

Approximating Mutant Fixation Probabilities in the Intestinal Crypt: From Microscopic Graphs to Macroscopic State Models

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Introduction & Motivation

- Fixation probability is a crucial metric for understanding mutant invasion and **Colorectal Cancer** initiation in the intestinal crypt.
- Cell-based models which use coupled ODEs to solve for cell mechanics and proliferation is computationally expensive.
- If we focus solely on fixation probability, can a topologically simplified (as shown in Fig 1) **Stochastic Model** efficiently approximate the results?

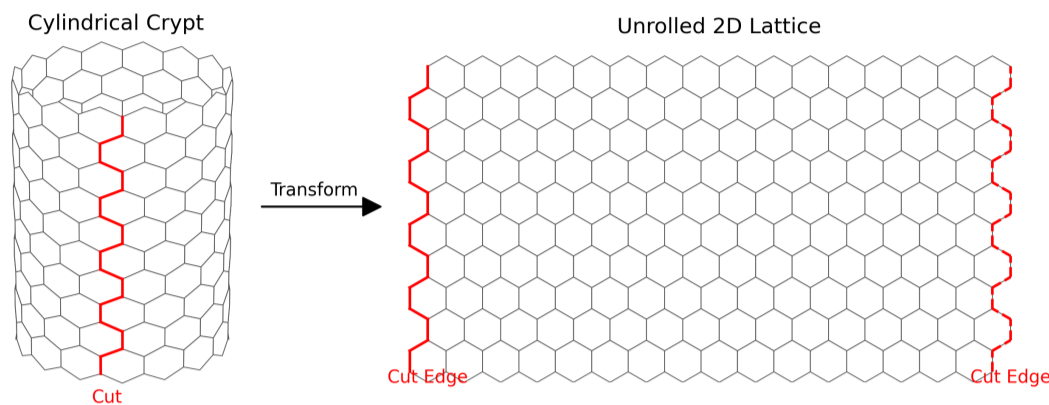


Fig. 1: From 3D simplified cylindrical crypt in [1] to 2D hexagonal grid used in this project.

One-Dimensional Moran Process

The classic **Moran process** models evolutionary dynamics in a **finite population** of size N with **two competing types**, tracking one type through time as either can proliferate and replace the other (**Birth-and-Death-Process**) [2].

One layer of the cylindrical crypt, represented as a **ring geometry** (Fig. 2), can be modeled as a 1D Moran process. The two cell types have **proliferative rates**: mutants (MT) λ and wild-type (WT) 1.

Crypt invasion initiates with 1 MT and transitions occur only at the MT-WT boundary (Fig. 2). $k = 0$ (Extinction) and $k = N$ (Fixation) are absorbing states.

Transition probabilities: Let k be the number of MTs. The process transitions are:

$$P(k \rightarrow k+1) = \frac{\lambda}{N + (\lambda-1)k}, \quad P(k \rightarrow k-1) = \frac{1}{N + (\lambda-1)k}$$

Tractable Solution: Fixation probability starting from 1 MT:

$$\rho(\lambda) = \frac{1 - \lambda^{-1}}{1 - \lambda^{-N}}$$

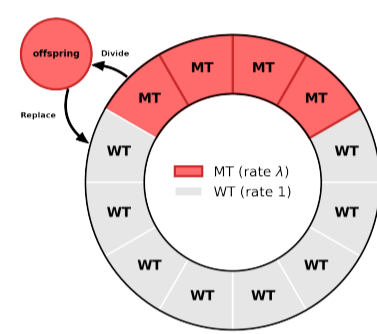


Fig. 2: 1D Ring Geometry.

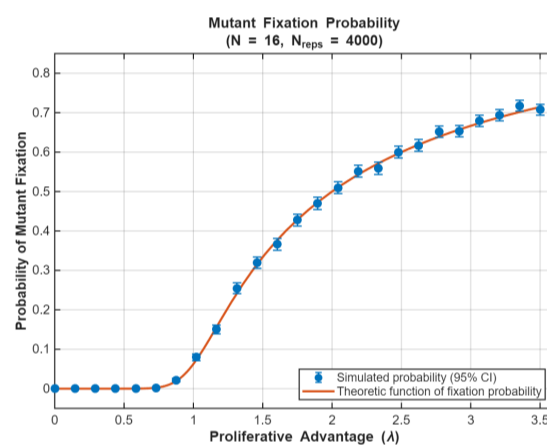


Fig. 3: Analytical and Simulated Fixation Probability for mutant invasion in 1D ring with λ as variable.

Microscopic Spatial Moran Process (MicSMP)

The **MicSMP** extends the classical Moran process to structured populations on an undirected graph $G = (V, E)$, where individuals occupy vertices V and interact through edges E .

