# Multiphase Tumour Growth 1-Dimensional Slab Model

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# Overview

## Main Purpose of Project

This project investigates modelling of tumour growth using a two-phase fluid model, with incorporating nutrient transport and mechanical stresses to describe how the tumour evolves over time.

## Outline

1. Derivation of Model
2. Simplification to 1D Model
3. Stability Analysis
4. Numerical Solutions
5. Critique on Model

# Main Variables and Unknowns

Before imposing a one-dimensional slab geometry, we model the tumour as a mixture of cells and water in a general spatial domain.

| Quantity | Meaning |
|---|---|
| $\alpha(\mathbf{x}, t),\ \beta(\mathbf{x}, t)$ | cell and water volume fractions |
| $\mathbf{v}_c(\mathbf{x}, t),\ \mathbf{v}_w(\mathbf{x}, t)$ | cell and water velocities |
| $p_c(\mathbf{x}, t),\ p_w(\mathbf{x}, t)$ | cell and water pressures |
| $\boldsymbol{\sigma}_c,\ \boldsymbol{\sigma}_w$ | cell and water stress tensors |
| $C(\mathbf{x}, t)$ | nutrient concentration |
| $S_c(\alpha, C)$ | net cell production rate |
| $Q_c(\alpha, C)$ | nutrient consumption rate |

## No-voids assumption

$$\alpha + \beta = 1.$$

All gradients are taken with respect to the general spatial variable $\mathbf{x}$.

# Mass Balance for each phase

For each phase, the rate of change equals transport plus a source term.

## cell phase and water phase balances

$$\frac{\partial \alpha}{\partial t} + \nabla \cdot (\alpha \mathbf{v}_c) = S_c,$$
$$\frac{\partial \beta}{\partial t} + \nabla \cdot (\beta \mathbf{v}_w) = S_w.$$

## Volume conversion

Cell proliferation converts water into cells, while cell death converts cells back into water, so

$$S_w = -S_c.$$

# Mixture Incompressibility

Add the two phase mass balances:

$$\frac{\partial}{\partial t}(\alpha + \beta) + \nabla \cdot (\alpha \mathbf{v}_c + \beta \mathbf{v}_w) = S_c + S_w.$$

Using

$$\alpha + \beta = 1, \qquad S_w = -S_c,$$

gives

**Mixture Incompressibility**

$$\nabla \cdot (\alpha \mathbf{v}_c + (1 - \alpha)\mathbf{v}_w) = 0.$$

The cell and water phases are treated as incompressible phases with volume conversion between them.

# Momentum Balance as Force Balance

Tumour growth is slow, so inertial terms are neglected and each phase is in force balance.

## Phase momentum balances

$$0 = \nabla \cdot (\alpha \boldsymbol{\sigma}_c) + \mathbf{F}_{wc},$$

$$0 = \nabla \cdot ((1-\alpha)\boldsymbol{\sigma}_w) + \mathbf{F}_{cw}.$$

## Action–reaction

$$\mathbf{F}_{cw} = -\mathbf{F}_{wc}.$$

# Mixture Force Balance

Adding the two momentum balances gives

## Mixture Force Balance

$$0 = \nabla \cdot \left( \alpha \boldsymbol{\sigma}_c + (1 - \alpha) \boldsymbol{\sigma}_w \right) .$$

This is still the **general** force balance.

No assumption has yet been made about a slab geometry or a coordinate $x$.

# Constitutive Laws and Cell-Cell Stress

The model is closed by specifying the stresses in the two phases.

## Cell Phase: Viscous Fluid

$$\boldsymbol{\sigma}_c = -p_c \mathbf{I} + \mu_c(\nabla \mathbf{v}_c + \nabla \mathbf{v}_c^T) + \lambda_c(\nabla \cdot \mathbf{v}_c)\mathbf{I}.$$

## Water Phase and Pressure Difference

$$\boldsymbol{\sigma}_w = -p_w \mathbf{I}, \qquad p_c = p_w + \Sigma_c(\alpha).$$

$\Sigma_c(\alpha)$ represents stress due to cell-cell interactions.

