My Findings

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Contents

Chapter 1

Modeling Attempts

1.1 Simple Model from Scratch

1.1.1 Simple ODE Model

Here, we develop a model that keeps track of the following variables

$n(t)$= density of tip cells in area of interest, (number per unit area).

$\rho(t)$ = density of blood vessels (length per unit area).

$c(t)$ = concentration of drug delivered to region by blood vessels (nano mole per unit area).

An updating list of model parameters:

- v [length/time]: The rate at which the tip cells move and extends the blood vessels.
- δ_v [1/time]: The rate at which the vascular structure gets degraded.
- λ_s [1/time]: Tip cell division rate (splitting rate).
- λ_b [1/time/length]: Tip cell emerging rate from stalk cells.
- δ_t [1/time]: Tip cell death/deactivation rate.
- κ [area/length/time]: Re-connection of tip cells to the other capillaries to form loops.
- μ [1/time]: Permeability of the capillary to the drug.
- σ [area/length]: The coverage of the blood vessels in the region.

And a list input functions

- $f(t)$: [nmol/length]: The amount of drug inside the capillary.

Studying dynamics of vessel formation

$$\frac{d\rho}{dt} = ??.$$

The active tip cells extend the vascular structure as they move. Assuming the tip cells move at rate v, then

$$\frac{d\rho}{dt} = vn + ??.$$

Also, assuming the vascular structure degrades with rate δ [per unit time], we can add the degradation term

$$\boxed{\frac{d\rho}{dt} = vn - \delta_v \rho}.$$

Studying the Dynamics of Tip Cells

Things important in the dynamics of the tip cells

- Generation of the tip cells: There are at least two ways for new tip cell generation listed as follows:
  - (i) Splitting mechanics: When the tip cells splits new vascular stem gets two heads. This should be proportional to the density of tip cells. The parameter λ_s [per unit time] reflects this mechanism.
  - (ii) Branching: New tip cells can form out the the endothelial stalk cells. This process should be proportional to the density of blood vessels. The parameter λ_b [per unit time per unit length] reflects this mechanism
- Loss of tip cells
  - (i) Death of the tip cells or getting deactivated: Reflected by the parameter δ_t
  - (ii) Joining the other branches of vascular network: When a tip cell reconnects another capillary branch, then they disappear. The parameter κ is for this mechanism. Note that the re-connection term is proportional to both number of tips cells, as well as the density of blood vessels. Thus the units of κ should be [area/length/time].
- The movement of tip cells and formation of new vascular networks along the way.

$$\boxed{\frac{dn}{dt} = (\lambda_s - \delta_t)n + \lambda_b \rho - \kappa n \rho}.$$

Nondimensionalization

In order the analyze the model more easily, we nondimensionalize the system with the following change of variable

$$\rho = R\tilde{\rho}, \qquad n = N\tilde{n}, \qquad t = T\tau.$$

There are many possible choice to choose the scaling factors R, N, T. However, we will choose them in a way that they are always positive, and the system of ODE becomes as simple as possible.

Substituting the change of variable above in the ODE system, we will get

$$\begin{aligned}\frac{d\tilde{\rho}}{d\tau} &= \frac{vNT}{R}\tilde{n} - \delta_v T\tilde{\rho},\\ \frac{d\tilde{n}}{d\tau} &= T(\lambda_s - \delta_t)\tilde{n} + \frac{\lambda_b TR}{N}\tilde{\rho} - T\kappa R\tilde{n}\tilde{\rho}.\end{aligned} \tag{♫}$$

We choose the following values for T, N, and R

$$T = \frac{1}{\delta_v}, \qquad R = \frac{\delta_v}{\kappa}, \qquad N = \frac{\lambda_b}{\kappa}.$$

This is a very suitable moment to pause and check the dimensions if they match (I did it and all of them matches!). With these choices from the coefficients, the system of ODEs will be

$$\frac{d\tilde{n}}{d\tau} = \frac{\lambda_s - \delta_t}{\delta_v}\tilde{n} + \tilde{\rho} - \tilde{n}\tilde{\rho}, \qquad \frac{d\tilde{\rho}}{d\tau} = \frac{v\lambda_b}{\delta_v^2}\tilde{n} - \tilde{\rho}.$$

To make the ODEs simpler to work with, we will write n, ρ in place of $\tilde{n}$ and $\tilde{\rho}$, and also we introduce the following parameters

$$\alpha = \lambda_s - \delta_t, \qquad \beta = \delta_v, \qquad \gamma = v\lambda_b. \tag{♣}$$

Then we can write

$$\boxed{\begin{aligned}\dot{n} &= \frac{\alpha}{\beta}n + \rho - n\rho,\\ \dot{\rho} &= \frac{\gamma}{\beta^2}n - \rho.\end{aligned}} \tag{☺}$$

Observation 1.1.1 — Other form of non-dimensionalization. After inspecting the non dimensionalization steps, we can see that the parameter κ somehow disappears, and there is no sign of it in the new parameters α, β, and γ. I tried another choices for R, T, and N, but still, I can not have the κ in the new parameters. The steps that I followed are the following.

$$T\kappa R = 1, \qquad NvT/R = 1, \qquad \delta_v T = 1.$$

Then we will have

$$T = 1/\delta_v, \qquad R = \delta_v/\kappa, \qquad N = \delta_v^2/(v\kappa).$$

Thus the system of ODEs will be

$$\dot{\rho} = n - \rho, \qquad \dot{n} = \alpha/\beta n - n\rho + \gamma/\beta^2 p,$$

where

$$\alpha = \lambda_s - \delta_t, \qquad \beta = \delta_v, \qquad \gamma = \lambda_b v.$$

Still, there is not κ in the new parameters.

In order to find the equilibrium points, we demand $\dot{n} = 0$ as well as $\dot{\rho} = 0$. This will lead to the following equations

$$\begin{aligned}\dot{n} = 0 : &\qquad \frac{\alpha}{\beta}n + \rho - n\rho = 0,\\ \dot{\rho} = 0 : &\qquad \frac{\gamma}{\beta^2}n - \rho = 0.\end{aligned}$$

After some algebra, it turns out that there are two equilibrium points for this system.

$$p_1^0 = (0,0), \qquad p_2^0 = (\frac{\alpha\beta}{\gamma} + 1, \frac{\gamma}{\beta^2} + \frac{\alpha}{\beta}) = (\frac{\alpha\beta+\gamma}{\gamma}, \frac{\gamma+\alpha\beta}{\beta^2}). \tag{E.1.1}$$

In order to analyze the stability of these equilibrium points, we first need to calculate the Jacobian matrix of the ODE system

$$DF = \begin{pmatrix} \alpha/\beta - \rho & 1-n \\ \gamma/\beta^2 & -1 \end{pmatrix}.$$

Stability Analysis of p_2^0

By evaluating the Jacobian matrix at the equilibrium point we will have

$$DF[p_2^0] = \begin{pmatrix} -\gamma/\beta^2 & -\alpha\beta/\gamma \\ \gamma/\beta^2 & -1 \end{pmatrix}.$$

The trace and determinant of this matrix is

$$\Delta = \gamma/\beta^2 + \alpha/\beta, \qquad \sigma = -\gamma/\beta^2 - 1.$$

By close inspection, it turns out that Δ is the same as the first component of p_2^0, which should be positive. This implies $\Delta > 0$. So the sign of the trace of the Jacobian matrix will determine the stability. From (♣), $\gamma > 0$. Thus $\sigma < 0$. This indicates that the equilibrium point p_0^2 is stable equilibrium. Also, note that since σ can never transversally become positive from being negative (i.e. passing through $\sigma = 0$, transversally), thus we can rule out the existence of any Hopf bifurcation with this particular model.

Observation 1.1.2 — stability of p_2^0. The Jacobian matrix evaluated at p_2^0 has

$$\Delta \geq 0, \qquad \sigma < 0.$$

Thus equilibrium point p_2^0 is a hyperbolic sink (when $\delta > 0$). This hyperbolic sink can be of the type stable node (with purely real eigenvalues) or stable focus (with complex valued eigenvalues whose real part is negative). But since these two kind of stability are topologically equivalent, we don't do further analysis to distinguish them at this point.

Observation 1.1.3 — No sustained oscillations. Note that since $\sigma < 0$ for all values of the parameters of the model, then there is no chance to observe a Hopf bifurcation, thus ruling out any sustained oscillations in the model.

Finding Lyapunov Function

In attempting to find a Lyapunov function, I thought it might be a good idea to have a different choices for the non-dimensionalization scaling so that I can have control on the nonlinear part $n\rho$. But it seems that there are no possible ways to achieve this. That is because in (♫), we can not make the first term of RHS of $\dot{\tilde{\rho}}$ and the second term of RHS of $\dot{\tilde{n}}$ simultaneously to be 1. Thus there are no choices for the scaling factors to make the coefficient of $\tilde{n}\tilde{\rho}$ to be 1.

Stability Analysis of p_1^0

The Jacobian matrix evaluated at p_1^0 is

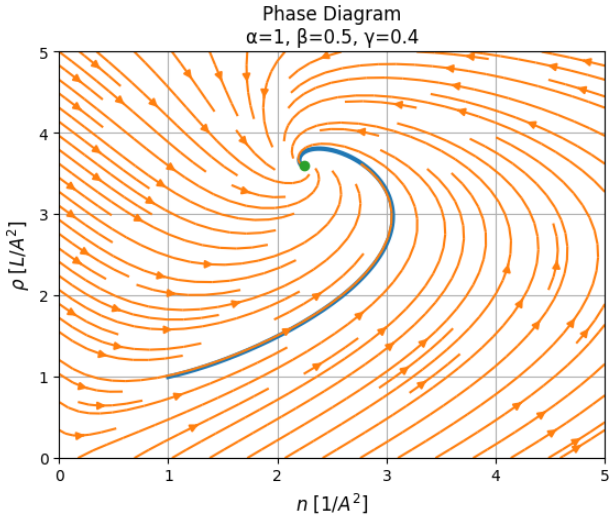
$$DF[p_1^0] = \begin{pmatrix} \alpha/\beta & 1 \\ \gamma/\beta^2 & -1 \end{pmatrix}.$$

The determinant and the trace will be

$$\Delta = -\alpha/\beta - \gamma/\beta^2, \qquad \sigma = \alpha/\beta - 1.$$

Observation 1.1.4 The determinant Δ is negative the first term of the p_2^0. Thus $\Delta \leq 0$. When $\Delta < 0$, then regardless of value of σ, p_1^0 is a hyperbolic saddle. However, when $\Delta = 0$, then p_1^0 is non-hyperbolic and further analysis is required to determine the stability.

The following shows the phase portrait of the system with some values for the parameters.



Furthermore, the following diagram shows the nullclines and the sign of the vector field at the different regions of the phase portrait.

Quantitative analysis with nullclines

Drawing the phase portrait and including the nullclines helps in understanding the quantitative effect of change in parameters (which causes by the drug-vessel interaction). To draw the nullclines, we require

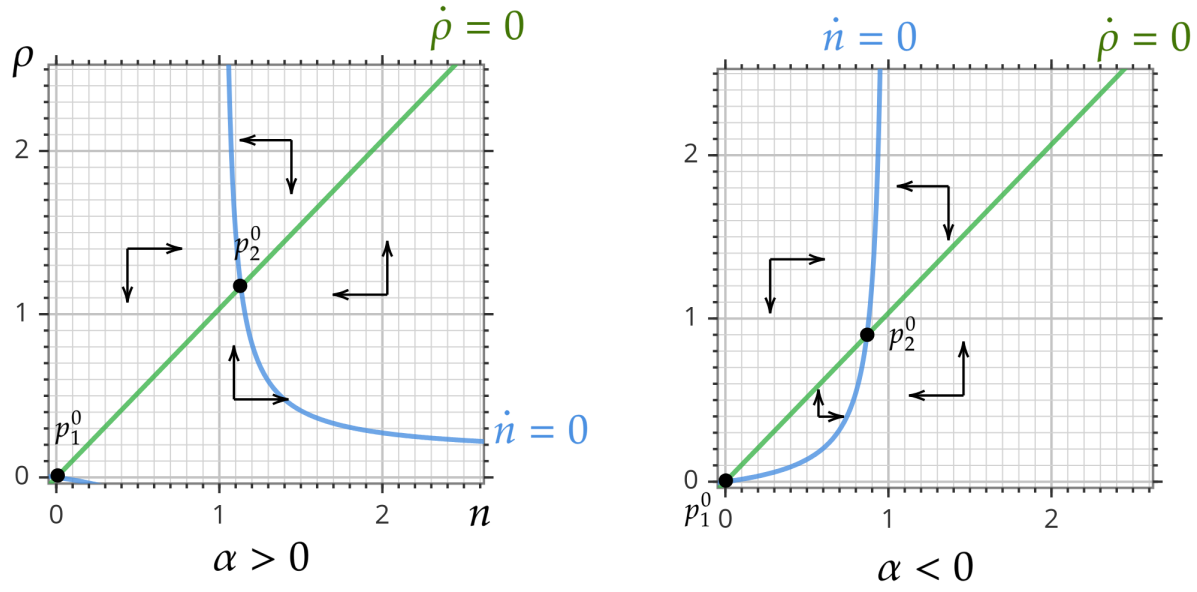
$$\begin{pmatrix} \dot{n} \\ \dot{\rho} \end{pmatrix} = \begin{pmatrix} f_1(n,\rho) \\ f_2(n,\rho) \end{pmatrix} = \begin{pmatrix} \frac{\alpha}{\beta} n + \rho - n\rho \\ \frac{\gamma}{\beta^2} n - \rho \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}.$$

After a little bit of algebra, we get

$$\dot{n} = 0: \qquad \rho = \frac{\alpha}{\beta} \cdot \frac{n}{n-1} \quad (n \neq 1),$$
$$\dot{\rho} = 0: \qquad \rho = \frac{\gamma}{\beta^2} n.$$

Observation 1.1.5 The reason that we get the restriction $n \neq 1$ for the $\dot{n} = 0$ nullcline is the following. From (E.1.1) we know that $f_1(p_2^0) = 0$. Thus we can use the implicit function theorem to get a continuous branch of equilibria near p_2^0 in the form of $\rho = \hat{\rho}(n)$ where $\hat{\rho}$ is a continuously differentiable function, where $\rho^* = \hat{\rho}(n^*)$ (note $p_2^0 = (n^*, \rho^*)$), and $f_1(n, \hat{\rho}(n)) = 0$ for some open neighborhood containing p_2^0. However, we can use this implicit function argument only when $\partial_\rho f_1 \neq 0$, which implies $n \neq 1$.
Also, it is interesting to note that $n = 1$ is equivalent to $\alpha = 0$. This can be observed from (E.1.1). The consequences of this are summarized in the following observation boxes.

We will have two cases of the phase portrait as shown in the figure below. Note that the stability of the equilibrium point p_2^0 will still remain the same as the value of α passes $\alpha = 0$ transversally. The results of this section is summarized in the observation box below.



Observation 1.1.6 — Two different phase portraits. As the parameter α passes through $\alpha_0 = 0$ transversally, we get two phase portraits that are not topologically equivalent (the results are shown in the figure above). Because of this, depending on the sign of α, we will observe totally different behaviours from the system as we change the parameter values.
I **emphasis** that in both of these phase portraits, the stability of both equilibria remains the same.

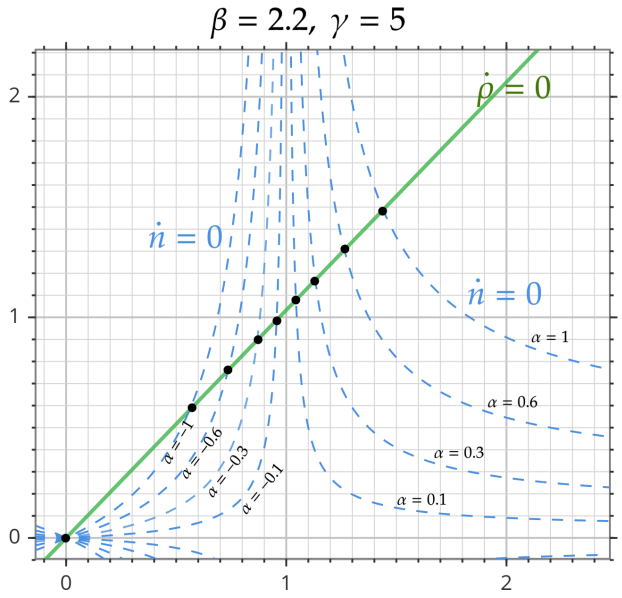
Observation 1.1.7 — Biological meaning of α. From (♣) we see that $\alpha = \lambda_s - \delta_t$, where λ_s is the tip cell division rate (which leads to vascular splitting), and δ_t is the death rate of the tip cells. Thus $\alpha > 0$ translates to larger division rate compared to the death rate for tip cells, and $\alpha < 0$ is the opposite.

Quantitative study of Effect of Changing the Parameters

This section will lay the foundations for studying the drug-vessel interaction and how that affects the system.

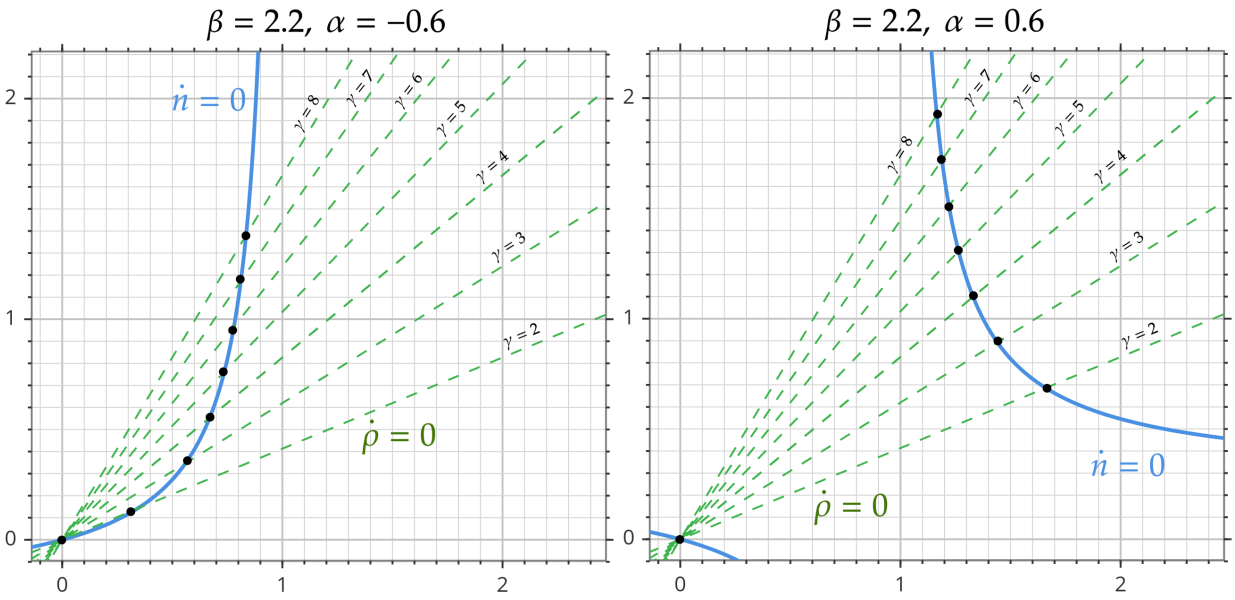
Effect of α

Regardless of the sign of α (i.e. being in either of phase portraits) increasing the value of alpha will move the p_2^0 higher. This observation is summarized in the following figure.



