My Findings

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Contents

Chapter 1

Modeling Attempts

1.1 Simple ODE model (First Iteration)

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

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

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 1.1.1 — 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 1.1.2 — 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

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

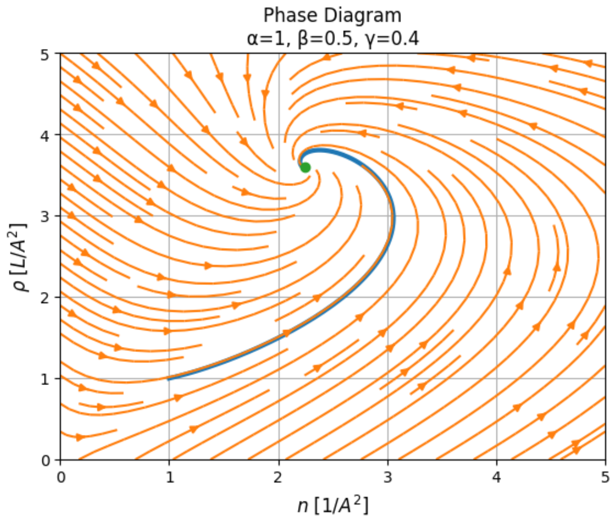
The determinant and the trace will be

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

Observation 1.1.3 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

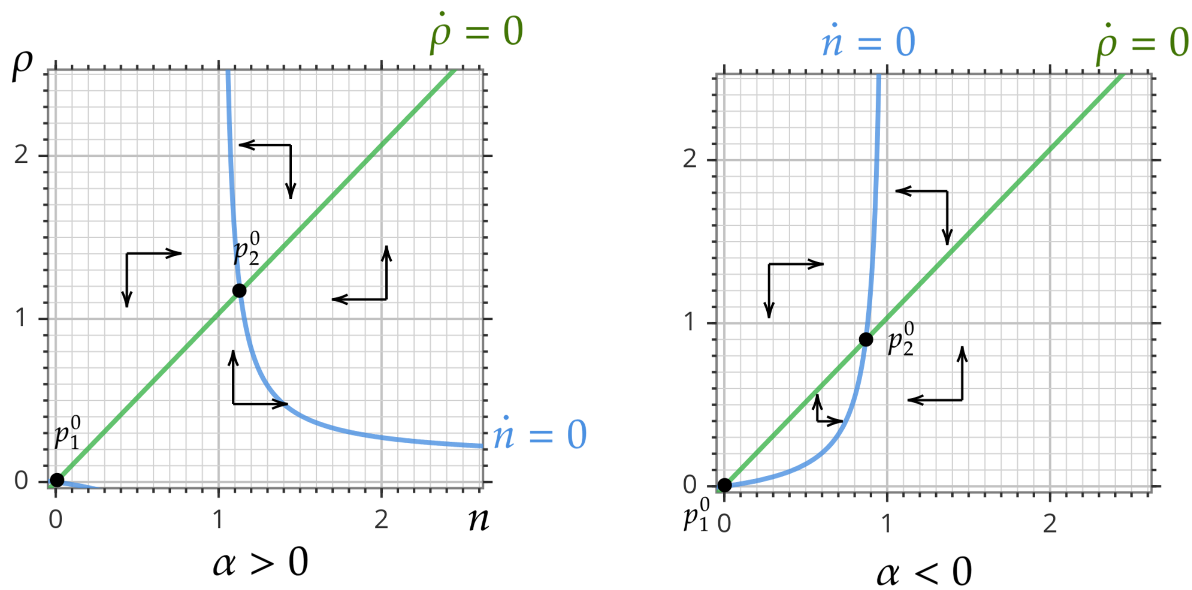
$$\begin{pmatrix} \dot{n} \\ \dot{\rho} \end{pmatrix} = \begin{pmatrix} f_1(n,\rho) \\ f_2(n,\rho) \end{pmatrix} = \begin{pmatrix} \frac{\alpha}{\beta} n + \rho - n\rho \\ \frac{\gamma}{\beta^2} n - \rho \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}.$$

After a little bit of algebra, we get

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

Observation 1.1.4 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 1.1.5 — 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.