# Drag Law and Nutrient Diffusion

The remaining ingredients are the interaction force between phases and the nutrient equation.

## Drag Relation

$$\mathbf{F}_{wc} = p\nabla(1-\alpha) - k(\alpha)(\mathbf{v}_w - \mathbf{v}_c),$$

$$-(1-\alpha)\nabla p = k(\alpha)(\mathbf{v}_w - \mathbf{v}_c).$$

## Pseudo-Steady Nutrient Equation

$$0 = \nabla^2 C - Q_c(\alpha, C), \qquad \nabla^2 C = Q_c(\alpha, C).$$

These general equations are the starting point for the one-dimensional reduction.

# Interpretation of the Source Term $S_c$

The source term is kept general at this stage, following the original paper.

## Net Cell Production

$$S_c(\alpha, C) = \text{cell birth} - \text{cell death}.$$

## Paper Form Used Later

$$S_c(\alpha, C) = \frac{s_0 C}{1 + s_1 C}\alpha(1-\alpha) - \frac{s_2 + s_3 C}{1 + s_4 C}\alpha.$$

Thus the basal death contribution is not ignored; it is contained in the second term of $S_c$.

# Specific Choices in Byrne et al. (2003)

The later analysis may use the following representative constitutive choices from the paper.

$$S_c(\alpha, C) = \left(\frac{s_0 C}{1 + s_1 C}\right)\alpha(1-\alpha) - \left(\frac{s_2 + s_3 C}{1 + s_4 C}\right)\alpha, \qquad Q_c(\alpha, C) = \frac{Q_0 C \alpha}{1 + Q_1 C}.$$

$$k(\alpha) = k_0 \alpha(1-\alpha), \qquad \Sigma_c(\alpha) = \begin{cases} 0, & 0 \le \alpha < \alpha_{\min}, \\ \dfrac{\hat{\Sigma}_c |\alpha - \alpha^*|^{r-1}}{(1-\alpha)^q}(\alpha - \alpha^*), & \alpha_{\min} \le \alpha < 1. \end{cases}$$

Here the first term in $S_c$ represents nutrient-dependent cell birth, while the second represents cell death.

# The 1-Dimensional Model

We assume that the tumour undergoes one-dimensional growth, parallel to the $x$-axis, that it occupies the region $-R(t) \leq x \leq R(t)$ at time $t$, and is symmetric about its midline $x = 0$. The governing equations are:

## Mass Conservation

$$\frac{\partial \alpha}{\partial t} + \frac{\partial}{\partial x}(\alpha v_c) = S_c(\alpha, C).$$

## Momentum Conservation

$$\frac{\partial}{\partial x}\left(\hat{\mu}_c \alpha \frac{\partial v_c}{\partial x} - \alpha \Sigma_c(\alpha)\right) = \frac{k(\alpha)}{(1-\alpha)^2} v_c \qquad \text{where} \qquad \hat{\mu}_c = 2\mu_c + \lambda_c.$$

## Nutrient Diffusion

$$\frac{\partial^2 C}{\partial x^2} = Q_c(\alpha, C).$$

# Boundary Conditions of the 1D Free-Boundary Model

## Symmetry at the Tumour Centre ($x = 0$)

$$v_c(0, t) = 0, \qquad \left.\frac{\partial C}{\partial x}\right|_{x=0} = 0.$$

No net cell motion or nutrient flux crosses the centreline.

## Conditions at the Tumour Boundary ($x = R(t)$)

$$\hat{\mu}_c \frac{\partial v_c}{\partial x} = \Sigma_c(\alpha), \qquad C(R, t) = C_\infty.$$

The boundary is stress-free and is exposed to a constant external nutrient concentration.

## Free-Boundary Condition

$$\frac{dR}{dt} = v_c(R, t).$$

The tumour edge moves with the local cellular velocity.

