

Buckling of Epithelial Cells: A Linear Spring Model

Lydia Colla, supervised by Prof. James Osborne and Mr. Patrick Grant

Introduction

The epithelium is the thin layer of protective tissue which forms the outer layer of organs. Under certain conditions the epithelium can undergo buckling, transforming it from a flat sheet of cells into a three-dimensional tissue. This project uses a linear spring model to investigate the conditions under which this buckling occurs, comparing numerical simulations and analytical approaches.

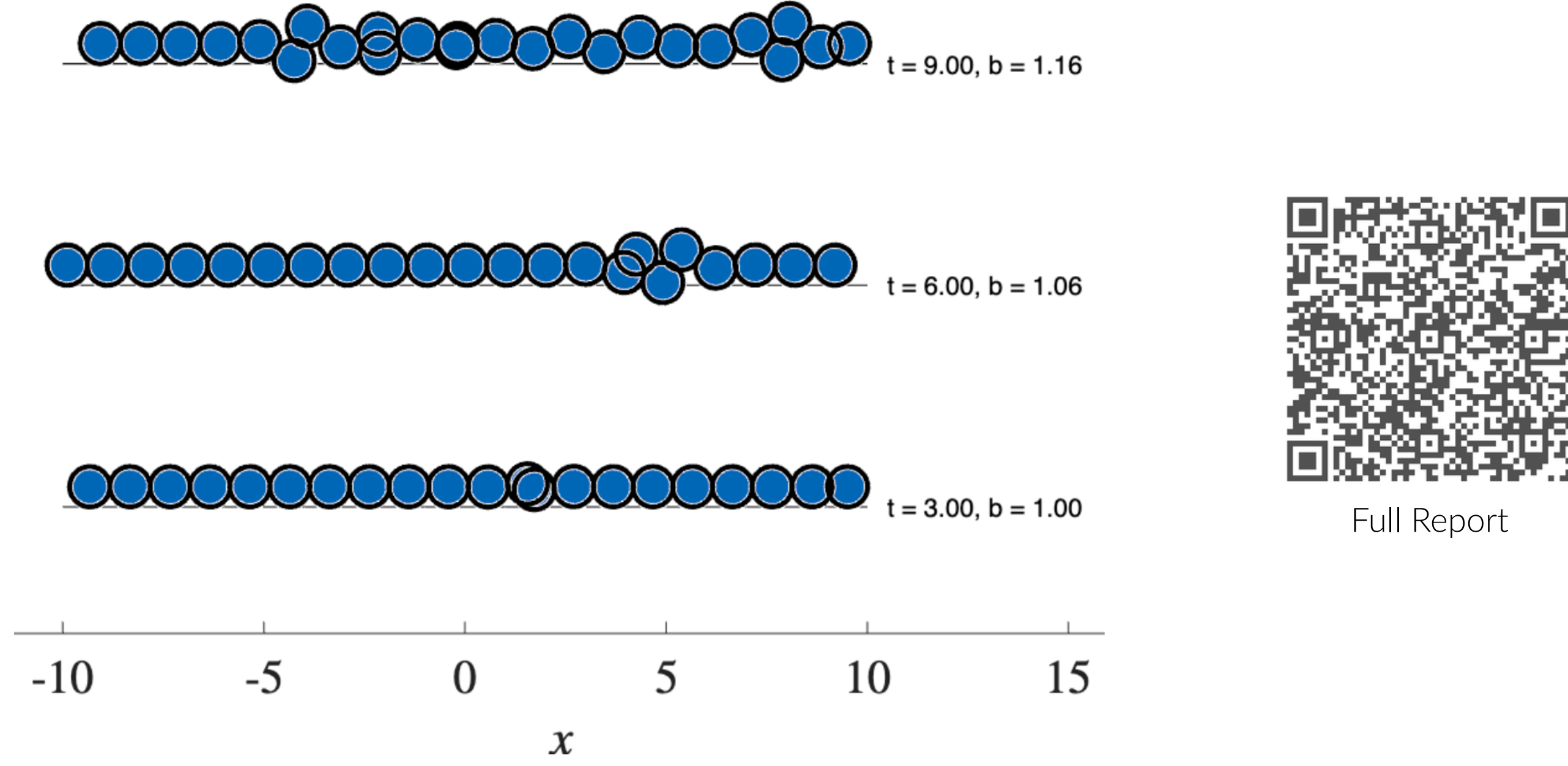


Figure 1. Example of MATLAB simulations, alongside QR code to access full written report. For the simulation we observe that buckling begins to occur at $t = 6.00$. Buckling ratio b is defined by Eqn. (5).

