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?
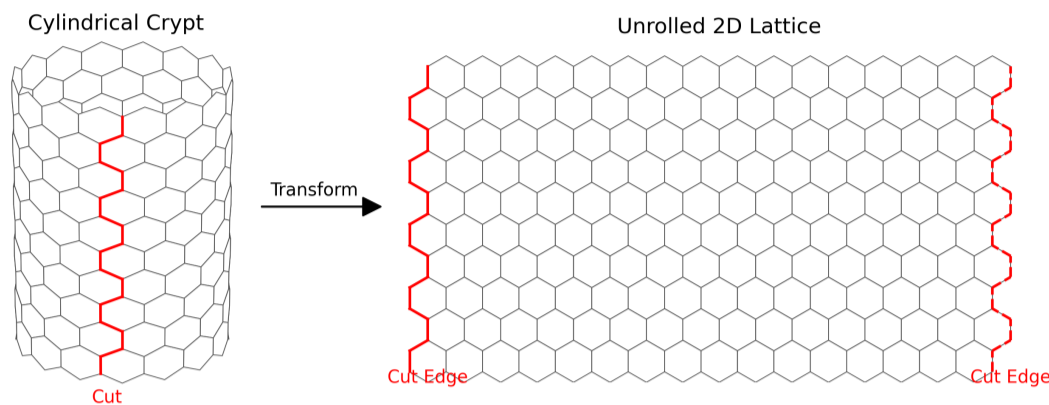

Fig. 1: From 3D simplified cylindrical crypt in [1] to 2D hexagonal grid used in this project.

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:

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

Tractable Solution: Fixation probability starting from 1 MT:

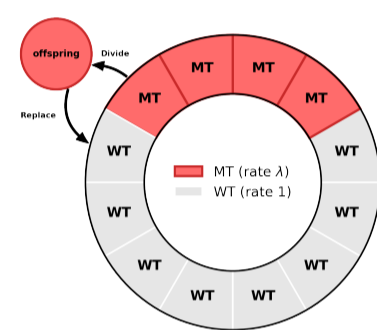$$\rho(\lambda) = \frac{1 - \lambda^{-1}}{1 - \lambda^{-N}}$$
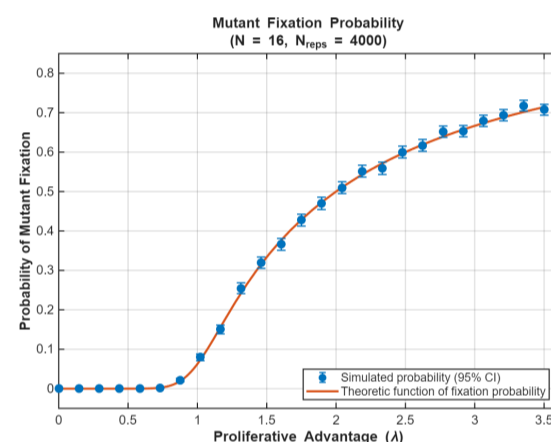

Fig. 2: Ring Geometry.