# Physical Intuition of the Limit $k, Q_c \to 0$

To isolate the core volumetric and boundary dynamics, we study a simplifying limit where external drag and nutrient consumption vanish:

- **No Nutrient Consumption ($Q_c \to 0$):** The diffusion equation simplifies to $\frac{\partial^2 C}{\partial x^2} = 0$. Subject to boundary conditions $\frac{\partial C}{\partial x}\big|_{x=0} = 0$ and $C(R,t) = C_\infty$, nutrients penetrate the domain uniformly:

$$C(x,t) = C_\infty \implies S_c(\alpha, C) = S_c(\alpha, C_\infty)$$

- **No Hydrodynamic Drag ($k \to 0$):** With zero resistance from the surrounding water phase, cells redistribute instantaneously to yield a spatially uniform cell fraction:

$$\alpha := \alpha(t) \implies \frac{\partial \alpha}{\partial x} = 0$$

- Under these spatial uniformity conditions, the explicit velocity field is linear in space:

$$\frac{\partial}{\partial x}\left(\hat{\mu}_c \alpha \frac{\partial v_c}{\partial x} - \alpha \Sigma_c(\alpha)\right) = 0 \overset{\partial_x \alpha = 0}{\Longrightarrow} v_c(x,t) = \frac{\Sigma_c(\alpha)}{\hat{\mu}_c} x.$$

# Deriving the ODE for Volume Fraction $\alpha(t)$

We substitute the spatially uniform conditions into the mass balance PDE:

$$\frac{\partial \alpha}{\partial t} + \frac{\partial}{\partial x}(\alpha v_c) = S_c(\alpha, C_\infty)$$

Applying the product rule and noting $\alpha$ depends only on time, $\frac{\partial \alpha}{\partial t} \to \frac{d\alpha}{dt}$. The expression reduces to:

$$\frac{d\alpha}{dt} + \alpha \frac{\partial v_c}{\partial x} = S_c(\alpha, C_\infty)$$

Differentiating the linear velocity profile $v_c = \frac{\Sigma_c(\alpha)}{\hat{\mu}_c} x$ with respect to $x$ gives:

$$\frac{\partial v_c}{\partial x} = \frac{\Sigma_c(\alpha)}{\hat{\mu}_c}$$

Substituting this back yields the final autonomous ODE for cellular density:

$$\boxed{\frac{d\alpha}{dt} = S_c(\alpha, C_\infty) - \frac{\alpha \Sigma_c(\alpha)}{\hat{\mu}_c}}$$

# Deriving the ODE for Tumor Boundary $R(t)$

The evolving boundary of the tumor is a free moving interface denoted by $x = R(t)$

## Kinematic Free-Boundary Condition

The edge of the tumor cluster must move exactly with the local velocity of the cells residing at that outermost boundary:

$$\frac{dR}{dt} = v_c(R, t)$$

Substituting the boundary velocity into the kinematic statement yields:

$$\boxed{\frac{dR}{dt} = \frac{R\Sigma_c(\alpha)}{\hat{\mu}_c}}$$

**Biological Insight:** If cellular packing density causes positive internal stress ($\Sigma_c > 0$), the tumor radius expands exponentially.

# Stability Analysis as $t \to \infty$

Stability analysis was performed on the differential equation

$$\boxed{\frac{d\alpha}{dt} = S_c - \frac{\alpha\,\Sigma_c(\alpha)}{\hat{\mu}_c}}$$

by considering the steady states of the system as $t \to \infty$.

Considering the two regimes for $\Sigma_c$, namely when

$$0 \leq \alpha < \alpha_{\text{min}}$$

and when

$$\alpha_{\text{min}} \leq \alpha < 1$$

The parameters $S_0$, $S_1$, $S_2$, $S_3$, and $S_4$ are held fixed as a positive value, while only the parameter $C$ is varied. This allows the effect of $C$ on the fixed points and stability of the system to be isolated and analysed directly.