Numerical Model: Linear Springs

We model each cell in the epithelial tissue as a circle of diameter $CD = 1$. Let $\mathbf{x}_i = (x_i, y_i)$ denote the centre of cell $i = 1, \dots, N$, where N is the number of cells in the simulation.

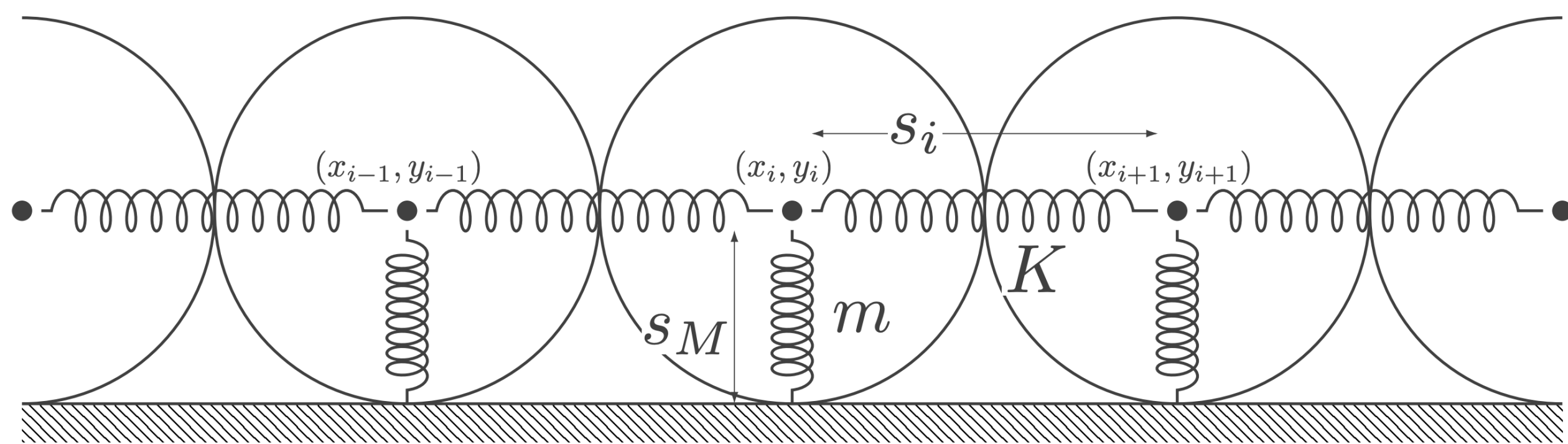


Figure 2. Forces acting on simulated cells. All springs are at their default rest lengths. We visualise the boundaries of the cells with the circles shown, although the only details included in this model are the centres given by (x_i, y_i) .

Given that it is not the first or last cell, the i^{th} cell in a chain of cells experiences the following forces:

$$\mathbf{F}_L = -K \left(\|\mathbf{x}_i - \mathbf{x}_{i-1}\| - s_{i-1} \right) \frac{(\mathbf{x}_i - \mathbf{x}_{i-1})}{\|\mathbf{x}_i - \mathbf{x}_{i-1}\|}, \quad (1)$$

$$\mathbf{F}_R = K \left(\|\mathbf{x}_i - \mathbf{x}_{i+1}\| - s_i \right) \frac{(\mathbf{x}_i - \mathbf{x}_{i+1})}{\|\mathbf{x}_i - \mathbf{x}_{i+1}\|}, \quad (2)$$

$$\mathbf{F}_M = -m(y_i - s_M) \begin{pmatrix} 0 \\ 1 \end{pmatrix}, \quad (3)$$

where s_i is the spring rest length between the i^{th} and $(i+1)^{\text{th}}$ cells for a spring of constant stiffness K , s_M is the spring rest length to the membrane for a spring of stiffness m , \mathbf{F}_L is the force from the "left" $(i-1)^{\text{th}}$ cell acting on the i^{th} cell, \mathbf{F}_R is similarly the force from the "right" cell, and \mathbf{F}_M is the force from the membrane. The system is in a non-inertial environment so all motion is governed by:

$$\eta \frac{d\mathbf{x}_i}{dt} = \mathbf{F}_i = \mathbf{F}_L + \mathbf{F}_R + \mathbf{F}_M. \quad (4)$$