Fig. 3: Analytical and Simulated Fixation Probability for mutant invasion in the 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 prolifertive rates to lower layers and weight matrix W defines the offset connectivity pattern (Fig 4).
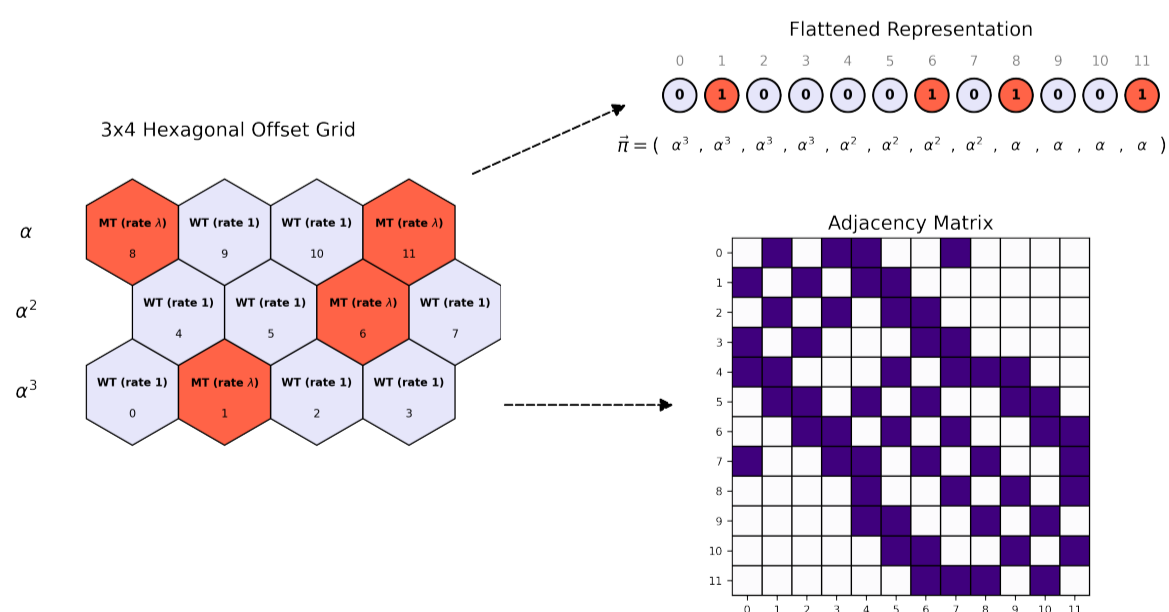

Fig. 4: Our crypt model as a MicSMP: selection policy $\hat{\pi}(\alpha)$ (layer-dependent birth rates) and adjacency weight matrix W (offset connectivity) in a small example of 3x4 crypt.

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:

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

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 $\mathbf{n} = (n_1, n_2, \ldots, n_M) \in \{0, 1, \ldots, N\}^M$ 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 $\hat{\pi} = (\hat{\pi}_1, \ldots, \hat{\pi}_M)$ 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.
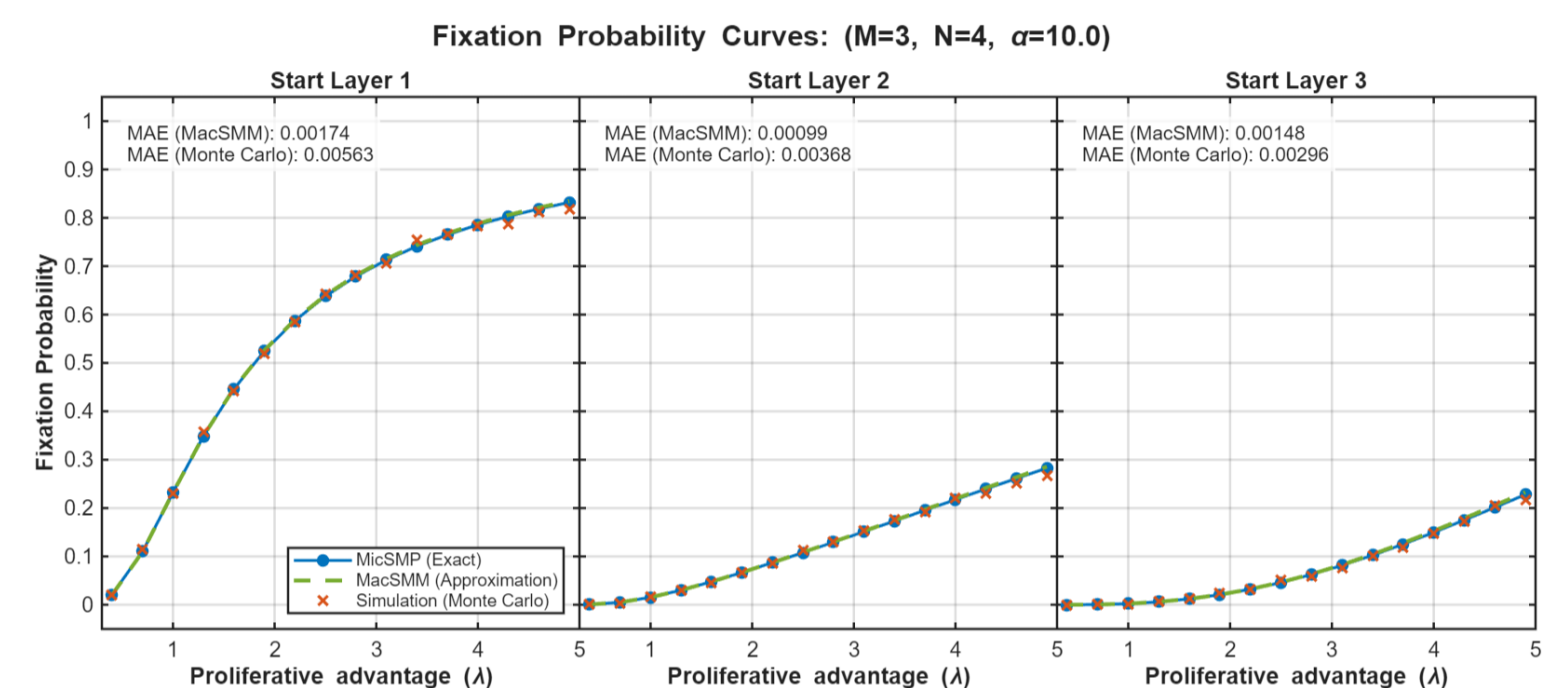
Numerical Results

