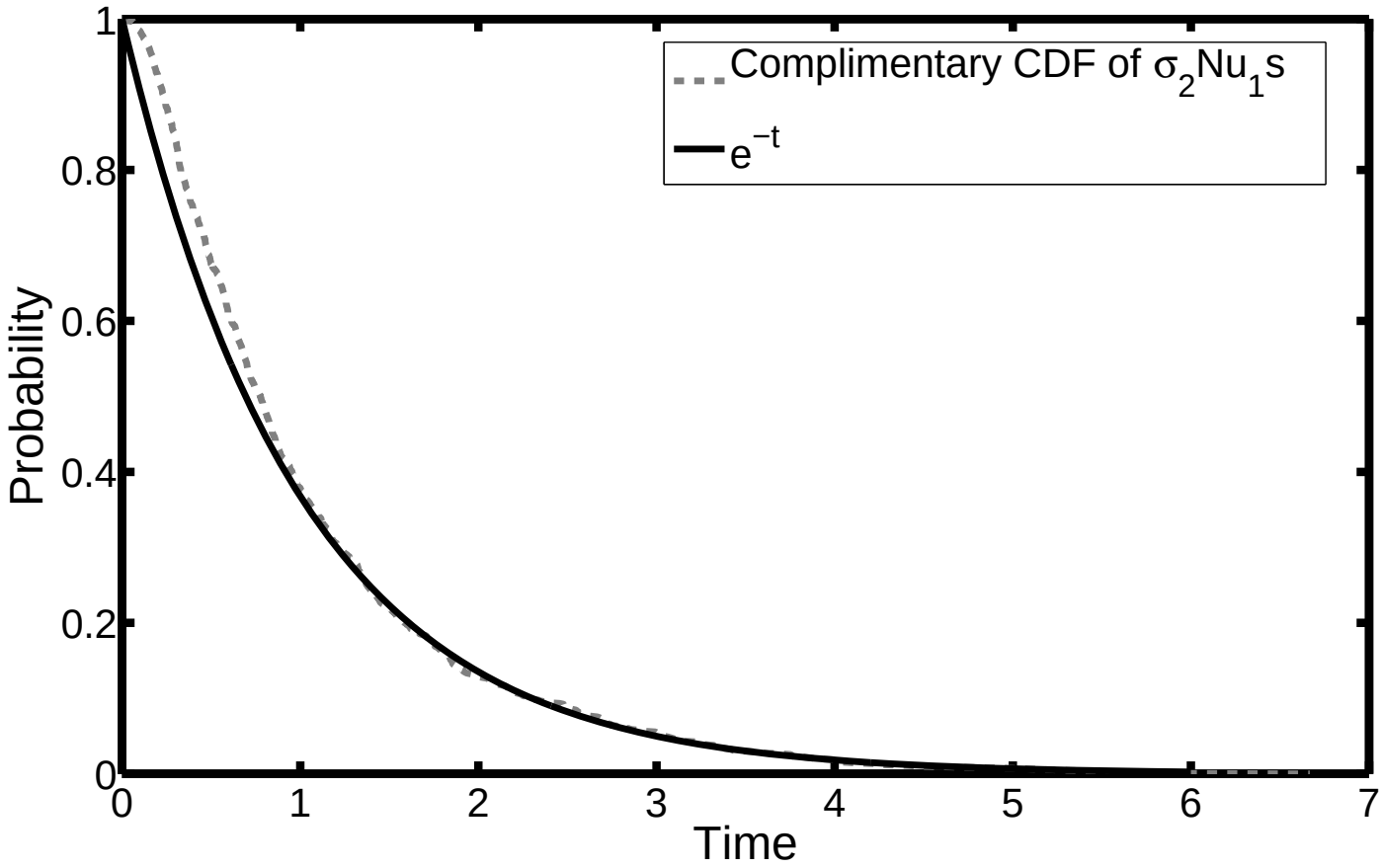


Figure: $N = 10^{5.5}$, $u_1 = 8 \times 10^{-8}$, $u_2 = 4.4 \times 10^{-4}$, $s = 0.01$ Deviation at small times due to contribution of $\sigma_2 - \sigma_1$.

σ_2, Second case

$$\Gamma = (Nu_1 s)^{d+1}(c_d^d u_2 s)^{-1}.$$

Intuitively, $\Gamma^{1/(d+1)}$ is the number of successful type 1 mutations needed (after the first one) to produce the first successful type 2.

