Symmetric and asymmetric cell division and modeling of interacting cell populations in the colonic crypt

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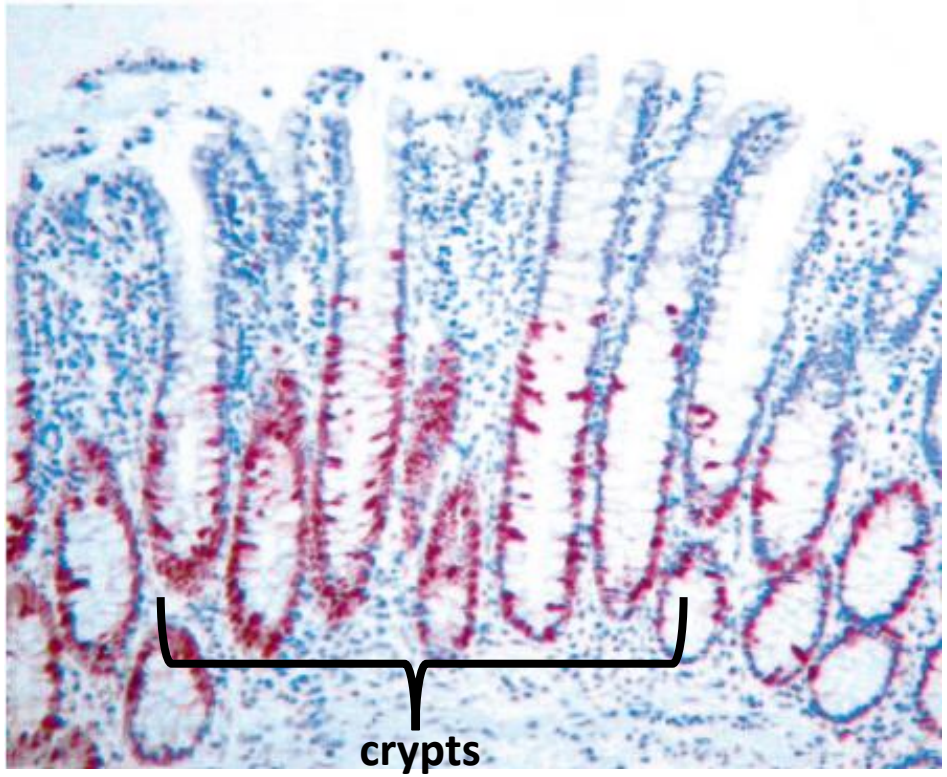
The Colonic Crypt

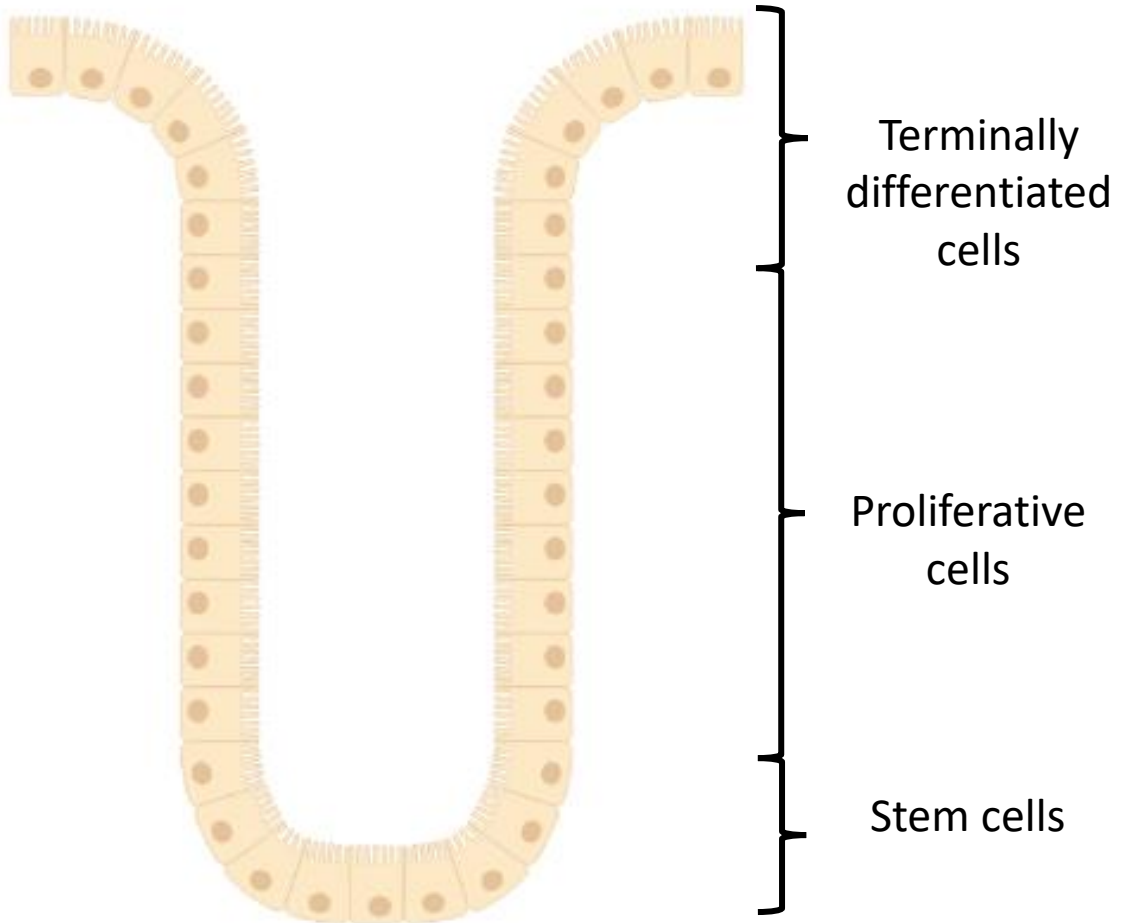
- Colon is responsible for the final stages of chemical digestion
- ~10 million crypts and length crypt depends on location in the intestine
- ~10 billion epithelial cells replaced daily