Fig. 5: Fixation probability for 3×4 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.
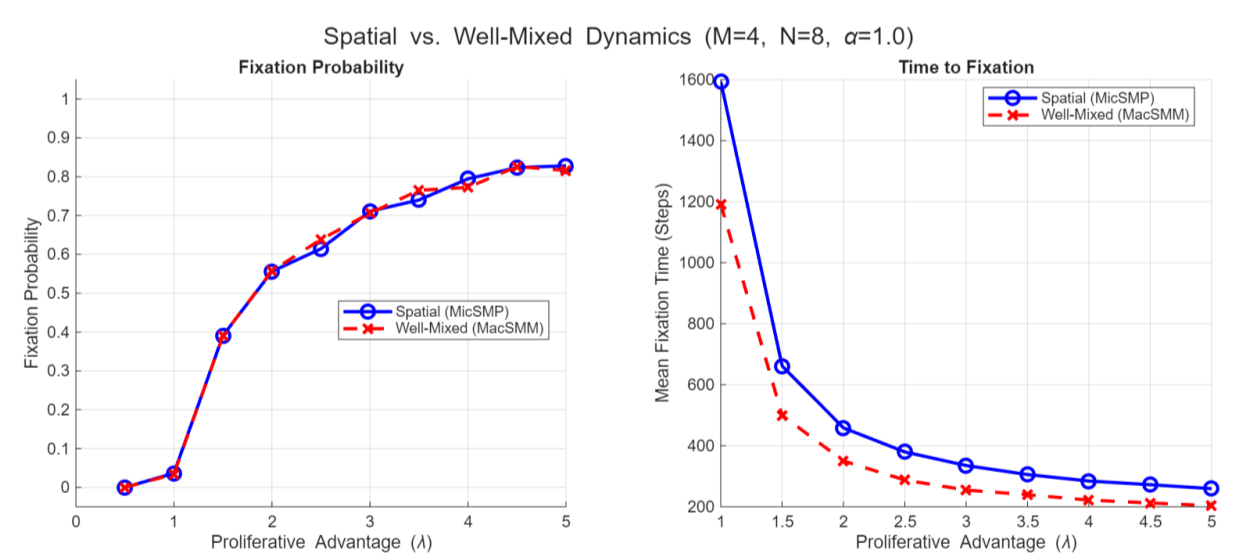

Fig. 6: Comparison of Fixation Probability and Time in an 4x8 ($\alpha = 1$) example through spatial (MicSMP) and well-mixed (MacSMM) Monte Carlo Simulation

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.