# First regime - $0 \leq \alpha < \alpha_{\min}$

In domain $0 \leq \alpha < \alpha_{\min}$, $\Sigma_c = 0$. The two fixed points are at:

**Fixed Points - when $\frac{d\alpha}{dt} = 0$**

$$\alpha_{F1} = 0 \quad \text{and} \quad \alpha_{F2} = 1 - \frac{(S_2 + S_3 C)(1 + S_1 C)}{(1 + S_4 C)(S_0 C)}$$

By conducting a simple bifurcation analysis on the fixed points, it is shown that the stability of the fixed points changes at:

**Bifurcation Point**

$$C^* = \frac{-\left(S_0 - S_1 S_2 - S_3\right) + \sqrt{\left(S_0 - S_1 S_2 - S_3\right)^2 + 4\left(S_0 S_4 - S_1 S_3\right) S_2}}{2\left(S_0 S_4 - S_1 S_3\right)}$$

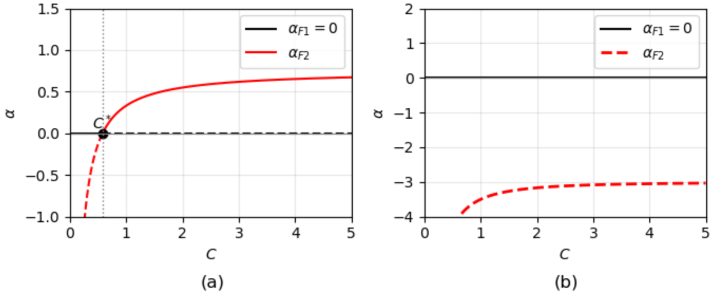


Figure: Bifurcation diagrams where $S_0S_4 > S_1S_3$ in (a) and $S_0S_4 < S_1S_3$ in (b). Solid lines indicate stable fixed points and dashed lines indicate unstable fixed points. In (a), it shows a stable fixed point at $\alpha_{F1}$ before $C^*$ and a stable fixed point at $\alpha_{F2}$ after $C^*$. In (b), it shows a stable fixed point at $\alpha_{F1}$ for all $C > 0$ values when $S_0S_4 > S_1S_3$ - this is due to $C^* < 0$ causing bifurcation to occur at negative values (unphysical ranges) of $C$.

Note: all stable regions of fixed points are in physical regions of $\alpha$.

# Second regime - $\alpha_{\text{min}} \leq \alpha < 1$

In domain $\alpha_{\text{min}} \leq \alpha < 1$, $\Sigma_c$ becomes:

$$\boxed{\Sigma_c = \frac{\hat{\Sigma}_c \left|\alpha - \alpha^*\right|^{r-1}}{(1-\alpha)^q}(\alpha - \alpha^*)}$$

Thus, the differential equation could be written as follows:

$$\frac{d\alpha}{dt} = f(\alpha) = \alpha \left( A(C)(1-\alpha) - B(C) - \frac{\hat{\Sigma}_c}{\hat{\mu}_c} \frac{\left|\alpha - \alpha^*\right|^{r-1}}{(1-\alpha)^q}(\alpha - \alpha^*) \right)$$

where

$$A(C) = \frac{S_0 C}{1 + S_1 C}$$

and

$$B(C) = \frac{S_2 + S_3 C}{1 + S_4 C}$$

Since $S_0$, $S_1$, $S_2$, $S_3$, $S_4$ and $C$ are all positive values, $A(C)$ and $B(C)$ are also positive.

# Second regime - $\alpha_{\min} \leq \alpha < 1$

## Fixed points - when $\frac{d\alpha}{dt} = 0$

$$\alpha_{F3} = 0 \qquad \text{(rej. } \because \text{ outside domain)}$$

$$A(C)(1-\alpha_{F4}) - B(C) - \frac{\hat{\Sigma}_c}{\hat{\mu}_c}\frac{|\alpha_{F4}-\alpha^*|^{r-1}}{(1-\alpha_{F4})^q}(\alpha_{F4}-\alpha^*) = G(\alpha_{F4}) = 0$$

Using the form of $G(\alpha)$, the differential equation can be further simplified:

$$\frac{d\alpha}{dt} = f(\alpha) = \alpha G(\alpha)$$

Since $f(\alpha)$ is not linear, system can be linearized through linearization theorem. Evaluating around fixed point $\alpha_{F2}$:

$$\boxed{\left.\frac{df}{d\alpha}\right|_{\alpha=\alpha_{F4}} = \alpha_{F4} G'(\alpha_{F4})}$$

Observing the modulus within $G(\alpha_{F4})$, three cases ($\alpha^* < \alpha_{F4}$, $\alpha^* = \alpha_{F4}$ and $\alpha^* > \alpha_{F4}$) were evaluated.