Boman 2004

Cell Populations

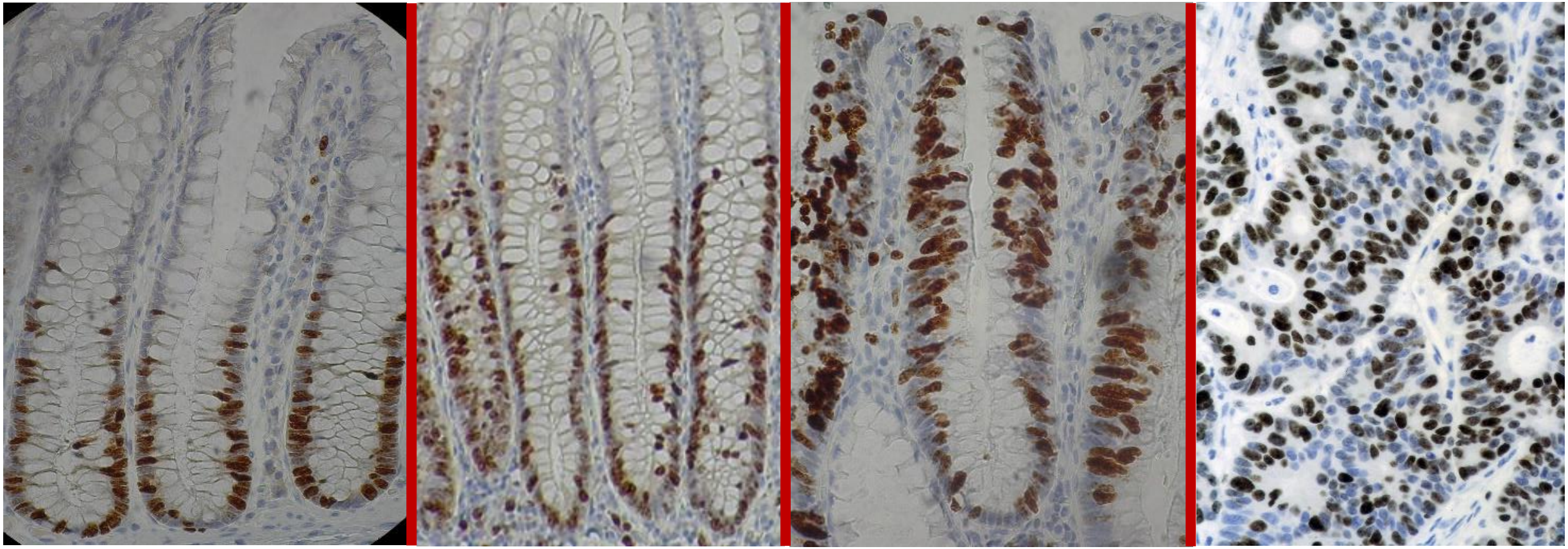
- Stem Cells (C)
  - Symmetric division: $C \rightarrow 2C$
  - Asymmetric division: $C \rightarrow C + P$
- Proliferative Cells (P)
  - Symmetric division: $P \rightarrow 2P$
  - Symmetric division: $P \rightarrow 2D$
  - Asymmetric division: $P \rightarrow P + D$
- Terminally differentiated Cells (D)
  - No division