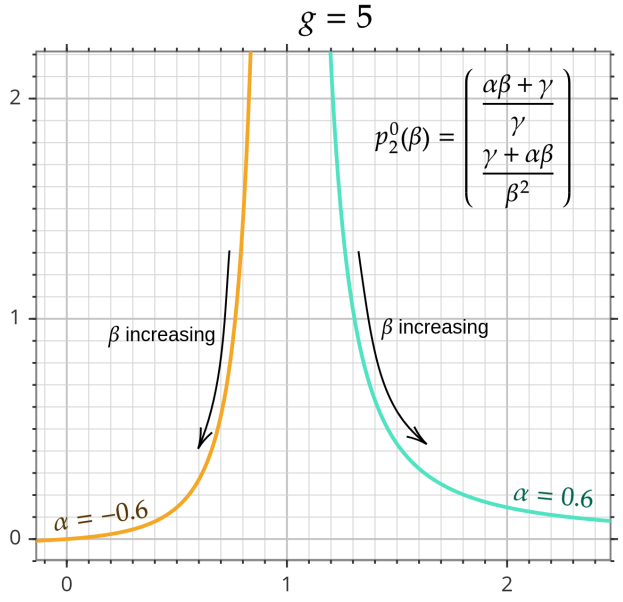
Effect of γ

γ is basically determining the slope of the $\dot{\rho} = 0$ nullcline. The higher the value of γ the more steeper is the slop. Thus changing the values of γ, the equilibrium point p_2^0 will move up or down on the $\dot{n} = 0$ nullcline. The sign of α determines the way p_2^0 changes. The following figure summarizes the results for the argument above.



Effect of β

Determining the effect of the parameter β is not as straight forward as the other two parameters as it appears in both ODEs. However, we can plot the parameterized curve of $p_2^0(\beta)$ using (E.1.1) to see the effect of β on the equilibrium point. The following figure summarizes the effect of β on p_2^0.



Drug delivery

In order to bring the drug-vessel interaction into play, we develop a ODE for $c(t)$ add approporite terms to the RHS of $\dot{n}$ and $\dot{\rho}$.

$$\frac{dc}{dt} = \mu(\rho(t)f(t) - \sigma c(t)\rho(t)) - \boxed{\lambda c}$$

where μ has the unit [1/time], and $f(t)$ is the amount drug inside the capillary that has the unit [nmol per unit length]. Note that we have assumed the exchange of drug between the vessels and the region of interest is proportional to the difference in the concentration of drug in two different environments. Furthermore, the coefficient σ has the units of [area/length] which is an indicator of the area coverage of the blood vessels. This parameter somehow characterizes the space filling and fractal structure of the blood vessels. This parameter should have some relations with the fractal dimension of a given vascular structure. Considering the dynamics of this parameter can possibly reflect some of the topological and non-local characterizations of the vascular network.

Basic and Simplified delivery scenario

We assume that there is an infinite pool of drug (i.e. the patient is getting injected continuously) so the amount of drug per unit length in the capillary is constant C_0 [nmol per unit length].

$$\frac{dc}{dt} = \mu\rho(t)(C_0 - \sigma c(t)).$$

Also, note that we have ignored the radiation decay term to keep stuff simpler at this stage. The reason behind this choice is that at this stage, in adding the drug-vessel interaction, we will only consider a mass-action type interaction (i.e. chemical interactions), and no radio-biological interaction will be assumed (which has more complexity).

Another assumption that we make is that since the molecules of the drug are much smaller and simpler than the cells in the body, then we assume that they reach to equilibrium much more faster than the characteristic time scale of tip cell movement, and the death/generation of the cells. This basically means that we can simply assume $dc/dt = 0$ to arrive at the following algebraic equation for c.

$$C_0 = \sigma c(t).$$

Adding the drug-vessel interaction

Presence of drug in the environment can have many different effects. It can kill/deactivate the existing tip cells (increasing δ_t). Or it can change the rate at which the endothelial cells turn into the tip cells (changing the value of δ_b). Or it can affect the tip cell division rate (λ_s). It can also affect the cellular migration of the tip cells and change the value of parameter v. The following lists the parameters corresponding to the amplitude of each of these interactions

- a_1: changing the tip cell movement/migration
- a_2: killing/deactivating the tip cells
- a_3: changing the endothelial-to-tip cell conversion rate
- a_4: changing the tip cell division rate

Some discussions on drug interaction

In mathematical modeling of biological processes, incorporating drug interactions can be complex, as the drug can influence various parameters of the system in different ways. The choice of interaction term often depends on the nature of the drug action and the available experimental data. Here are a few common approaches to include drug interactions in the model:

1. **Linear Interaction**: If the drug effect is proportional to its concentration, we can model the interaction linearly. For instance:

$$\begin{aligned} v(c) &= v_0 - a_1 c, \\ \delta_v(c) &= \delta_{v0} + a_2 c, \\ \lambda_b(c) &= \lambda_{b0} + a_3 c, \\ \lambda_s(c) &= \lambda_{s0} - a_4 c. \end{aligned}$$

   Here, v_0 and δ_{v0} are the baseline motility and degradation rates without the drug, while a_1 and a_2 represent the sensitivity of these rates to the drug concentration. Similarly λ_{b0} and λ_{s0} are the baseline rates without the drug, and a_3, a_4 are the sensitivities of these rates to the drug concentration.

2. **Hill Function**: If the drug effect exhibits saturation – meaning it has a maximum effect regardless of concentration – a Hill function can be appropriate:

$$\begin{aligned} v(c) &= v_0 \left(1 - \frac{a_1 c^h}{K_d^h + c^h}\right), \\ \delta_v(c) &= \delta_{v0} \left(1 + \frac{a_2 c^h}{K_d^h + c^h}\right), \\ \lambda_b(c) &= \lambda_{b0} \left(1 + \frac{a_3 c^h}{K_{d3}^h + c^h}\right), \\ \lambda_s(c) &= \lambda_{s0} \left(1 - \frac{a_4 c^h}{K_{d4}^h + c^h}\right), \end{aligned}$$

   Here, h is the Hill coefficient that determines the steepness of the response curve, and K_d is the drug concentration at which the effect is half of its maximum. With h as the Hill coefficient, and K_{d3}, K_{d4} as the half-maximal effective concentrations for λ_b and λ_s, respectively.

3. **Michaelis-Menten Kinetics**: If the drug interaction is enzyme-like, you can model it using Michaelis-Menten kinetics:

$$\begin{aligned} v(c) &= v_0 \left(1 - \frac{a_1 c}{K_m + c}\right), \\ \delta_v(c) &= \delta_{v0} \left(1 + \frac{a_2 c}{K_m + c}\right), \\ \lambda_b(c) &= \lambda_{b0} \left(1 + \frac{a_3 c}{K_m + c}\right), \\ \lambda_s(c) &= \lambda_{s0} \left(1 - \frac{a_4 c}{K_m + c}\right), \end{aligned}$$

   Where K_m is the Michaelis constant, representing the drug concentration at which the rate of reaction is half of its maximum. where K_m is the Michaelis constant, indicative of the concentration at which the reaction rate is half its maximum.

4. **Exponential or Sigmoidal Functions**: For more complex drug effects, such as those that have a threshold effect or exhibit a sigmoidal dose-response, exponential or sigmoidal functions can be used.

These interaction terms would be incorporated into the model by modifying the differential equations as follows:

$$\frac{d\rho}{dt} = v(c)n - \delta_v(c)\rho,$$

$$\frac{dn}{dt} = (\lambda_s(c) - \delta_t)n + \lambda_b(c)\rho - \kappa n\rho,$$

where $\lambda_b(c)$ and $\lambda_s(c)$ are now functions of the drug concentration that reflect the modulation of the endothelial-to-tip cell conversion rate and the tip cell division rate by the drug.

The form of the interaction should be chosen based on the biological mechanism of the drug action, the type and quality of experimental data available, and the ability to estimate the additional parameters introduced by these functional forms with the available data. To decide which model to use, consider the following:

- **Biological Mechanism**: Does the drug interact with its target in a manner that is competitive, non-competitive, or does it follow some form of cooperative binding? This will guide whether you use linear, Hill, or Michaelis-Menten kinetics.
- **Data Availability**: What kind of data do you have? If you have dose-response data, you can fit these models to the data to estimate parameters like a_1, a_2, h, K_d, or K_m.
- **Parameter Estimation**: Can you estimate the additional parameters introduced by these functions? More complex models require more data for accurate parameter estimation.

1.1.2 Simple Spatially Distributed 1D System

In this section, we extend a simple ordinary differential equation (ODE) model for angiogenesis to include spatial dynamics. The original model captures the temporal evolution of the density of tip cells, the density of blood vessels, and the concentration of a drug delivered to a region. We now consider these variables as functions of both space and time, $\rho(x,t)$, $n(x,t)$, and $c(x,t)$, to develop a partial differential equation (PDE) model that accounts for spatial growth and diffusion processes.

Flux of Tip Cells

A key concept in extending the model to incorporate spatial dynamics is the introduction of the flux of tip cells, denoted as J. Flux is defined as the rate of flow of a property per unit area, which in this context is the flow of tip cells moving into a region. Mathematically, the flux J is given by the product of the density of tip cells $n(x,t)$ and their velocity v, i.e., $J = nv$. This formulation allows us to quantify how the movement of tip cells contributes to the spatial development of blood vessels.

Spatial Model Development

We now proceed to develop the spatial model by modifying the equations from the original ODE model to incorporate spatial derivatives, reflecting the spatial dynamics of vessel formation, tip cell movement, and drug diffusion.

Equation for Blood Vessel Density

The blood vessel density $\rho(x,t)$ is primarily affected by the extension of vascular structures due to the movement of tip cells and the degradation of these structures over time. Assuming homogeneous conditions without specific spatially-dependent growth mechanisms, the equation for ρ remains similar to the non-spatial model but now includes a spatial component:

$$\boxed{\frac{\partial \rho}{\partial t} = vn - \delta_v \rho}, \tag{1.1.1}$$

where δ_v represents the rate of vascular degradation.

Equation for Tip Cell Density

The spatial dynamics of tip cell density $n(x,t)$ are influenced by their flux across the spatial domain. Incorporating the concept of flux, the balance equation for n in one dimension is given by:

$$\boxed{\frac{\partial n}{\partial t} + \frac{\partial (nv)}{\partial x} = (\lambda_s - \delta_t)n + \lambda_b \rho - \kappa n \rho}, \tag{1.1.2}$$

where the terms on the right-hand side represent the generation and loss of tip cells, and the spatial derivative term accounts for their movement.

Equation for Drug Concentration

The drug concentration $c(x,t)$ is affected by diffusion, permeation through the capillary walls, and any external sources of the drug. The equation accounting for these processes is:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - \mu c + f(x,t), \tag{1.1.3}$$

where D is the diffusion coefficient, μ represents the drug's permeability through capillaries, and $f(x,t)$ is a source term for the drug.

1.2 Anderson Chaplain Model of Angiogenesis

1.2.1 Biological Facts and Basics

The sequences of angiogenesis is assumed to be

(i) Tumor angiogenic factors (TAF) are secreted by the tumors under low oxygen stress.
(ii) Emergence of a chemical gradient of TAF between the tumor and the pre-existing vasculature.
(iii) Endothelial cells lining the interior of the existing vasculature respond to this chemical clue by

- Secreting digestive enzymes to loosen the basal lamina.
- Migrate from the disrupted membrane, up in the TAF gradient towards the tumor (i.e. chemotaxis). Look at the citations in the corresponding section)
- The endothelial cells form into a few cell clusters Muthukkaruppan u. a. (1982); Orme und Chaplain (1996) which eventually become sprouts. Small, finger-like capillary sprouts are formed by accumulation of endothelial cells which are recruited from the parent vessel.
- The sprout grow in length and continue to move toward the tumor directed by the motion of the leading endothelial cells at the sprout tip.

(iv) Further sprout extension occurs when some of the endothelial cells of the sprout wall begin to proliferate. Cell division is largely confined to a region just behind the cluster of mitotically inactive endothelial cells that constitute the sprout time. Note that Sholley u. a. (1984) demonstrated that in the absence of endothelial cell proliferation, a restricted capillary network, which stops after a few days and never reaches the tumor, is formed. Thus, unless the endothelial cells undergo mitosis, the capillary sprouts cannot complete vascularization completely.
(v) This process of sprout tip migration and proliferation of sprout-wall cells forms solid strands of endothelial cells amongst the extracellular matrix.
(vi) The tip cells find their way through the extracellular matrix that consist of itersitial tissue, collagen fiber and fibronectin as well as other components.
(vii) Interactions between the endothelial cells and the extracellular matrix, in particular fibronectin.

- **Initial distribution of fibronectin:** At the very early stages of angiogenesis, when the endothelial cells lining the parent vessels, are stimulated by TAF, they secrete enzymes to digest through the basal lamina of the parent vessel. This initial damage results in an increased vessel permeability Clark u. a. (1981). This allows the plasma fibronectin from the blood to leak from the parent vessel and diffuse through the domain Hynes (1989). The diffusion coefficient of fibronectin has been measured to be $2 \times 10^{-7} \mathrm{cm}^2 \mathrm{s}^{-1}$ Williams u. a. (1982); Rocco u. a. (1987). This plasma fibronectin eventually binds to the extracellular matrix Oh u. a. (1981); Deno u. a. (1983); Clark u. a. (1983), thus prior to the start of angiogenesis we will have a gradient of fibronectin that is high near the parent vessel and gets lower away from the parent vessel. This has been experimentally observed by Paku und Paweletz (1991) and Clark u. a. (1982, 1981, 1983). It has also been experimentally observed that a higher concentration of laminin (another matrix macromolecule with similar adhesive properties to fibronectin) are initially found around the parent vessel Hynes (1989); Paku und Paweletz (1991)
- Cultured endothelial cells are known to synthesize and secrete cellular fibronectin (i.e. the insoluble form) Birdwell u. a. (1978, 1980); Jaffee (1978); Macarak u. a. (1978); Ner-

lich und Schleicher (1991). Note that the insoluble form is first secreted in the soluble form and then assembles into insoluble matrix.

- The expression of secreted fibronectin in cultured endothelial cells closely reflects the distribution of pre-existing fibronectin observed in matrices *in vivo* Vlodavsky u. a. (1979); Hynes (1989)
- The fibronectin secreted by the endothelial cells do not diffuse and bound the to extracellular matrix Birdwell u. a. (1980); Hynes (1989).
- Fibronectin secreted by the endothelial cells is a major ligand between cells and matrix material in many situations.
- Endothelial cells use fibronectin for attachment to the matrix via integrins, a family of cell surface receptors Johansson u. a. (1987); Hynes (1989); Alberts u. a. (2002b).

(viii) Haptotaxis of the endothelial cells: migration of the endothelial cells up the gradient of adhesiveness Everitt u. a. (1996); McCarthy und Furcht (1984); Carter (1965).

(ix) Thus in addition to the chemotaxis of endothelial cells following the chemical gradient of TAF, there is a complementary haptotactic response to the fibronectin present within the extracellular matrix Bowersox und Sorgente (1982).

(x) Modes of the spatial growth:

- Initially, the sprouts arising from the parent vessel are essentially parallel to each other.
- Tend to incline towards each other when the finger-like capillary sprouts have reached a certain distance from the parent vessel Paweletz und Knierim (1989) leading to numerous tip-to-tip and tip-to-sprout fusions known as anastomoses. This anastomoses leads to a network of poorly perfused loops and arcades.
- Form this process of anastomoses, the first signs of circulation can be recognized and from the primary loops, new buds and sprouts emerge repeating the angiogenic sequence of events.
- The process of emerging new capillary sprouts from the existing sprout tips is often called *sprout branching*.
- As the sprouts approach the tumor, their branching dramatically increases until the tumor is eventually penetrated.

(xi) The repeated steps of angiogenesis: endothelial cell migration, sprout extension, cell proliferation and loop formation.

1.2.2 A Review of previous mathematical models

- Continuum and deterministic models for one dimension developed by Liotta u. a. (1977); Balding und McElwain (1985); Chaplain und Stuart (1993); Byrne und Chaplain (1995b); Orme und Chaplain (1996). These models were able to capture some features like average sprout density and network expansion rates. But was not able to capture more detailed information concerning the actual structure and morphology of the capillary network.

- More realistic 2D continuum models by Chaplain (1995); Orme und Chaplain (1997): These models allowed a more detailed qualitative comparison with *en vivo* observations about the spatial morphology of the networks. However, even these models were not able to capture the events like repeated sprout branching and hence overall dendrictic structure of the network.

- Important: More general continuum branching models Meinhardt (1976, 1982); Ermentrout und Edelstein-Keshet (1993).
- Discrete probabilistic framework by Stokes und Lauffenburger (1991) using stochastic differential equations. This model incorporated chemotaxis but not the Haptotaxis. Also, was not able to capture the fact that more branched appear as the network gets closer to the tumor. This effect is called the **brush border** effectGimbrone u. a. (1974); Ausprunk und Folkman (1977); Zawicki u. a. (1981); Muthukkaruppan u. a. (1982); Sholley u. a. (1984).

Some notes about the fibronectin: Fibronectin is a high molecular weight (about 500 kD) Glycoprotein (i.e. protein + an Oligosaccharide) that binds to the membrane-spanning receptor protein called Integrin. On the other hand, they also bind to other extracellular matrix proteins like collage, fibrin, etc.

Fibronectin in blood plasma, is in soluble form (made in Liver), however, in the extracellular matrix, the Fibronectin is first secreted in soluble form (mostly by the fibroblast cells) and then assembles into an insoluble matrix in a complex cell mediated process. In the terminology above, the soluble fibronectin is called *plasma fibronectin* and the insoluble form is called *cellular fibronectin*.

1.2.3 Details of the model

Here in this section I will follow the model described in Anderson und Chaplain (1998). This model is based on the experimental data presented in Gimbrone u. a. (1974) and Muthukkaruppan u. a. (1982). The variables of the model are as the following.

- $n = n(X,t) : \Omega \times \mathbb{R} \to \mathbb{R}$: the endothelial-cell density (per unit area).
- $c = c(X,t) : \Omega \times \mathbb{R} \to \mathbb{R}$: the tumor angiogenic factor (TAF) concentration (nmol per unit area).
- $f = f(X,t) : \Omega \times R \to \mathbb{R}$: the fibronectin concentration (nmol per unit area).

