Modeling I
Non-dimensionalization
Consider a chemical species $C$ that is contained in a long thin tube with constant cross sectional area $A$. The concentration of the species, $c(x, t)$, varies in time and space, where (for now) the spatial variation is restricted to one spatial variable $x$.

In any fixed region $R$ along the tube, the conservation of $C$ can be expressed in words as:

\[
\frac{\text{time rate of change of the total amount of } C \text{ within } R}{\text{rate at which } C \text{ flows in to } R} - \frac{\text{rate at which } C \text{ flows out of } R}{+ \frac{\text{rate at which } C \text{ is produced within } R}{- \frac{\text{rate at which } C \text{ is destroyed within } R}}
\]
The total amount of chemical C contained in a small slice of tube between \( x \) and \( x + dx \) is \( c(x, t) A \). At any time \( t \), the total amount of \( C \) in some arbitrary interval \( x_a < x < x_b \) can be computed by integrating \( c(x, t) A \) over the interval:

\[
\text{total amount of } C \text{ in the interval } [x_a, x_b] = \int_{x_a}^{x_b} c(x, t) A \, dx
\]  

(20.2)

Note that:

• concentration (or, amount/volume), units: micromolar (or micromol/liter)
• total amount, units: micromoles
Continuum Modeling of Movement

Now suppose that $C$ is free to move about inside the tube, so that $C$ moves in and out of the interval by crossing the boundaries of the interval at $x = x_a$ and $x = x_b$. If we denote by $J(x, t)$ the rate at which $C$ moves across the boundary at position $x$ from the left to right at time $t$, then the net movement, or flux, of $C$ into the interval is

$$\text{net rate of entry of } C = A J(x_a, t) - A J(x_b, t) \quad (20.3)$$

Note that the units of
- net rate of entry : amount/time
- area $A$ : area
- flux rate $J(x, t)$ : amount/(area×time)
Continuum Modeling of Movement

When C moves to the right \( \rightarrow J(x, t) \) is positive
When C moves to the left \( \rightarrow J(x, t) \) is negative

If we let \( f(x, t, c) \) denote the net rate of increase of \( C \) (production – destruction) per unit volume at location \( x \) and time \( t \), then the total amount of \( C \) produced in the interval at time \( t \) is

\[
\text{net rate of production of } C = \int_{x_a}^{x_b} f(x, t, c(x, t)) A \, dx
\]

(20.4)

Note that the presence of \( c \) in the definition of \( f \) allows for the possibility that the rate of production of \( C \) depends on \( c \) itself.
Continuum Modeling of Movement

Since the units of the net of rate of production of $C$ are amount/time, the units of $f$ must be amount/(time×volume).

When $f$ is positive, the region is a source (leading to an increase in the total amount of $C$), and when $f$ is negative, the region is a sink. The function $f$ is often called a source function.

Equation (20.1) can now be written in mathematical symbols as

$$\frac{d}{dt} \int_{x_a}^{x_b} c(x, t) \, dx = J(x_a, t) - J(x_b, t) + \int_{x_a}^{x_b} f(x, t, c(x, t)) \, dx$$

(20.5)

where the constant $A$ has been factored out.
Continuum Modeling of Movement

The flux terms can be replaced by

$$- [J(x_b, t) - J(x_a, t)] = - \int_{x_a}^{x_b} \frac{\partial}{\partial x} J(x, t) \, dx \quad (20.6)$$

allowing all the terms in (20.5) to be written as integrals:

$$\frac{d}{dt} \int_{x_a}^{x_b} c(x, t) \, dx = - \int_{x_a}^{x_b} \frac{\partial}{\partial x} J(x, t) \, dx + \int_{x_a}^{x_b} f(x, t, c(x, t)) \, dx \quad (20.7)$$

If the function $c(x, t)$ is smooth enough, the differentiation and integration can be interchanged, and equation (20.7) can be rewritten as

$$\int_{x_a}^{x_b} \left[ \frac{\partial}{\partial t} c(x, t) \, dx + \frac{\partial}{\partial x} J(x, t) \, dx - f(x, t, c(x, t)) \right] \, dx = 0 \quad (20.8)$$
Since the interval is arbitrary, the only way this equality can hold is if the integrand is zero. Therefore we replace equation (20.8) by an equivalent form:

$$\frac{\partial c}{\partial t} + \frac{\partial J}{\partial x} = f(x, t, c)$$  \hspace{1cm} (20.9)