Idealized crypt schematic and distribution

Expected vs Unregulated Behavior

Healthy | **Healthy-appearing FAP** | **Adenomatous** | **Cancerous**



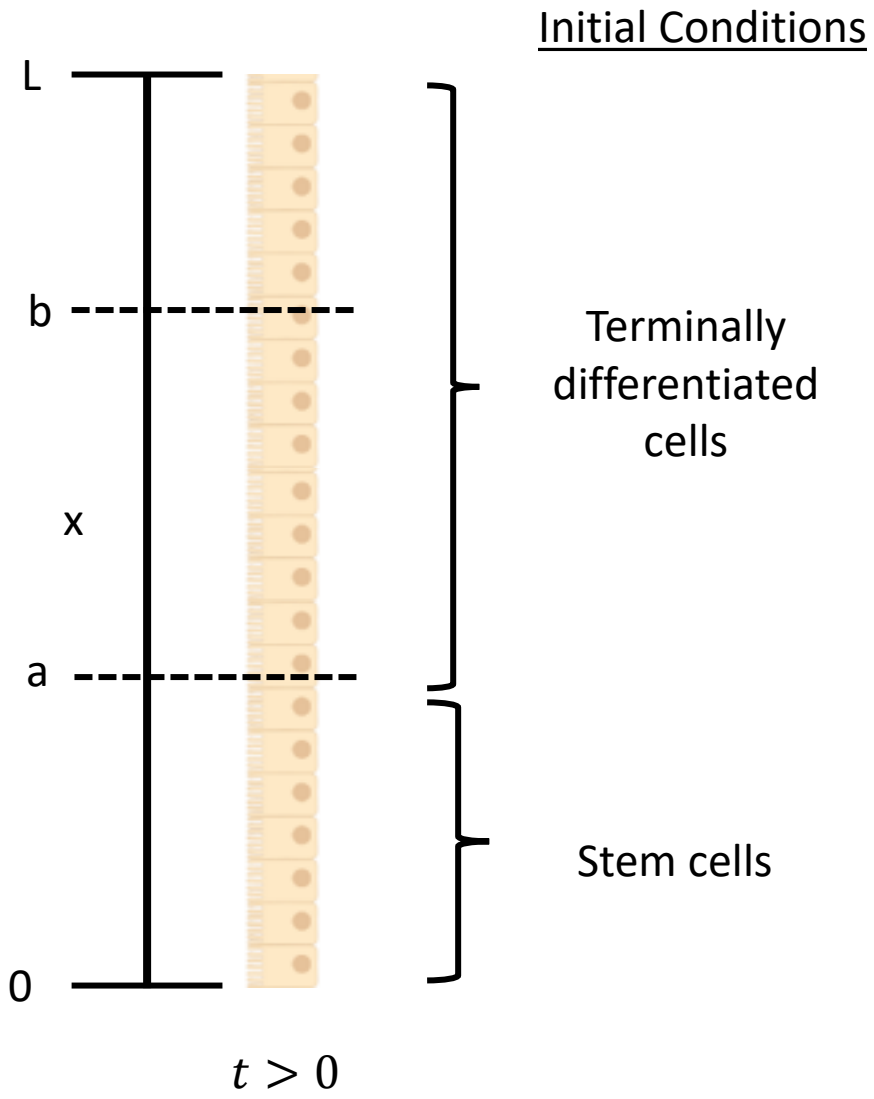
Adapted from Boman 2004

Proposed Model Components

- Only stem cells capable of asymmetric division:

$$C \xrightarrow{k_1} C + D$$

- Reduce size of crypt to a 1D line of cells
- Tracking density of cells for continuous equations
- Removal of cells from the system dependent on spatial location
- No apoptosis
- Incorporate a stochastic model for further analysis



Methods: Creating PDE System

By Conservation Law:

$$\frac{\partial}{\partial t}\int_a^b C dx = \int_0^a k_1 C dx \left[\frac{C}{C+D}\right]\Big|_{x=a}^{-} - \int_0^b k_1 C dx \left[\frac{C}{C+D}\right]\Big|_{x=b}$$

$$\underbrace{\frac{\partial}{\partial t}\int_a^b D dx}_{\text{Change in Cell Population}} = \underbrace{\int_0^a k_1 C dx \left[\frac{D}{C+D}\right]\Big|_{x=a}^{-}}_{\text{Flux In}} \underbrace{\int_0^b k_1 C dx \left[\frac{D}{C+D}\right]\Big|_{x=b}}_{\text{Flux Out}} + \underbrace{\int_a^b k_1 C dx}_{\text{Cell Production}}$$

Conversion to PDEs:

$$\begin{cases} \dfrac{\partial C}{\partial t} + \dfrac{\partial}{\partial x}\left[\displaystyle\int_0^x k_1 C dz \left[\frac{C(x)}{\rho_{max}}\right]\right] = 0 \\ \dfrac{\partial D}{\partial t} + \dfrac{\partial}{\partial x}\left[\displaystyle\int_0^x k_1 C dz \left[\frac{D(x)}{\rho_{max}}\right]\right] = k_1 C \end{cases}$$

Methods: Solving PDE System

Localized Model Substitution:

$$S(x,t) = \int_0^x C(z,t)dz$$

$$T(x,t) = \int_0^x D(z,t)dz$$

$$\begin{cases} \dfrac{\partial S}{\partial t} + \dfrac{k_1}{\rho_{max}} S \dfrac{\partial S}{\partial x} = 0 \\ \dfrac{\partial T}{\partial t} + \dfrac{k_1}{\rho_{max}} S \dfrac{\partial T}{\partial x} = k_1 S \end{cases}$$

Solving by Characteristic Method:

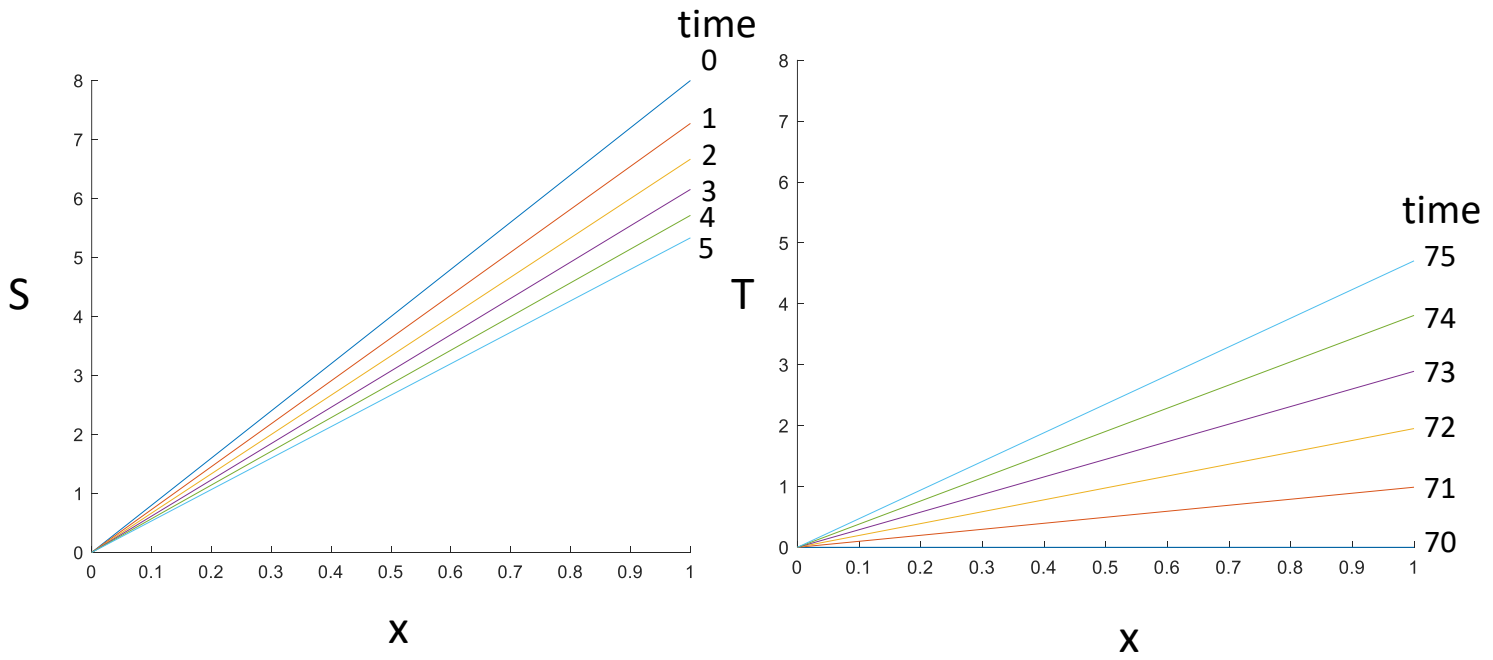
$$C(x,t) = \frac{\rho_{max}}{k_1 t + 10}$$

$$D(x,t) = \rho_{max}\left(1 - \frac{1}{k_1 t + 10}\right)$$

Initial Conditions:

$$C(x,0) = \frac{\rho_{max}}{10}$$

$$D(x,0) = \frac{9\rho_{max}}{10}$$



Methods: Numerical Analysis

PDE System:

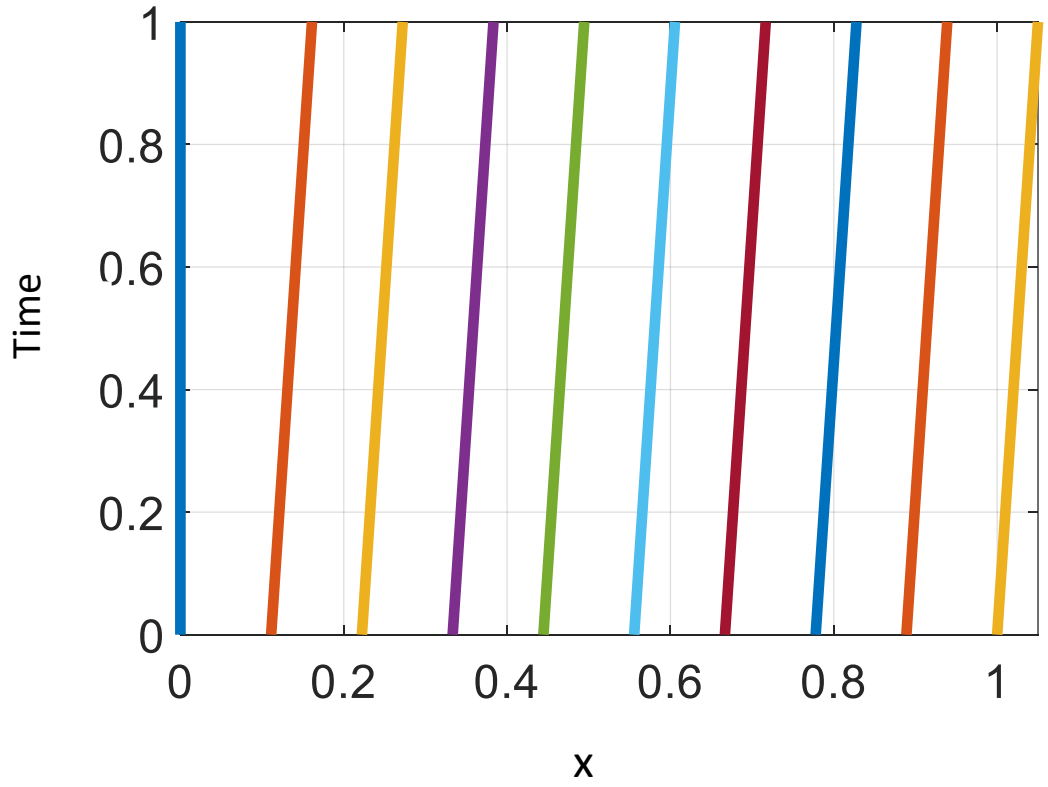
$$\begin{cases} \dfrac{\partial S}{\partial t} + \dfrac{k_1}{\rho_{max}} S \dfrac{\partial S}{\partial x} = 0 \\ \dfrac{\partial T}{\partial t} + \dfrac{k_1}{\rho_{max}} S \dfrac{\partial T}{\partial x} = k_1 S \end{cases}$$