> **Strange Observation 1.2.1 — Ambiguity in the definition of one of the parameters.** As we read in Anderson und Chaplain (1998), n is introduced to be the "endothelial-cell density". However, I feel that it is not true and this variable should represent the "endothelial *tip* cell density". I feel this way because it is the tip cells that are doing a random walk (thus diffusion) and reacting to the TAF and fibronectin gradients.

Equations for endothelial cells

The endothelial cells are moving in the space due to (1) their random motion (i.e. diffusion), (2) chemotaxis (moving up in the gradient of TAF), and (3) haptotaxis (moving up in the gradient of fibronectin). Combining these factors we will come up with the following flux for the tip cells

$$J_n = -D_n \nabla n + \chi n \nabla c + \rho_0 n \nabla f.$$

where D_n is the diffusion coefficient of the endothelial cells, and χ, ρ_0 are the sensitivity of chemotaxis and haptotaxis of endothelial cells due to the TAF and fibronectin gradients respectively. Putting this in the continuoity equation, we will get

$$\frac{\partial n}{\partial t} = -\nabla \cdot (-D_n \nabla n + \xi n \nabla c + \rho_0 n \nabla f) = D_n \nabla^2 n - \nabla \cdot (\chi n \nabla c) - \nabla \cdot (\rho_0 n \nabla f).$$

Strange Observation 1.2.2 — Growth of the tip-cells are not considered in the model. As we discussed in subsection 1.2.1 in item (iv), the endothelial tip cells are dividing (otherwise the vascularization will not be completed). But in the PDE above, we didn't have any term for the tip cells proliferating or degrading.

Strange Observation 1.2.3 — A problem with the diffusion coefficient of endothelial cells. As explained above, we are modeling the random mobility of endothelial tip cells by diffusion. However, according to the discussion (page 865 in Anderson und Chaplain (1998)), it has been observed Rupnick u. a. (1988) that when the migration of the endothelial cells are constrained by the surrounding cells, then their estimate for the for the diffusion coefficient the tip cells was too large and did not agree with experimental results.

Because of this observations, authors of Anderson und Chaplain (1998) used a diffusion coefficient that was about 100 times smaller! (they cite to Bray (2000) for this decision). I feel like this is not a good approach! The biological observation above is a signal that capturing the random mobility of the cell simply by diffusion is not a correct framework to use.

Also, according to the discussion on page 886 of Anderson und Chaplain (1998)), there are some in vivo experiments that indicate that there appear so the very little random mobility of endothelial cells at the capillary sprout tops Paweletz und Knierim (1989); Paku und Paweletz (1991).

In the PDE for tip cell density, the parameter χ can depend on the concentration of TAF. We can model this interaction as (see the strange observation box below).

$$\chi(c) = \chi_0 \frac{k_1}{k_1 + c}.$$

Strange Observation 1.2.4 — The chemotaxis sensitivity seems not to be correct. In the model above by Anderson und Chaplain (1998), the authors are assuming that the functional form of χ is given as

$$\chi(c) = \chi_0 \frac{k_1}{k_1 + c}.$$

They say that the more realistic assumption is that the chemotactic sensitivity decreases with increased TAF concentration. They present the following references for this claim Lapidus und Schiller (1976); Lauffenburger u. a. (1984); Sherratt (1994); Woodward u. a. (1995); Olsen u. a. (1997). This does not make sense for me. I feel like since the cell feels the chemicals by cell surface receptor binding, then the more chemicals available, the more strong is the signal for chemotaxis. So I feel that the appropriate model for this will be

$$\chi(c) = \chi_0 \frac{c}{k_1 + c}.$$

Equations for TAF

To derive the equation for TAF concentration, first observe that TAF is secreted by the tumor cells where it starts diffusing into the space. I.e. the governing equation for TAF will be

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c - \theta c, \tag{1.2.1}$$

where D_c is the TAF diffusion constant and θ is the decay rate. We assume that during the initial stage of tumor secreting TAF, its distribution in the environment reaches a steady state which gives us the initial condition for the concentration of c in the domain.

In the stage that the angiogenesis begins (when we have an established steady state for c), while the tip cells move up the gradient, TAF is used by uptake and binding to the cells Ausprunk und Folkman (1977); Hanahan (1997). This interaction can be modeled by

$$\frac{\partial c}{\partial t} = -\lambda n c,$$

where λ is a constant.

Strange Observation 1.2.5 — TAF interaction with cells does not seem to be correct. In the model above (from Anderson und Chaplain (1998)), the uptake and binding of TAF to the tip cells is modeled in a mass action kinetic way. I have a feeling that this might not be true and it should be modeled by Michaelis-Menten equation. Also, this model assumes that the used TAF is not get replaced, but I feel that as long as tumor is under oxygen stress, the secreting mechanism of TAF in tumor will still be active.

Be Careful! — To much intuition is not good. The way that the model above is presented is not appealing for me at all. This is the way that Anderson und Chaplain (1998) does, and I think there are more than enough common sense floating around! For instance, they say that in the initial stage, the tumor secretes the TAF and it starts diffusing in the environment while degrading and eventually reaches steady state (which is fair up to now). Then, they say that during the angiogenesis stage the differential equation governing the concentration of TAF is different (Which also makes sense). My problem is that I want to see both of the terms in a single PDE and then by appropriate mathematical treatment (slow-fast dynamics, perturbation theory, etc) arrive at the conclusions that they stated using the commons sense. I need to do this for my thesis.

Equations for fibronectin

As we discussed in the biology background subsection, the endothelial tip cells tend to move up in the gradient of fibronectin. Fibronectin is present in the domain before angiogenesis. As the tip cells do haptotaxis (moving up (up or down?) in the gradient of fibronectin) they use some fibronectin to connect to the ECM. Tip cells also secrete fibronectin which dose not diffuse. Thus the corresponding differential equation will be

$$\frac{\partial f}{\partial t} = \omega n - \mu n f,$$

where ω is the production rate of f by the tip cells and μ is the rate at which the tip cells use fibronectin to bind to the ECM.

Strange Observation 1.2.6 — The model for fibronectin dynamics is too simple. The model above for the time evolution of fibronectin is given by Anderson und Chaplain (1998). According to our detailed discussion in item (vii), I feel like this model is too simple to capture the time evolution of the fibronectin. We are assuming that the fibronectin is used and produced only by the tip cells (if by Strange observation 1.2.1 we come to the conclusion that n represents the tip cells). This implies that the stalk cells are not producing fibronectin which might not be true.

Also, as assume that as soon as the process of angiogenesis starts, the leakage of fibronectin from the parent vessel into the domain stops. According to the parameters in Table 1.1, the time scale happens to be $\tau = L^2/D_c \approx 2$ days. Since in item (vii) we discussed that the reason of the initial distribution of fibronectin is the damage to the basal lamina of the parent vessels, then I feel like in the span of several days that dame might still persist so we might still have the leakage of fibronectin to the domain.

Strange Observation 1.2.7 — The initial condition for fibronectin is too intuitive. As we will see in [add the cross reference for the fibronectin initial condition here], the initial condition for fibronectin concentration, although makes sense, but it is not appropriately modeled compared to what we did for TAF (see Equation (1.2.1))

Summary 1.1 The complete set of equations will be give as

$$\begin{aligned}
\frac{\partial n}{\partial t} &= D_n \nabla^2 n - \nabla \cdot (\chi n \nabla c) - \nabla \cdot (\rho n \nabla f), \\
\frac{\partial c}{\partial t} &= -\lambda n c, \\
\frac{\partial f}{\partial t} &= \omega n - \mu n f,
\end{aligned}$$

■ **Remark** We assume that non of species, i.e. tip cells, TAF and fibronectin leave the domain of simulation. Thus the boundary condition is give as

$$\hat{\xi} \cdot J_n = 0.$$

1.2.4 Non dimensionalization of the system

For an easier analysis of the system we first need to write the system in non dimensionalized way. Consider the following change of variables

$$\begin{aligned}
&n = N_0 \tilde{n}, && c = C_0 \tilde{c}, && f = F_0 \tilde{f}, \\
&t = \underbrace{\tau}_{\tau = L^2/D_c} \tilde{t}, && x = L\tilde{x}.
\end{aligned}$$

Substituting these change of variables in the model we will get the following non dimensionalized form of the model. Note that we remove the tilde symbol for more clear look.

$$\begin{aligned}
\frac{\partial n}{\partial t} &= D \nabla^2 n - \nabla \cdot \left(\frac{\chi}{1+\alpha c} n \nabla c\right) - \nabla \cdot (\rho n \nabla f), \\
\frac{\partial c}{\partial t} &= -\eta n c, \\
\frac{\partial f}{\partial t} &= \beta n - \gamma n f,
\end{aligned}$$

where

$$\begin{aligned}
&D = \frac{D_n}{D_c}, && \chi = \frac{C_0 \chi_0}{D_c}, \ \alpha = \frac{C_0}{k_1} && \rho = \frac{f_0 \rho_0}{D_c}, \\
&\eta = \frac{L^2 \lambda N_0}{D_c}, && \beta = \frac{L^2 \omega N_0}{F_0 D_c}, && \gamma = \frac{L^2 \mu N_0}{D_c}.
\end{aligned}$$

1.2.5 Some discussions on the parameters used

The following table summarizes the realistic values for the model parameters discussed in Anderson und Chaplain (1998).

Parameter	Value [units]	Reference
D_n	10^{-10} $[\text{cm}^2\text{s}^{-1}]$	Bray (2000)
D_c	2.9×10^{-7} $[\text{cm}^2\text{s}^{-1}]$	Bray (2000); Sherratt und Murray (1990)
χ_0	2600 $[\text{cm}^2\text{s}^{-1}\text{M}^{-1}]$	Stokes u. a. (1990)
ρ_0	same as χ_0 but $\chi_0 > \rho_0$	Anderson und Chaplain (1998)
c_0	10^{-10} $[M]$	Stokes u. a. (1990)
f_0	10^{-10} $[M]$	Terranova u. a. (1985)
λ, ω, μ	no available estimates.	Hynes (1989)
L	2 $[mm]$	Gimbrone u. a. (1974)

Table 1.1: The biologically realistic parameter values for the Anderson-Chaplain model.

1.2.6 Simulating the model

Simulation Domain

The simulation domain is the square $[0,1] \times [0,1]$. With the tumor located at $\{1\} \times [0,1]$ and the parent vessel located at $\{0\} \times [0,1]$.

I implemented this model in the Visual PDE online solver, with the parameters that both their result look good and also the default solvers of this tool are stable. You can find the model here.

Initial condition for tip cell density

As we discussed in item (iii) the tip cells, after getting stimulated by TAF form small clusters. Thus we assume that the initial concentration of the tip cells are give as

$$n(x, y, 0) = e^{-x^2/\xi_3} \sin^2(3\pi y).$$

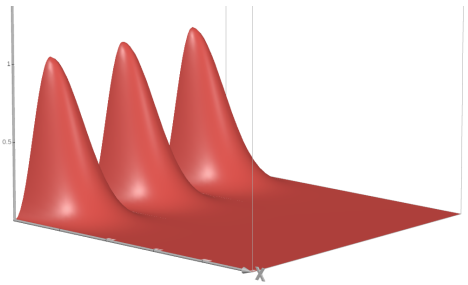


Figure 1.2.1: Tip cell initial density.

Initial condition for TAF

Assuming Equation 1.2.1 models the initial phase of the time evolution of TAF, then we can assume that the steady state of that equation is the initial condition for the phase that the angiogenesis

starts happening. Depending on the initial configuration of the tumor in the domain, Anderson und Chaplain (1998) came up with two biologically interesting initial condition.

Case 1: A column of tumor cells or larger circular implant. For this case the initial concentration of TAF will be

$$c(x, y, 0) = e^{-(1-x)^2/\xi_1}, \qquad (x, y) \in [0, 1] \times [0, 1].$$

Case 2: A small circular tumor centered at (1,1/2). In this case the initial concentration of TAF is given by (Anderson und Chaplain (1998) and they reference Chaplain (1995, 1996) for the equation)

$$c(x, y, 0) = \begin{cases} 1, & 0 \le r \le r_0, \\ \frac{(\nu - r)^2}{\nu - r_0}, & r_0 \le r \le 1, \end{cases}$$

where ν is a positive constant and r is given by

$$r = \sqrt{(x-1)^2 + (y-1/2)^2},$$

assuming that the tumor is centered at $(1, 1/2)$ with a radius of r_0. Note that ν is in fact showing the concentration right at the edge of the tumor. To make the transition between concentration c inside the tumor (i.e. $0 \le r \le r_0$) and outside the tumor (i.e. $r_0 \le r \le 1$) continuous, the value of ν should be $\boxed{\nu = r_0 + 1}$. We can see this by simply trying to force the function $c(x, y, 0)$ to be continuous. The following figure illustrates the initial concentration of TAF for $r_0 = 0.2$ (thus $\nu = 1.2$).

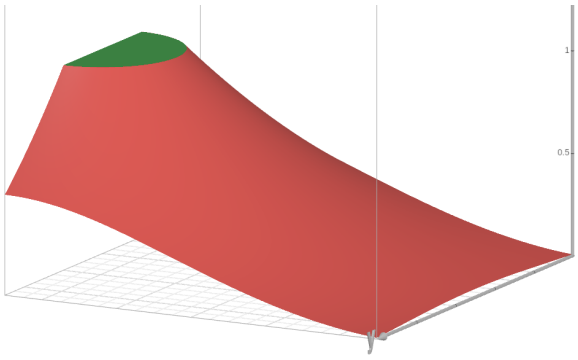


Figure 1.2.2: Initial concentration of TAF for small tumor with radius $r_0 = 0.2$ centered at $(1, 1/2)$. The green region shows the tumor inside which the concentration of TAF is assumed to be 1.

⚠ **Be Careful! — I am not sure if the formulas above are really the steady state solution of TAF PDE.** Note that the initial concentration of TAF should be the steady state of Equation 1.2.1. Anderson und Chaplain (1998) claims that the two cases above are the steady state solutions for the early stage TAF PDE. I have not checked this yet and I need to evaluate if this is really true.

Initial condition for Fibronectin

The initial condition for fibronectin has been a more phenomenological one in Anderson und Chaplain (1998). They Assumed the initial concentration of fibronectin is given by

$$f(x, y, 0) = ke^{-x^2/\xi_2}, \qquad (x, y) \in [0, 1] \times [0, 1],$$

where $0 < k < 1$ and $\xi_2 > 0$. As discussed in item (vii) this choice of initial conditions is justified up to some degree. However look at Strange observation 1.2.7 for a discussion about possible alternative approaches to find a more realistic initial condition.

1.2.7 Make it a Combo! Adding Stochastic Model to Generate Vascular Networks

1.2.8 Some Thoughts

Discrete vs. continuous model

For me, the distinction between discrete model and the continuous model discussed above is just the difference between solving a SDE (which will give us some trajectories) vs. solving the corresponding Fokker-Plank equation. However observe that, in SDE trajectories, we can measure some quantities like the number of branches, number of loops, the tortuosity, distribution of the length segments, etc. On the other hand, the corresponding Fokker-Plank equation (the advection-diffusion PDE) gives us the time evolution of the tip cell density. So the following is my question

🎓 **Open Question 1.1** Given an SDE, is it possible to write down a differential equation (like the Fokker-Plank equation) that can capture a measurement of interest? Like the time evolution of the average number of collisions between n trajectories of the SDE.

Here are some possible steps to find the answer to the question above.

Observation 1.2.1 — Steps to solve the question above. The overall theme of solving the question above is to generalize the Fokker-Plank equation of an SDE such that we can write down a similar PDE for any measurement of interest.

(I) First, try to think about the Fokker-Plank equation in this framework. I.e. try to observe what kind of measurement is the variable ρ whose time evolution is captured by the Fokker-Plank equation.

(II) Try to abstract the notion of ρ. I.e. What are the properties of ρ that help in developing the Fokker-Plank equation?

1.2.9 Important citations of this paper

- biology of the angiogenesis
  - Embryo angiogenesis Graham und Lala (1992).
  - Angiogenesis in tissue repair Arnold und West (1991); Pettet u. a. (1996).
  - Uncontrolled angiogenesis in tumors, arthritis, abnormal neovascularization of the eye, duodenal ulcers, and following myocardial infarction Folkman (1985, 1995); Folkman und Klagsbrun (1987).
  - Pathological examples of angiogenesis Muthukkaruppan u. a. (1982); Ribatti (2008).
- Angiogenic factors:
  - Several angiogenic factors like vascular endothelial growth factor (VEGF), acidic and basic fibroblast growth factor (aFGF, bFGF), angiogenin, etc has been isolated Folkman und Klagsbrun (1987); Relf u. a. (1997).

  - Endothelial cell receptors for these angiogenic factors Millauer u. a. (1993); Hatva u. a. (1995); Mandriota u. a. (1995); Fong u. a. (1995); Hewett und Murray (1996); Patterson u. a. (1996); Kappel u. a. (1999); Duh u. a. (1997); Hanahan (1997)
  - Effect of disrupting the angiogenic factors on the final structure of the capillary network Dumont u. a. (1994); Fong u. a. (1995); Sato u. a. (1995); Hanahan (1997).
- Initial response of the endothelial cells to the angiogenic factors is a chemotatic one Sholley u. a. (1984); Terranova u. a. (1985); Paweletz und Knierim (1989); Stokes u. a. (1990).
- New finger-like capillary sprout formation Cliff (1963); Warren und Shubik (1966); Ausprunk und Folkman (1977); Sholley u. a. (1984)
- New tip cells finding their way through the extracellular matrix Liotta u. a. (1983); Paweletz und Knierim (1989).

1.3 Idea Bin!

This section might have very simple, basic and sometimes silly ideas that came into my mind during developing some models and I thought they might worth trying

- Developing a model for a weighted graph generation. I suspect a weighted graph might have all the necessary information we want.

Chapter 2

A Theoretical Investigation

In this chapter I will be trying to appropriately formalize the problem in hand while being very careful about the hidden structures in the problem.

2.1 The Set of All Vascular Structures. Is That a Manifold?

I start with my formal definition of a valid vascular structure.

Definition 2.1 Consider $\Omega = [0,1] \times [0,1]$ as a closed subset of $\mathbb{R}^2$. A valid vasculature, is a network in the domain, where there is at least one path that starts from $\{0\} \times (0,1)$ and reaches $\{1\} \times (0,1)$.

■ **Remark** The definition above needs to further formalized. For instance, what is a network? if I mean a graph theoretical concept, then I need to formally define it.

Let $\mathcal{N}$ denote the set of all valid vascular systems. Introducing the notion of the set of all valid vascular structures, if we have no information about the topology or algebraic properties of that set is no more useful than re-naming an object.

We can consider a particular vascular system as a mapping $s : \Omega \to \mathbb{R}$, where a given vascular network will be just a domain coloring of the map s. Then the set of all vascular systems $\mathcal{N}$ will be the same as the function space of all functions mapping Ω to $\mathbb{R}$. This set is far too complex than being useful. So I will follow an alternative approach.We will use the notion of graphs to represent a particular vascular system.