Equation (20.9) above is undetermined because it is a single equation relating two unknowns: the concentration $c$ and the flux $J$. To resolve this problem, an additional equation relating $c$ and $J$ is needed.
Diffusion

One such relation is called Fick’s law which states that $C$ moves from regions of high concentration to regions of low concentration, at a rate proportional to the concentration gradient:

$$J(x, t) = -D \frac{\partial c}{\partial x} \quad (20.10)$$

where the proportionality constant $D$ is called the diffusion constant. The negative sign signifies that $C$ moves spontaneously from regions of high concentrations to regions of low concentrations. The value of $D$ depends on the size of $C$, as well as properties of the medium in which it is diffusing. The constant $D$ has units of length$^2$/time.
Taxis

If the movement of $C$ is due to concentration gradient of another species $u(x, t)$ that also varies over space and time, the flux relation is given by

$$J(x, t) = \chi c \frac{\partial u}{\partial x} \tag{20.11}$$

This flux is called “chemotactic flux”, which refers to flux movement in the presence of concentration gradient of (usually) chemical substances, either towards high gradient (attractant) or towards low gradient (repellent). The proportionality constant $\chi$ is called chemotactic sensitivity and has units of length$^2$/(micromolar$\times$time).
Advection

Suppose that there is a uniform macroscopic flow of the solvent, with speed $v$ along the $x$–axis, which carries solutes along with it. Then during a small time $\Delta t$, all of the $C$ between $x = x_a$ and $x = x_a - v\Delta t$ will cross the point $x = x_a$. The total amount of $C$ crossing $x_a$ during this time is found by multiplying the concentration $c(x, t)$ by the fluid volume $A \nu \Delta t$. The corresponding flux is therefore

$$J(x, t) = v c \quad (20.12)$$

This flux is called the “advective flux”. Note that this flux is proportional to the concentration itself.
Using the flux described in (20.10), equation (20.9) becomes

\[
\frac{\partial c}{\partial t} = \frac{\partial}{\partial x} \left( D \frac{\partial c}{\partial x} \right) + f(x, t, c) \tag{20.13}
\]

Using the flux described in (20.11), equation (20.9) becomes

\[
\frac{\partial c}{\partial t} = -\frac{\partial}{\partial x} \left( \chi c \frac{\partial u}{\partial x} \right) + f(x, t, c) \tag{20.14}
\]

Using the flux described in (20.12), equation (20.9) becomes

\[
\frac{\partial c}{\partial t} = -\frac{\partial}{\partial x} (v c) + f(x, t, c) \tag{20.15}
\]
Modeling Cancer Invasion

Adenocarcinoma (human liver)
Modeling Cancer Invasion

In this model, the key physical variables that involve in the invasion of extracellular matrix/tissue by cancer cells are:

- cancer cell density, denoted by $c(x,t)$
- extracellular matrix protein density, denoted by $v(x,t)$
- proteolytic enzyme (uPA), denoted by $u(x,t)$

**Cancer cells**
The rate of change of cancer cells is due to migration and growth/proliferation. It is assumed that the dominating factors that govern cancer cell migration are random motion, chemotaxis due to a proteolytic enzyme (e.g., uPA or urokinase-type plasminogen activator) secreted by the cells, haptotaxis due to component of extracellular matrix (ECM).
Modeling Cancer Invasion

Beside migration, cancer cell proliferation is also included in the model in the form of a logistic growth law.

Extracellular matrix (ECM)
It is known that ECM does not diffuse. The components of ECM are degraded by the proteolytic enzyme. A logistic growth term accounts for the remodeling of the ECM by fibroblast cells present in the tissue.

Proteolytic enzyme (uPA)
Factors influencing the protease concentration are assumed to be diffusion, protease production, and protease decay. Specifically, uPA is produced by cancer cells, diffuses throughout the ECM with constant diffusion, and decays.
Modeling Cancer Invasion

The rate of change of cancer cell density is described by

$$\frac{\partial c}{\partial t} + \nabla \cdot (J_{\text{random}} + J_{\text{chemotaxis}} + J_{\text{haptotaxis}}) = \text{proliferation}$$

Using (20.10) and (20.11), the rate of change of cancer cell density becomes

$$\frac{\partial c}{\partial t} = \nabla \cdot (D_1 \nabla c) - \nabla \cdot (\chi_1 c \nabla u) - \nabla \cdot (\chi_2 c \nabla v) + \mu_1 c \left(1 - \frac{c}{c_0}\right)$$

where $D_1$ is random motility coefficient, a constant, $\chi_1$ and $\chi_2$ are the chemotactic and haptotactic coefficients, respectively, and $\mu_1$ is the proliferation rate of the cells. (20.16)
Modeling Cancer Invasion

The equation for ECM density is given by

\[
\frac{\partial v}{\partial t} = -\delta u v + \mu_2 v(1 - \frac{v}{v_0})
\]  \hspace{1cm} (20.17)

where \( \delta \) is ECM degradation rate, and \( \mu_2 \) remodeling rate.