Initial Conditions:

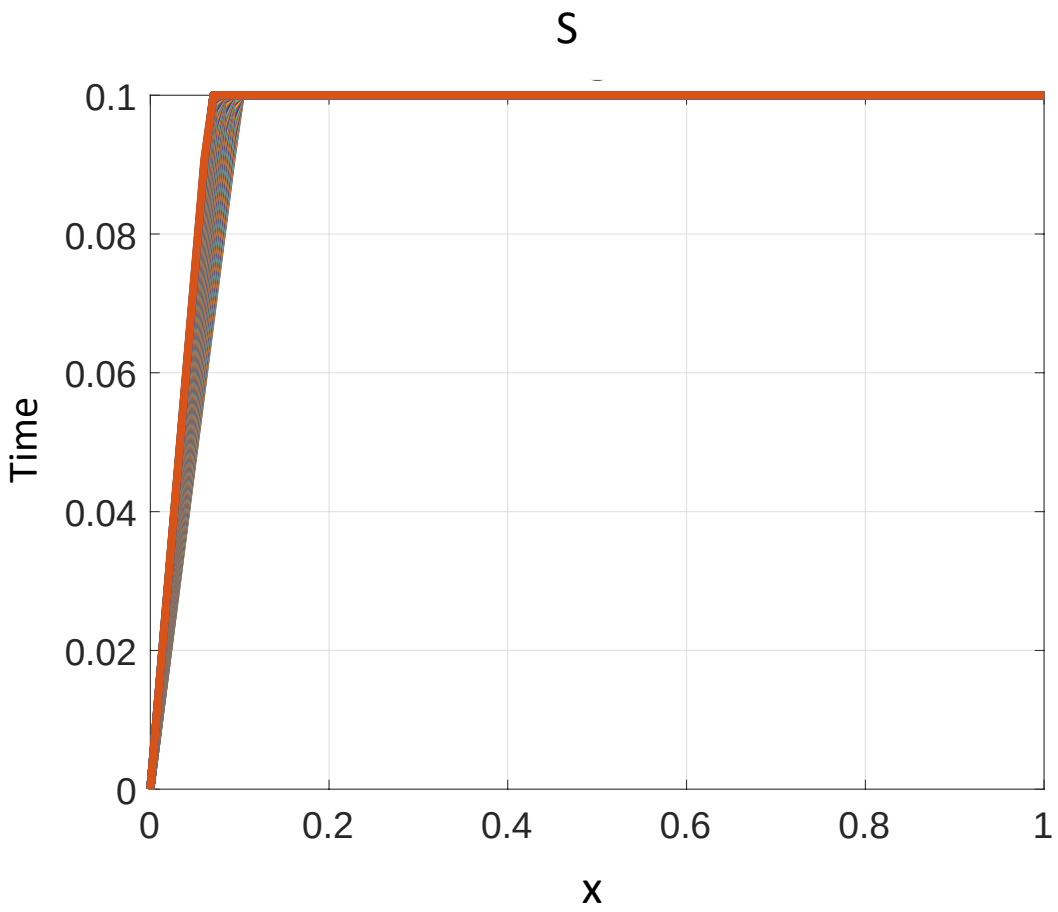
$$S(x,0) = \begin{cases} \dfrac{\rho_{max} x}{10} & 0 \le x \le \dfrac{L}{10} \\ \dfrac{\rho_{max} L}{100} & \dfrac{L}{10} \le x \le L \end{cases}$$