A MicSMP is uniquely characterised by: (1) an adjacency **weight matrix** W where $W(v, v')$ represents the probability from vertex v to v' ; (2) a **selection policy** $\hat{\pi}$ predefines a rule to select vertex to action; and (3) the advantage λ between different types.[2]

Our crypt model is an instance of MicSMP: The selection policy $\hat{\pi}(\alpha)$ assigns higher proliferative rates to lower layers and weight matrix W defines the offset connectivity pattern (Fig 4).

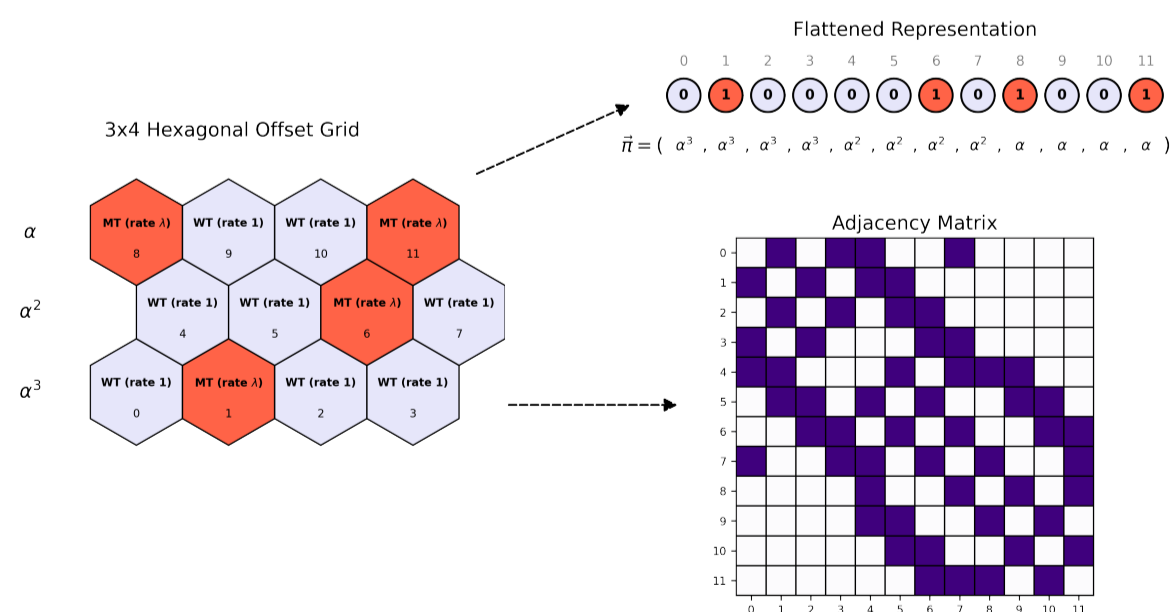


Fig. 4: Our crypt model as a MicSMP: selection policy $\hat{\pi}(\alpha)$ (layer-dependent birth rates) and adjacency weight matrix W (offset connectivity) in a small example of 3x4 crypt.

Markov chain structure: MicSMP defines a DTMC $\{\mathbf{X}_n\}$ on state space $\mathcal{X} = \{0, 1\}^{|V|}$ (1 for MT, 0 for WT) where each state $\mathbf{x} \in \mathcal{X}$ represents a cell-type configuration. Transition probabilities can be expressed as:

$$P(x_j : 0 \rightarrow 1) = \sum_{i \in \mathcal{N}(j)} \underbrace{\left(\frac{\lambda \hat{\pi}_i}{1 + (\lambda-1)\mathbf{x}\hat{\pi}^T} \right)}_{\text{select MT at } i} \cdot W_{ij}, \quad P(x_j : 1 \rightarrow 0) = \sum_{i \in \mathcal{N}(j)} \underbrace{\left(\frac{\hat{\pi}_i}{1 + (\lambda-1)\mathbf{x}\hat{\pi}^T} \right)}_{\text{select WT at } i} \cdot W_{ij}$$

where $\mathcal{N}(j)$ denotes spatial neighbors of cell j . $\mathbf{0}$ and $\mathbf{1}$ are absorbing states.

Key constraints:

- State space explosion: 2^{MN} configurations (M layers, N cells per layer)
- Fixation probability only solvable via linear system for small crypt ($MN \leq 14$, yielding $|\mathcal{X}| \lesssim 16000$ states) within reasonable computational time on MATLAB.

Macroscopic Spatial Moran Model (MacSMM)

To coarsen the MicSMP, direct projection $\mathbf{Y}_n = \mathbf{X}_n \mathbf{1}^T$ (summing cell states per layer) yields a process $\{\mathbf{Y}_n\}$ but does not preserve the Markov property [2].

