

# My Findings

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# 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.
- $\delta_v$  [1/time]: The rate at which the vascular structure gets degraded.
- $\lambda_s$  [1/time]: Tip cell division rate (splitting rate).
- $\lambda_b$  [1/time/length]: Tip cell emerging rate from stalk cells.
- $\delta_t$  [1/time]: Tip cell death/deactivation rate.
- $\kappa$  [area/length/time]: Re-connection of tip cells to the other capillaries to form loops.
- $\mu$  [1/time]: The rate at which
- $\sigma$  [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  $\delta$  [per unit time], we can add the degradation term

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

### 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  $\lambda_s$  [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  $\lambda_b$  [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  $\delta_t$
  - (ii) Joining the other branches of vascular network: When a tip cell reconnects another capillary branch, then they disappear. The parameter  $\kappa$  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  $\kappa$  should be [area/length/time].
- The movement of tip cells and formation of new vascular networks along the way.

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

### Nondimensionalization

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

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

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

$$\begin{aligned} \frac{d\tilde{\rho}}{d\tau} &= \frac{vNT}{R}\tilde{n} - \delta_v T\tilde{\rho}, \\ \frac{d\tilde{n}}{d\tau} &= T(\lambda_s - \delta_t)\tilde{n} + \frac{\lambda_b TR}{N}\tilde{\rho} - T\kappa R\tilde{n}\tilde{\rho}. \end{aligned} \tag{1}$$

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

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

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

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

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

$$\alpha = \lambda_s - \delta_t, \quad \beta = \delta_v, \quad \gamma = v\lambda_b. \quad (\clubsuit)$$

Then we can write

$$\boxed{\begin{aligned} \dot{n} &= \frac{\alpha}{\beta} n + \rho - n\rho, \\ \dot{\rho} &= \frac{\gamma}{\beta^2} n - \rho. \end{aligned}} \quad (\odot)$$

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

$$p_1^0 = (0, 0), \quad p_2^0 = \left( \frac{\alpha\beta}{\gamma} + 1, \frac{\gamma}{\beta^2} + \frac{\alpha}{\beta} \right) = \left( \frac{\alpha\beta + \gamma}{\gamma}, \frac{\gamma + \alpha\beta}{\beta^2} \right).$$

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

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

By close inspection, it turns out that  $\Delta$  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  $(\clubsuit)$ ,  $\gamma > 0$ . Thus  $\sigma < 0$ . This indicates that the equilibrium point  $p_2^0$  is stable equilibrium. Also, note that since  $\sigma$  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

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

Thus equilibrium point  $p_2^0$  is a hyperbolic sink (when  $\delta > 0$ ). When  $\Delta > 0$ , then we have two imaginary eigenvalues

$$\lambda_1 = \sigma/2 + i\sqrt{\Delta}, \quad \lambda_2 = \sigma/2 - i\sqrt{\Delta}.$$

where  $\sigma$  is always negative. This implies that  $p_2^0$  will always be a stable focus and the equilibrium point will be approached in a damping oscillatory way.

In the special case where  $\Delta = 0$ , we will have  $p_2^0 = p_1^0$ , thus it will inherit the stability of  $p_0^1$ .

**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  $(\mathcal{N})$ , we can not make the first term of RHS of  $\dot{\rho}$  and the second term of RHS of  $\dot{n}$  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

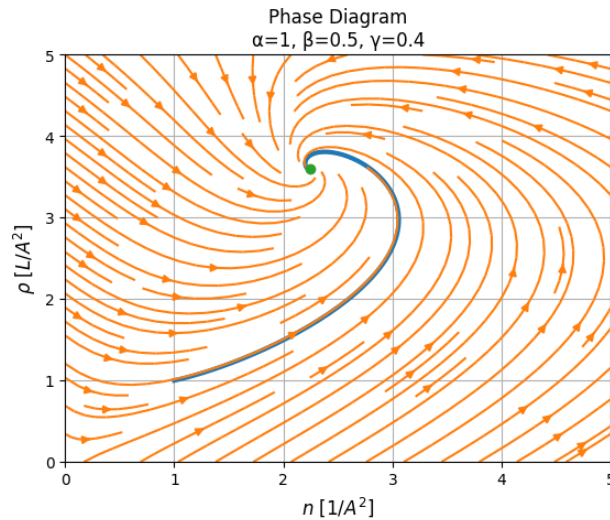
$$DF[p_1^0] = \begin{pmatrix} \alpha/\beta & 1 \\ \gamma/\beta^2 & -1 \end{pmatrix}.$$

The determinant and the trace will be

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

**Observation 1.1.3** The determinant  $\Delta$  is negative the first term of the  $p_2^0$ . Thus  $\Delta \leq 0$ . When  $\Delta < 0$ , then regardless of value of  $\sigma$ ,  $p_1^0$  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.



### Adding the drug-vessel interaction

In order to bring the drug-vessel interaction into play, we develop a ODE for  $c(t)$  add appropriate 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  $\mu$  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  $\sigma$  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.

## 1.2 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 on:** 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

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

where  $\mathcal{A} : P \rightarrow M$  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 nutrient 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. (2007)

### 2.1.6 Results

## 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 hollow 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 ([cornealMicroPocketAssayJOVE](#))

## Chapter 4

# Meeting log

### 4.0.1 29 Jan Meeting with Leah

Things to discuss

- Citation with Year-Author style, or Number Style?

## 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 collaboration 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 measuring 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  $\delta$  (per unit time). Write down an ODE for the rate at which capillary density changes with time.

$$\frac{d\rho}{dt} = ?? \quad (5.1.1a)$$

Assume that new tip cells are created by branching along sides of vessels (or possibly by splitting of existing tip cells) at a rate  $\beta$  per unit length per unit time, and that tips disappear when they reconnect to a capillary at some rate  $\kappa$  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  $\kappa$ ?] Write down an equation for the rate of change of tip density.

$$\frac{dn}{dt} = ?? \quad (5.1.1b)$$

Complete the ODE model equations (5.1.1). Analyse the model so far by determining the steady state densities  $\rho_{ss}, n_{ss}$ , and how they depend on the parameters  $v, \delta, \beta, \kappa$ . 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.

$$\frac{dc}{dt} = ?? \quad (5.1.1c)$$

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  $\rho$ . 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.

$$\frac{\partial \rho}{\partial t} = ? \quad (5.1.2a)$$

$$\frac{\partial n}{\partial t} = ? \quad (5.1.2b)$$

$$\frac{\partial c}{\partial t} = ? \quad (5.1.2c)$$

Remark: see above for timescale separation.

### Step 2a: Analysis of wave of invasion

Consider looking for traveling wave solutions of the  $\rho, n$  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  $\rho n$  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 like 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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