Observation 2.1.1 — Vascular System as a Graph. A weighted multi graph (where we allow to have multiple weights on an edge, and also allow assigning weights to nodes) can capture any necessary information of a vascular system that determines the flow of blood through it. For instance, we can have the following correspondence between a given vascular system and a multi graph.

- Denoting the branching points as nodes.
- Denoting the vessel segments as edges.
- Assigning a weight $w \in \mathbb{R}^n$ to each edge, where n is the number of important characters of the vessel segment that affects the dynamic of blood flow. These weights can be the length of segment, the radius of segment, etc.

- Assigning a weight to $v \in \mathbb{R}^m$ to each node, where m is the number of important parameters at each node affecting the fluid dynamics of blood in the vessels. For instance, the hematocrit splitting ration depends on the number of branches in a given node (which is reflected by the degree of a given node), and also the angle between branches. The angle between branches, etc can all be considered in the weight assigned to each node.

The observation above is just a general blue print. We can obviously make some simplifications and reduce the number of weights at each edge.

Observation 2.1.2 — The Set of All Vascular Systems is a Manifold. For now, let's consider that for each vessel segment we assign one weight that can be the radius of the vessel segment, or a combination of parameters, like flow as given by the Poiseuille's law. For each node we assign no weights (for instance we assume that the hematicrit splitting is not significant). Then we can identify each vascular network with an adjacency matrix of the associated graph. Thus the set of all vascular systems with n nodes will be the same as the set of all $n \times n$ matrices.

Proposition 2.1 The set of all $n \times n$ matrices topologized with the subspace topology of $\mathbb{R}^{n \times n}$, is a smooth manifold.

Thus the set of all vascular systems with n nodes is a smooth manifold.

■ **Remark** In the observation box above we stated that the set of all manifolds with n nodes is a the same as the set of all $n \times n$ matrices. But can we have any statements about the set of all vascular structures with any number of nodes? For this case I think I need to design a graded structures (as in the case of graded algebra) that can capture the whole set of all vascular structures.

Intuitively, we tend to identify the vascular systems that have the same total flow across the network. To put this in a useful theoretical ground we have the following observation box.

Observation 2.1.3 — Vascular Systems Identification Based on the Total Flow in the Network. Let $\mathcal{N}_n$ denote the set of all vascular networks that has n nodes. Define the map

$$F : \mathcal{N}_n \to \mathbb{R}$$

which is the total flow of the network. Then we define the following equivalence relation. For $x, y \in \mathcal{N}_n$

$$x \sim y \quad \Leftrightarrow \quad x, y \text{ are on the same level set of } F \ .$$

As we will see later, this map is very important and can be computed by considering the rheology of blood and the geometry of the network. The observation box below shows that any intervention induces a vector field on the manifold $\mathcal{N}$ and as we will see later, the interplay between this vector field and the gradient of the map F turns out to be very important.

Observation 2.1.4 — Any Intervention Induces a Vector Field on $\mathcal{F}$. First, I need to mention that since I have not yet developed a graded structure to handle different vascular systems with different total number of nodes as a graded manifold (or some similar construct) I will assume that the interventions do not change the number of nodes. But this is just a bureaucracy and I will resolve it as soon as I develop rich structures.

Every intervention induces a vector field on the manifold $\mathcal{N}$ denoted by $\mathcal{I}$. So the time evolution of a given vascular system due to particular intervention (like radiotherapy or chemotherapy) will be given be a one-parameter group of diffeomorphisms of $\mathcal{N}$. In other words, the time

evolution of a given vascular system $p \in \mathcal{N}$ will be the integral curve of $\mathcal{I}$ starting at p.

■ **Remark** According to the remark above, we can model the angiogenesis process as a background vector field on the space of all vascular systems. Any other background biological mechanisms can also be lumped in this vector field. We denote this vector field as $\mathcal{G}$.

🎓 **Open Question 2.1 — How to Determine These Vector Fields?.** Our ultimate goal in this project is to determine the mapping F as well as the intervention vector field $\mathcal{I}_i$, along with any background vector field $\mathcal{G}$. Denote the intervention and the background vector fields as

$$\mathcal{I} = \mathcal{I}_i + \mathcal{G}.$$

I am still thinking actively how my modeling attempts (like agent based model, or the PDE model) manifest themselves in this general framework? How these models can ultimately help to determine these vector fields, at least locally.

🎓 **Open Question 2.2 — Can a Machine Learning System Learn These Vector Fields?.** One possible parallel approach to determine these vector fields is to use appropriate machine learning system along with a suitable simulator the learn these vector fields.

Observation 2.1.5 — Effectiveness of the Intervention is the Lie Derivative of ∇F with respect to $\mathcal{I}$. Formalizing the problem in the structure above is useful from many points of view and can be a unifying theme.

For instance, let $F : \mathcal{N} \to \mathbb{R}$ denote the total flow mapping and $\mathcal{I}$ be the induced vector field due to intervention (and possibly plus any background process like angiogenesis). Then if $\mathcal{I}$ align with ∇F we will have the maximum effect due to therapy, and if $\mathcal{I}$ gets perpendicular to ∇F we will have no effect (i.e. the intervention will have no effect on the flow). Thus we can introduce a notion of effectiveness of intervention which is the Lie derivative of ∇F with respect to $\mathcal{I}$. In other words

$$E = \mathcal{L}_{\mathcal{I}} \nabla F = [\mathcal{I}, \nabla F].$$

Alternatively, we can define other measures. For instance, assuming that the manifold $\mathcal{N}$ is a Riemannian manifold, hence we have the notion of inner product at a given tangent space, we can define

$$E = \langle \mathcal{I}, \nabla F \rangle.$$

2.2 Statistical Properties of Vascular System

For me, the phenomena of angiogenesis if very similar to the phenomena of percolation. I am not claiming that it is the same phenomena, but I am emphasizing the similarities. For instance, some fluid is percolating, then instead of a uniform flow of fluid through the porous media, individual channels form (I think due to the surface tension of water, the water molecules tend to follow the pre-existing water channels rather than making a new one through wetting the surface).

Observation 2.2.1 — Homogenization and Darcy's Law. I think at some step, I would need to consider percolation models and their statistical signatures to see if I can use somewhat modified versions of that. After making this connection. I can apply the idea of homogenization and

possibly Darcy's law suggested by Leah.

Chapter 3

Papers Reviewed

In this section I will keep the notes of the papers I have reviewed, or reproduced their results.

Paper Summary

Title: Topological data analysis distinguishes parameter regimes in the Anderson-Chaplain model of angiogenesis
Author(s): Nardini, Byrne
Published: 2021-PLOS CB

3.1.1 Introduction

This paper studies the Anderson Chaplain Anderson und Chaplain (1998) model of angiogenesis and partitions the parameter spaces based on the morphology of the vascular structure generated by the model. In other words, let $P = R^d$ be the parameter space of the model, M the space of all possible morphology for the vascular networks. Also, define the equivalence relation $\sim$ defined on the parameter space P to be

$$\text{for } p_1, p_2 \in P \text{ we have } p_1 \sim p_2 \qquad iff \qquad \mathcal{A}(p_1) \equiv \mathcal{A}(p_2),$$

where $\mathcal{A} : P \to M$ a mapping from the parameter space to the morphology space. The $\equiv$ is yet another equivalence relation defined on the morphology space M where for $m_1, m_2 \in M$ we write $m_1 \equiv m_2$ if and only if m_1 and m_2 has the same topological characterization. These topological characterizations are computed using the topological data analysis techniques.

3.1.2 Method

Chaplain-Anderson model of angiogenesis used in this paper keeps track of the spatio-temporal evolution of three variables: endothelial tip cells, tumor angiogenesis factor, and fibronectin.

Topological data analysis: Two filtration methods were used: sweeping plane method, and flooding filtration. The filtration is performed on the binary images generated with the Chaplain-Anderson model.

3.1.3 Useful facts

- The growth factors the cancer cells release when under low nutritient and oxygen: vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and basic fibroblast growth factor (bFGF).

3.1.4 Points that are not clear yet

(a) In the introduction, the authors claim that "The morphology of a vascular network can reveal the presence of an underlying disease, or predict the response of a patient to treatment", without any citation of explanation. I think this needs more discussion.

3.1.5 Useful papers cited

- Papers related to biology of the tumor induced angiogenesis Gupta und Qin (2003); Folkman (1971).
- More modern descriptions of the angiogenesis Lugano u. a. (2020); Saman u. a. (2020)
- The role of the mechanical stress on the angiogenesis Li und Harris (2005); Li u. a. (2002); Vavourakis u. a. (2017)
- Some old and classic models for the angiogenesis Anderson und Chaplain (1998); Balding und McElwain (1985); Byrne und Chaplain (1995a); Stokes und Lauffenburger (1991).
- More detailed theoretical models for angiogenesis Byrne (2010); Hadjicharalambous u. a. (2021); Metzcar u. a. (2019); Scianna u. a. (2013).
- Alternative models of angiogenesis Vilanova u. a. (2017); Stepanova u. a. (2021); Perfahl u. a. (2017); Grogan u. a. (2017); Vavourakis u. a. (2017); Cai u. a. (2017); Sefidgar u. a. (2015)
- Statistical and single scale methods to quantify the vascular networks Perfahl u. a. (2017); Folarin u. a. (2010); Kannan u. a. (2018); Konerding u. a. (1999, 2001)
- Biological angiogenesis experiments Bauer u. a. (2007b)

Paper Summary

Title: Quantitative Angiogenesis Assays in vivo – A Review
Author(s): J. Hasan
Published: 2004, Angiogenesis

This paper discusses various angiogenesis assays, highlighting the corneal micropocket and the CAM assay as established methods. It emphasizes the importance of selecting complimentary assays to best replicate tumor angiogenesis for studying the effects of pro- or anti-angiogenic compounds. The development of non-invasive techniques for quantifying angiogenesis is highlighted as a significant advancement for the field Hasan u. a. (2004)

Paper Summary

Title: Characterization of lymphocyte-dependent angiogenesis using a SCID mouse: human skin model of psoriasis
Author(s): B. Nickoloff
Published: 2000, The journal of investigative dermatology

This review updates the understanding of angiogenesis in psoriasis, integrating the characterization of endothelial cells in plaques and discussing a novel animal model for triggering neovascularization and plaque formation, providing insights into the angiogenic process in skin disorders Nickoloff (2000)

Paper Summary

Title: Integration of experimental and computational approaches to sprouting angiogenesis
Author(s): S. Peirce
Published: 2012, Current Opinion in Hematology

This paper summarizes the integration of experimental tools and computational modeling in studying sprouting angiogenesis, showcasing how such interdisciplinary approaches can lead to new understandings and therapeutic targets by accounting for molecular data and cell-level behaviors Peirce u. a. (2012)

Paper Summary

Title: Mathematical models of developmental vascular remodelling: A review
Author(s): Jessica R. Crawshaw
Published: 2023, PLOS Computational Biology

Focusing on the less-explored area of developmental remodeling of vascular networks, this review discusses mathematical models that have contributed to understanding the transformation of primitive vessel networks into functional ones, highlighting the multiscale nature of this problem Crawshaw u. a. (2023)

Paper Summary

Title: Assessment Methods of Angiogenesis and Present Approaches for Its Quantification
Author(s): G. J. Khan
Published: 2014, Cancer Research

This paper provides an overview of angiogenesis assessment methods, including in vitro, in vivo, and in ovo models, focusing on the calculation modes and considerations necessary for concluding the angiogenic or antiangiogenic properties of agentsKhan u. a. (2014)

Paper Summary

Title: Endogenous inhibitors of angiogenesis.
Author(s): P. Nyberg, et. al.
Published: 2005, Cancer research

Highlighting the balance between proangiogenic and antiangiogenic factors, this review explores the role of endogenous inhibitors in the body, providing insight into the potential of leveraging these natural inhibitors for therapeutic purposes in cancer treatment Nyberg u. a. (2005)

Paper Summary

Title: Mathematical Models of Avascular Tumor Growth
Author(s): T. Roose, et. al.
Published: 2007, SIAM Rev

Offering a comprehensive list and discussion of models for avascular tumor growth, this review emphasizes the importance of mathematical modeling in understanding tumor development and outlines potential future directions for research in this area Roose u. a. (2007)

Paper Summary

Title: Mathematical Modelling of Angiogenesis
Author(s): Chaplain
Published: 2000, Journal of Neuro-Oncology

Discusses a variety of mathematical models used to describe capillary network formation, focusing on a model that generates 2D and 3D vascular structures. This model incorporates the migratory response of endothelial cells to tumor angiogenic factors, cell proliferation, and interactions with extracellular matrix macromolecules, among other factors Chaplain (2000)

Paper Summary

Title: Computational and Mathematical Modeling of Angiogenesis
Author(s): S. Peirce
Published: 2008, Microcirculation

Reviews mathematical and computational models developed over two decades to study various aspects of angiogenesis. This work emphasizes the insights gained from these models in normal physiological growth, tumorigenesis, wound healing, and therapeutic strategy design Peirce (2008)

Paper Summary

Title: Mathematical modelling of angiogenesis using continuous cell-based models
Author(s): F. D. Bookholt, et. al
Published: 2016, Biomechanics and Modeling in Mechanobiology

By Bookholt et al. (2016) introduces a 3D in vitro model simulating early stages of angiogenesis. The model addresses endothelial cell migration due to chemotaxis and durotaxis and includes various proteins impacting angiogenesis Bookholt u. a. (2016)

Paper Summary

Title: Mathematical modelling of dynamic adaptive tumour-induced angiogenesis: clinical implications and therapeutic targeting strategies
Author(s): S. McDougall, et. al.
Published: 2006, Journal of theoretical biology

Presents a model that couples vessel growth with blood flow, offering insights into the adaptive and dynamic nature of tumor-induced angiogenesis and identifying new therapeutic targets for tumor management McDougall u. a. (2006)

Paper Summary

Title: Angiogenesis—Understanding the Mathematical Challenge
Author(s): Pamela F Jones
Published: 2006, Angiogenesis

Explains the mathematical modelling strategy in biological terms, aiming to bridge the gap between mathematics and life sciences. The paper discusses the assumptions and simplifications foundational to modeling and their implications for understanding angiogenesis Jones und Sleeman (2006)

Paper Summary

Title: On the mathematical modeling of wound healing angiogenesis in skin as a reaction-transport process
Author(s): Samik Ghosh
Published: 2015, Frontiers in Physiology

Provides a comprehensive review of mathematical models of angiogenesis in skin wound healing. It introduces the continuum reaction-transport framework as a useful tool for exploring unresolved questions in angiogenesis research Ghosh u. a. (2015)

Paper Summary

Title: Multiscale Agent-based Model of Tumor Angiogenesis
Author(s): Megan M, et. al.
Published: 2013

Olsen and Siegelmann (2013) developed a three-dimensional multiscale ABM focusing on breast cancer. The model encompasses cellular (genetic control), tissue (cells, blood vessels, angiogenesis), and molecular (VEGF, diffusion) levels. A novel discrete approach to model angiogenesis is proposed to decrease computational cost, offering potential new directions for modeling in cancer research Olsen und Siegelmann (2013)

Paper Summary

Title: Simulating cancer growth with multiscale agent-based modeling.
Author(s): Zhihui Wang, et. al.
Published: 2015, Seminars in cancer biology

Discusses the utility of ABMs in simulating diverse cancer behaviors, including tumor morphology, adaptation to the microenvironment, angiogenesis, and response to therapies. The review highlights the capability of ABMs to simulate the complex interplay between tumor cells and their microenvironment, paving the way for new therapeutic insights Wang u. a. (2015)

Paper Summary

Title: Agent-based model of angiogenesis simulates capillary sprout initiation in multicellular networks.
Author(s): Joseph Walpole, et. al.
Published: 2015, Integrative biology

Presents an ABM that incorporates both stochastic and deterministic rules to simulate the initiation of sprouting angiogenesis. The model accurately simulates sprout initiation frequency and location, offering a deeper understanding of the balance between stochasticity and determinism in biological processes Walpole u. a. (2015)

Paper Summary

Title: Agent-Based Modeling of Vascularization in Gradient Tissue Engineering Constructs
Author(s): E. S. Bayarak, et. al.
Published: 2015, IFAC-PapersOnLine

Develops an ABM to simulate vascular growth in engineered biomaterials, investigating the influence of growth factor release rate on angiogenesis. The model's results, validated against experimental studies, suggest microsphere properties that promote angiogenesis, offering insights into tissue engineering applications Bayrak u. a. (2015)

Paper Summary

Title: A cell-based model exhibiting branching and anastomosis during tumor-induced angiogenesis.
Author(s): A. Bauer, et. al.
Published: 2007, Biophysical journal

Describes a cell-based ABM that integrates endothelial cell migration, growth, division, and the evolving structure of the stroma at the cellular Potts model level. The model successfully reproduces various morphologies of capillary sprouts observed in vivo, demonstrating the emergence of branching and anastomosis without prescribed rules Bauer u. a. (2007a)

Paper Summary

Title: Coupled mathematical model of tumorigenesis and angiogenesis in vascular tumours
Author(s): M. Cooper, et. al.
Published: 2010, Cell Proliferation

Developed a model that combines the processes of avascular tumor growth and the development of capillary networks through tumor-induced angiogenesis. This comprehensive model offers insights into the growth and development mechanisms of vascular tumors Cooper u. a. (2010)

Paper Summary

Title: Tree topology analysis of the arterial system model
Author(s): V. Kopylov
Published: 2018, Journal of Physics

Presented an algorithm for constructing an arterial system model with physiologically significant geometric properties. Their analysis of the bifurcation exponent's effect on the arterial network's topology provides valuable insights into the optimal network topology for efficient vascular function Kopylova u. a. (2018)

Paper Summary

Title: Mathematical Model of Blood Flow in an Anatomically Detailed Arterial Network of the Arm
Author(s): Sansuke M, el. al.
Published: 2013, Mathematical Modelling and Numerical Analysis

Watanabe, Blanco, and Feijóo (2013) developed a detailed model for hemodynamics simulations in the arm's arterial network. Their model includes a comprehensive arterial topology and offers a systematic estimation of involved parameters, allowing for accurate simulations of blood flow and pressure Watanabe u. a. (2013)

Paper Summary

Title: An integrated approach to quantitative modelling in angiogenesis research
Author(s): A. J. Connor, et. al.
Published: 2015, Journal of The Royal Society Interface

Discusses a multidisciplinary approach combining experiments, image processing, analysis, and mathematical modeling focused on angiogenesis in the cornea micropocket assay. This approach aims to provide mechanistic insights into the action of angiogenic factors through quantitative data extraction and model parametrization Connor u. a. (2015)

Paper Summary

Title: Integration of experimental and computational approaches to sprouting angiogenesis
Author(s): S. Peirce, et. al.
Published: 2012, Current Opinion in Hematology

Peirce et al. (2012) summarize recent advancements in computational modeling of angiogenesis, driven by detailed molecular data and experimental tools. These models help predict hypothetical experiment outcomes and generate new hypotheses for understanding angiogenesis at a system-wide level Peirce u. a. (2012)

Paper Summary

Title: A Computational Tool for Quantitative Analysis of Vascular Networks
Author(s): E. Zudaire, et. al.
Published: 2011, PLoS ONE

developed AngioTool, a user-friendly software for the quantification of vascular networks in microscopic images. AngioTool computes several morphological and spatial parameters and is open source, available for free download, facilitating standardized analysis in angiogenesis research Zudaire u. a. (2011)

Paper Summary

Title: Consensus guidelines for the use and interpretation of angiogenesis assays
Author(s): Many authors
Published: 2018, Angiogenesis

Published the first edition of consensus guidelines for the use and interpretation of angiogenesis assays. This collaborative work aims to serve as a reference for current and future angiogenesis research, promoting standardized methodologies across the field Nowak-Sliwinska u. a. (2018)

Paper Summary

Title: Zebrafish as an Emerging Model Organism to Study Angiogenesis in Development and Regeneration
Author(s): Myra N Chávez, et. al.
Published: 2016, Front Physiol

Focuses on the zebrafish (Danio rerio) as an emerging model organism for studying angiogenesis in development and regeneration, highlighting its potential for understanding vascularization in artificial tissues and organs, as well as for drug discovery Chávez u. a. (2016)

Chapter 4

Molecular Biology

Here in this chapter, I will be covering the basics of the relevant molecular biology concepts. This chapter will serve as a reference for the biological claims throughout the document, as well as the foundation for the review chapters of my thesis.