At $\alpha_{F4}$:

$$G'(\alpha_{F4}) = -A(C) - \frac{\hat{\Sigma}_c}{\hat{\mu}_c}\left(\frac{r(\alpha_{F4}-\alpha^*)^{r-1}}{(1-\alpha_{F4})^q} + \frac{q(\alpha_{F4}-\alpha^*)}{(1-\alpha_{F4})^{q-1}}\right)$$

Since $G'(\alpha_{F4}) < 0$:

### Stability Analysis of $\alpha_{F4}$ in Case 1

$$\left.\frac{df}{d\alpha}\right|_{\alpha=\alpha_{F4}} < 0$$

Hence, according to linearization theorem, this is a stable point.

At $\alpha_{F4}$:

$$G'(\alpha_{F4}) = -A(C)$$

Since $G'(\alpha_{F4}) < 0$:

### Stability Analysis of $\alpha_{F4}$ in Case 2

$$\left.\frac{df}{d\alpha}\right|_{\alpha=\alpha_{F4}} < 0$$

Hence, according to linearization theorem, this is also a stable point.

# 2nd Regime Case 3 - $\alpha^* > \alpha_{F4}$

At $\alpha_{F4}$:

$$G'(\alpha_{F4}) = -A(C) + \frac{\hat{\Sigma}_c}{\hat{\mu}_c}\left(-\frac{r(\alpha^* - \alpha_{F4})^{r-1}}{(1-\alpha_{F4})^q} + \frac{q(\alpha^* - \alpha_{F4})^r}{(1-\alpha_{F4})^{q+1}}\right)$$

This shows that the stability depends on the value of parameters $A(C)$, $\hat{\Sigma}_c$, $\hat{\mu}_c$, $r$ and $q$.

## Stability Analysis of $\alpha_{F4}$ in Case 3

**If $\alpha_{F4}$ is stable:** as $t \to \infty$, $\alpha \to \alpha_{F4}$.

**If $\alpha_{F4}$ is unstable:** $\alpha$ will tend towards the direction of perturbation.

# Numerical Results: Spatially-Uniform Model

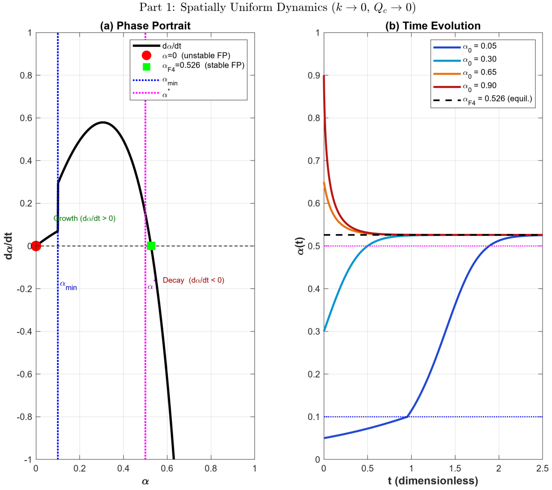


Figure: Spatially-uniform dynamics in the limit $k \to 0$, $Q_c \to 0$. (a) Phase portrait of $\dot{\alpha} = f(\alpha)$. (b) Time evolution for four initial conditions.

# Spatially-Uniform Model: Key Results

- Two equilibria are obtained:[$\alpha = 0$ ;(unstable), $\alpha_{F4} = 0.526$ ;(stable).]
- Cell–cell interaction stress shifts the equilibrium from the uncoupled value $\bar{\alpha} = 0.8$ to $\alpha_{F4} = 0.526$.
- The phase portrait shows $f(\alpha) > 0$ for $\alpha < \alpha_{F4}$ and $f(\alpha) < 0$ for $\alpha > \alpha_{F4}$, indicating global attraction.
- All initial conditions converge to $\alpha_{F4}$, confirming stability.