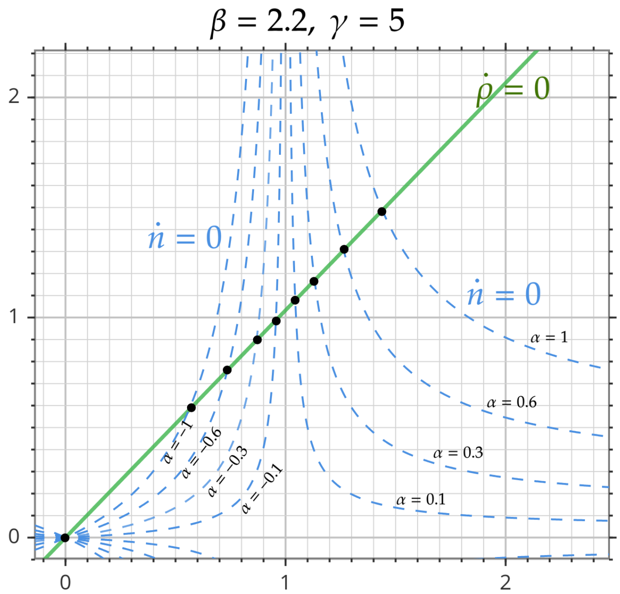
Observation 1.1.6 — Biological meaning of α. From (♣) we see that $\alpha = \lambda_s - \delta_t$, where λ_s is the tip cell division rate (which leads to vascular splitting), and δ_t is the death rate of the tip cells. Thus $\alpha > 0$ translates to larger division rate compared to the death rate for 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.

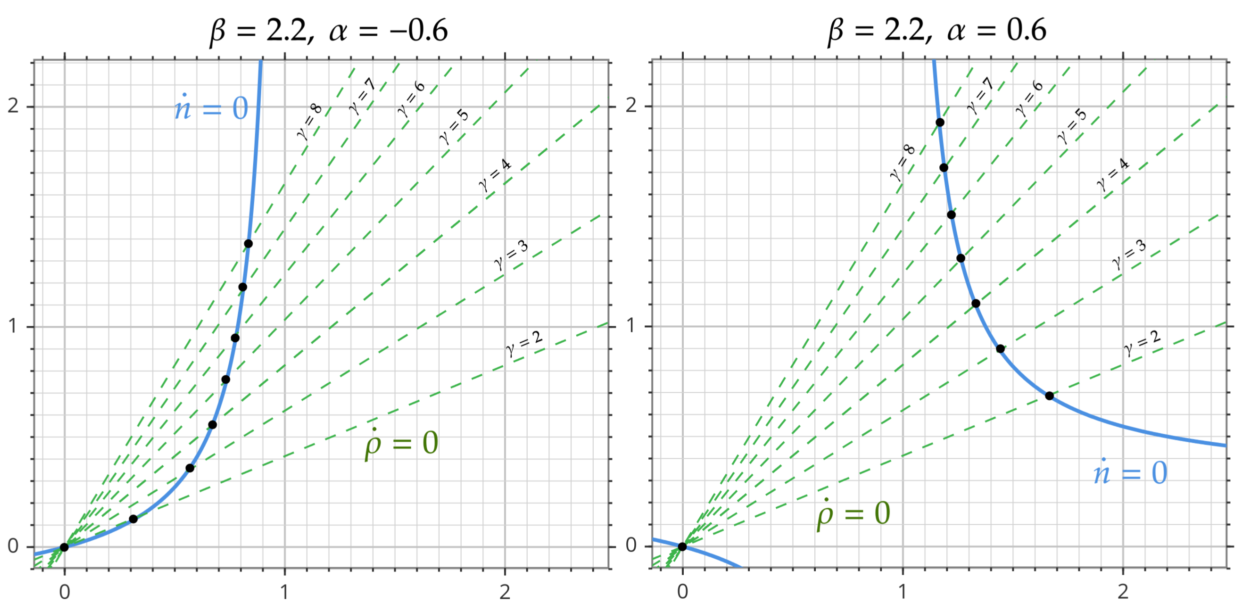
Effect of α

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.