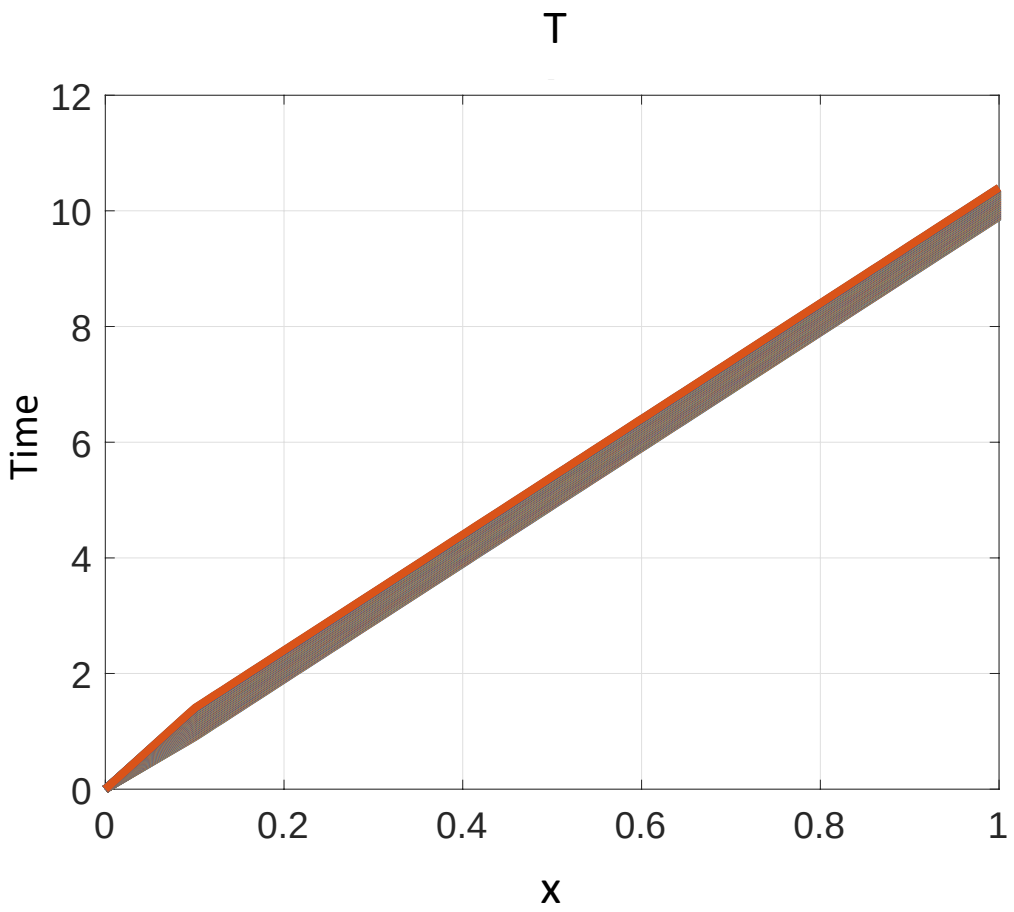
$$\rho_{max} = 10$$

$$L = 1$$



Results: Numerical Analysis