4.1 Molecular Mechanism of Angiogenesis

Blood vessels and the vascular structure are formed by the differentiation of the cells in the mesoderm layer during the embryo development (the layer which also give rise to blood cells, kidney, liver, connective tissue, etc.) Alberts u. a. (2002a).

4.1.1 A Brief Anatomy of Vessels

Endothelial cells line all of the vessels. Blood vessels (like the arteries and the veins that are the largest vessels of the body) have a thick and tough wall of connective tissue with several layers of smooth muscles. The wall is lined by a very thin layer of endothelial cells (i.e. the endothelium) separated from the outer surrounding layers by basal lamina Alberts u. a. (2002a). It is worth noting that the amount of connective tissue and smooth muscle depends on the diameter of the blood vessel as well as its function, **but the endothelial lining is always present**. In the finest branches of the vasculature (i.e. capillaries and sinusoids) the wall is just made up of endothelial cells and basal lamina. One of the major roles of the endothelial cells is to control to transport of material in an out of the bloodstream.

A study of embryo development reveals that the even larger vessels (like arteries and veins) start developing from smaller vessels that has only endothelial cells and basal lamina. The connective tissue, smooth muscles and pericytes are added later on, by the signaling from endothelial cells. In particular, the recruitment of pericytes are driven by PDGF (platelet driven growth factor) secreted by the endothelial cells.

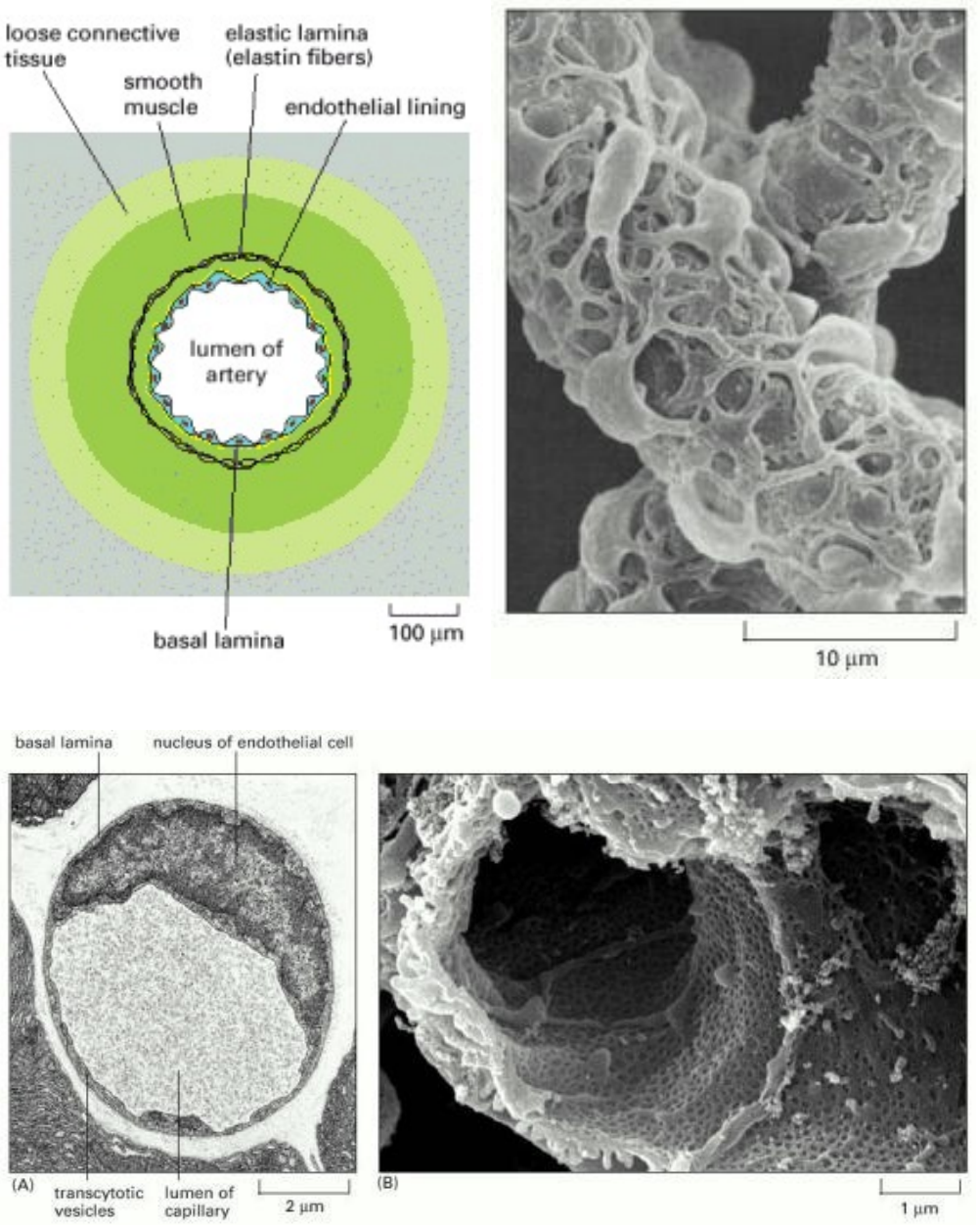


Figure 4.1.1: **Figure Top Left:** This figure shows the anatomy of a large vessel, like vein or arteries. Note that smaller vessels, like capillaries as well as sinusoids consists of only endothelial cells and basal lamina, except for some scattered pericytes wrapped around the walls (see figure Top Left). **Figure Top Right:** Electron micro graph showing small pericytes wrapped around small blood vessels. **Figure Bottom Left:** A capillary that its wall consists of only endothelial cell and basal lamina. **Figure Bottom Right:** Electron micro graph showing a cross section of small capillary in pancreas. All of the figures are from Alberts u. a. (2002a)

Also, the following figure summarizes the cross section of different types of vasculature.

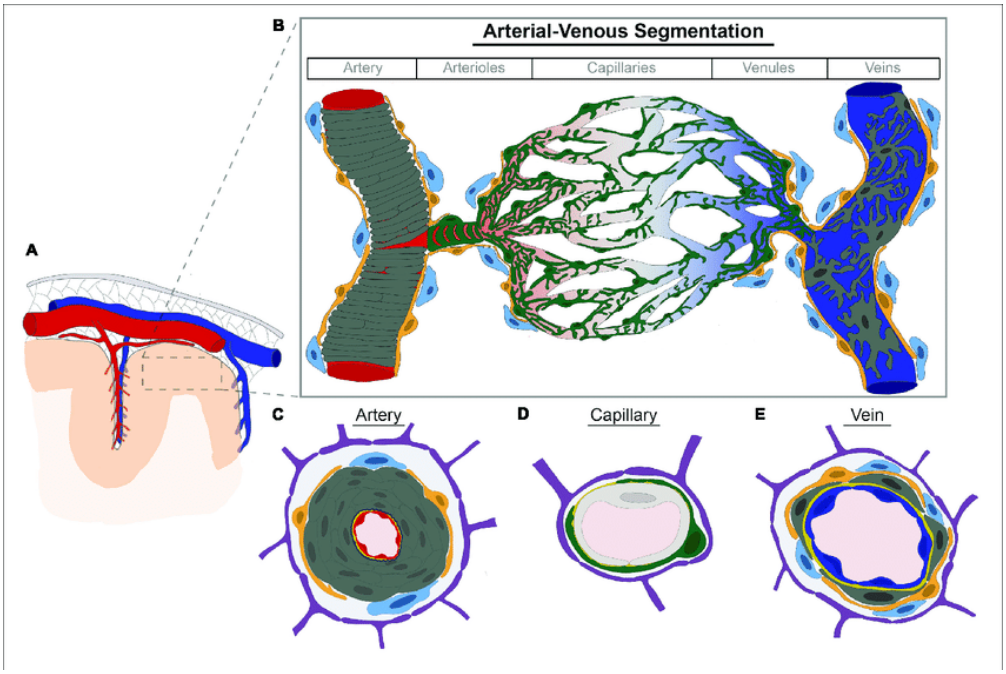


Figure 4.1.2: The cross section of vessels in the form of arteries, capillaries, and vein. Note the single lining of the endothelial cells for the capillary.

4.1.2 Molecular Biology of Vascular Structure

New vessels in the adults originate as capillaries, which sprout from the existing small vessels. Endothelial cells on the arterial and venous side of the developing networks of vessels differ in their surface properties. In the embryo at least, the plasma membrane of the arterial cells contains trans membrane protein ephrine-B2, while the membrane of the venous cells contain the corresponding receptor protein Eph-B4, which is a receptor tyrosine kinase. These molecules mediate a signal delivered at sites of cell-cell contact, and they are essential for the development of a properly organized network of vessels. One suggestion is that they somehow define the rules for joining one piece of growing capillary tube to another Alberts u. a. (2002a).

Observation 4.1.1 The difference in the surface properties of endothelial cells on the arterial and venous side of the developing networks of vessels control the rate an which one piece of growing capillary tube joins another. This becomes very interesting if we consider it along the observations in Köry u. a. (2024). They observed that the blunt-ended capillaries with small diameter are more susceptible for degradation after irradiation. And since the presence of blunt-ended vessels with small diameter increase the flow resistance of the network, pruning these branches “normalizes” the blood flow, hence increase the perfusion after irradiation.

Steps involved in angiogenesis

Individual endothelial cells responds to the signals produced by the organ that they invade. The signal is complex, but the main part of the signal is vascular endothelial growth factor (**VEGF**) (which is a distant relative of platelet driven growth factor (**PDGF**)). The control on the production of VEGF is through its mRNA stability and its rate of transcription. Under a low oxygen concentration, the intracellular concentration of an active form of gene regulatory protein called

hypoxia inducible factor 1 (HIF-1) increases. HIF-1 stimulates the transcription of VEGF gene (and the production of other genes that are needed when the oxygen supply is low). When the VEGF protein is secreted, it is then diffuses through the tissue and acts on nearby endothelial cells.

Endothelial cells that are to form a new capillary, grow out from the side of an existing capillary by forming long pseudopodia pioneering the formation of new capillary sprout that hallows out to form a tube. This process continues until the sprout encounters another capillary, where they merge. In the tumor micro environment, The growth rate of tumor increases abruptly as soon as the vessels reach it.

There are two general balancing forces acting on the angiogenesis

- Inhibitors:
  - endostatin
  - angiostatin
  - thrombospondin
- Angiogens
  - VEGF: Vascular Endothelial Growth Factors.
  - bFGF: Basic Fibroblast Growth Factor.
  - PDGF: Platelet Driven Growth Factor.

The Response of Endothelial Cells to VEGF

The response of endothelial cells to VEGF has four components. First, they produce proteases to digest through the basal lamina of the parent vessels. For the second step, they migrate towards the source of VEGF, and for the third step they proliferate. Finally, they form hallow tubes. It is worth mentioning that VEGF stimulates endothelial cells selectively, while other angiogens, like fibroblast growth factor stimulates other cell types as well. The following figure summarizes these steps.

Controlling Capillary Joining Process

In the following text from Alberts u. a. (2002a), there is some vague hints about the mechanisms that are controlling capillary joining to each other

> Observations such as these reveal that endothelial cells that are to form a new capillary grow out from the side of an existing capillary or small venule by extending long pseudopodia, pioneering the formation of a capillary sprout that hollows out to form a tube (Figure 22-25). This process continues until the sprout encounters another capillary, with which it connects, allowing blood to circulate. Endothelial cells on the arterial and venous sides of the developing network of vessels differ in their surface properties, in the embryo at least: the plasma membranes of the arterial cells contain the transmembrane protein ephrin-B2 (see Chapter 15), while the membranes of the venous cells contain the corresponding receptor protein, Eph-B4, which is a receptor tyrosine kinase (discussed in Chapter 15). These molecules mediate a signal delivered at sites of cell-cell contact, and they are essential for the development of a properly organized network of vessels. One suggestion is that they somehow define the rules for joining one piece of growing capillary tube to another.

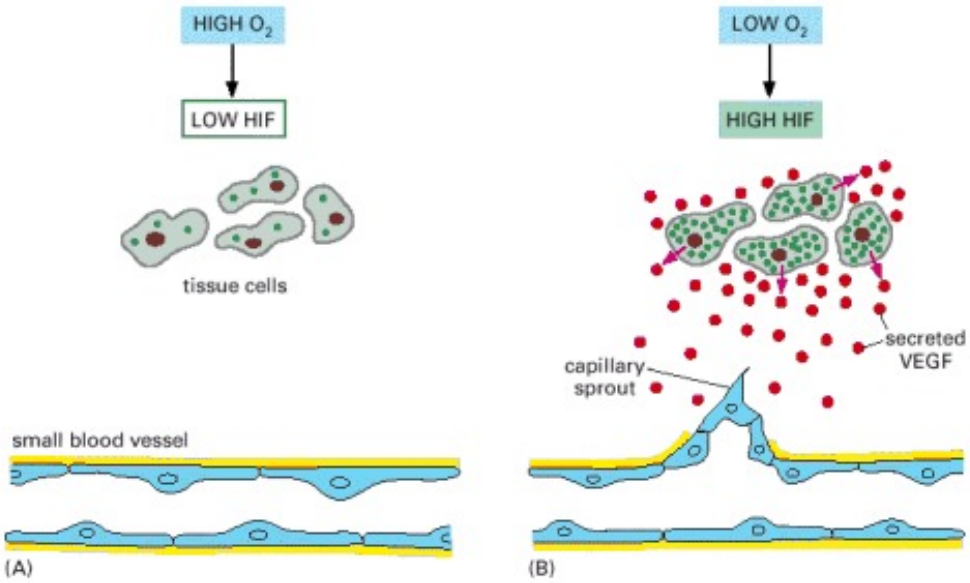


Figure 4.1.3: A summary of the response of the endothelial cells to VEGF. Under low oxygen concentration, the intracellular concentration of HIF-1 increases. This gene regulatory protein in turn increases the transcription of VEGF protein. Then VEGF diffuses through the tissue and stimulates the endothelial cells lining the vessels. Figure is from Alberts u. a. (2002a).

Formation of tube structures by endothelial cells

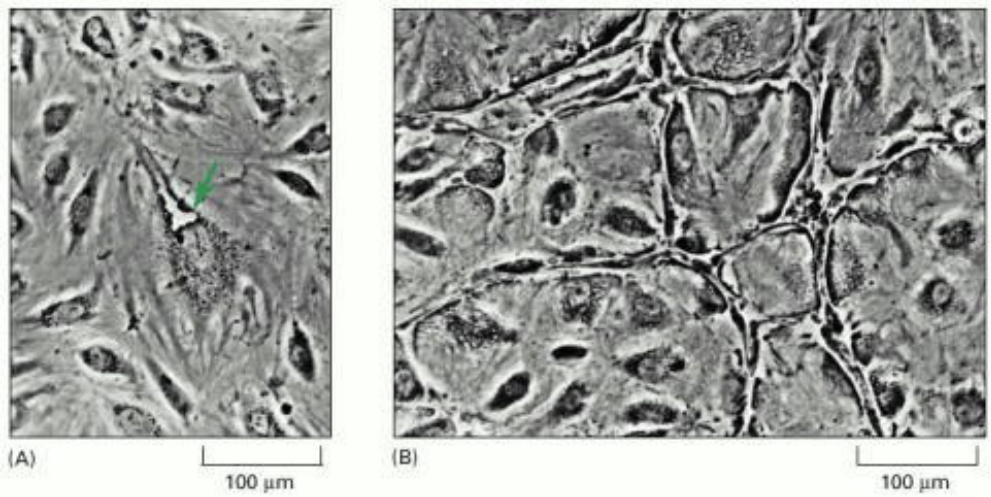


Figure 4.1.4: The endothelial cells, when supported by suitable growth medium and signals, start to form hallow structure, that do not contain any blood, and not fluid passes through them. This indicates that the no mechanical trigger (i.e. pressure) is required to form the hallow structure for the new vessels. Image from Alberts u. a. (2002a).

It was one of my main concerns that what is the process in which a single lining of endothelial cells following a tip cell forms a hallow tube (i.e. vessel). The following text from Alberts u. a. (2002a) explains this clearly. This process has also been described in angiogenesisYoutube.

Experiments in culture show that endothelial cells in a medium containing suitable growth factors will spontaneously form capillary tubes, even if they are isolated from all other types of cells (Figure 22-26). The capillary tubes that develop do not contain blood, and nothing travels through them, indicating that blood flow and pressure are not required for the initiation of a new capillary network. Endothelial cells in culture spontaneously develop internal vacuoles that appear to join up from cell to cell, giving rise to a network of capillary tubes. These photographs show successive stages in the process.

4.2 Biological Assays to Study Angiogenesis

4.2.1 Corneal Micropocket Assay

This is one of the simple and reproducible assays to study angiogenesis in a eye. The process involves introducing growth factors in the eye ball of mouse, and then letting the vascular network to form. This is a video from JOVE explaining the details of the protocol (conealMicroPocketAssayJOVE)

4.3 Some Histology

In short, histology is the study of the animal tissue in the microscopic scale (which is also known as the microscopic anatomy or micro anatomy). Studying different types of animal tissue falls in the realm of histology.
There are four types of animal tissue

(i) Epithelium
- squamous: endothelial lining of the vascular structure is of this type.
- cuboidal
- columnar

(ii) Muscle tissue
- smooth muscle
- skeletal muscle
- cardiac muscle

(iii) Connective tissue
- cartilage
- bone
- blood
- lymph
- hemopoietic

(iv) Nervous tissue
- central nervous system
- peripheral nervous system

Among this list of the four basic types of the animal tissue, we will focus on the Epithelium.