Instead, we introduce a MacSMM that assumes **lumpability**: cells within each layer are uniformly distributed (well-mixed). Therefore it only tracks the MT count per layer and discard exact spatial positions.

State space: The macroscopic state $\mathbf{n} = (n_1, n_2, \dots, n_M) \in \{0, 1, \dots, N\}^M$ records the number of mutants in each of M layers, giving $(N+1)^M$ states (versus 2^{MN} for MicSMP).

Transition probabilities: Under the well-mixed assumption, let $\xi = (j, \uparrow)$ denote an event where the mutant count increases in layer j (and similarly \downarrow for decrease). Using the similar selection policy $\hat{\pi} = (\hat{\pi}_1, \dots, \hat{\pi}_M)$ from MicSMP:

$$P(\xi = (j, \uparrow)) = \frac{2}{d_j} \cdot \left(\frac{\lambda n_j \hat{\pi}_j}{N + (\lambda-1)\mathbf{n}\hat{\pi}^T} \cdot \frac{N - n_j}{N-1} + \sum_{i \in \mathcal{N}(j)} \frac{\lambda n_i \hat{\pi}_i}{N + (\lambda-1)\mathbf{n}\hat{\pi}^T} \cdot \frac{N - n_i}{N} \right)$$

$$P(\xi = (j, \downarrow)) = \frac{2}{d_j} \cdot \left(\frac{(N - n_j) \hat{\pi}_j}{N + (\lambda-1)\mathbf{n}\hat{\pi}^T} \cdot \frac{n_j}{N-1} + \sum_{i \in \mathcal{N}(j)} \frac{(N - n_i) \hat{\pi}_i}{N + (\lambda-1)\mathbf{n}\hat{\pi}^T} \cdot \frac{n_i}{N} \right)$$

where d_j is the degree of cells in layer j .

Numerical Results

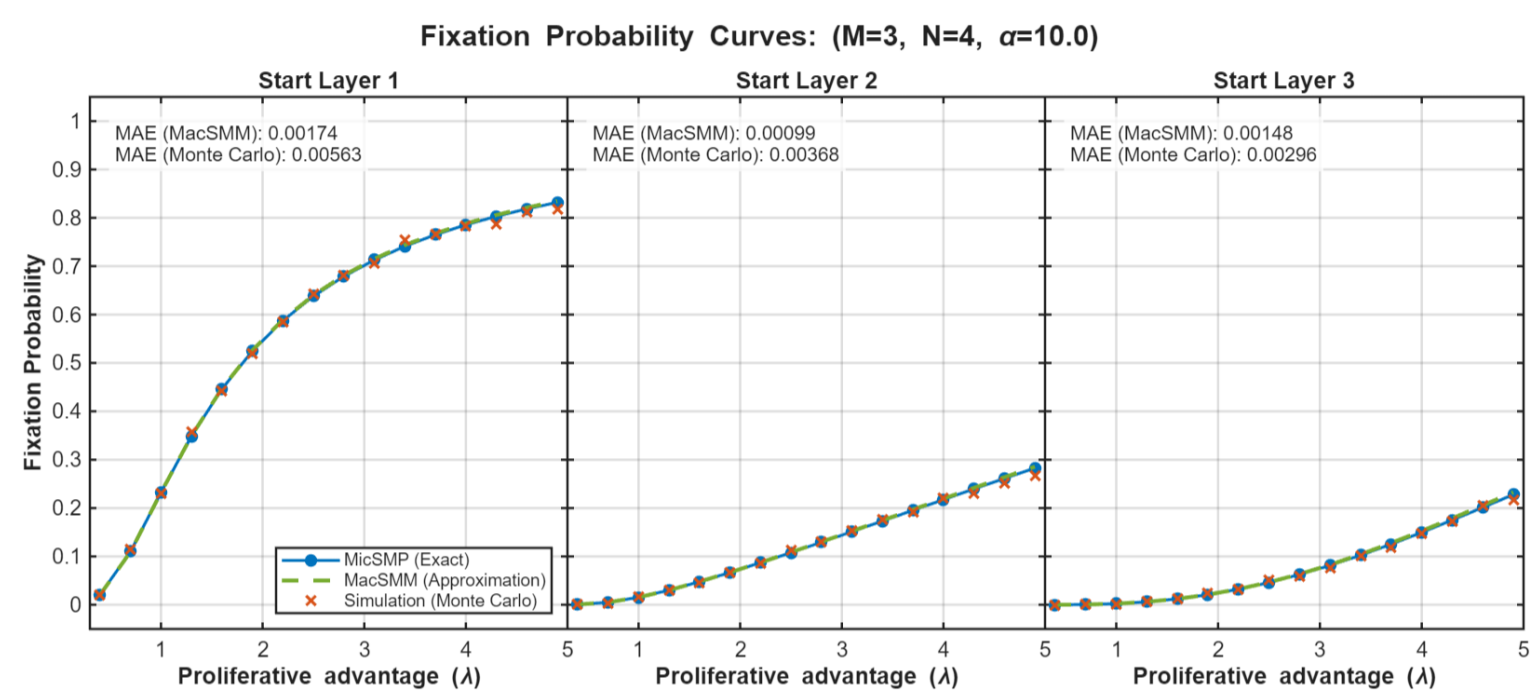


Fig. 5: Fixation probability for 3x4 crypt with MT initiating in each layer ($\alpha = 10$). Mean absolute errors (MAE) for MacSMM and Monte Carlo to MicSMP are shown.