The equation governing the evolution of the proteolytic enzyme uPA concentration is given by

\[
\frac{\partial u}{\partial t} = D_2 \nabla^2 u + \alpha c - \beta u \]

\hspace{1cm} (20.18)

\[
\text{proteolysis} \quad \text{remodeling}
\]

\[
\text{diffusion} \quad \text{production degradation}
\]
Non-dimensionalization

where \( D_2 \) is constant diffusion coefficient of uPA, \( \alpha \) is the rate of uPA production by cancer cells, and \( \beta \) is the natural decay of uPA.

We non-dimensionalize equations (20.16), (20.17), and (20.18) by using the following reference variables:

1) Reference length scale, \( L_0 \), (e.g., the maximum invasion distance of the cancer cells at this early stage of invasion 0.1 – 1 cm.

2) Reference time unit, \( \tau = \frac{L_0^2}{D} \), where \( D \) is a reference chemical diffusion coefficient, e.g., \( 10^{-6} \) cm\(^2\)s\(^{-1}\).

3) Reference cancer cell density \( c_0 = 6.7 \times 10^7 \) cells/cm\(^3\), ECM density \( \nu_0 = 1 \) nM, and uPA concentration \( u_0 = 1 \) nM.
Non-dimensionalization

The non-dimensional length $X$ (in 1D) is defined as

$$X = \frac{x}{L_0}$$

or $x = L_0X$. Spatial derivative gives $\partial x = L_0 \partial X$.

The non-dimensional time $T$ is defined as

$$T = \frac{t}{\tau}$$

or $t = \tau T$. Time derivative gives $\partial t = \tau \partial T$.

The non-dimensional dependent variables are defined as

$$c^* = \frac{c}{c_0} \quad v^* = \frac{v}{v_0} \quad u^* = \frac{u}{u_0}$$
Non-dimensionalization

Time and spatial derivatives of the dependent variables are

\[
\frac{\partial c}{\partial t} = \frac{\partial (c_0 c^*)}{\partial (\tau T)} = \frac{c_0}{\tau} \frac{\partial c^*}{\partial T} \quad \frac{\partial c}{\partial x} = \frac{\partial (c_0 c^*)}{\partial (L_0 X)} = \frac{c_0}{L_0} \frac{\partial c^*}{\partial X}
\]

\[
\frac{\partial v}{\partial t} = \frac{\partial (v_0 v^*)}{\partial (\tau T)} = \frac{v_0}{\tau} \frac{\partial v^*}{\partial T} \quad \frac{\partial v}{\partial x} = \frac{\partial (v_0 v^*)}{\partial (L_0 X)} = \frac{v_0}{L_0} \frac{\partial v^*}{\partial X}
\]

\[
\frac{\partial u}{\partial t} = \frac{\partial (u_0 u^*)}{\partial (\tau T)} = \frac{u_0}{\tau} \frac{\partial u^*}{\partial T} \quad \frac{\partial u}{\partial x} = \frac{\partial (u_0 u^*)}{\partial (L_0 X)} = \frac{u_0}{L_0} \frac{\partial u^*}{\partial X}
\]

Second-order spatial derivatives are defined as

\[
\frac{\partial^2 c}{\partial x^2} = \frac{\partial}{\partial x} \left( \frac{\partial c}{\partial x} \right) = \frac{\partial}{\partial (L_0 X)} \left( \frac{\partial (c_0 c^*)}{\partial (L_0 X)} \right) = \frac{c_0}{L_0^2} \frac{\partial^2 c^*}{\partial X^2}
\]
Non-dimensionalization