Quantifying Buckling

We quantify the buckling of the system using the following:

$$b = \frac{\sum_{i=1}^{N-1} \|\mathbf{x}_{i+1} - \mathbf{x}_i\|}{x_N - x_1}, \quad (5)$$

where $b = 1$ indicates a perfectly flat system. We claim that the system has buckled once it reaches a point at which it can no longer re-stabilise to flat; that is, if the system achieves some b_{buckled} at time t_b , then for all $t > t_b$, $b > 1$.

Simulation Results

We apply a Forward Euler simulation and observe the following buckling behaviour. Note that these simulation results took >4h to produce, thus motivating the need for an efficient analytical prediction.

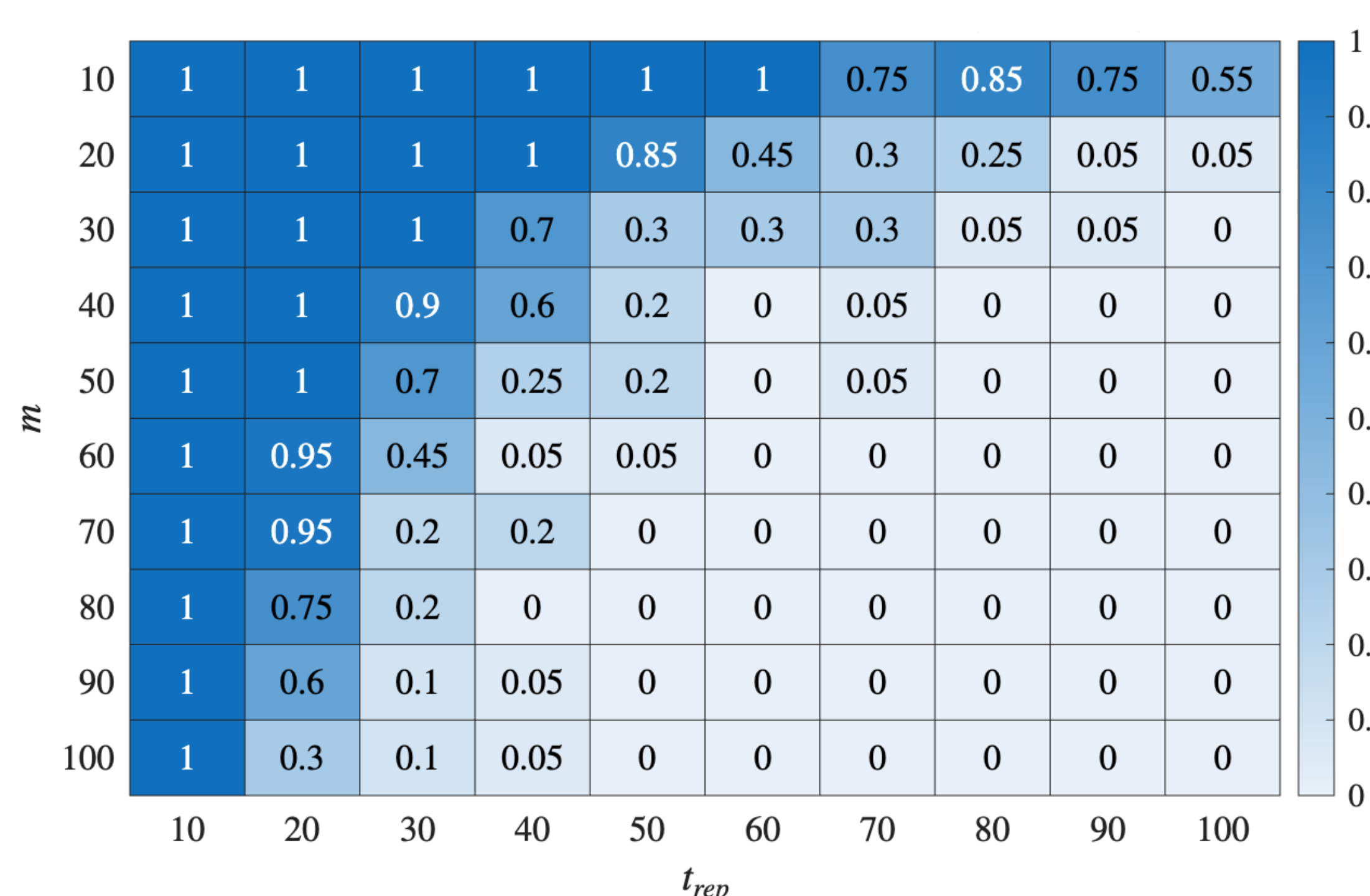


Figure 3. Proportion of simulations buckled over varying median proliferation ages t_{rep} and membrane spring constants m . $K = 100$, $t_{runtime} = 500$. Note that in this model a normal force has also been applied to prevent non-neighbour cells from occupying the same physical space.

Analytical Approach: Stability Analysis

To predict whether a system will buckle, we consider a flat chain of cells with all springs at their rest lengths. Suppose a proliferation event occurs. The system reacts as follows:

- Fast Step:** The cells "pop" out of the flat layer and move into a stable state. Since this happens almost immediately, we fix the positions for all cells other than two new daughter cells. We balance forces and solve for nullclines to determine the stable solutions, which can be either symmetric (Fig. 4 (a), (c)) or antisymmetric (Fig. 4 (b), (d)).