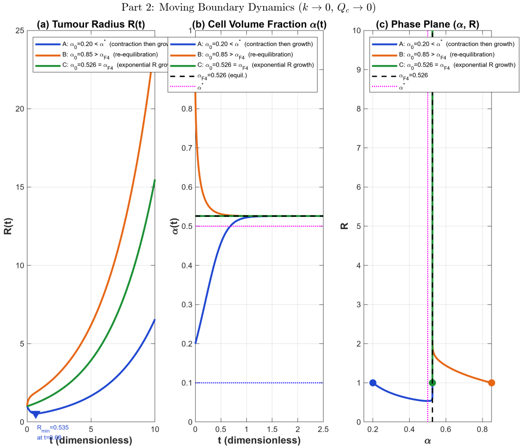


Figure: Moving-boundary dynamics for three initial conditions. (a) Radius $R(t)$. (b) Cell volume fraction $\alpha(t)$. (c) Phase plane $(\alpha, R)$.

# Moving-Boundary Model: Key Results

- **Case A ($\alpha_0 = 0.20$):** initial negative stress causes tumour contraction, followed by re-expansion once $\alpha > \alpha^*$.
- **Case B ($\alpha_0 = 0.85$):** tumour radius grows monotonically while $\alpha$ relaxes toward equilibrium.
- **Case C ($\alpha_0 = \alpha_{F4}$):** $\alpha$ remains constant and $R(t) = e^{0.274t}$ exhibits pure exponential growth.
- In all cases, $\alpha(t) \to \alpha_{F4} = 0.526$, confirming the globally stable equilibrium.
- The transient dynamics differ, but the long-time behaviour is identical. "'

# Spatially Uniform Model

**Biological Interpretation**

- The tumour is treated as well-mixed.
- Nutrient concentration and cell density are spatially uniform.
- Growth depends only on average proliferation and stress.

**Strengths**

- Simple and analytically tractable.
- Useful for studying steady states and long-term growth.

**Limitations**

- Ignores nutrient gradients and spatial structure.
- Cannot capture proliferative rims or nutrient-deprived regions.

# Moving Boundary Model

**Biological Interpretation**

- Nutrients diffuse into the tumour from the boundary.
- Cell density, stress, and velocity vary with position.
- The tumour boundary moves as cells proliferate and push outward.

**Strengths**

- Captures spatial heterogeneity.
- Includes nutrient transport and mechanical effects.

**Limitations**

- Assumes a simple 1D geometry.
- Neglects necrosis, angiogenesis (no asymptote for $R(t)$), and irregular tumour shapes.

# Appendix: Spatially-Uniform Model

**Parameters** $[s_0 = 1, \quad s_2 = 0.2, \quad C_\infty = 1, \quad \hat{\mu} = 0.1, \quad \hat{\Sigma} = 0.5,]$
$[\alpha^* = 0.5, \quad \alpha_{\min} = 0.1, \quad q = 1.]$

**Equilibria** $[\alpha = 0; \text{(unstable)}, \qquad \alpha_{F4} = 0.5260; \text{(stable)}.]$

- Uncoupled equilibrium: $\bar{\alpha} = 0.8$.
- Stress at equilibrium: $\Sigma_c(\alpha_{F4}) = 0.0274$.
- Initial conditions: $\alpha_0 = 0.05, , 0.30, , 0.65, , 0.90$.
- All trajectories satisfy $\alpha(t) \to \alpha_{F4}$.

# Appendix: Moving-Boundary Model

**Case A ($\alpha_0 = 0.20$)**

- $\Sigma_c(0.20) = -0.1875$.
- $R_{\text{min}} = 0.535$ at $t \approx 0.68$.
- $R(10) = 6.56$.

**Case B ($\alpha_0 = 0.85$)**

- $\Sigma_c(0.85) = 1.167$.
- $R(10) = 24.35$.

**Case C ($\alpha_0 = \alpha_{F4}$)**

- $\dot{\alpha} = 0$.
- $\dot{R} = 0.274R, \quad R(t) = e^{0.274t}$.
- $R(10) = 15.49$.

[$\alpha(t) \to \alpha_{F4} = 0.526$ for all cases.]