The spatial derivatives for chemotaxis and haptotaxis terms (in 1D) are defined as

\[
\frac{\partial}{\partial x} \left( \chi_1 c \frac{\partial u}{\partial x} \right) = \frac{\partial}{\partial (L_0 X)} \left( \chi_1 (c_0 c^*) \frac{\partial (u_0 u^*)}{\partial (L_0 X)} \right)
\]

\[
= \frac{\chi_1 u_0 c_0}{L_0^2} \frac{\partial}{\partial X} \left( c^* \frac{\partial u^*}{\partial X} \right)
\]

\[
\frac{\partial}{\partial x} \left( \chi_2 c \frac{\partial v}{\partial x} \right) = \frac{\partial}{\partial (L_0 X)} \left( \chi_2 (c_0 c^*) \frac{\partial (v_0 v^*)}{\partial (L_0 X)} \right)
\]

\[
= \frac{\chi_2 v_0 c_0}{L_0^2} \frac{\partial}{\partial X} \left( c^* \frac{\partial v^*}{\partial X} \right)
\]
Non-dimensionalization

The reaction terms are scaled as

\[ \mu_1 c \left( 1 - \frac{c}{c_0} \right) = \mu_1 (c_0 c^*) \left( 1 - \frac{c_0 c^*}{c_0} \right) = \mu_1 c_0 c^* \left( 1 - c^* \right) \]

\[ \mu_2 v \left( 1 - \frac{v}{v_0} \right) = \mu_2 (v_0 v^*) \left( 1 - \frac{v_0 v^*}{v_0} \right) = \mu_2 v_0 v^* \left( 1 - v^* \right) \]

\[ \delta u v = \delta (u_0 u^*) (v_0 v^*) = \delta u_0 v_0 u^* v^* \]

\[ \alpha c = \alpha c_0 c^* \]

\[ \beta u = \beta u_0 u^* \]
Non-dimensionalization

Substituting the non-dimensional terms and variables into equations (20.16), (20.17), and (20.18) gives

\[
\frac{c_0}{\tau} \frac{\partial c^*}{\partial T} = \frac{D_1 c_0}{L_0^2} \frac{\partial^2 c^*}{\partial X^2} - \frac{\chi_1 u_0 c_0}{L_0^2} \frac{\partial}{\partial X} \left( c^* \frac{\partial u^*}{\partial X} \right) \\
- \frac{\chi_2 v_0 c_0}{L_0^2} \frac{\partial}{\partial X} \left( c^* \frac{\partial v^*}{\partial X} \right) + \mu_1(c_0 c^*) \left( 1 - \frac{c_0 c^*}{c^*} \right)
\]

\[
\frac{v_0}{\tau} \frac{\partial v^*}{\partial T} = -\delta u_0 v_0 u^* v^* + \mu_2 v_0 v^* (1 - v^*)
\]

\[
\frac{u_0}{\tau} \frac{\partial u^*}{\partial T} = \frac{D_2 u_0}{L_0^2} \frac{\partial^2 u^*}{\partial X^2} + \alpha c_0 c^* - \beta u_0 u^*
\]
Nondimensionalization

Multiplying equation (20.19) by $\tau$ and dividing by $c_0$ gives

$$\frac{\partial c^*}{\partial T} = \frac{\tau D_1}{L_0^2} \frac{\partial^2 c^*}{\partial X^2} - \frac{\tau \chi_1 u_0}{L_0^2} \frac{\partial}{\partial X} \left( c^* \frac{\partial u^*}{\partial X} \right)$$

$$- \frac{\tau \chi_2 v_0}{L_0^2} \frac{\partial}{\partial X} \left( c^* \frac{\partial v^*}{\partial X} \right) + \tau \mu_1 c^* (1 - c^*)$$

$$= \frac{L_0^2}{D} \frac{D_1}{L_0^2}$$

$$= \frac{D_1}{D} \text{[cm}^2\text{[s}^{-1}]\text{]}$$

$$= D_c$$

(new dimensionless parameter)
Non-dimensionalization

From which we get a dimensionless equation for cancer cell density:

$$\frac{\partial c^*}{\partial T} = D_c \frac{\partial^2 c^*}{\partial X^2} - \chi_u \frac{\partial}{\partial X} \left( c^* \frac{\partial u^*}{\partial X} \right) - \chi_v \frac{\partial}{\partial X} \left( c^* \frac{\partial v^*}{\partial X} \right) + \mu_c c^*(1 - c^*)$$  \hspace{1cm} (20.23)

In the same fashion, we get dimensionless equations for ECM and uPA:

$$\frac{\partial v^*}{\partial T} = -\gamma u^* v^* + \mu_v v^*(1 - v^*)$$  \hspace{1cm} (20.24)

$$\frac{\partial u^*}{\partial T} = D_u \frac{\partial^2 u^*}{\partial X^2} + k_c c^* - k_u u^*$$  \hspace{1cm} (20.25)
Non-dimensionalization