- Slow Step:** The system spreads outwards, pulling the disturbed cells back into a flat state. We approximate this behaviour by isolating the two disturbed daughter cells in a high-drag environment. We run a once-off simulation to find the best drag coefficient.

Sample of Calculations: Symmetric System

Fast Step: Stabilisation

For the symmetric cases in Fig. 4(a) and (c), we have the following solution:

$$x_{eq} = \frac{K - m \cdot x_{GC}}{2K - m}, \quad (6)$$

$$(y_{eq} - \frac{1}{2})^2 = \left(\frac{1}{1 - \frac{m}{K}} \right)^2 - (x_{GC} - x_{eq})^2, \quad (7)$$

where x_{GC} is the position of the right "ghost cell" (i.e. first fixed neighbour on the right) and (x_{eq}, y_{eq}) is the equilibrium point of the right daughter cell.

Slow Step: Relaxation

The settling time of the slow step is given by:

$$t_x = \frac{\eta_S}{2K} \log \left(\frac{x_{eq} - \frac{1}{2}}{x_{99\%} - \frac{1}{2}} \right), \quad (8)$$

$$t_y = \frac{\eta_S}{m} \log \left(\frac{y_{eq} - \frac{1}{2}}{y_{99\%} - \frac{1}{2}} \right), \quad (9)$$

$$t_{\text{settle, sym}} = \frac{t_x + t_y}{2}, \quad (10)$$

where $x_{99\%}$ and $y_{99\%}$ give the position of the cell when it has moved 99% of the way from its disturbed state to its flat state. η_S is the drag coefficient in the high-drag approximation; for this symmetric solution, tests indicate that $\eta_S = 7.7$ makes this approximation valid.

For complete calculations, see full report.

