STOCHASTIC CONVEYOR BELT FOR QUANTITATIVE MODELING

We base our modelling strategy on recent results demonstrating that the dynamics of epithelial renewal in the intestine can be adequately described by the so called Stochastic Conveyor Belt (SCB) theory [1, 2]. We expanded the SCB framework, introducing a single modified cell with increased proliferation rate at the start of a simulation to mimic the experimental setup.

The basics of the SCB model is rooted in two independent Poisson processes:

- **Cell division** at rate k_d: The daughter cell can isotropically move with equal probability along the crypt-villus axis or laterally. Whatever the new position it takes, it pushes up the column of cells immediately above the newly arrived cell.
- **Cell relocation** at rate k_r: cells swap positions along the crypt-villus axis.

The model also incorporates geometry. The cylindrical geometry of the crypt is represented as a square lattice with periodic boundary conditions in the lateral direction. Each row contains five cells, and the height is set to 20 rows, based on the observation that this number has minimal impact on the dynamics when $L \gg \sqrt{k_r/k_d}$ [2]. Each cell position is defined by coordinates (i, j) where $i \in [0, 5]$ and $j \in [0, 20]$.

Simulation Initialization

At $t = 0$, a single random cell from the bottom row ($j = 0$) is labeled, while all other cells remain unlabeled. This differs from the setup in [2], where a random cell was labeled from the first four rows. At initialization, we restrict labeled cells to the bottom-most row, as low relocation rates in the proximal colon would prevent labeled cells originating from higher rows from effectively competing for monoclonalization at the crypt base. We consider two scenarios:

- **Neutral competition:** All cells share the same k_d and k_r.
- **Biased competition:** The initial labeled cell has an increased division rate k_d^μ, while wild-type cells keep dividing at k_d; being $k_d^\mu > k_d$. k_r remains the same for all cells. Daughter cells inherit the parental rates.

Simulation Update

At each simulation step, a random cell is chosen from the whole lattice. Possible events, such as cell divisions or relocations, are modeled as independent Poisson processes.

- **Division events** are spatially isotropic:
  - 50% percent of the divisions are axial, producing a labeled copy at $(i, j+1)$ and displacing all cells above in the same column by one position.
  - 50% percent of the divisions are lateral, producing a labeled copy at $(i \pm 1, j)$ (with periodic lateral boundaries) and shifting the displaced cell upward within its column.
- **Relocation events** occur only axially: a cell at (i, j) swaps position with the cell at either $(i, j+1)$ or $(i, j-1)$ [2].

Simulations run until the bottom row becomes monoclonal or for 100 days.

Parameters

For neutral competition in the proximal colon, we fixed $k_r/k_d = 0.25$ [2], as the experiments demonstrated comparable monoclonal conversion times for the entire large intestine and the proximal colon. We varied k_d between 0.18–0.27. The best fit, according to the minimal RMSE for the monoclonal conversion of the proximal colon, was obtained for the following parameters:

$$k_r = 0.0525, \quad k_d = 0.21 \quad .$$

For biased competition, the best fit was obtained for the modified cells:

- **BRAF:** $k_d^\mu = 0.46, \quad k_r = 0.0525 \quad ,$
- **BRAF; MHCII fl/fl:** $k_d^\mu = 0.74, \quad k_r = 0.0525 \quad ,$
- **BRAF; IL10RA fl/fl:** $k_d^\mu = 0.59, \quad k_r = 0.0525 \quad ,$
- **BRAF+DT:** $k_d^\mu = 0.73, \quad k_r = 0.0525 \quad ,$
- **BRAF+anti-IL10RA:** $k_d^\mu = 0.66, \quad k_r = 0.0525 \quad .$

Wild-type cells retained the values determined under neutral competition.

Simulation Replicates

Each simulation run comprised 100 crypts over $T = 100$ days. For each parameter set, 1000 independent repetitions were performed.

Computed Observables

Percent Fixed Clones The percentage of fixed clones at time t is defined as the ratio of monoclonal crypts to visible crypts:

$$\text{Percent Fixed Clones}(t) = \frac{\text{Monoclonal}[t]}{\text{Visible}[t]} \quad .$$

This value is averaged over 1000 independent simulation repetitions, with standard deviations reported.

Extinction Probability The extinction probability at time t is defined as the number of crypts whose labels became extinct divided by the total number of crypts per run ($N_{\text{crypts}} = 100$):

$$\text{Extinction Probability}(t) = \frac{\text{Extinction}[t]}{N_{\text{crypts}}} \quad .$$

Unlike the percent fixed clones, this metric normalizes by the total crypt count rather than visible clones. Averages and standard deviations are computed across 1000 repetitions.

Replacement Probability To compute the replacement probability, we simulate interactions at the boundary between labeled and unlabeled cells, for a comparable measure of replacement as in *CryptDriftR* [3]. Since our model is two-dimensional and includes axial movements, we restrict labeled cells to the bottom-most row at initialization. This makes our setup comparable to the one-dimensional *CryptDriftR* model, while accounting for the possibility that labeled cells may be lost due to upward movements. For the proximal colon, this restriction is a reasonable approximation, as relocation rates are low and the effect of random relocations is therefore expected to be minor. For each of the 100 crypts in a simulation, we record the frequency of labeled cells replacing unlabeled ones and vice versa:

$$P_{\text{labeled}} = \frac{N_{\text{labeled}}}{N_{\text{labeled}} + N_{\text{unlabeled}}} \quad .$$

This yields a replacement value per simulation. Across all 1000 simulations, we compile a histogram of these values, with the y-axis normalized to represent the probability density.

[1] Corominas-Murtra, B., et al. (2020). Stem cell lineage survival as a noisy competition for niche access. Proceedings of the National Academy of Sciences of the United States of America, 117(29), 16969–16975.

[2] Azkanaz, M., et al. (2022). Retrograde movements determine effective stem cell numbers in the intestine. Nature, 607(7919), 548–554.

[3] Vermeulen, L., et al. (2013). Defining stem cell dynamics in models of intestinal tumor initiation. Science (New York, N.Y.), 342(6161), 995–998.