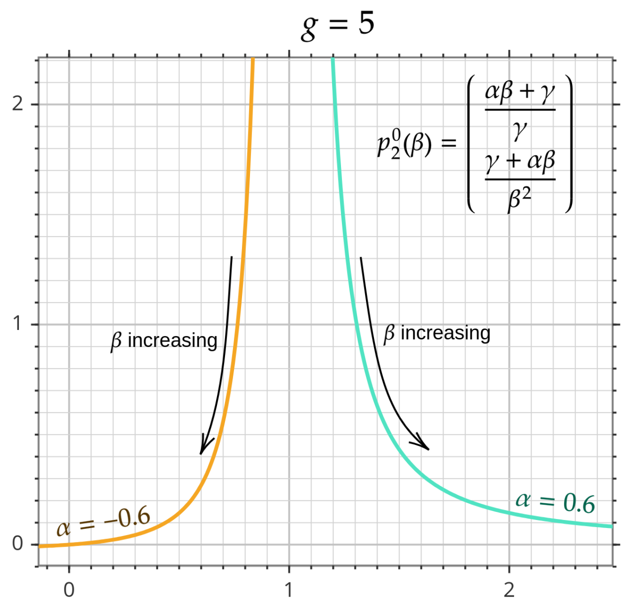
Effect of γ

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.

1.2 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.

1.2.1 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.

1.2.2 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:

$$\frac{\partial \rho}{\partial t} = vn - \delta_v \rho, \tag{1.2.1}$$

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:

$$\frac{\partial n}{\partial t} + \frac{\partial (nv)}{\partial x} = (\lambda_s - \delta_t)n + \lambda_b \rho - \kappa n \rho, \tag{1.2.2}$$

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:

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} - \mu c + f(x,t), \tag{1.2.3}$$

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.

1.3 Some Ideas to Try

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

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

2.1.1 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.

2.1.2 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.

2.1.3 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).

2.1.4 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.

2.1.5 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 (1995); 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

discuss 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

present 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

develop 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

describe 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

discuss 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

ocus 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 3

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.

3.1 Molecular Mechanism of Angiogenesis

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.

Controlling Capillary Joining Process

In the following text from Alberts u. a. (2002), 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.

Formation of tube structures by endothelial cells

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. (2002) 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.

3.2 Biological Assays to Study Angiogenesis

3.2.1 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)

Chapter 4

Meeting log

4.1 Meetings with Leah

4.1.1 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

4.1.2 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.

4.1.3 12 Feb Meeting (Joint Meeting with Arman)

- Add the axis labels for the qualitative analysis, and edit the title.

4.2 Meetings with Arman

Chapter 5

Comments

5.1 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.

5.1.1 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

5.1.2 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.

$$\frac{d\rho}{dt} = ?? \tag{5.1.1a}$$

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.

$$\frac{dn}{dt} = ?? \tag{5.1.1b}$$

Complete the ODE model equations (5.1.1). 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.

$$\frac{dc}{dt} = ?? \tag{5.1.1c}$$

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.

5.1.3 (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.

$$\frac{\partial \rho}{\partial t} = ? \tag{5.1.2a}$$
$$\frac{\partial n}{\partial t} = ? \tag{5.1.2b}$$
$$\frac{\partial c}{\partial t} = ? \tag{5.1.2c}$$

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.

5.1.4 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.

5.1.5 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.

5.1.6 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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