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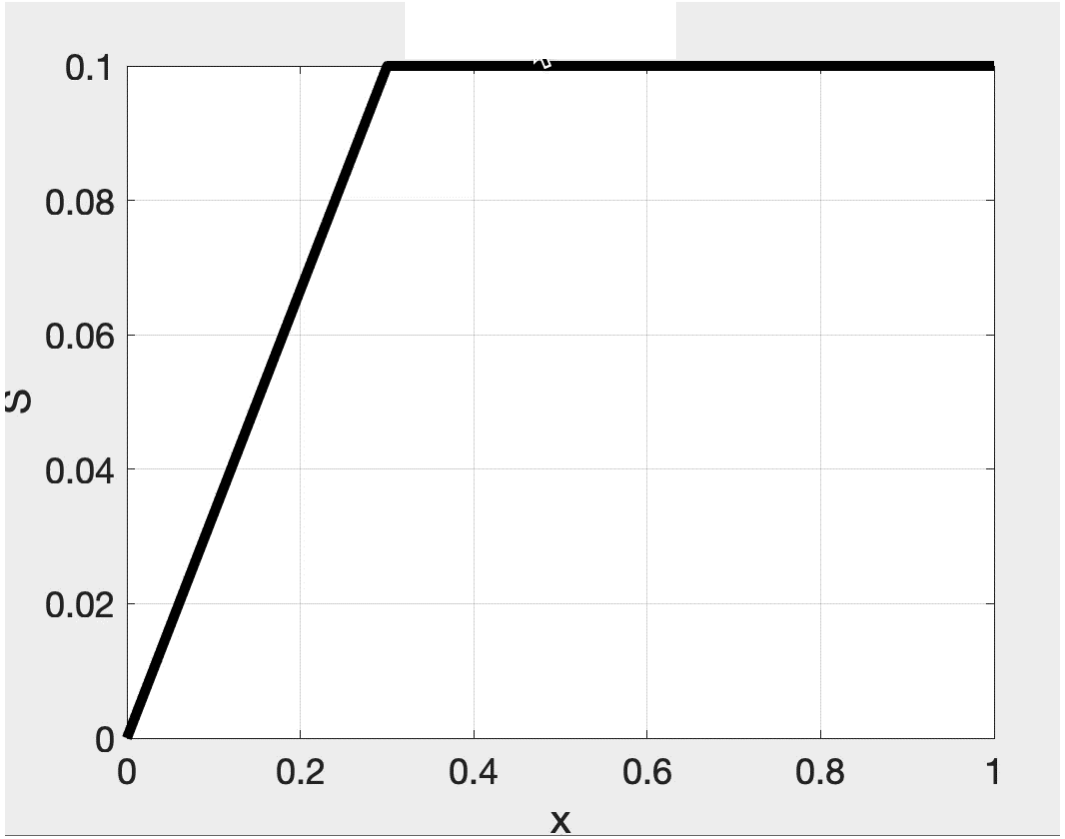
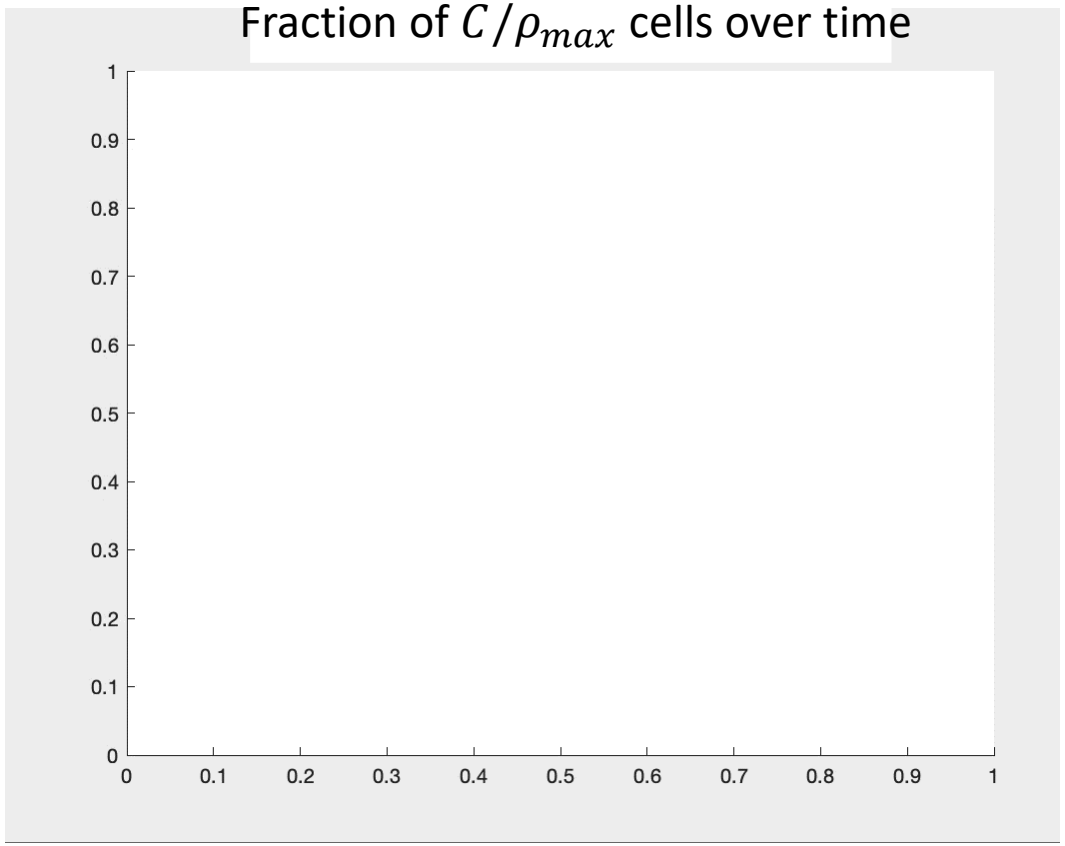