Theorem 4. *If we assume (A1), (A3), and* $\Gamma \to I \in (0,\infty)$ *then as* $s \to 0$

$$P(\sigma_2 > t/Nu_1 s) \to \exp\left(-\int_0^t 1 - \exp\left[-\frac{\gamma_d}{I} \cdot \frac{y^{d+1}}{d+1}\right] dy\right)$$

(A1) Balls fit in torus. [(A2) in Th 3 is $\Gamma \to 0$.]

(A3) Successful type 2 does not come from unsuccessful type 1.

Proof: Show whp cones don't overlap, compute volume, use Poisson.

Simulation (0.116) vs. Theorem $I = 0.4$

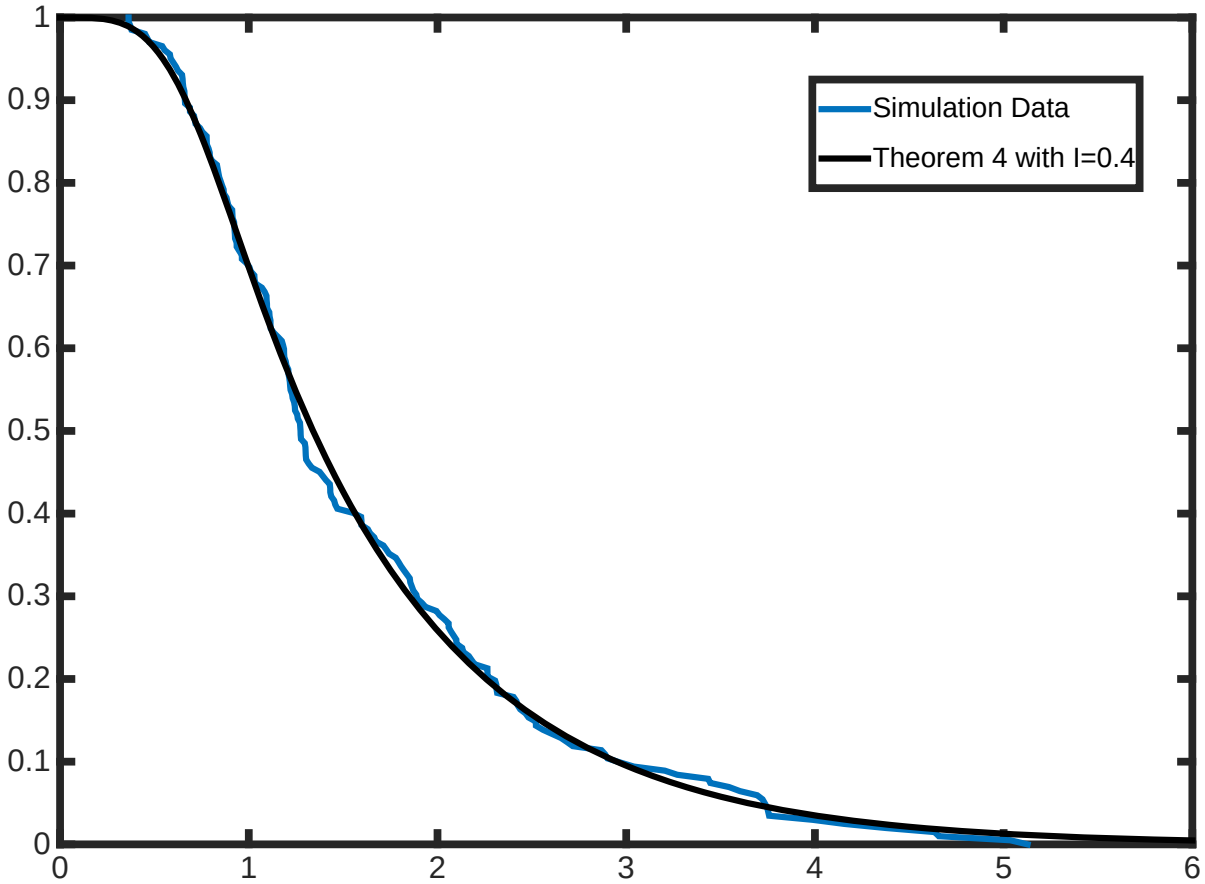


Figure: $N = 10^{5.5}$, $u_1 = 8 \times 10^{-8}$, $u_2 = 8 \times 10^{-6}$, $s = 0.01$