4.3.1 Epithelium

Epithelium forms continuous sheets of cells that line internal surfaces and cover the external surfaces of the organs. A **basement membrane** separates an epithelium from the underlying connective tissue.

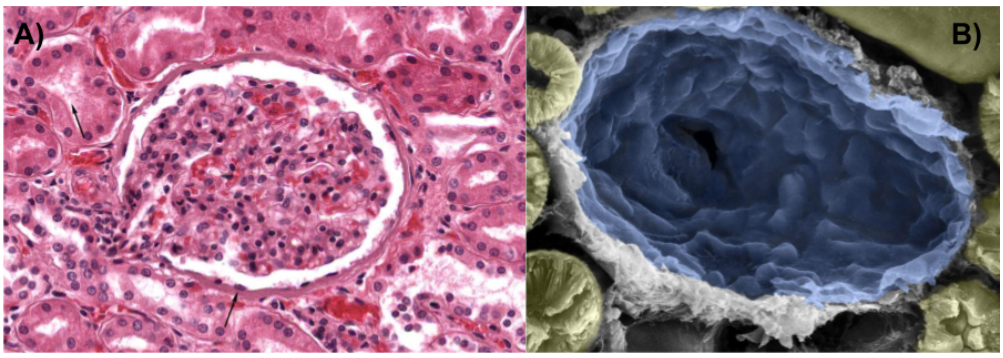


Figure 4.3.1: A) A microscopic image of renal corpuscle that contains a glomerulus (a tuft of capillaries) surrounded by Bowman's capsule. The interior of the capsule, is lined with a simple squamous epithelial that rests on a thick basement membrane. The only part of these cell visible is their nuclei bulging into the interior. B) Scanning electron microscope of renal corpuscle that its glomerulus is removed. The simple squamous epithelial can be seen in blue (borders of individual cells are not visible). Both images are from histologyguide.com.

Figure 4.3.2: A pathology image of bile duct (the large lumen at the center). There are many blood vessels in the surrounding connective tissue. Blood vessels are lined with simple squamous epithelial. The only par of these cells visible is their flatten nuclei. **Epithelium that lines blood vessels, heart, and lymphatic vessels is also known as endothelium.**

Chapter 5

Some Notes on Mathematical Modeling

These are the steps for mathematical modeling that I have gathered by thinking deep and observing what is happening around me. How my supervisors attack a problem, what is the thought process of professor X in dealing with a problem at one glance, what are the concerns about a specific type of problem (like Stock's problem in PDE theory which is a saddle-node type problem), and what are the main tools to address that problem. These steps in modeling a phenomena mathematically gives me a sense of orientation in a busy world full of new things. This section will be developed overtime, and at some point it can be a chapter of my thesis.

Summary 5.1 The primary purpose of these notes is to locate the stage of any ongoing project. Also, I will do my best to prepare a kind of checklist for each step that can be used to evaluate the progress of the sub-steps of the project.

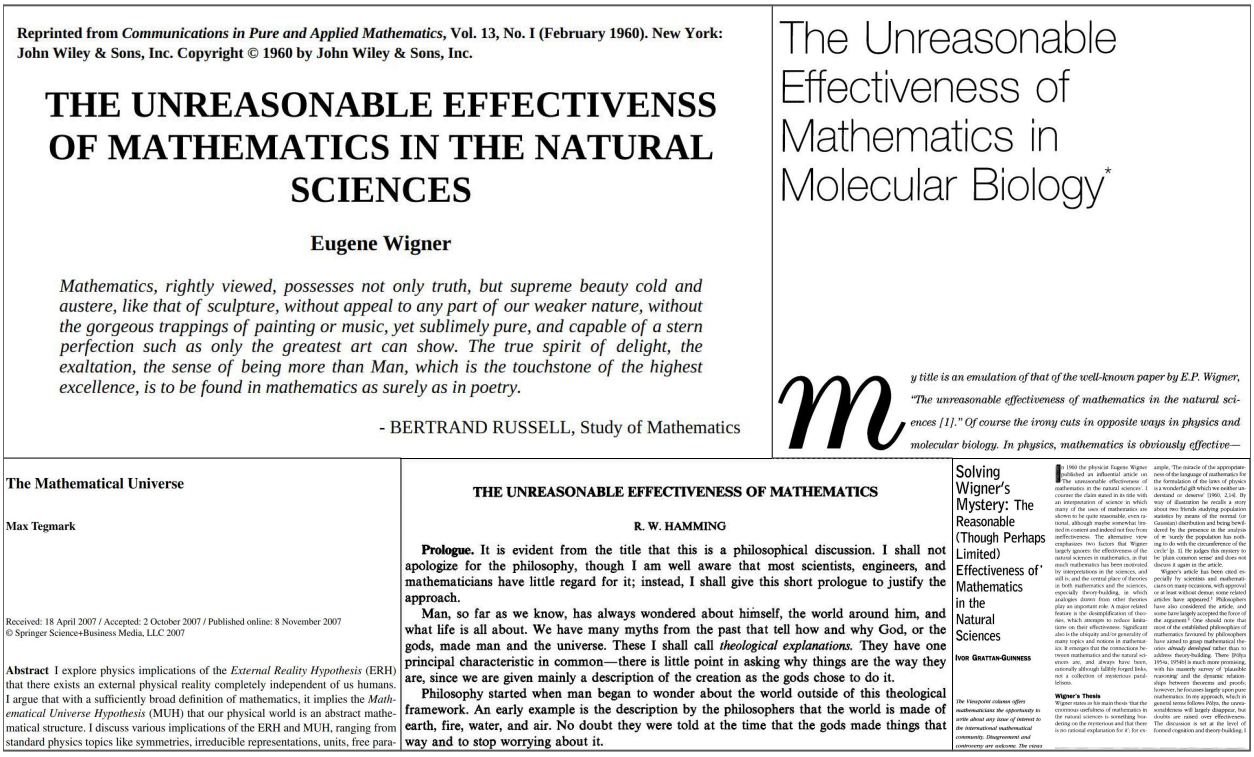
5.1 STEP 0: Understanding the phenomena we want to study

5.2 STEP I: Converting Natural Phenomena to a Mathematical Problem

This step is one of the steps that looks very strange for me. Early from calculus courses and elementary ODE, PDE courses, we can see phrase like "this Dirichlet boundary condition along with an elliptic PDE models a rod that its two ends are covered with ice at temperature 0", or "This saddle-point problem named Stokes problem models a non-compressible fluid". But they never talk about why this is true, and even how this is possible? Why a bunch of numbers and functions should mimic a very complex phenomena?

There are some very interesting papers written to explain why the mathematics is so effective in modeling the natural world (see Figure 5.2.1). In my opinion, this step, although innocent looking, is a totally non-trivial step. Because the nature is what it is, and the fact that some abstract notions and objects can mimic those natural phenomena with nuance details (like the things that happens in bifurcation) is very strange.

At this step, we need to first **identify the questions** that we want to answer. This is the most important step that affects all of the subsequence analysis. We need to ask ourselves **to what level of accuracy** we want our answer? **To what level of generality** we want our answer be?



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THE UNREASONABLE EFFECTIVENSS OF MATHEMATICS IN THE NATURAL SCIENCES

Eugene Wigner

Mathematics, rightly viewed, possesses not only truth, but supreme beauty cold and austere, like that of sculpture, without appeal to any part of our weaker nature, without the gorgeous trappings of painting or music, yet sublimely pure, and capable of a stern perfection such as only the greatest art can show. The true spirit of delight, the exaltation, the sense of being more than Man, which is the touchstone of the highest excellence, is to be found in mathematics as surely as in poetry.

- BERTRAND RUSSELL, Study of Mathematics

The Unreasonable Effectiveness of Mathematics in Molecular Biology*

My title is an emulation of that of the well-known paper by E.P. Wigner, "The unreasonable effectiveness of mathematics in the natural sciences [1]." Of course the irony cuts in opposite ways in physics and molecular biology. In physics, mathematics is obviously effective—

The Mathematical Universe

Max Tegmark

Received: 18 April 2007 / Accepted: 2 October 2007 / Published online: 8 November 2007
© Springer Science+Business Media, LLC 2007

Abstract I explore physics implications of the *External Reality Hypothesis* (ERH) that there exists an external physical reality completely independent of us humans. I argue that with a sufficiently broad definition of mathematics, it implies the *Mathematical Universe Hypothesis* (MUH) that our physical world is an abstract mathematical structure. I discuss various implications of the ERH and MUH, ranging from standard physics topics like symmetries, irreducible representations, units, free para-

THE UNREASONABLE EFFECTIVENESS OF MATHEMATICS

R. W. HAMMING

Prologue. It is evident from the title that this is a philosophical discussion. I shall not apologize for the philosophy, though I am well aware that most scientists, engineers, and mathematicians have little regard for it; instead, I shall give this short prologue to justify the approach.

Man, so far as we know, has always wondered about himself, the world around him, and what life is all about. We have many myths from the past that tell how and why God, or the gods, made man and the universe. These I shall call *theological explanations.* They have one principal characteristic in common—there is little point in asking why things are the way they are, since we are given mainly a description of the creation as the gods chose to do it.

Philosophy started when man began to wonder about the world outside of this theological framework. An early example is the description by the philosophers that the world is made of earth, fire, water, and air. No doubt they were told at the time that the gods made things that way and to stop worrying about it.

Solving Wigner's Mystery: The Reasonable (Though Perhaps Limited) Effectiveness of Mathematics in the Natural Sciences

IVOR GRATTAN-GUINNESS

The Viewpoint column offers mathematicians the opportunity to write about any issue of interest to the international mathematical community. Disagreement and controversy are welcome. The views

Figure 5.2.1: A series of papers written after Wigner's famous article published in 1960 Wigner (1995). Several famous scientists of the time responded to this paper, by expanding the ideas to particular fields, among which are Hamming (1980), Lesk (2000), Tegmark (2008), and Grattan-Guinness (2008).

This step is the step in which we make our decisions. We decide what details to include or ignore. We decide what are the concrete questions we want to answer. This will determine the right mathematical tools that we can use.

Summary 5.2 — Step I: Converting a natural phenomena to a mathematical problem.

(i) The most important thing: What is the question that we want to answer?

(ii) We make lots of decisions:

- What is the precision in the answer that we are looking for?
- What is the generality that we are after?
- What is an appropriate mathematical tool that can be used to model?

5.3 STEP II: Mathematical Analysis of the Model in Hand

After doing the STEP I appropriately, we will have a mathematical description of the phenomena in our hand. This mathematical formulation on the problem can come in my different flavors and forms, We can categorize them by considering their different aspects, like being a discrete or continuous model, being a deterministic or stochastic model, etc. Each of these formulations will

have its own appropriate way of treating. So I will discuss their subsequence steps separately.

5.3.1 STEP II: PDE models

After converting the natural phenomena to a mathematical model containing PDEs, we will have a domain, and a PDE. For instance, let $\Omega \subset \mathbb{R}^2$, and we define

$$\begin{aligned} -\Delta u &= g, && \text{on } \Omega, \\ u &= 0, && \text{on } \partial\Omega. \end{aligned}$$

In this particular problem, we have a domain, on which we are interested in finding a mapping $u : \Omega \to \mathbb{R}$ whose partial derivatives satisfies a certain equation. Our first goal is to determine if this problem has a solution (existence), and then to see if the problem as a unique solution (uniqueness), and then to see if the solution is stable (i.e. bounded by the given data).

Summary 5.3 Given a PDE in hand, it is important to see if the problem is well-posed (in the sense of Hadamard). I.e.

- a solution exists,
- the solution is unique, and
- the solution is stable.

Different Formulations of the Problem: Strong vs. Weak Formulation

To find the answers to these questions, we can formulate our problem in different ways, i.e. strong formulation, or a weak formulation. In the weak formation, we have more relaxed requirements on the solutions. For instance, for a classic solution to satisfy an elliptic Dirichlet boundary value problem, by definition, it needs to have two derivatives while being zero at the boundary (i.e. $u \in C_c^2(\Omega)$). However, we can relax this requirement by a kind of axiomatic extension of the set of possible solutions. For instance, we know that all $C_c^2(\Omega)$ functions has a nice interaction with $C_c^\infty(\Omega)$ functions through the integration by parts formula.

$$\int_\Omega \nabla u \nabla v = -\int_\Omega u \nabla v \qquad \forall v \in C_c^\infty(\Omega).$$

Thus we can use this property as a definition of derivative, and define the notion of the weak derivative. We can use this property to formulate the problem in weak sense.

$$\int_\Omega \nabla u \, \nabla v = \int_\Omega g v \qquad \forall v \in H_0^1(\Omega).$$

We can now write the problem in a more abstract form by defining bi-linear forms

$$a : H_0^1 \times H_0^1 \to \mathbb{R}, \qquad l : H_0^1 \to \mathbb{R}$$

and define

$$a(u, v) = \int_\Omega \nabla u \, \nabla v, \qquad l(v) = \int_\Omega g v.$$

Thus we can now write the weak formulation as the following abstract equation, i.e. we say u satisfies the boundary value problem stated above if it satisfies

$$\begin{aligned} &a(u, v) = l(v), && \forall v \in H_0^1, \\ &u = 0 \quad \text{on } \partial\Omega. \end{aligned}$$

well-Posedness

Writing the problem in hand in abstract form, helps us to use other existing mathematical infrastructure to understand if a solution exists, if it is unique, and if it is stable. For instance, writing the elliptic problem in the form of $a(u, v) = l(v)$ allows us to use the infrastructure developed in functional analysis to find the answers to our questions. For instance, in this particular case, we can use the Lax-Milgram theorem (which is a kind of generalization to the Ritz-representation theorem) to show that under certain conditions (i.e. the bi-linear form a being coercive and bounded, and the linear form l being bounded.) a solution exists, and is unique and stable (i.e. bounded by the data). Or in the case of the Stokes problem for the non-compressible fluid, we have the Ladyzhenskaya-Babuška-Brezzi condition (or LBB in short) which is also often called inf-sup condition, is a set of conditions under which the Stokes problem as a unique solution that is stable.

Summary 5.4 — Importance of formulating the mathematical problem appropriately. Formulating a mathematical problem in an appropriate way is very crucial. Appropriate formulations allows us to use the existing important theorems in a specific field of mathematics to our advantage. For instance, by formulating a PDE in weak form and using suitable forms, we can use

- Lax-Milgram theorem (generalized form of Ritz-representation theorem) to show the well-posedness of an elliptic problem under certain conditions.
- Ladyzhenskaya-Babuška-Brezzi theorem (or LBB in short) to show the well-posedness of the Stokes problem for non compressible fluid.

What kind of solutions do we need?

The well-posedness of a problem is a hunting license to find the actual solutions. Again, we need to revisits our main question in step I. What are we looking for? Is having a solutions in closed form necessary? Can having the solution in a series form (with a high or low convergence rate) enough? Can we get the answers to our question by some sort of qualitative analysis? Is a numerical solution necessary? **The exact answer to these questions depends on the questions that we want to answer with mathematical modeling.**

Summary 5.5 — Solutions to the PDE. After getting the hunting license and being sure about the well-posedness of the problem, we need to revisit our original question to decide what we want to do with the solution? The solution can be found in many ways that might be suitable for some cases and and overkill for other cases.

- closed form solution
- series solution (with poor or good convergence rate)
- some contracting map
- local solution (for local behaviour analysis)
- numerical solution
- etc.

Numerical Solution

After deciding on if we need a numerical solution, we can use different approaches, each of which has its own treatment. Here I will only talk about the finite element methods. In the finite element method, we find a suitable finite dimensional sub-space of the solution space (H_0^1 in the case of the elliptic Dirichlet problem) and formulate the problem in discrete form. For instance, if we can generate a triangulation of a domain Ω and define some local basis functions e.g. some continouse and piece-wise affine functions that each of them is non-zero only at one node. Thus we can express our function in the weak formulation in this form

$$u = \sum_{i=1}^{n} U_i \phi_i(x), \qquad g = \sum_{i=1}^{n} G_i \phi_i(x).$$

By substituting this in the weak formulation, we will get the following system of linear equations

$$AU = G,$$

where the matrix A (stiffness matrix) and the vector G are the given data and we want to find the vector U. Or in the case of the Stokes problem, we will get the following system of equations.

$$\begin{aligned} AU + BP &= F, \\ B^T U &= 0. \end{aligned}$$

Note: After projecting the problem to a finite dimensional sub-space, it is not necessarily true the the well-posedness of the problem in the infinite dimensional Hilbert space carries over to the finite dimensional sub-space. For instance, in the case of the Stokes problem, the well-posedness does not carry over and we need to study the well-posedness of the discrete problem.

Error Estimate

Projecting an infinite dimensional space to a finite dimensional space introduces some errors that we need to be sure we can quantify and understand how does that error scales with the mesh size (i.e. the dimension of the finite dimensional sub-space).

5.4 What Is the Flux, Really?

Here in this section we will go deeper into the notion of flux in particle transport which is the central part mathematical modeling of living systems. I will try to connect this notion with mathematical objects with clear definitions rather than providing vague intuition.

Generally speaking, flux is a surface integral of some vector field, and by designing that vector field accurately, we can use the notion of flux in different contexts. Here we will design the notion of flux to study particles and their densities assuming they are non-compressible fluids. Let $\Omega \subset \mathbb{R}^3$. Define

$$J = \rho v$$

where

$$\rho : \Omega \times \mathbb{R} \to \mathbb{R}, \qquad v : \Omega \times \mathbb{R} \to \mathbb{R}^3,$$

representing the density and the velocity of the scalar field respectively. But what is the velocity of ρ? Here is the part where the notion of volume preserving diffeomorphisms become useful. Let

$X_0 \in \Omega$ denote the position of a point particle in the domain. Then its trajectory over time is determined by the action of the group $\{g^t\}_{t\in T}$ on X_0. For instance $X(t) = g^t X_0$. Since we have assumed that the species are in form of non-compressible fluids, then the group $\{g^t\}$ is a subgroup of the group of all diffeomorphisms that preserves the volume. For a fixed $X_0 \in \Omega$ its orbit is defined to be

$$\text{Orbit}(X_0) = \{g^t X_0 \mid t \in T\}.$$

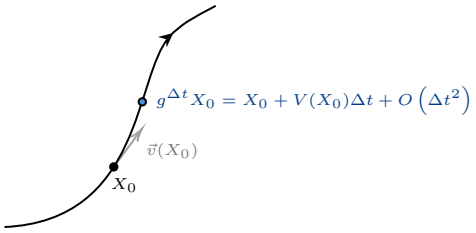
At any time t, $v(X,t)$ is defined to be

$$v(X,t) = \lim_{\Delta t \to 0} \frac{g^{t+\Delta t}X - g^t X}{\Delta t}$$

This means that for $X_0 \in A$ we can write

$$g^{\Delta t} X_0 = X_0 + \vec{v}(X_0)\Delta t + O(\Delta t^2)$$

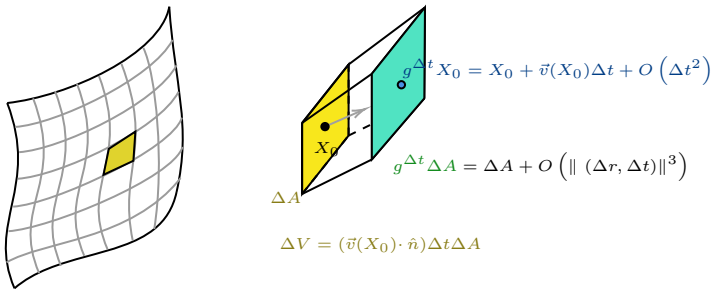
which means that the effect of $g^{\Delta t}$ on the point X_0 just shifting X_0 in the direction $\vec{v}(X_0)\Delta t$. In the figure below we can see this approximation on a particular orbit. Let σ be any surface given



in the domain. We claim that the rate of volume passing through this membrane is given by

$$\frac{dV}{dt} = \int_\sigma \vec{v} \cdot \hat{n}\, dA.$$

To see this ΔA be the area of a flat square tangent to the membrane at point X_0 on the surface. See the figure below.