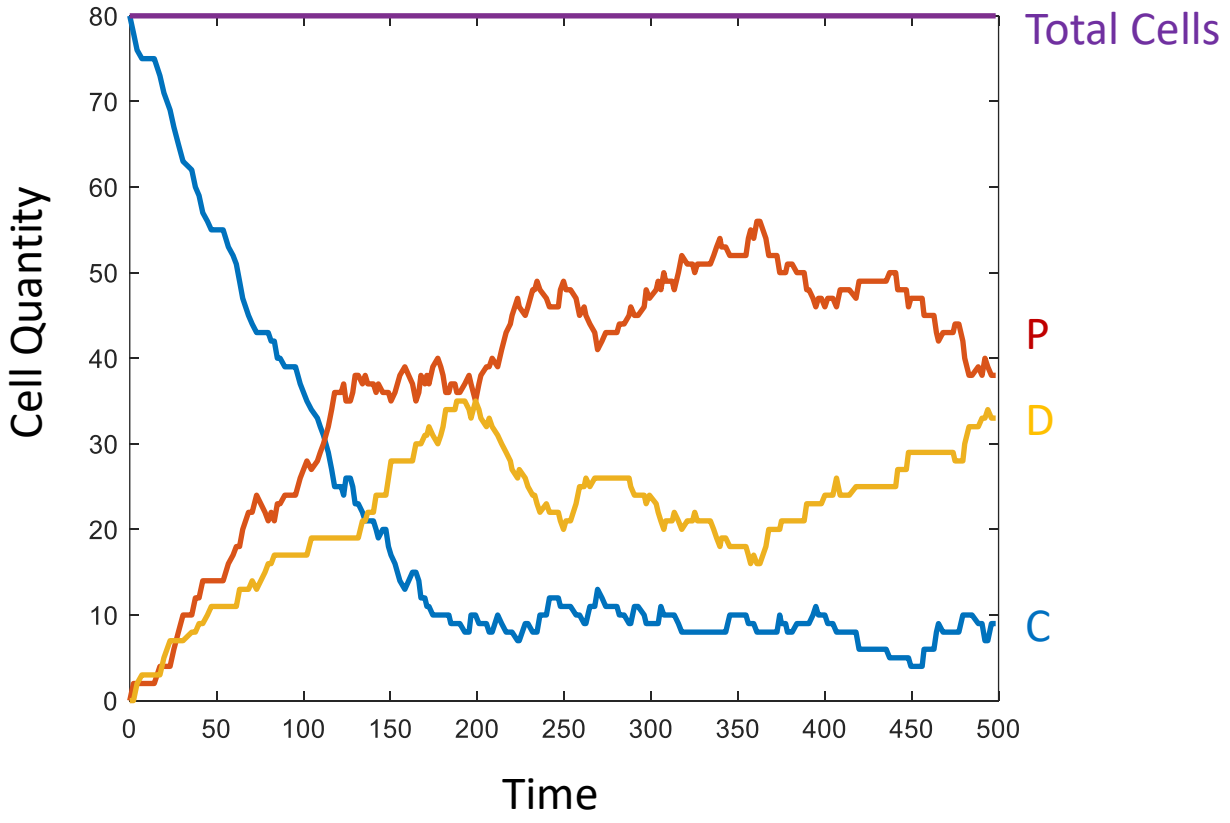
Fraction of C/ρ_{max} cells over time



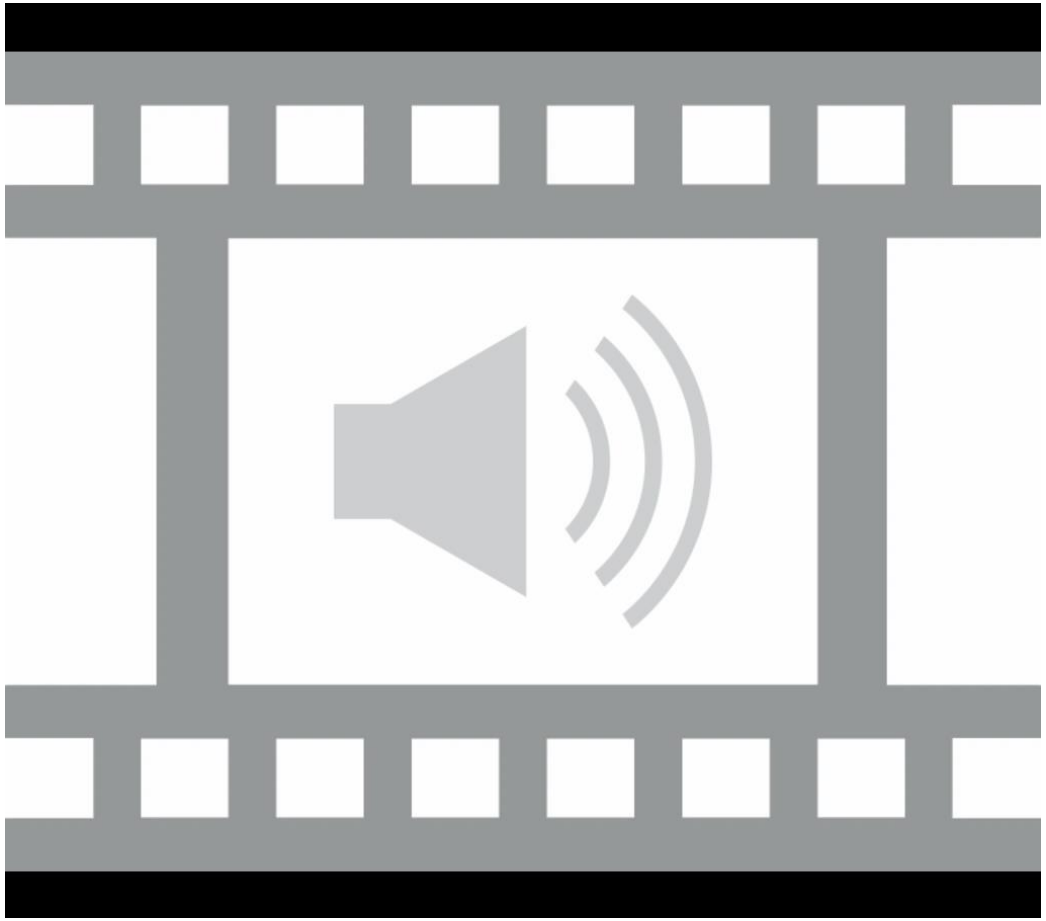
Results: Stochastic Model

- C cells divide at rate k_1 by:
  - Symmetric: $C \xrightarrow{k_1} 2C$
  - Probability: $1 - p$
  - Asymmetric: $C \xrightarrow{k_1} C + P$
  - Probability: p

- P cells divide at rate k_2 by:
  - Symmetric: $P \xrightarrow{k_2} 2P$
  - Probability: $1 - q$
  - Asymmetric: $P \xrightarrow{k_2} P + D$
  - Probability: q



Results: Stochastic Model



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Conclusions

- Simple mathematical models can produce complicated systems and solutions which is reflective of in vivo scenarios
- Varying initial parameters results in either stable, periodic solutions or unstable, chaotic solutions
- Stochastic analysis can improve understanding of the spatial results, especially when translating the mathematical results for clinicians

- Future work suggestions:
  - Validate parameters through experimental data
  - Include proliferative cells to expand model to include all cell types
  - Division reaction rates (k_i) as functions of local cell concentration
  - Include signaling pathways

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