The source of the problem

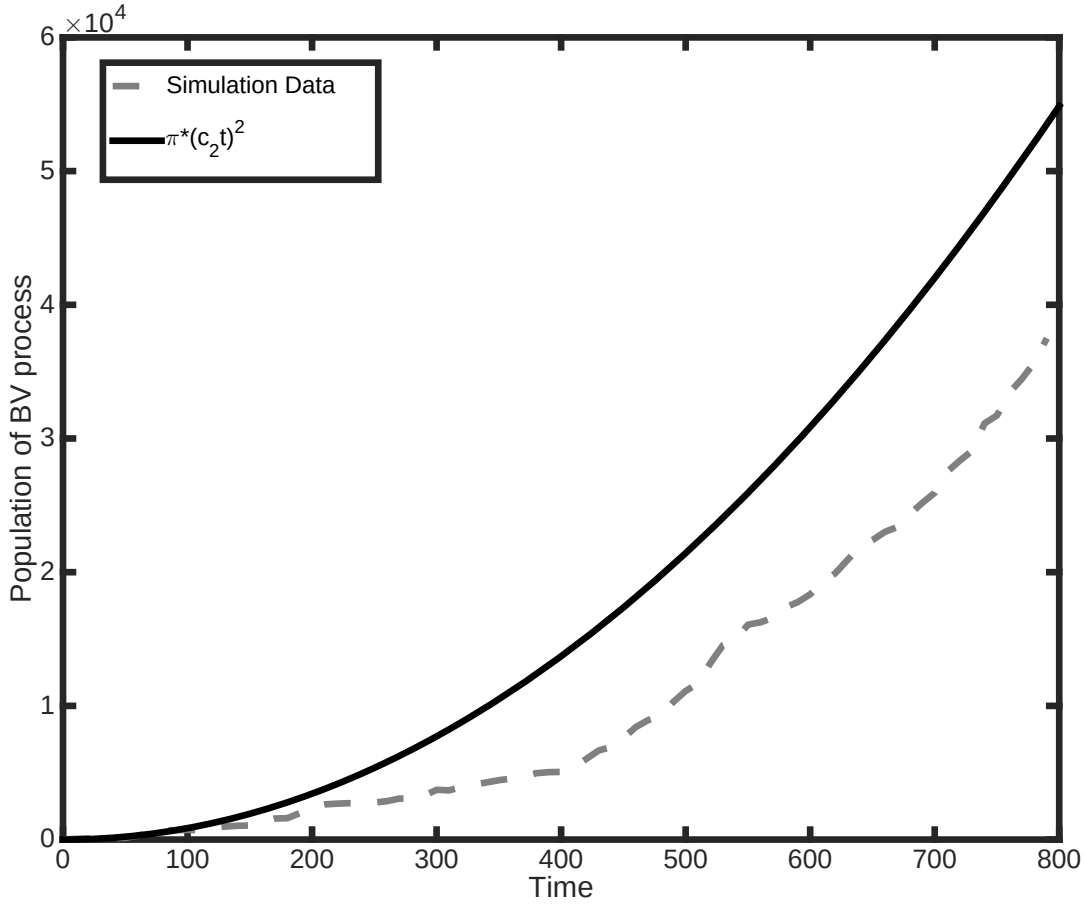


Figure: Simulated volume versus formula $s = 0.01$. Only 50,000 cells at end of simulation. Even a small $d = 2$ tumor will have 10^6 cells.

Connections with Cancer

Slaughter (1951) coined the term **cancer field effect** to reflect the fact that in Head and Neck Squamous Cell Carcinoma (HNSCC) and other epithelial cancers, a malignancy is surrounded by a region that has undergone premalignant transformation, which is what our model predicts.

He also noticed that often there was a **distant recurrence** which might be as far as 7cm from the original malignancy. The original hypothesis was that these were metastases but sequencing studies show that they have a different genotype. In Case 2 of of result for σ_2 there are multiple cancer fields.

References

R.D. and Stephen Moseley (2014) Spatial Moran Model, I. Tunneling in the Neutral Case. *Ann. Applied. Probab.* 25, 104–115

R.D., Jasmine Foo, Kevin Leder (2015) Spatial Moran Model, II. Cancer Initiation in Spatially Structured Tisse. *J. Math. Biol.*, to appear

Jasmine Foo, Kevin Leder, and Marc Ryser (2014) **Multifocality and recurrence risk: a quantitative model of field cancerization.** *J. Theor. Biol.* 355, 170–184

The first two papers and the slides for this talk are available on my web page.