We observe that the point X_0 moves to $X_0 + \vec{v}(X_0)\Delta t + (\Delta t^2)$. Also, observe that the area any point on ΔA distance Δr away from X_0 will be transferred to

$$g^{\Delta t}(X_0 + \Delta r) = X_0 + \Delta r + \vec{v}(X_0 + \Delta r)\Delta t + O(\Delta t^2) = (X_0 + \Delta r) + \vec{v}(X_0)\Delta t + O(\Delta t^2 + \Delta t \Delta r).$$

Thus the area of the green surface in the figure above will be the same as ΔA up to order $O((\Delta t^2 + \Delta t \Delta r)^2)$. Note that by the action of $g^{\Delta t}$, everything in between the yellow and green surfaces will move through the green surface. So the volume that will pass through the green surface is

$$\Delta V = (\vec{v}(X_0)\Delta t) \cdot \hat{n} \Delta A + O(\Delta t^2)$$

Given that the density of species is u, then the number species passed through the green membrane after time Δt will be

$$\frac{\Delta N}{\Delta t} = \vec{v}(X_0) \cdot \hat{n} \Delta A + O(\Delta t^2 + \Delta A^2)$$

I.e. we can write

$$\frac{dN}{dt} = \int_\sigma \vec{v} \cdot \hat{n} \, dA$$

Summary 5.6 In a nutshell, If we define

$$J = \rho v$$

where $\rho : \Omega \times \mathbb{R} \to \mathbb{R}$ is a function representing the density, and $v : \Omega \times \mathbb{R} \to \mathbb{R}^3$ is the tangent vector to the orbit of particles generated by the action of group of diffeomorphisms that preserve the volume element $\{g^t\}_{t \in T}$, then, for any surface $\sigma \subset \Omega$, the rate of particles passing through the membrane will be

$$\frac{dN}{dt} = \int_\sigma J \cdot \hat{n} \, dA.$$

Then by assuming that no particles will by destroyed to the thin air, and also no particles will born out of blue sky, then we can derive the continuity equation. In any volume V of our domain enclosed by the surface σ, we can write

$$\frac{d}{dt} \int_V \rho \, dV = - \int_\sigma J \cdot \hat{n} \, dA = - \int_V \nabla \cdot J dV.$$

By dropping the integration signs we will get

$$\frac{d\rho}{dt} + \nabla \cdot J = 0.$$

Observation 5.4.1 Reading the summary box above, one might conclude that the flux for diffusion might be something like $J = -\rho \nabla \rho$ as the particles are moving opposite to their gradient. But this is wrong! In the case of diffusion, the velocity field is

$$v = -\frac{1}{\rho} \nabla \rho$$

so the flux (Fick's law) will be of the form

$$J = -\nabla \rho.$$

At first, it was as very bizarre observation for me. I still do not understand how I can derive this velocity profile (i.e. flow velocity or simply flow).

5.5 Some cool PDE simulations

Living in this level of abstraction, we can now do some stuff with PDEs that might look magic at the first glace. Here, I will show case some of these simulations.

5.5.1 Diffusion and Advection

Be aware of the context. Note that in this section, when we talk about the vector field F, we are actually talking about the vector field that determines the advection term of the flux. I.e. we assume F is

$$J_{\text{advection}} = \rho F$$

To have diffusion and advection at the same time, we need to design the flow in a way that can produce this. The first term of will be for the diffusion, where according to the observation box above will be of the form

$$J = -\nabla\rho + \underbrace{\cdots}_{\text{advection term}}$$

To design the advection term, we need to observe that the particles should move along side some vector field. So it will be of the form

$$\boxed{J_{\text{advection}} = \rho F(X)}$$

where $F : \Omega \to \mathbb{R}^3$ is the desired vector field. So the advection-diffusion PDE will be

$$\frac{\partial \rho}{\partial t} = \nabla \cdot (-\nabla\rho + \rho F).$$

Now we can come up with all sort of creative vector fields.

Simple velocity field

For instance, for the vector field $F(x, y) = (-1, 0)$, we will have

$$\frac{\partial \rho}{\partial t} = \nabla^2\rho - \frac{\partial \rho}{\partial x}.$$

Then the solution of this model will be like the following figure.

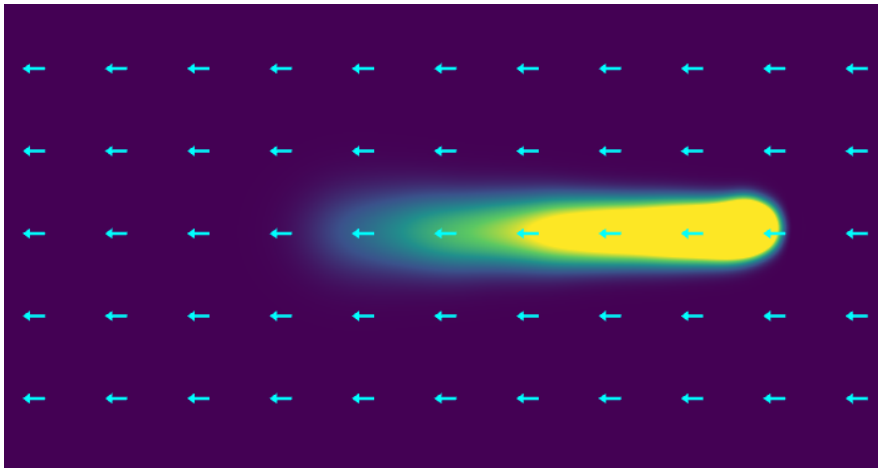


Figure 5.5.1: Advection diffusion with the vector field $F(x, y, z) = (-1, 0, 0)$. The designed PDE forces the particles to move in this velocity field (or velocity profile).

Particles Moving Down the Hill

Here, we design a vector field that resembles particles moving down a potential hill to get to their minimum potential state. To design such a vector field, we simply first define an appropriate potential function and define the vector field to be its gradient. The potential that we will using for this purpose is

$$f(x, y) = 1/2(x^2 + y^2).$$

Then the corresponding vector field will be

$$F(x, y) = -\nabla f(x, y) = (x, y).$$

So the desired PDE will be

$$\frac{\partial \rho}{\partial t} = \nabla^2 \rho + x\frac{\partial \rho}{\partial x} + y\frac{\partial \rho}{\partial y} + \rho.$$

Simulating this PDE we will get

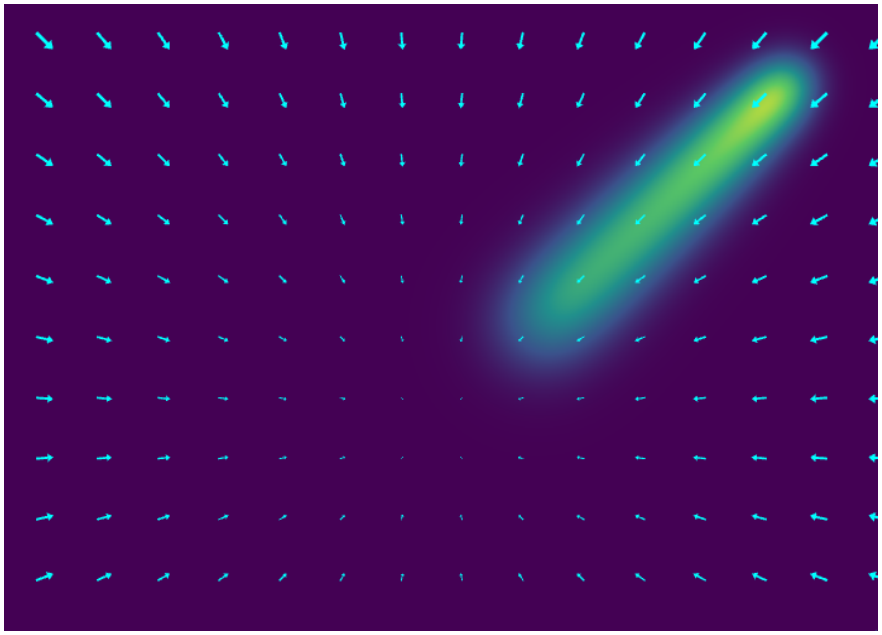


Figure 5.5.2: Advection diffusion with the vector field $F(x, y) = (x, y)$ which is the gradient of potential function $f(x, y) = 1/2(x^2 + y^2)$.

Moving Around the Origin

What if at each point, we rotate the vector vector of the previous example by 90 degrees so that the particles will move around the origin. The vector field in previous example was $F(x, y) = (x, y)$. To do the rotation we need ot multiply that in the rotation matrix

$$F_{\text{new}}(x, y) = \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix} F(x, y) = \begin{pmatrix} -y \\ x \end{pmatrix}.$$

Thus the desired PDE will be

$$\frac{\partial \rho}{\partial t} = \nabla^2 \rho - y\frac{\partial \rho}{\partial x} + x\frac{\partial \rho}{\partial y}.$$

By simulating this PDE we will get

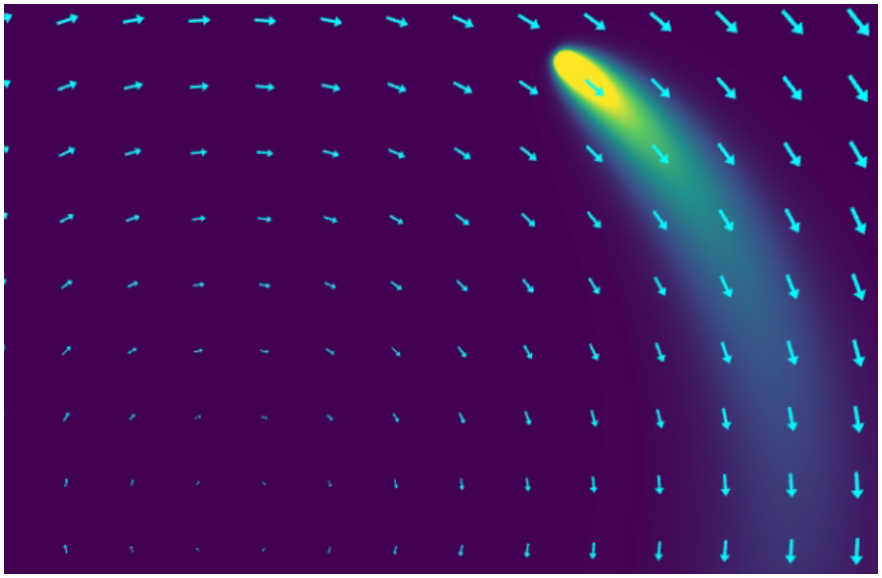


Figure 5.5.3: Advection diffusion with the vector field $F(x, y, z) = (-y, x)$. This vector field is derived by rotating the vectors in the previous example by 90 degrees. Surprisingly, there are no potentials that F ce be its gradient! In other words, we can not derive F from any potential.

Spiraling in to the Origin

We can start with the vector field $F(x, y) = (x, y)$ and this time, instead of rotating it with a rotation matrix, we can rotate that using a matrix corresponding to a complex number $z = \mu + i\omega$, i.e.

$$F_{\text{new}}(x, y) = \begin{pmatrix} \mu & -\omega \\ \omega & \mu \end{pmatrix} F(x, y).$$

We can take this complex number to be $z = -1 + i$. Thus our new vector field will be

$$F_{\text{new}}(x, y) = (-x + y, -x - y).$$

So our PDE will read

$$\frac{\partial \rho}{\partial t} = \nabla^2 \rho + (-x + y)\frac{\partial \rho}{\partial x} + (-x - y)\frac{\partial \rho}{\partial y} - 2\rho.$$

Simulating this PDE we will get

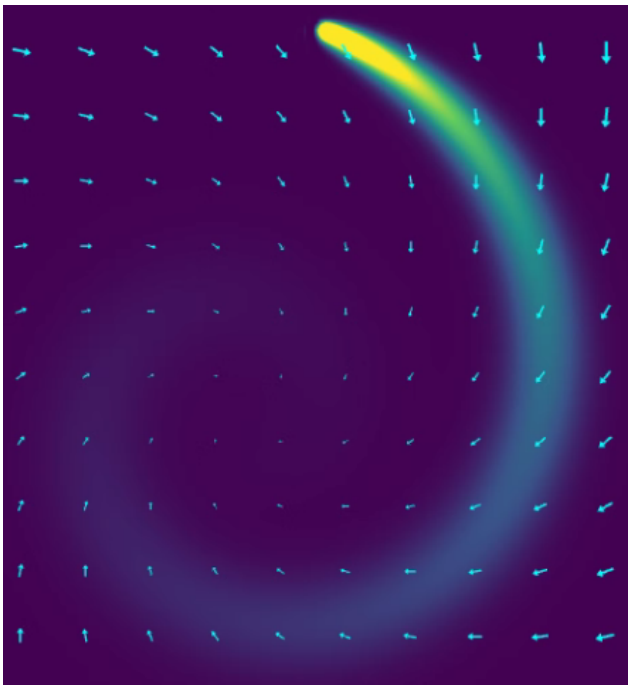


Figure 5.5.4: Advection diffusion with the vector field $F_{\text{advection}}(x, y, z) = (-x + y, -x - y)$.

Now the interesting question is why do we see this? To observe this, remember that the velocity profile is the same as the vector field that we specify for the model (in this case $F_{\text{new}}(x, y)$). On the other hand, we know that the velocity profile is in fact the right hand side of the ODE for flow

$$\frac{d\phi}{dt} = F_{\text{new}}(x, y).$$

Note that ϕ is flow, or following the terminology of Summary 5.6, it is one element of the group diffeomorphisms that preserve the volume element (in the that terminology we denote it by g^t). For the simulation above, ODE for $\phi : \mathbb{R}^2 \to \mathbb{R}^2$ is

$$\begin{pmatrix} \dot{\phi_1} \\ \dot{\phi_2} \end{pmatrix} = \begin{pmatrix} -1 & 1 \\ -1 & -1 \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix}.$$

The phase plane of flow will be

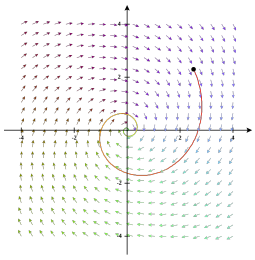


Figure 5.5.5: The phase plane of flow $\phi_{\text{advection}} = (\phi_1, \phi_2)$

The following summary box summarizes our observation.

Summary 5.7 — Advection-Diffusion PDE. In an advection diffusion PDE for ρ the flux will have two terms,

$$J = \underbrace{-D\nabla\rho}_{J_{\text{diffusion}}=\rho v_{\text{diffusion}}} + \underbrace{\rho F}_{J_{\text{advection}}=\rho v_{\text{advection}}}$$

where F is a vector field, which is the velocity profile of advection (i.e. $v_{\text{advection}} = F$). Thus the flow (or in the terminology of Summary 5.6 the diffeomorphism preserving the volume element) will be given with the following ODE

$$\frac{d\phi_{\text{advection}}}{dt} = v_{\text{advection}}.$$

In the cases where we have small diffusion, the solution of the advection-diffusion PDE will look like the phase plane diagram of $\phi_{\text{advection}}$. Compare Figure 5.5.4 with Figure 5.5.5 to see this.

Observation 5.5.1 Given what we discussed above, I have the following idea to study the phase plane of an ODE system in a wise way! Consider the following ODE system

$$\dot{\Phi} = F(\Phi).$$

In the corresponding phase space diagram, we usually plot the vector field $F(X)$ and roughly draw some important orbits (see Figure 5.5.5). However, using the machinery we discussed in the summary box above, we can also evaluate what will happen for a given volume of initial positions (i.e. a volume of phase space). We can design a PDE whose flow is given by Φ. Thus this PDE will be

$$\frac{\partial\rho}{\partial t} = -\nabla\cdot(\rho F(\Phi)),$$

where ρ represents the density of states in the phase space. Note that the equation above is nothing more that just inserting an appropriate choice of flux into the continuity equation.

Observation 5.5.2 — A proof for Liouville's theorem (Hamiltonian). After doing some research, I found out that the approach I have had in the observation above can be used to prove the Liouville's theorem for Hamiltonian. This was an independent discovery and proof of this theorem!

Proof. consider the following Hamiltonian system

$$\Phi = \begin{pmatrix}\dot{q}\\ \dot{p}\end{pmatrix} = \begin{pmatrix}\partial H/\partial p\\ -\partial H/\partial q\end{pmatrix} = F(\Phi).$$

Let ρ be the density of states in the phase plane, since all of these points are following the flow profile, thus the corresponding flux will be

$$J = \rho\Phi.$$

Inserting this into the continuity equation we will get

$$\frac{\partial\rho}{\partial t} = -\nabla\cdot(\rho\Phi) = -\nabla\rho\cdot\Phi - \rho\nabla\cdot\Phi.$$

For the first term in the right hand side we have

$$\nabla\rho\cdot\phi=\frac{\partial\rho}{\partial q}\cdot q+\frac{\partial\rho}{\partial p}\cdot p.$$

And for the second term we can write

$$\rho\nabla\cdot\Phi=\rho(\frac{\partial^2H}{\partial q\partial p}-\frac{\partial^2H}{\partial p\partial q})=0.$$

Thus we can write

$$\frac{\partial\rho}{\partial t}+(\frac{\partial\rho}{\partial q}\cdot q+\frac{\partial\rho}{\partial p}\cdot p)=0.$$

This completes the proof. □

Observation 5.5.3 The time evolution of the density of a die in an *incompressible fluid* due to *advection*, i.e. with the flux given by

$$J=\rho v$$

is analogous to the time evolution of the density of states in the phase plane of its flow Φ (determined by the equation $\dot{\Phi}=v$).