- Layer hierarchy:** Layer 1 exhibits significantly higher fixation probabilities than layers 2 and 3 (Fig. 5). All curves resemble scaled versions of 1D Moran fixation curve (Fig. 3).
- MacSMM accuracy:** Despite discarding spatial information, MacSMM closely approximates MicSMP with lower error than Monte Carlo simulation.
- Fixation time discrepancy:** The fixation times highlights the difference between two models (Fig. 6). MacSMM's well-mixed assumption allows proliferation anywhere within layers, whereas MicSMP constrains proliferation to spatially adjacent cells.

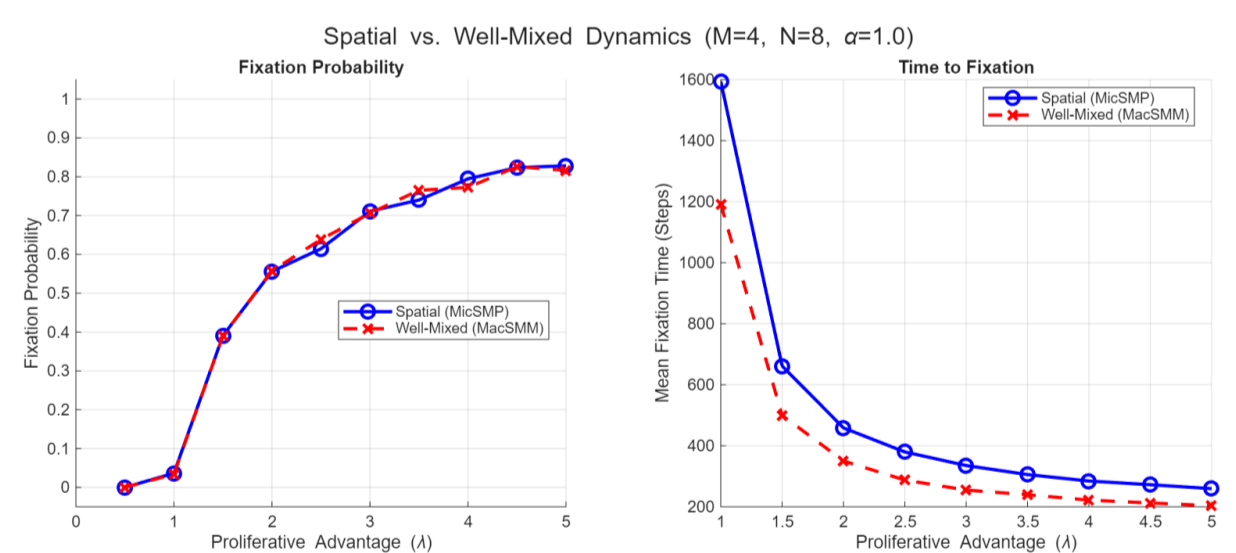


Fig. 6: Comparison of Fixation Probability and Time in an 4x8 ($\alpha = 1$) example through spatial (MicSMP) and well-mixed (MacSMM) Monte Carlo Simulation

Discussion & Conclusion

We developed a MicSMP model for intestinal crypts that provides exact numerical solutions for fixation probabilities. However, the model is computationally constrained.

Our results suggest that the MacSMM serves as a robust approximation for MicSMP, yielding comparable fixation probabilities with significantly reduced computational cost.

Future directions:

- Do analytical analysis on MacSMM and MicSMP to understand the approximation and define conditions under which the approximation remains valid.
- Investigate non-regular topologies and alternative selection policies in MicSMP to understand dynamics beyond current dimensional constraints.

References

- [1] G. R. Mirams, A. G. Fletcher, P. K. Maini, and H. M. Byrne, "A theoretical investigation of the effect of proliferation and adhesion on monoclonal conversion in the colonic crypt," *Journal of Theoretical Biology*, vol. 312, pp. 143–156, Nov. 2012, doi: <https://doi.org/10.1016/j.jtbi.2012.08.002>.
- [2] P. Keller and M. Ugurlu, "Fixation probability in Moran-like Processes on graphs," *arXiv preprint arXiv:2403.12598*, 2024.