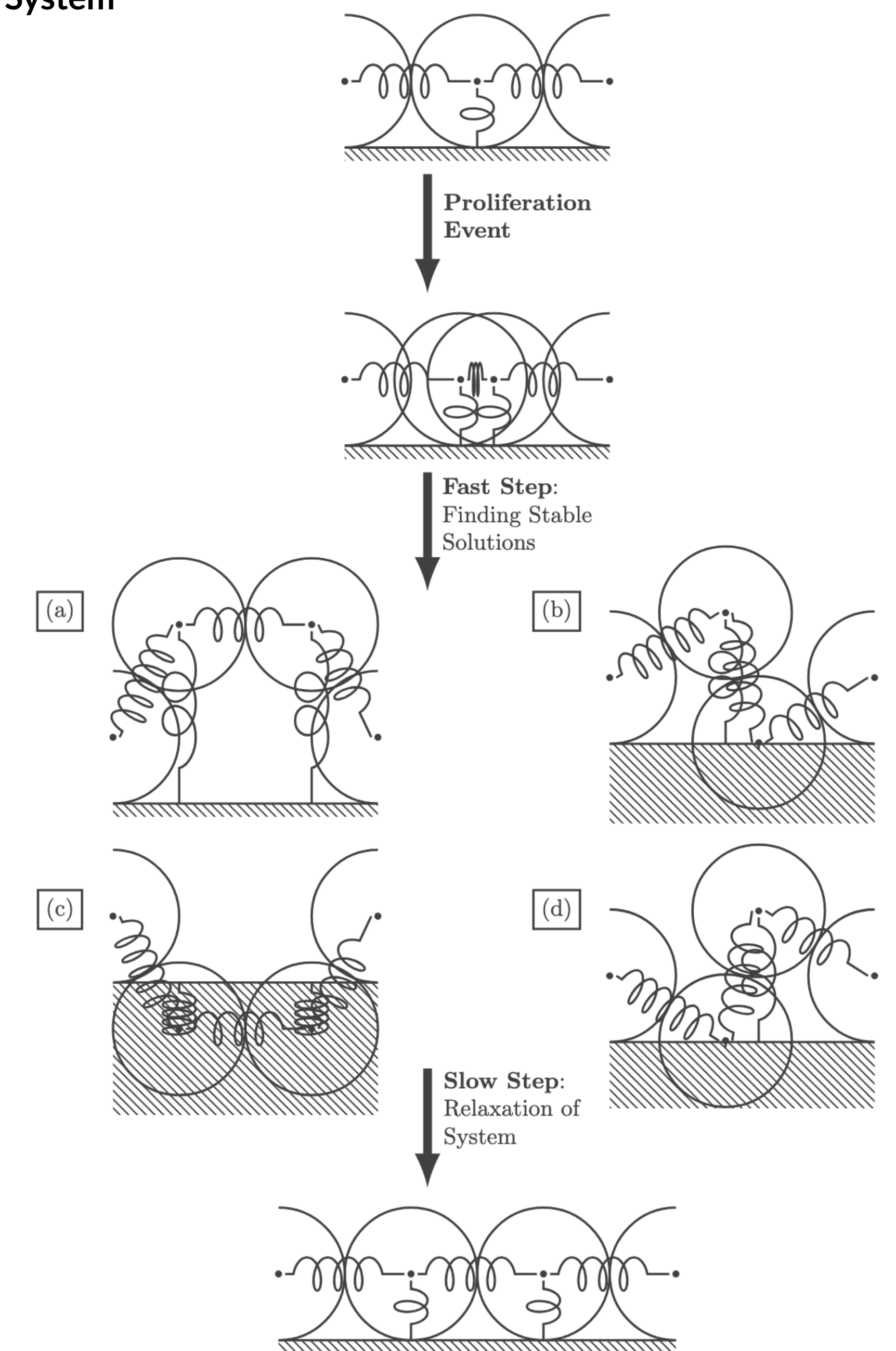


Figure 4. Sequence of events after a proliferation event.

Buckling Probabilities

Define a "buckling event" as the case in which a disturbed subsystem undergoes a second proliferation event before it has finished its relaxation step. We define the "subsystem" as the two new daughter cells and their four immediate neighbours, noting that the new cells are too young to proliferate. We have:

$$P(\text{buckle event in subsystem}) = P(\text{prolif.}) \cdot \left[\frac{1}{2} \cdot P(\text{antisym. buckling event}) + \frac{1}{2} \cdot P(\text{sym. buckling event}) \right], \\ = \frac{1}{2t_{rep}} \left[\left(1 - \left(1 - \frac{1}{t_{rep}} \right)^{4t_{\text{settle, asym}}} \right) + \left(1 - \left(1 - \frac{1}{t_{rep}} \right)^{4t_{\text{settle, sym}}} \right) \right], \quad (11)$$

where $t_{\text{settle, sym}}$, $t_{\text{settle, asym}}$ are the predicted settling times of the symmetric and antisymmetric proliferation events respectively. Given that we have $\frac{N}{6}$ subsystems in the total system, we have

$$P(\text{buckle}) = 1 - \left(1 - P(\text{buckle event in subsystem}) \right)^{\frac{N}{6} t_{\text{runtime}}}. \quad (12)$$

Analytical Predictions

The above probabilities predict the following behaviour. The predicted results are very similar to those simulated in Fig. 3, suggesting that the analytical method works well to predict buckling.