In the observation box above, we have only talked about the rationale behind the PDEs that contains only the advection term. But what about the diffusion term? What are the ODE systems where the density of states in its phase plane will have a diffusion like behaviour? The following important observation box answers this important question.

Observation 5.5.4 — Diffusion of the density of states in phase space. The statement of the question is as follows.

> I was studying the PDEs governing the time evolution of the concentration of some die in an incompressible fluid. I noticed this general framework behind that which can be applied to the time evolution of the density of states in the phase plane of an ODE system. Once we know the governing ODE for the state of a system, lets say
>
> $$\dot{X}=F(X)$$
>
> Then we can draw the phase plane with some important orbits in it. However, in order to find out what is the time evolution of the density of states, then we can easily find a corresponding PDE given by first defining $J=\rho F$ and then writing
>
> $$\rho_t=-\nabla\cdot(\rho F)=-\nabla\cdot(J).$$
>
> This gives the time evolution of a given density of states. In order to have a diffusion like behaviour in the phase plane, we should have $J=\rho F=-\nabla\rho$. This means that the corresponding RHS for ODE should be $F=-1/\rho\nabla\rho$ which does not make sense for me, as when writing the ODE for X the right hand side depends on the density of the states which does not makes sense in an ODE. So my question is that in what situation the density of states in and ODE system will have a diffusion like behaviour?

The answer to this question has very deep roots in the stochastic vs. deterministic systems. The fact is that in *deterministic* ODEs, we will *never* observe a *diffusion like behaviour* in the density of states of phase plane. The diffusion like behaviour of the density of states happens only in the case of Stochastic Differential Equations (SDE). As in the case of deterministic ODE systems, defining a suitable flux and inserting it into the continuity equation gives us the PDE for the time evolution of the density of states, doing a similar process gives us the Fokker-Plank equation that describes the time evolution of the density of states (which is called probability density function in this context) of the corresponding SDE. Consider the following SDE

$$dX_t = \mu(X_t, t)dt + \sigma(X_t, t)dW_t,$$

where $\mu(X_t, t)$ is the drift and $D(X_t, t) = \sigma^2(X_t, t)/2$ is the diffusion coefficient. The corresponding Fokker-Plank equation for the probability density function $p(x, t)$ of the random variable X_t (analogous to the notion of the density of states in what we had discussed above) is given by

$$\frac{\partial}{\partial t}p(x, t) = -\frac{\partial}{\partial x}[\mu(x, t)p(x, t) - \frac{\partial}{\partial x}(D(x, t)p)].$$

Similarly, for the higher dimensions, the SDE will be of the form

$$d\mathbf{X_t} = \boldsymbol{\mu}(\mathbf{X_t}, t)dt + \boldsymbol{\sigma}(\mathbf{X_t}, t)d\mathbf{W_t},$$

where $\mathbf{X_t}$ and $\boldsymbol{\mu}$ are N dimensional vectors, and $\boldsymbol{\sigma}$ is $N \times M$ matrix, and $\mathbf{W_t}$ is an M dimensional Wiener process. Then the corresponding Fokker-Plank equation will be given as

$$\frac{\partial p}{\partial t} = -\nabla \cdot (p\boldsymbol{\mu} + \boldsymbol{\nabla} \cdot (p\mathbf{D}))$$

where the bold letter $\boldsymbol{\nabla}\cdot$ applied on a matrix outputs a vector where each row is the divergence of the rows of the input matrix, and the matrix $\mathbf{D} = \frac{1}{2}\boldsymbol{\sigma}\boldsymbol{\sigma}^{\boldsymbol{T}}$. See examples below for more details.

■ **Example 5.1 — 1D Diffusion Equation.** Consider the following SDE

$$dX_t = \sqrt{D}dW_t.$$

The PDE governing the density of states (or the probability density function), i.e. the Fokker-Plank equation is given by

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial x}(-D\frac{\partial p}{\partial x}) = D\frac{\partial^2 p}{\partial x^2},$$

which gives rise to the 1D diffusion equation. ■

■ **Example 5.2 — 2D Diffusion Equation.** Consider the following system of SDEs

$$\begin{pmatrix} dX_t \\ dY_t \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} dW_t^{[1]} \\ dW_t^{[2]} \end{pmatrix}.$$

The corresponding Fokker-Plank equation will be

$$\frac{\partial p}{\partial x} = \nabla \cdot (\boldsymbol{\nabla} \cdot \begin{pmatrix} p & 0 \\ 0 & p \end{pmatrix}) = \nabla \cdot (\begin{pmatrix} p_x \\ p_y \end{pmatrix}) = p_{xx} + p_{yy},$$

Which is the 2D diffusion equation. ■

■ **Example 5.3 — Advection Diffusion Equation.** For instance, if we have

$$\begin{pmatrix} dX_t \\ dY_t \end{pmatrix} = \mathbf{F}(X_t)dt + \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} dW_t^{[1]} \\ dW_t^{[2]} \end{pmatrix}.$$

Then the corresponding Fokker-Plank equation will be

$$\frac{\partial p}{\partial t} = -\nabla \cdot (-\boldsymbol{\nabla} \cdot (\begin{pmatrix} p & 0 \\ 0 & p \end{pmatrix}) + p\mathbf{F}) = -\nabla \cdot (-\nabla p + p\mathbf{F}).$$

which is nothing but the familiar advection-diffusion system. Note that first term inside the parenthesis is the Fick's first law and the second term is taking care of the fact that the particles are advecting according to the vector field $\mathbf{F}$. ■

■ **Example 5.4 — Boltzmann Distribution at the Thermodynamic Equilibrium.** Consider the following SDE that is the overdamped Langevin equation

$$dX_t = -\frac{1}{k_B T}(\nabla U)dt + dW_t.$$

Observe that similar to the example corresponding to Figure 5.5.2 we defined the vector field for advection (drift) term as the gradient of a potential function. Thus similar to the example mentioned above, the particles will following trajectories down the potential well. The corresponding Fokker-Plank equation will be

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial x}(-\frac{\partial p}{\partial x} - p\frac{1}{k_B T}\nabla U),$$

where we have kept writing the derivative of U as ∇U to emphasis it is the gradient of a potential, but in fact we have $\nabla U = \frac{\partial U}{\partial x}$. The steady state solution for the PDE above is

$$\frac{dp}{dx} = \frac{-p}{k_B T}\frac{dU}{dx}.$$

The solution of the ODE above is given by

$$\boxed{p(x) = Ae^{-\frac{U(x)}{k_B T}}}.$$

■

■ **Example 5.5 — Ornstein-Uhlenbeck process.** Consider the following SDE

$$dX_t = -X_t dt + dW_t.$$

Then the corresponding Fokker-Plank equation will be

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial x}(-px - p_x).$$

The steady state solution of this PDE will be given as

$$\frac{dp}{dx} = -px + c.$$

The solution of this differential equation is given as

$$\boxed{p(x) = Ae^{-x^2/2}}.$$

This model is used to model the financial markets. ■

Chapter 6

Meeting log

6.1 Meetings with Leah

6.1.1 29 Jan Meeting

- Fixing some errors in the eigenvalues for the main differential equations.
- Add the nullclines plot.
- Add the possible interactions between vascular networks and the drug

6.1.2 5 Feb Meeting

- Thinking again about including the decay of radiopharmaceuticals: This has both pros and cons. The pros is that
  - more realistic model,
  - it is always good to have same sort of decay in the model to ensure the stability.

  However, the downside is that radiation interacts more wildly with the the cells present in the mode. It can inhibit them (by killing them) which is in a non mass action or Hill function style. The killing mechanism follows the linear quadratic rule. Also, the radiation can have activation functionality on the same cells by simply causing crazy genetic mutations. **So decision on including the radiation term in the basic model should be done with extra care.**
- Doing qualitative analysis (not quantitative) with the nullclines and the change in parameters due to the drug interaction. This way we can capture the possible interactions with out considering the actual functional form of the interaction.
- After doing the qualitative analysis, I need to do some literature review to see what are the possible drug-vessel interactions (both radiation and chemical)
- Consider adding the tumor compartment. The tumor compartment can interact with the vascular network by
  - increasing the mobility of the tip cells: both by increasing chemotaxis agents, and also by loosens the extracellular matrix,
  - Any other interaction that needs to be determined carefully.
- Adding the condition under which the stability of p_2^0 is focus or node.

6.1.3 12 Feb Meeting

- Add the axis labels for the qualitative analysis, and edit the title.
- Consider the non-dimensionalization process to see if you can control the non-linear term.
- Add the section for drug-tissue interaction. Consider the possible simplifications of the model.

6.1.4 8 March Meeting

- To develop the PDEs for the model: Note the following facts: The blood vessels are not moving, but they are deposited by the moving endothelial cells.
- There should be no diffusion or advection terms in the PDE for ρ.
- Although the tip cells are diffusing as well, but we can consider their dynamics to be advection dominated diffusion. Thus no diffusion term at the moment.
- The advection speed of the tip cells is the same as the speed that they move in the bulk model.
- Try the traveling wave solution to the derived PDE.
- Be careful about the terms that can be simplified by the time scale separation argument.

6.1.5 12 March Meeting

- Things to discuss: going through the qualitative study once again, discussing why we can not have κ directly appearing in the non-dimensionalized version, discussing the effect of κ on the dynamics.
- $$\frac{\partial n}{\partial t} = D\frac{\partial^2 n}{\partial x^2} - \frac{\partial (nv)}{\partial x} + (\lambda_s - \delta_t)n - \kappa_2 n^2.$$
  This can be thought of as a model that $\lambda_b \to 0$.

6.1.6 20 March Meeting

- Jupiter: More analysis on the vertical asymptotic.
- Laurent: Drawing a diagram summerizing all of the different interactions happening
  - Effect of drug on vasculature
  - Effect of vasculature on tumor response
  - Effect of vasculature on drug delivery
  - Effect of tumor on all of these
  - what is the topology of the reaction graph?
- Jupiter: adaptive systems

- Leah: (1) I agree that vessel density is a good metric, and I suppose that often this is more easy to measure in scans of images than any other network property. I seriously doubt that you can estimate the number of loops or tips in 2D images for all but the very low density of vessels.

  (i) Eric asked: How do veins and arteries connect up. Good to look into this.

  (ii) He asked what causes more/less resistance to radiotherapy. Eric asked if you were thinking about devising some fractionation protocol that would result in tumor reduction overall.

  There was also a question about the effect of hypoxia - pro or anti tumor, pro or anti vessel growth etc.

  (iii) Tim asked if you were considering vessels to be tubes. I think it's OK to assume that the tubes emerge once the branches grow.

  (iv) Eric was asking what the model is describing, e.g. what timescale, etc. Do the vessels degrade over such timescale? Or do you want to consider a model where the growth rate v goes to 0 at steady state? [LEK: we are currently exploring a basic simple model with all parameters assumed to be constants.. but the eventual goal is to include the effect of tumor, and drug.. etc, and feedback between treatment and vessels.]

  (v) You did not yet mention the drug c, and how you might include it.

  (vi) Talk to Tim about his microtubule branching ABM.

  (vii) Do you really want to nondimensionalize the model? Jupiter as confused why n –> 1 always. It's due to the scaling. If you keep the original parameters, you can see how they affect the n and rho steady states.

  (viii) Jimmy said so far you focused on the angiogenesis, what about the tumor. It would be good to mention that this will be considered later.

  (ix) Laurent: will drug feed back on vasculature? will tumor affect vasculature?

  He and Jack also asked if tips diffuse.

  [We do not want to redo the model by the Helen Byre group, but we could include later the chemotaxis of tips towards the tumor, as well as a bit of tip diffusion.]

  (x) Talk to Jupiter about adaptive systems.

  (xi) Discussion about TA.

  (xii) General comments from me:

  - On every slide you show, you need to give credit to where you got images, tables, data, graphs etc that you did not create yourself, even if available on the web. It can be in small font, but it is essential in all talks.
  - I know you are still learning about TDA. But I am doubtful whether it will be helpful to us since (1) we have few images, if any to analyse (2) the images are all in 2D, so vessels overlap or disappear into the 3rd dimension (what you called blunt ends) making it tricky or impossible to detect true loops or other features. Density seems reasonable.

6.2 Meetings with Arman

Chapter 7

Comments

7.1 Leah Comments Jan 24, 2024

Please change the citation style to Author et al (year) in place of [number], so it is easier to see who you are citing without having to flip to the bibliography. Thanks for linking the bibliography to the URLs of the papers so it's possible to scan them.

When citing papers, it is best if you can also say 1-2 sentences about those papers, even based on their abstract (in your own words, of course, never copied directly). For example:

Byrne (2010) reviews theoretical cancer models and demonstrates the advantages of colaboration between modelers and experimentalists.

7.1.1 Suggested research style and flavour

Since it is unlikely that we will get data for the detailed mechanochemical mechanisms for blood vessel growth in the prostate tumors, it makes sense to (a) start simple from very minimal models that can be linked to data and (b) avoid introducing variable that we have no hope of measuing in the obtained data. My understanding is that (for now) we will have to make do with at best some bulk properties of the blood vessels, so models with a lot of detail will hardly help us.

Here is a possible minimalistic stepwise approach, where we start very simple and gradually build up more detail, starting with simple assumptions.

Definitions:

$n(t)$= density of tip cells in area of interest, (number per unit area)

$\rho(t)$ = density of blood vessels (length per unit area),

$c(t)$ = concentration of drug delivered to region by blood vessels

7.1.2 Step 1: Bulk model

Ignoring spatial structure, we only track the density of vessels. Assume everything is spatially uniform, so there will be no spatial derivatives to consider. We construct an ODE model, and make an elementary assumption.

Assumption 1: The drug is delivered by diffusion from the capillaries into the tissue. Hence, as a rough approximation, and (for now) neglecting the detailed structure of the vessel network, the amount of drug delivered to the region per unit time is proportional to the density of the blood vessels.

Step 1a: Elementary model:

Assume that tips extend at some rate v (units of length/time), creating additional length of capillaries as they extend. Assume capillaries may also have some loss rate δ (per unit time). Write down an ODE for the rate at which capillary density changes with time.

$$\frac{d\rho}{dt} = ?? \tag{7.1.1a}$$

Assume that new tip cells are created by branching along sides of vessels (or possibly by splitting of existing tip cells) at a rate β per unit length per unit time, and that tips disappear when they reconnect to a capillary at some rate κ to form a loop. [Note: reconnection requires the interaction of tips with capillaries, and would thus be handled as mass action term. What are the units of κ?] Write down an equation for the rate of change of tip density.

$$\frac{dn}{dt} = ?? \tag{7.1.1b}$$

Complete the ODE model equations (7.1.1). Analyse the model so far by determining the steady state densities ρ_{ss}, n_{ss}, and how they depend on the parameters v, δ, β, κ. Determine stability of SS. Create a phase plane diagram that shows the expected dynamics. Simulate the simple ODE system assuming some values of the parameters.

We made the assumption that drug delivery is roughly proportional to the vessel density. Write down an approximate ODE for concentration of drug in the region.

$$\frac{dc}{dt} = ?? \tag{7.1.1c}$$

Explain how this level of drug depends on the vessel branching and growth parameters.

So far, the blood vessels affect the drug but not the other way around.

Step 1b: Coupling vessel dynamics to drug

Consider how the level of drug might affect the vessel parameters (branching or growth rate or death rate, etc). This will introduce feedback from the drug to the vessel density.

Write down one or two variants of such a model and analyse them fully (including steady states, simulations, and some interpretation of what it means for overall treatment of the tissue.)

Note that the drug dynamics would be fast on the timescale of vessel growth, so there is some time-scale separation that you can take advantage of.

7.1.3 (Optional) Step 2: Simple spatially distributed 1D system

We continue with simplest model but now take spatial growth of vessels into a region. So we consider $\rho(x,t), n(x,t), c(x,t)$ as variables of interest. We make the same assumptions as above, but now we take into account the fact that there is a flux of tips growing into a region,

$$J = nv.$$

Explain why this is a flux. The equations will be modified to form PDEs. Use the 1D balance equation to create that equation for n. Explain whether you need to add any spatial derivatives to the equation for ρ. The drug diffusion in the spatial variable will also introduce spatial derivatives in the equation for c. Write down the modified 1D spatial model. Note that we do not assume anything like chemotaxis or other fancy mechanisms for the tip motion at this point.

$$\frac{\partial \rho}{\partial t} = ? \tag{7.1.2a}$$

$$\frac{\partial n}{\partial t} = ? \tag{7.1.2b}$$

$$\frac{\partial c}{\partial t} = ? \tag{7.1.2c}$$

Remark: see above for timescale separation.

Step 2a: Analysis of wave of invasion

Consider looking for traveling wave solutions of the ρ, n system on its own to ask how blood vessels spread along a 1D direction and invade a tissue. (Write down ODEs by transforming variables to $z = x - ct$ where c is wave speed, then analyze existence of traveling was in the ρn phase plane. See one of my books or ask Jack Hughes for help if you are not yet familiar with this idea.)

Step 2b: Simulations For simulations of the whole system: You will need to assume some boundary conditions on n and on c, as well as some initial distribution in order to simulate this system.

7.1.4 Step 3: An agent-based (CPM) model:

Look up the simplest work on Merks and Rens and co and find their CPM model. Ask whether a Morpheus xml file already exists for this model (can ask the Morpheus team or Merks). If not, create one.

Set up this model and adapt it to describing a simple branching vessel structure, similar to what we have above.

ADD: assume that the cells in this network "secrete" drug that then diffuses into the tissue and has some decay time. Find ways of plotting properties of the vessels and the drug concentration.

Here you can get creative, and assume that the tip cell growth etc are affected by drug level, etc. (Again, time scale separation is important.)

Your role will be to extend the Merks model to include this drug aspect.

NOTE: some of Merk's work includes the dynamics of an ECM. I would suggest to avoid extending the model with such a dynamic variable, and to assume instead, that it is a static field or vector-field that affects the rate or direction of tip cell motion.

7.1.5 Step 4: Look for data

This can be done in parallel with other steps: look for specific data on blood vessel density in normal and cancerous tissue. There may be animal studies in which the vessel density is tracked over time.

Find if there is data that we can use to help constrain any of these simple models.

For sure it's easier to find bulk vessel density than to find its spatial distribution and the chemical factors liek VEGF that are modeled in some papers.

7.1.6 Step 5: More details and other variants

You can later (after all the early steps) extend and improve the model in various ways. Some suggestions include the following:

- Write down an equation for the number of loops that accumulate as tips reconnect to blood vessels (extend simple model).
- Find a way to associate these with "tortuosity" of vessel network that could affect its conductivity of drug to tissue.
- Consider some kind of D'Arcy's Law (porous medium) as a measure of how vessel structure can reduce net drug delivery.
- Vessels have various radii and sizes. You may want to consider how this affects the model as well as the implications on drug delivery. A PDE model with a distribution of vessel diameters would likely be a bit newer than the above simple branching equations.

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