Or, we rewrite the equations after dropping the * signs:

\[
\frac{\partial c}{\partial T} = D_c \frac{\partial^2 c}{\partial X^2} - \chi_u \frac{\partial}{\partial X} \left( c \frac{\partial u}{\partial X} \right) - \chi_v \frac{\partial}{\partial X} \left( c \frac{\partial v}{\partial X} \right) + \mu_c c(1 - c)
\]

\[
\frac{\partial v}{\partial T} = -\gamma uv + \mu_v v(1 - v)
\]

\[
\frac{\partial u}{\partial T} = D_u \frac{\partial^2 u}{\partial X^2} + k_c c - k_u u
\]
Non-dimensionalization

where the dimensionless parameters are

\[ D_c = \frac{D_1}{D} \quad \chi_u = \frac{\chi_1 u_0}{D} \]
\[ D_u = \frac{D_2}{D} \quad \chi_v = \frac{\chi_2 v_0}{D} \]

\[ \mu_c = \tau \mu_1 \]
\[ \mu_v = \tau \mu_2 \]
\[ \gamma = \delta u_0 \tau \]
\[ k_c = \alpha \frac{c_0}{u_0} \tau \]
\[ k_u = \beta \tau \]
Steady State, Eigenvalues

A homogeneous steady state of a PDE model is a solution that is constant in space in time. For equations (20.23), (20.24), and (20.25) we take

\[
\frac{\partial c^*}{\partial T} = \frac{\partial v^*}{\partial T} = \frac{\partial u^*}{\partial T} = 0
\]

\[
\frac{\partial c^*}{\partial X} = \frac{\partial v^*}{\partial X} = \frac{\partial u^*}{\partial X} = 0
\]

which gives us

\[
0 = \mu_c c_{ss} (1 - c_{ss})
\]

\[
0 = -\gamma u_{ss} v_{ss} + \mu_v v_{ss} (1 - v_{ss})
\]

\[
0 = k_c c_{ss} - k_u u_{ss}
\]
Steady State, Eigenvalues

If we take

\[ c_{ss} = 0 \quad \rightarrow \quad u_{ss} = 0 \quad \text{and} \quad v_{ss} = 0 \quad \text{or} \quad v_{ss} = 1 \]

\[ c_{ss} = 1 \quad \rightarrow \quad u_{ss} = \frac{k_c}{k_u} \quad \text{and} \quad v_{ss} = 0 \quad \text{or} \quad v_{ss} = -\frac{\gamma}{\mu_v} u_{ss} + 1 \]

We look at solutions that are consisted of steady state and perturbation:

\[ c^*(X, T) = c_{ss} + \tilde{c}(X, T) \]
\[ v^*(X, T) = v_{ss} + \tilde{v}(X, T) \]
\[ u^*(X, T) = u_{ss} + \tilde{u}(X, T) \]
Exercise 1

Solve the dimensionless equations using MATLAB’s built-in function `pdepe`, with zero-flux boundary conditions.

The parameter values:

\[ D_c = 10^{-4} \quad \mu_c = 0.25 \quad k_c = 0.05 \]
\[ D_u = 10^{-2} \quad \mu_v = 0.15 \quad k_u = 0.3 \]
\[ \chi_u = 0.05 \quad \chi_v = 0.035 \quad \gamma = 8.15 \]

Initial conditions:

\[ c(X, 0) = \exp(-|X|^2/0.01) \]
\[ v(X, 0) = 1 - \exp(-|X|^2/0.01) \]
\[ u(X, 0) = \frac{1}{2} \exp(-|X|^2/0.01) \]
Exercise 2

Solve the dimensionless equations using Method of Lines (MOL), with zero-flux boundary conditions.

The parameter values:

\[ \begin{align*}
D_c &= 10^{-4} & \mu_c &= 0.25 & k_c &= 0.05 \\
D_u &= 10^{-2} & \mu_u &= 0.15 & k_u &= 0.3 \\
\chi_u &= 0.05 & \chi_v &= 0.035 & \gamma &= 8.15
\end{align*} \]

Initial conditions:

\[ \begin{align*}
c(X, 0) &= \exp(-|X|^2/0.01) \\
v(X, 0) &= 1 - \exp(-|X|^2/0.01) \\
u(X, 0) &= \frac{1}{2} \exp(-|X|^2/0.01)
\end{align*} \]
References

(1) Computational Cell Biology, Christopher Fall et al.
(3) http://blogs.scientificamerican.com/guest-blog/2013/10/30/the-hallmarks-of-cancer-6-tissue-invasion-and-metastasis/ (figure on slide 13)