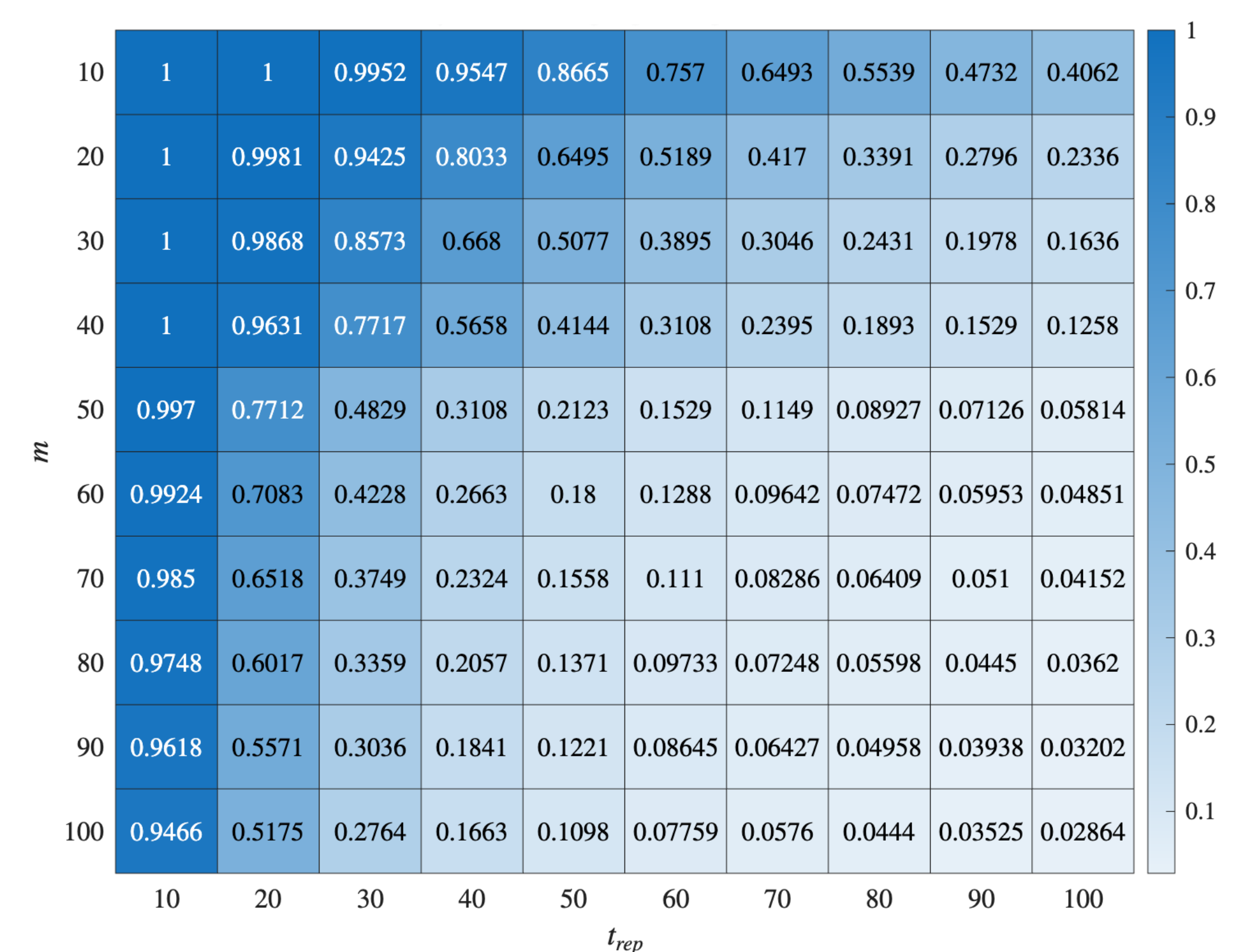


Figure 5. Buckling probabilities over varying median proliferation ages t_{rep} and membrane spring constants m . $K = 100$, $t_{runtime} = 500$. Where the symmetric solution is undefined we assumed zero probability of buckling.

References

Brown, P. J., Green, E. F., Binder, B. J., & Osborne, J. M. (2025). Understanding the mechanisms causing buckling of epithelial monolayers. *Mathematical Biosciences*, 380. <https://doi.org/10.1101/2024.04.01.587527>